CPQ Medicine (2023) 15:1
Review Article

Cannabidiol as a Novel Therapeutic for Skin Treatments

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Received: 16 June 2023

Published: 13 July 2023

Keywords: *Cannabidiol; Endocannabinoid System; Psoriasis; Acne; Skin Aging*

Abstract

Cannabinoids display potential therapeutic applications. Regarding cannabidiol (CBD) to skin application, it shows an anti-inflammatory and antioxidant effect. Therefore, it has potential application in the treatment of acne, dermatitis, psoriasis, and on aged skin. CBD modulates several receptors of the endocannabinoid system of the skin (ECS) which are found all over skin components such as fibroblasts, keratinocytes, and sebaceous glands. In this review, CBD applications to skin treatments as well as the proposed mechanisms of action of CBD were described. The reports evaluated CBD effects alone or associated with other ingredient, *in vitro* or *in vivo* assays. The clinical trials, although incipient, showed the potential applications of CBD. Moreover, modulation of transient receptors potential channels family is believed to be related to its anti-acne, anti-atopic dermatitis and anti-aging properties. On the other hand, the anti-psoriasis activity is probably related to modulation of G protein-coupled receptor 55 and peroxisome proliferator-

activated receptor gamma. The use of CBD for skin disorders is promising. Nonetheless, further research and a better understanding of CBD mechanisms of action are required.

Introduction

For thousands of years, *Cannabis spp*. has been employed with therapeutic purposes and as a source of phytocannabinoids. The two best-known phytocannabinoids are Δ9-tetrahydrocannabinol (Δ9-THC), and cannabidiol (CBD) [1]. The former is the main psychoative compound found in *Cannabis* while cannabidiol shows therapeutical potential for nervous system disorders. Beyond phytocannabinoids, endocannabinoids and synthetic cannabinoids also features therapeutic value [2,3]. Phytocannabinoids come from *C. sativa, C. indica e C.ruderalis* [3]. Diversely, endocannabinoids are cannabinoids of endogenous source. On the other hand, synthetic ones do not come from a natural source and they are not produced endogenously [2,3].

Biological effects of cannabinoids are due to their ability to modulate the endocannabinoid system (ECS), a complex molecular system found all over human organs. Currently, reports are directed towards understanding the modulation mechanisms of cannabinoids on the ECS [4]. As the endocannabinoid system is present in the skin, the understanding of the mechanisms and receptors involved in the skin ECS have been researched [5-7]. As a consequence, new skin treatments may be developed [4, 8-15]. Therefore, this report aims to highlight the potential of CBD to formulations designed to skin diseases treatment or cosmetic therapy. Furthermore, as ESC plays a fundamental role in cannabidiol effect, the main aspects and the most recent evidences regarding skin ECS will be discussed.

Endocannabinoid System of the Skin (ECS)

Endogenously, the human body produces several endocannabinoids, where anandamide and 2-arachidonoylglycerol (2-AG) are the most important ones [16]. These endogenous molecules are synthesized and metabolized by enzymes. In addition to endocannabinoids and enzymes, the ECS is composed of receptors, in which endocannabinoids and phytocannabinoids bind [4].

The cannabinoid receptor type 1 (CB1) and cannabinnoid receptor type 2 (CB2) are the oldest identified receptors, but several other receptors have already been identified such as the transient receptor potential channels (TRP), peroxisome proliferator-activated receptor (PPAR) [4], G protein-coupled receptores[16]. About TRP channels, there are the following subptypes: transient receptor potential vanilloid channels (TRPV), transient receptor potential ankyrin channels (TRPA), transient receptor potential melastatin channels (TRPM) [5]. TRPV channels are further divided into: TRPV1, TRPV2, TRVP3, TRPV-4 [17]. Regards to TRPA and TRPM, the most important are TRPA-1 and TRPM-8, respectively [5]. For PPAR and skin application, PPARγ is the principal [17]. TRPV channels, PPARγ as well as TRPA-1 and TRPM-8 are secundary targets of cannabinoids [17].

Concerning endocannabinoid system, skin components have more than one ECS receptor. Table 1 shows the main ECS receptors and the skin site where they are found. For instance, the fibroblasts and keratinocytes express CB1, CB2, PPARy, TRPV1, TRPV2, TRPV3, TRPV4, TRPA1. On the other hand, for sebaceous gland the following receptores CB1, CB2, TRPV1 are found. In immune cells, CB1, CB2, TRPV1, TRPV2, TRPV3, TRPV4, TRPA1, TRPM-8 are expressed. Hence, by knowing the receptors found in each skin component, cannabinoids can be topical applied to target one or several of these receptors [4].

Table 1: *Skin Endocannabinoid system*

Receptor	Subtype	Skin components
CB	CB1	Fibroblasts, Keratinocytes, Sebaceous glands, Nerve endings, Immune cells
	CB2	
PPAR	PPARγ	Keratinocytes, Fibroblasts
TRPV	TRPV1	Keratinocytes, Immune cells, Nerve endings, Sebaceous gland, Fibroblasts
	TRPV2	Keratinocytes, Fibroblasts, Nerve endings, Immune cells
	TRPV3	
	TRPV4	
TRPA	TRPA-1	Keratinocytes, Immune cells,Nerve endings,Fibroblasts
TRPM	TRPM-8	Immune cells, Nerve Endings

CB: cannabinoid receptor, CB1: cannabinoid receptor type 1, CB2: cannabinoid receptor type 2, PPAR: peroxisome proliferator-activated receptor, PPARγ: peroxisome proliferator-activated receptor gamma, TRPV : transient receptor potential channel, TRPV1: transient receptor potential vanilloid type-1, TRPV2: receptor potential vanilloid type-2, TRPV3: receptor potential vanilloid type-3, TRPV4: receptor potential vanilloid type-4, TRPA: transient receptor potential ankyrin channel, TRPA1: transient receptor potential ankyrin type-1, TRPM: transient receptor potential melastin channel, TRPM-8: transient receptor potential melastatin type-8.

Skin Applications of Cannabidiol

Cannabinoids may be used to improve skin health either in the treatment of skin disorders [15,18] or as cosmeceutical [15]. Regarding skin disorders, they may be useful in the treatment of inflammatory diseases such as psoriasis and acne [18]. Besides, cannabinoids also shows ability to reduce melanoma and non-melanoma skin cancer proliferation, and would then have a potential application to the treatment of these diseases [15]. As cosmeceuticals, phytocannabinoids improve skin healing [19] which is compromised in aged skin [20]. Therefore, an improved skin appearance can be achieved [19]. Moreover, cannabidiol features promising applications due to its anti-inflammatory and antioxidant effects [11].

Acne

As one of the most prevalent skin diseases, acne is an inflammatory disease causing increased sebum production [21] resulting in comedo and in inflammatory acne forms when there is *Cutibacterium acnes* [22]. Once traditional treatments are often associated with adverse effects, more effective new treatments need to be developed [22].

Cannabidiol have lipolytic an anti-inflammatory effect, which is essential for acne treatment [12]. Furthermore, *Cannabis* seed extract was able to reduce sebum production in a clinical study. In that report, isolated CBD was not used. Then, possibly the observed effects may be due to the association of cannabinoids found in *Cannabis* seed [23]. Nevertheless, there is a likely use of cannabinoids, including cannabidiol, in acne therapy.

Concerning mechanisms of action of cannabidiol in acne, its effect is possibly due to the activation of TRPV1[12,24], since it has low affinity to CB1 e CB2 [24]. Besides, CBD caused a upregulation of tribbles homolog 3 receptor, related to anti-inflammatory activity. The mechanisms, receptors and mediators involved in the CBD anti-acne activity [12] need to be better investigated in order to CBD-based acne treatments be more effective.

Skin Barrier Disorders

Stratum corneum is the outermost skin layer responsible for skin protection and to create the skin barrier. Disturbance of this barrier is related to dehydration of the skin and to atopic dermatitis and psoriasis [25,26]. Atopic dermatitis and psoriasis are complex diseases combining environmental and genetic factors [26] and they are related to systemic diseases [27,28]. Since patients affected by these diseases may have low life quality [29], alternatives to conventional treatments have been developed [27, 28, 30, 31].

The benefits of topical cannabidiol in atopic dermatitis have been shown both in clinical trials [32, 33] and in animal assays [14]. However, the number of volunteers in clinical trials is small [32, 33]. About animal assay, it is valuable in an initial development of CBD as drug candidate. However, further investigation in humans are necessary. Accordingly, additional studies need to be conducted to prove CBD efficaccy on atopic dermatitis.

The combination of CBD with other anti-inflammatory ingredients is also interesting. In this sense, aspartame associated with CBD had a greater anti-inflammatory activity than CBD alone, probably due to the synergistic anti-inflammatory effect of both CBD and aspartame [32]. Likewise, palmitoylethanolamide associated with CBD reduced inflammation. However, the results were not as satisfactory as the one obtained to mometasone, the traditional treatment. This denotes the need to better understand the effects of CBD and its associations in atopic dermatitis [14].

Apart from that, CBD topical use reduced the psoriasis severity [9]. Adverse effects were the same for the CBD-based product and for the control treatment [9], showing the probable safety of CBD use. Beyond that, reports aiming to detect oxidative stress markers [34, 35] showed that CBD inhibited reactive oxigen

species [34] and lipid peroxidation [35]. Oxidative stress occur in psoriasis. Then, the reduction of free radicals and of other secundary molecules oxidative stress-related may be of interest in achieving successful psoriasis therapy. Nonetheless, additional researches are need to to prove CBD efficacy in psoriasis.

With respect to the probable CBD mechanisms on psoriasis, its action on CB1, CB2, G-protein coupled receptor 55 (GPR55) and PPARy is postulated [9]. Even though the CBD affinity to CB1 and CB2 is low, it is still able to bind in both receptors [36]. To atopic dermatitis, the probable mechanism of action is related to pruritus reduction through TRPV1, TRPV2, TRPV3, TRPV4, TRPA1[4], found in mast cells, keratinocytes and nerve endings. In addition, TRPM8 which is found mast cells and nerve endings, can be implicated as well [4].

Antiaging

Oppositely to stated so far, the view of aging as a solely physiological aspect is currently changing. Skin aging should be considered a disease, as other dysfunctions can occur as consequence of it. Among them, cancer may develop [37]. Therefore, the search for new anti-aging ingredients is essential to develop new more effective anti-aging products, which can prevent/avoid dysfunctions resulting from skin aging.

Beyond wrinkles [38], sun exposure increase the risk of developing skin cancer [39]. Cyclobutane pyrimidine dimers (CPD) are the main markers of ultraviolet B damage and of a possible skin cancer [40]. In keratinocytes, CBD reduced CPD content [41] and then it can be beneficial to prevent skin cancer, as reported previously [2, 42]. In addition, antioxidant ingredients are desired in anti-aging products[38]. In that regard, CBD promoted a photoprotective effect against UVB radiation [41] and against phospholipids upregulation or downregulation due to ultraviolet exposure [43]. Also, as photoaged skin is dehydrated, the increase of aquaporine-3 expression would be useful to improve skin hydration [44]. In that sense, the use of topical CBD is interesenting for this purpose [45]. Additionally, a topical product bearing retinol and CBD reduced wrinkles and skin laxity [46].

As to CBD mechanisms on the antiaging activity, it possibly involves the ones already described. However, as skin aging is complex and multifactorial [38], several mechanisms may be associated. Hence, TRP channels receptors are implicated in preventing skin dehydration [7]. Moreover, CBD antiaging effects is explained by its antioxidant ability, scavanging free radicals. In that case, the possible mechanism is through inhibition of BACH1 receptors on keratinocytes [47]. BTB and CNC homology (BACH1) is a transcrition factor related to free radicals production [48], which which makes this receptor a potential antiaging target for CBD.

Conclusion and Trends

Cannabidiol has potential applications in the treatment of skin disorders, mainly for those whose current treatments are side-effect related or the treatment efficacy is limited. Then, it may be a promise treatment for chronic skin diseases such as psoriasis and atopic dermatitis. Moreover, as cannabidiol can be used as a multifunctional ingredient, it may be interesting in increasing patient adherence to treatment, as the number of products required may be reduced.

Nevertheless, more researches on the mechanisms of action of canabidiol are needed in order to better establish its use in the treatment of skin diseases, as well as for new applications to be investigated. Further research addressing safety and possible adverse effects of topical cannabidiol should also be conducted.

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