REVIEW

# Therapeutic Potential of Cannabidiol (CBD) for Skin Health and Disorders

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**Abstract:** Though there is limited research confirming the purported topical benefits of cannabinoids, it is certain that cutaneous biology is modulated by the human endocannabinoid system (ECS). Receptors from the ECS have been identified in the skin and systemic abuse of synthetic cannabinoids, and their analogs, have also been associated with the manifestation of dermatological disorders, indicating the effects of the ECS on cutaneous biology. In particular, cannabidiol (CBD), a non-psychoactive compound from the cannabis plant, has garnered significant attention in recent years for its anecdotal therapeutic potential for various pathologies, including skin and cosmetic disorders. Though a body of preclinical evidence suggests topical application of CBD may be efficacious for some skin disorders, such as eczema, psoriasis, pruritis, and inflammatory conditions, confirmed clinical efficacy and elucidation of underlying molecular mechanisms have yet to be fully identified. This article provides an update on the advances in CBD research to date and the potential areas of future exploration.

**Keywords:** cannabidiol, CBD, cannabinoids, endocannabinoids, endocannabinoid system, skin, CB1, CB2, FAAH, AEA

## Introduction

### The Endocannabinoid System in Skin

The ECS is an evolutionarily conserved network of molecular signaling that plays a role in bodily homeostasis.[1–3] The ECS is made up of multiple components: (a) signaling molecules called endocannabinoids, (b) specific receptors, and (c) enzymes that synthesize and breakdown endocannabinoids and transporters of endocannabinoids. The most well-researched functions of the ECS are related to modulation of the central nervous system (CNS) and immune function in the body. Recent research has indicated the critical role of the ECS in maintaining skin homeostasis and barrier function, and its dysregulation has been implicated in various skin disorders like atopic dermatitis, itch, acne, hair growth/loss, and hyper/hypopigmentation.[4–7]

### Endocannabinoids

The existence of an endogenous ECS ligand was first reported by Devane et al in 1988 when they showed that N-arachidonoylethanolamine glycerol (AEA/Anandamide) binds to the cannabinoid brain receptor in a murine model.[8,9] Since then, detection of numerous endocannabinoids has also been reported in the human body including the peripheral organs like skin.[10] Amongst all endocannabinoids present in skin, anandamide (N-arachidonoyl ethanolamide, AEA) and 2-arachidonoyl glycerol (2-AG) are the most widely studied.[11,12] Anandamide and 2-AG were detected and quantified in

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the femtomolar range in both keratinocytes and fibroblast cells by Gegotek et al.[13] The biosynthesis pathways and cellular uptake of these two lipid mediators are described in multiple review articles.[2,14,15] Other less know endocannabinoids detected in skin by Kendall et al are N-palmitoyl ethanolamide (PEA), N-alpha-linolenoyl ethanolamide (ALEA) N-linoleoyl ethanolamide (LEA), N-oleoyl ethanolamide (OEA), N-stearoyl ethanolamide (SEA), N-eicosapentaenoyl ethanolamide (EPEA), and, N-docosahexaenoyl ethanolamide (DHEA).

## Receptors

Cannabinoid (CB) 1 receptors are generally present in abundance in the central nervous system (brain and spinal cord) and CB2 receptors are present in the peripheral nervous system (nerves in extremities), the digestive system, and immune system. Research indicates that both CB1 and CB2 receptors are also found in epidermal keratinocytes, cutaneous nerve fibers, dermal cells, melanocytes, eccrine sweat glands and hair follicles.[13,16,17,19–21,22] While cannabinoid receptors remain the primary targets for endocannabinoids, they have also been shown to bind to Transient Receptor Potential (TRP) receptors present in various types of skin cells (Figure 1) and are involved in different functions like formation and maintenance of the skin barrier, cell growth, cell differentiation, immunological and inflammatory processes.[23]

In addition, endocannabinoids also interact with peroxisome proliferator-activated receptors (PPAR) via direct (endocannabinoid) or indirect (secondary metabolite of endocannabinoids) signaling pathways. PPAR (α and γ) activation partially mediates major biological functions of endocannabinoids like neuroprotection, antiinflammation, and analgesic actions. The ECS and some other non-cannabinoid (indirect) targets influencing the ECS in different cellular compartments of the skin are also shown in Figure 1. A simplistic mechanism of action of endocannabinoids like AEA and 2-AG on CB1 and CB2 receptors in presynaptic neurons in the central
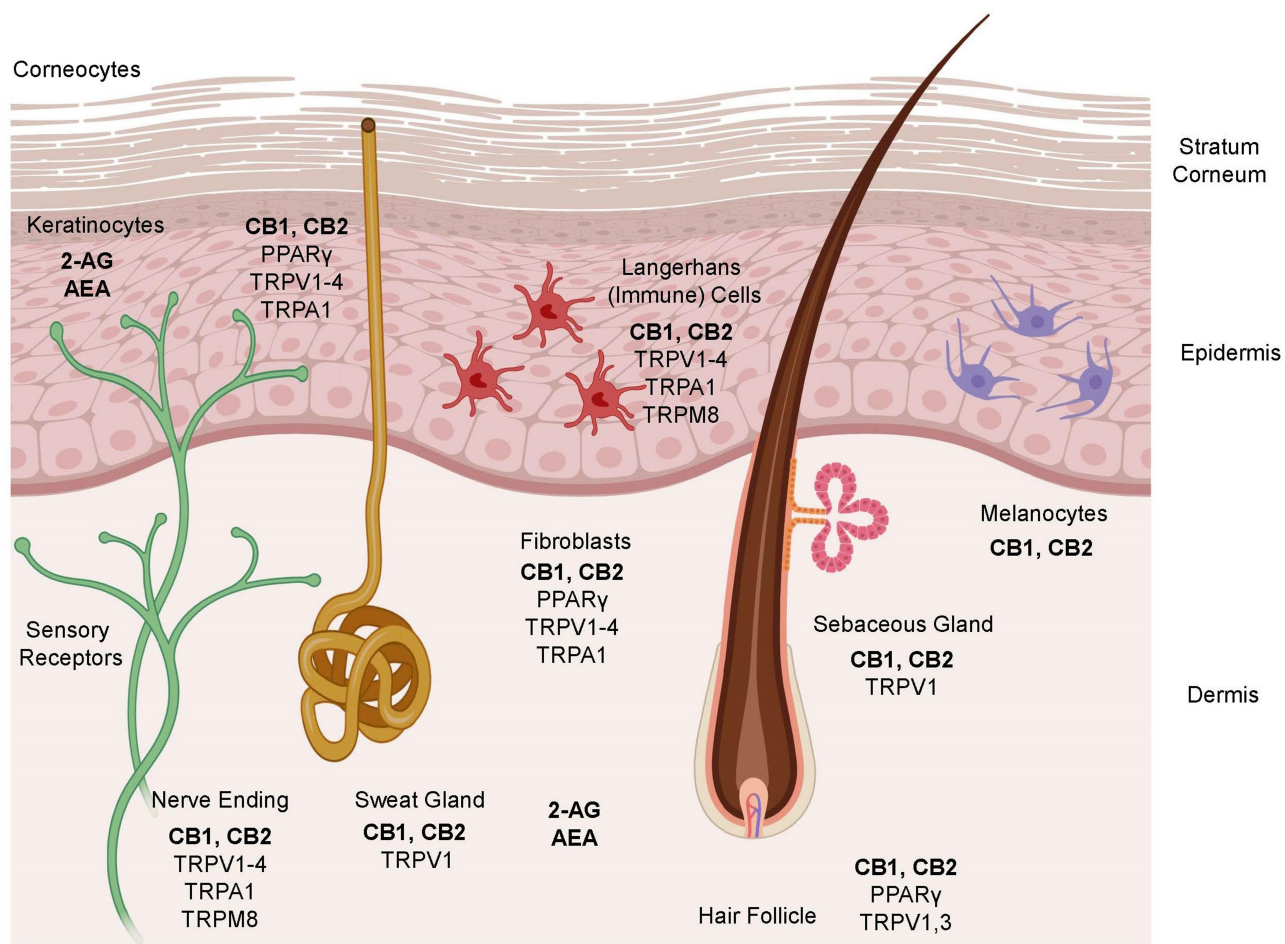


**Figure 1** Schematic representation of the key components of the ECS in different cellular compartments of the skin.
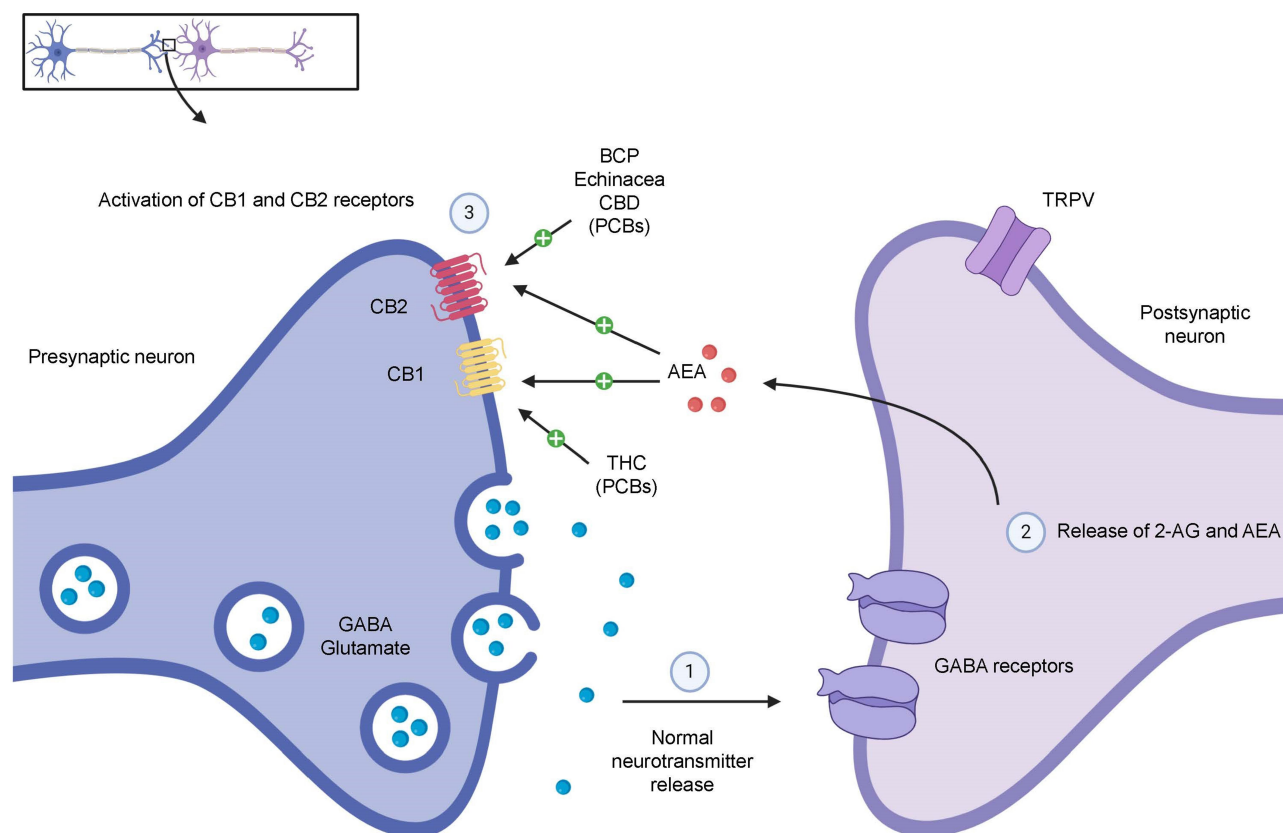
**Figure 2** Modulation of the ECS by endocannabinoids and phytocannabinoids in presynaptic neurons in the central and peripheral nervous systems.

and peripheral nervous systems is shown in Figure 2, which also shows the modulation of the ECS by phytocannabinoids (PCBs) by direct activation of CB1 (like THC). Indirect mechanisms of the ECS (not shown in the figure) include inhibition of enzymatic breakdown of endocannabinoids (ECBs) and/or receptor modulation.

### Enzymes and Transporters

The synthesis of endocannabinoid AEA is mediated by Phospholipase D while diacylglycerol lipase (DAGL) regulates the synthesis of 2-AG.[24,25] The degradation of AEA and 2-AG primarily is regulated by two enzymes, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively.[2] The biological signaling of endocannabinoids via interaction with their receptors is inhibited by a two-step mechanism. The endocannabinoids are first removed from the intracellular space by a membrane transporter known as anandamide membrane transporter (AMT) and then, after reuptake, the endocannabinoids entering the cells are metabolized by enzymes like FAAH and MAGL.[26]

## Types of Cannabinoids

Cannabinoids can be broken into three general categories based on where they are produced. Endocannabinoids (ECBs) are the cannabinoids compounds biosynthesized within the human body. Figure 3 represents the chemical structures of nine endocannabinoids found in human skin by Kendall et al.[10] Phytocannabinoids (PCBs) are the cannabinoids obtained from plants while synthetic cannabinoids (SCs) are generated synthetically using various chemical processes (e.g., Dronabinol, Nabilone). Phytocannabinoids are found in abundance in the resin-producing trichomes of the *Cannabis sativa L.* plant (*C. sativa*). While there are many cultivars of *C. sativa*, regulatory bodies typically segment them into one of two different chemotypes. Industrial hemp is the chemotype with a minimal amount of tetrahydrocannabinol (THC) and higher levels of CBD, while the marijuana chemotype contains high levels of THC (e.g., above 0.3% w/w by dry weight). Figure 4 represents the most common phytocannabinoids found in hemp.
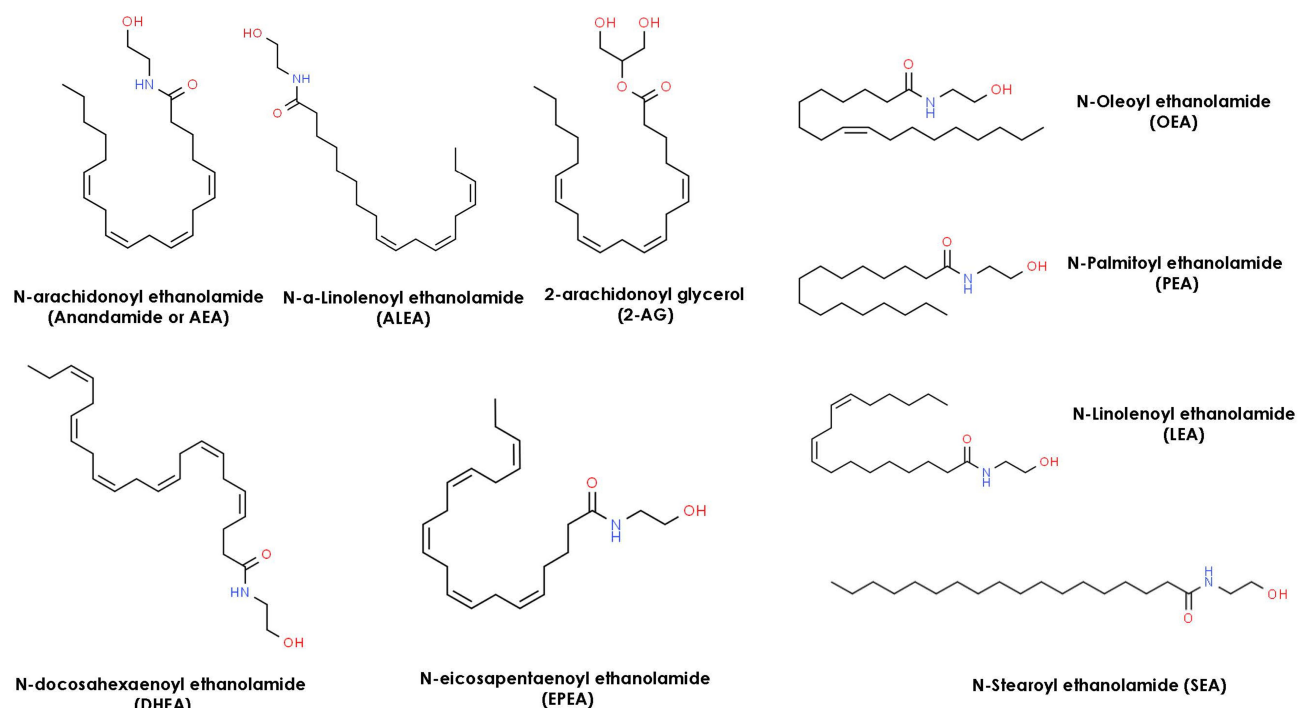
**Figure 3** Chemical Structures of 9 endocannabinoids found in human skin.



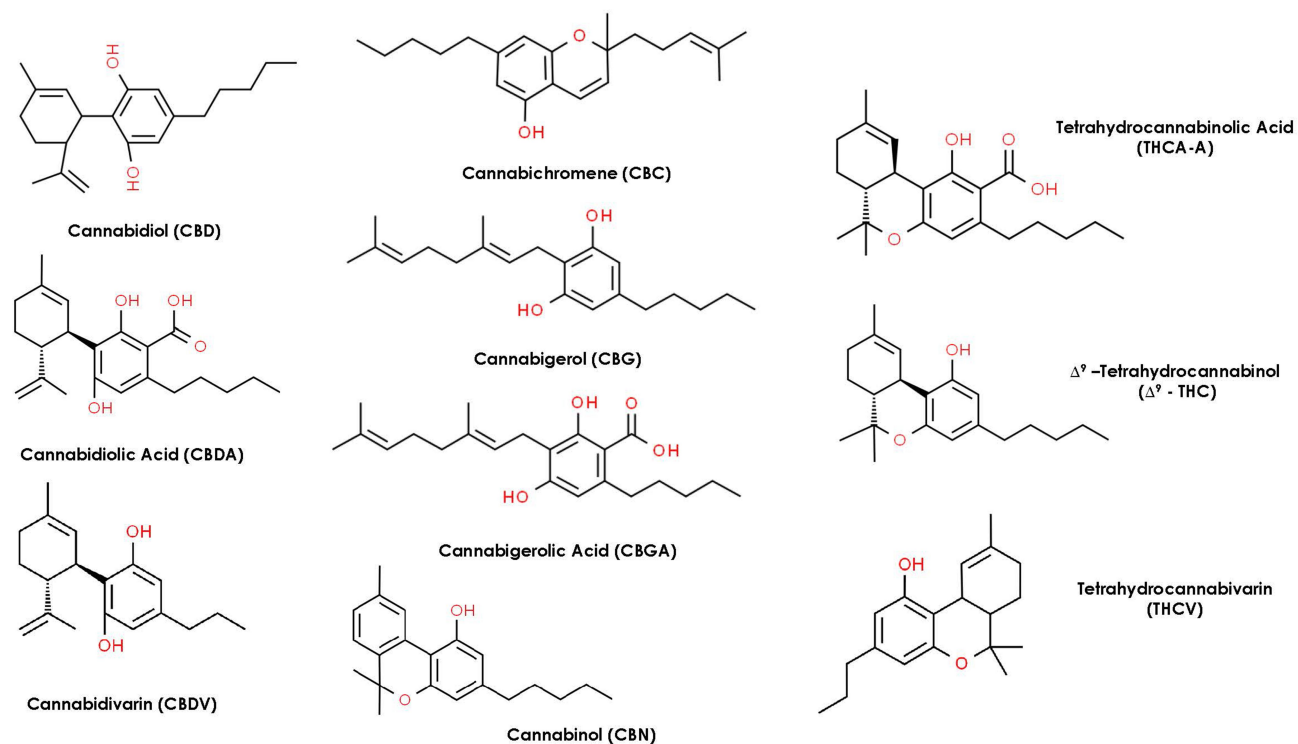**Figure 4** Chemical structures of the most common phytocannabinoids found in the hemp plant.

Historically, hemp has been cultivated for its fiber, which can be used to produce paper or clothing, or for its nutritious seeds. More recently, hemp has gained popularity for its beneficial cannabinoid constituents including CBD. While the flowering tops and leaves of hemp have significant levels of CBD, the hemp stems/

stalks and seeds have little to none. Hemp seeds contain nutritious omega-3 fatty acids and are high in protein, but only contain trace amounts of PCBs and no terpenoids.[27] Steam distillation of hemp flowering tops and leaves is commonly used to produce an essential oil containing terpenoids such as myrcene, α-pinene, and β-caryophyllene.[28] However, the volatile fraction produced from steam distillation will not contain appreciable amounts of PCBs.[29] Ethanolic and supercritical CO2 extracts of whole hemp plant or flowering tops and leaves can have significant levels of CBD.[30] These extracts have various commonly known nomenclatures like full spectrum hemp extract, broad spectrum hemp extract, hemp oil, and, phytocannabinoid-rich hemp oil/extract.

## Potential of Cannabidiol for Skin Health and Dermatological Conditions

Because the ECS plays an important regulatory function in the skin, it is plausible that treatment with topical cannabinoids could be efficacious for certain disorders or skin health in general. However, most of the clinical evidence to date has focused on the effects of CBD and other cannabinoids when consumed, inhaled, or injected. There is limited research investigating the therapeutic potential for topical applications. Yet, there is evidence to suggest applying cannabinoids, and specifically CBD, topically may be a viable route of administration for certain conditions. Although CBD has a reasonable molecular weight (314.46 Da), its high log P value (lipid/water partitioning) of ~6.3, poses unique challenges to its transdermal delivery.[31] However, this challenge may be overcome if appropriate carrier systems are used, as seen with CBD being absorbed transcutaneously in preclinical models. In 2003, Lodzki et al reported successful transdermal delivery of CBD in a murine model by using ethosomal carriers.[32] Similarly, Hammel et al investigated the efficacy of topically applied CBD (1–10%) in a gel format, specifically for reduction of inflammation-associated symptoms in a monoarthritic rat model, and found that it was well-absorbed, as the plasma concentration showed a linear relationship with the dose applied.[33] In vitro diffusion studies using human tissue have demonstrated CBD's permeation potential.[34] However, at present no clinical trials investigating the topical absorptive capability in humans have been identified. Further work is warranted to better understand the appropriate doses and delivery methods for therapeutic CBD skin applications.

## Skin Protection | Barrier Function

Skin serves as a protective barrier against environmental insults which can lead to the generation of reactive oxygen species (ROS).[35,36] Oxidative stress induces cell damage and can result in chronic inflammation if left unchecked. It is also implicated in skin disorders and skin aging.[36] Keratinocytes are the main cell type in the epidermis and are particularly sensitive to environmental stressors.[37]

The harmful accumulation of ROS is countered in healthy skin by activation of numerous defense mechanisms. Many of these systems are controlled by the master regulator of cellular antioxidant defense system, NRF2 (nuclear factor erythroid 2-like 2) and PPAR-γ.[38] The stress-induced enzyme Hemeoxygenase1 (HMOX1) is one of the key NRF2 target genes and exhibits antioxidant and anti-inflammatory properties.[39] In in vitro studies, CBD has demonstrated the ability to induce expression of HMOX1 and other NRF2-regulated genes.[40,41] One study done in Normal Human Epidermal Keratinocytes (NHEK), reported that CBD induced the expression of several NRF2 target genes, with HMOX1 being the most upregulated by CBD.[42] In the same study, increased levels of HMOX1 and expression of proliferation and wound repair keratins 16 and 17 were observed in mice epidermis after topical application of CBD. In another in vitro study using human keratinocytes, researchers showed that CBD was able to penetrate the cells and balance the oxidative stress response resulting from UVB irradiation and hydrogen peroxide. They also demonstrated that CBD had a protective effect against the peroxide-induced reduction of polyunsaturated fatty acids in the cell membrane, helping to protect membrane integrity.[43] There is evidence to suggest CBD can activate PPAR-γ, as well. Treating 2D and 3D fibroblast cells with CBD resulted in activation of PPAR-γ with a corresponding decrease in levels of NF-kB.[44] Since HMOX1 and PPAR-γ play strong cytoprotective roles with anti-inflammatory, antioxidant, and anti-apoptotic properties, treatments regulating their expression could be beneficial for skin conditions characterized by inflammation and keratin disorders, such as eczema or atopic dermatitis.

## Pain and Muscle Relief

Tissue damage typically triggers an inflammatory response in the body which could result in irritation, ulcers, sensitization of peripheral tissues, neuropathies, and chronic wounds.[45] If left unresolved, a chronic inflammatory

state in the body leads to increased tissue damage and pain.[46] Current therapies (cannabinoids, antidepressants, NSAIDs and anticonvulsants) for chronic pain management target the peripheral and central nervous system often producing undesirable side effects.[47,48] Preclinical and clinical models have shown that targeting peripheral inflammation by topical therapy (e.g., clonidine[49,50] capsaicin)[51,52] is not only effective in reducing pain for specific conditions but also circumvents the CNS, thereby reducing the negative side effects, ie, respiratory depression, sedation, and tolerance. While preclinical models strongly indicate that ingestible cannabinoids may produce antinociceptive effects in neuropathic and inflammatory pain models[53,54] and a moderate level of clinical evidence supports the use of ingestible cannabinoids for chronic pain (primarily THC and combination of THC+ CBD + lower levels of other cannabinoids)[18,55,56] the clinical application of topically applied CBD for pain management has not yet been validated by robust scientific and clinical studies.

## Eczema or Atopic Dermatitis

Atopic Dermatitis (AD) is a chronic inflammatory skin disorder associated with multifactorial causes like environmental triggers, damaged skin barrier function, microbiome imbalance, genetic predisposition, and an altered immune response.[57] Phytocannabinoids have been shown to modulate inflammatory responses by regulating more than one underlying mechanism. Adelmidrol, a PEA derivative, has been shown to be effective in treating mild AD in a pediatric population.[58] Though the efficacy of CBD is yet to be clinically validated, in a recent study by Petrosino et al, CBD was shown to exhibit anti-inflammatory properties in an experimental, allergic contact dermatitis model.[59]

The influence of microbiome imbalance, especially due to colonization and biofilm formation of *Staphylococcus aureus (S. aureus)*, has also emerged as an influencing factor which can contribute towards the severity of dermatitis.[60,61] The preliminary data indicating the antimicrobial and antibiofilm activity of hemp come from the essential oil (steam distillate) fraction of hemp which is composed mainly of terpenoids such as myrcene, α-pinene, β-caryophyllene and other terpenes, but no significant levels of CBD.[28,62] Zengin et al evaluated the antimicrobial and antibiofilm efficacy of hemp essential oil (EO) against a reference strain (*S. aureus* American Type Culture Collection (ATCC) 29,213) and three clinical

strains (*S. aureus* 101 TV, *S. aureus* 104, and *S. aureus* 105). The effective Minimum Inhibitory Concentration (MIC), Minimum Bactericidal Concentration (MBC), and the Minimum Biofilm Eradication Concentration (MBEC) hemp EO values against all *S. aureus* strain types were reported as 8, 16 and 24 mg/mL, respectively, which indicated the hemp EO may disrupt and eradicate a mature biofilm of *S. aureus*. Thus, the antimicrobial and antibiofilm activities of hemp EO against *S. aureus* suggest its therapeutic potential to prevent skin disorders like atopic dermatitis.[63]

## Itch (Pruritis)

When it becomes chronic, itch or pruritis can severely affect one's quality of life. The pathogenesis of pruritis is well researched and is described comprehensively in various recent review articles.[64–66] Though most of the ECS research indicates that the itch response is primarily modulated through CB1 receptors in the CNS,[67–69] some reports argue the involvement of peripheral CB1 receptors could also be a potent contributor to itch.[70,71] The available data thus far for the involvement of peripheral CB2 receptors are conflicting and more research is needed to conclusively determine its role in pruritis.[72,73] It has also been shown that all ionotropic cannabinoid responsive receptors (e.g., TRPV1−4, TRPA1 and TRPM8) play a vital role in the complex cutaneous communication between keratinocytes, immune (Mast) cells and the sensory nerves which leads to an itch sensation.[74–78] Thus, inhibiting the activity of such ionotropic channels by selective PCBs may be helpful in alleviating pruritis.

FAAH and MAGL inhibitors, which can increase the levels of endocannabinoids and modulate cannabinoid and non-cannabinoid receptor responses, were found to demonstrate anti-pruritic effects on murine models when administered via intraperitoneal and intrathecal routes.[79–81] Though cannabinoids like THC and PEA have been shown to reduce itching in murine models,[82] the human clinical data for testing the antipruritic potential of PEA have resulted in conflicting results.[83,84] To add to the dilemma, a study by Spradley et al indicated that peripheral endocannabinoids have opposite effects on itching behavior in spinally versus trigeminally innervated skin of mice, and therapeutic treatment of itch might be more relevant for treating the lower body than itch arising from trigeminal innervated skin of the face or scalp.[85] Since CBD is a FAAH inhibitor, a CB2 inverse agonist[86] (antagonist of CB2 agonists) and TRPV1 agonist, it could

potentially play a role in modulating itch response, but the scientific evidence remains scarce for this application to-date.

## Wound Healing

Wound healing is an intricate process which includes three overlapping phases – inflammation, proliferation, and maturation/tissue remodeling.[87–89] It is plausible that the complex process of wound healing is influenced by ECS signaling, as it modulates epidermal proliferation and differentiation, fibroblast functions, and cutaneous inflammation. CB1 and CB2 receptor involvement during the wound healing process in various immune and fibroblast cells are based on murine models.[90–92] In these models, various cannabinoid analogs have generated a wound healing response possibly associated with activation of CB1 and/or CB2 receptors, upregulation of anti-inflammatory factors, indirect activation of TRPV1 and epidermal growth factor receptors, and inhibition of the FAAH enzyme.[91,93,94] The evidence of the clinical application of PCBs, especially CBD, for wound healing is scarce. A single study reported three patients suffering from Epidermolysis bullosa (a rare skin disorder characterized by pain and blistering) had faster wound healing, less blistering and amelioration of pain with self-reported topical use of cannabidiol.[95,96]

Though there is a dearth of clinical evidence, the preclinical models indicate an optimistic outlook. A study by Sangiovanni et al reported the effects of CBD and Cannabis Sativa Extract (CSE, standardized to 5% CBD) on human keratinocytes (HaCaT cells) and human dermal fibroblast (HDF) cells.[97] In keratinocytes, TNF-α (Tumor Necrosis Factor alpha) treatment resulted in upregulated expression of 26 genes involved in inflammatory pathways and included chemokines like CXCL8 and CXCL10, interleukins like IL−17C and IL−1B, and VEGF-A. Treatment with CSE downregulated all 26 inflammatory related genes, and CBD alone downregulated 15 genes. In HDF cells, TNF-α treatment upregulated 16 genes involved in the process of wound healing. While CSE was again able to downregulate all genes, CBD only downregulated 11 genes and did not exhibit any inhibitory effects on genes playing a role in inflammation and matrix remodeling, including IL−6 and MMP−9. These results indicate that the additional components within the complex cannabinoid extract, such as the other cannabinoids, flavonoids, and terpenes, may exert a synergistic anti-inflammatory effect greater than that of CBD alone. More robust preclinical

and clinical studies are needed to draw a conclusion on the cutaneous wound healing response of the CBD and its related compounds.

## Acne/Seborrhea

The major factors involved in acne onset are sebum overproduction, unwanted sebocyte proliferation, and inflammation. It is known that the ECS plays a key role in homeostasis of the skin, and specifically in lipogenesis. The endocannabinoid AEA, has been shown to stimulate lipid production in human sebocytes at low concentrations but induces apoptosis at higher levels.[98] Although current research is limited, several in-vitro studies indicate that CBD could be a novel therapeutic in the management of acne by acting on pathways relating to sebum production, sebocyte proliferation, and inflammation. One notable study performed by Oláh et al addresses CBD's potential effects on several of these outcomes. First, researchers investigated the effects of CBD on sebaceous gland function in human SZ95 cells. They found that a 24-hour treatment of CBD (1–10 μM) alone caused no changes in cellular lipid synthesis; however, when cells were first treated with AEA, CBD was able to quell the lipogenic actions in a dose-dependent manner. The researchers went on to test other lipogenic substances, including arachidonic acid and a mixture of linoleic acid and testosterone, and found that CBD was able to inhibit extraneous lipid synthesis induced by those compounds, as well. This finding suggests that CBD's effect is a universal action and is not limited to direct ECS interaction.[99] Also, it is important to note that CBD does not simply reduce lipid production but rather it is able to normalize lipogenesis in a state of imbalance. The same researchers went on to investigate the anti-proliferation abilities of CBD in-vitro. They found that CBD did not suppress cell counts beyond the starting number (did not reduce the number of viable cells) but did significantly reduce the overall proliferation of cells at 1−10 μM doses. Higher doses of CBD (50 μM) or elongated application (6 days) did result in apoptosis-driven cytotoxicity and overall viable cell count was reduced.

Finally, Oláh's research group examined CBDs anti-inflammatory actions and found that it was able to prevent pro-acne mediators from elevating TNF-α mRNA expression. It also was able to normalize the LPS-induced expression of IL−1B and IL6. This data provided further evidence for CBD's substantial anti-inflammatory actions. Notably, it is believed the control of sebocyte proliferation

and lipid production was mediated through TRPV4 signaling, while the anti-inflammatory effects of CBD application were not.[99]

In addition to previously mentioned factors, imbalance in the skin microbiome may also contribute to the pathogenesis of acne. Specifically, *Cutibacterium acnes* (*C. acnes*) overgrowth has been linked to the establishment of acne for over 100 years.[100] Therefore, the known anti-microbial effects of CBD may also prove effective in acne treatment. In an in-vitro study by Jin et al, a hemp seed hexane extract (HSHE) exhibited anti-microbial activity on *C. acnes* while inducing inflammation, and lipogenesis in sebocytes at the molecular and cellular level.[101] With 20% HSHE treatment, complete inactivation of *C. acnes* was observed. In this study, the content of CBD in HSHE was not reported; hence, it is difficult to attribute the contribution of CBD alone towards inactivation of *C. acnes*. Similarly, in a small clinical study involving men with buccal facial acne, a 3% Cannabis seed extract containing cream led to decreased sebum content and erythema. As cannabis seed extract contains minimal CBD content, it limits our understanding of application of CBD for acne and seborrhea therapy.[102] Likewise, hemp essential oil contains many terpenes which were shown to have anti-microbial effects against *C. acnes* (formerly known as *Propionibacterium acnes*).[103,104]

We speculate that Hemp seed extract or hemp EO could also have potential for treating acne vulgaris because of its anti-lipogenic, anti-proliferative, anti-inflammatory, and anti-microbial, properties, which may target similar or independent mechanisms than that of CBD. Unfortunately, no large-scale human trials have investigated the role of CBD for the management of acne. Larger studies will help to understand how CBD may impact acne at the clinical level.

## Modulation of Hair Growth

The human hair follicle is an immune-privileged miniaturized organ consisting of epithelial and mesenchymal tissue. As part of the pilosebaceous complex, the hair follicle is extensively regulated, the extent of which is still not completely understood. Human scalp hair growth is a complex and dynamic process including a period of keratinocyte proliferation and hair fiber growth (anagen), followed by a stage of apoptotic follicle regression (catagen) and a semi-quiescent stage (telogen).[105] Hair growth abnormalities include lack of hair growth (alopecia), and excessive hair growth (hirsutism and hypertrichosis).

Given the success of topically applied compounds to treat hair loss[106] coupled with the detection of major cannabinoid compounds in hair fibers, including CBD, following cannabis consumption[107] and topical application of hemp oil[108] further understanding of how cannabinoid compounds can potentially benefit hair-related issues is needed.[109–111]

Immunohistochemical analysis of human skin revealed differential expression of CB1 and CB2 receptors within the hair follicle. CB1 was detected in portions of the infundibulum and the inner root sheath, but absent from the outer root sheath, the bugle, hair bulb, and arrector pili muscle. CB2 was present in the outer root sheath and hair bulb, but absent in the inner root sheath, bulge, and arrector pili muscle.[19] Surgically isolated facial hair follicle cultures showed production of ECBs - AEA and 2-AG. Intriguingly, AEA, and $\Delta^9$-THC suppressed hair follicle growth and induced the catagen cycle. The effects of these endo-exo cannabinoids were ameliorated by the addition of a CB1 antagonist. 2-AG treatment, however, resulted in comparable follicle growth compared to vehicle control-treated follicles.[112]

An orally administered synthetic antagonist of CB1 promoted hair growth stimulation in obese mice but had no effect when applied topically. Whether oral administration of the CB1 antagonist specifically targeted CB1 to induce hair growth was not discussed by Srivastava et al.[113] Bodo et al identified the expression of TRPV1 in human hair follicles and outer root sheath keratinocytes.[114] Activation of TRPV1 in follicle organ cultures leads to inhibition of cell proliferation, while inducing apoptosis and catagen entry. Hair growth activators, HGF, IGF1, and SCF, were also suppressed with TRPV1 stimulation. TRPV3 and TRPV4 were also detected in human hair follicles and outer root sheath keratinocytes, and receptor activation, though not exclusively by cannabinoids, resulted in suppression of hair follicle elongation.[115,116] A metabolite of the endocannabinoid anandamide, bimatoprost, is recognized as a topical prostamide treatment for eyebrow hypotrichosis.[117] Khidhir et al also showed human scalp hair follicles possess select prostamide receptors within the dermal papilla. Working with human scalp, organ-cultured hair follicles, bimatoprost treatment resulted in follicle growth and it stimulated hair regrowth when applied to mouse skin.[118] A limited clinical study showed bimatoprost application also accelerated hair regrowth in alopecia areata patients to a greater extent than a topical steroid treatment.[119] Szabo et al in a pilot

study using ex vivo human hair follicles and primary outer root sheath keratinocytes found systemic-like application of CBD had dose-dependent opposing effects on hair growth dynamics.[116] At the 0.1 μM and 1.0 μM doses, the hair shafts grew similar to controls, while at the 10 μM dose, growth was significantly suppressed and follicle catagen was induced. As CBD dosage increased, keratinocyte proliferation decreased. The researchers proposed that CBD concentration may lead to differential receptor activation, with low doses favorably affecting hair growth pathways and higher doses activating suppression targets such as TRPV4.

As the hair follicle contains ECS and cannabinoid-responsive receptors, coupled with the evidence of cannabinoid deposition within the fiber followed by cannabis consumption and topical application, there may be potential to use compounds like CBD to treat certain hair disorders. However, given the complexity of hair growth dynamics, research conducted employing hair follicle organ culture and systemic-like treatment, and the potential of pleiotropic effects of certain cannabinoids seen to date, additional research is needed, including clinical trials, to determine if phytocannabinoids like CBD can be effective topical interventions to treat hair loss or excessive hair growth conditions.

## Skin and Hair Pigmentation

The pigmentation of human skin is the manifestation of synthesis of dark pigment, melanin, which is regulated by a melanogenesis process in melanocytes.[120,121] Melanogenesis is a complex process regulated by more than 250 genes.[122] Microphthalmia Transcription Factor (MITF) acts as a master regulator of melanogenesis, directly controlling the transcription of key genes involved in pigmentation such as tyrosinase (TYR), tyrosinase-related protein (TYRP)-1, and TYRP-2.[123]

Due to a limited number of studies, the involvement of the ECS in the cascades of the melanogenesis process is not clear. In 2012, Pucci et al showed that a fully functional ECS was present in normal human primary epidermal melanocytes. Lower concentrations of AEA, as well as other endocannabinoids like Arachidonoyl-2′-chloroethylamide (ACEA), and 2-AG, demonstrated induction of melanogenesis in a dose-dependent manner via the CB1 receptor.[21] However, other studies demonstrated contrasting results with CB1 agonism inhibiting melanogenesis or having no influence. Zhou et al demonstrated that OEA acts as an inhibitor of melanin synthesis

and MITF production in α-MSH stimulated B16 cells via activation of ERK, Akt, and p38 pathways and inhibition of the CREB pathway.[124] Another study by Magina et al demonstrated that CB1 agonism, under UVB exposure in a co-culture model using HaCat and SK-mel-1 cells, inhibited basal melanogenesis, whereas the inhibition was reversed when a CB1 antagonist was introduced.[125] Kim et al demonstrated that a major metabolite from JWH-073, a synthetic cannabinoid, had no significant effect on hair pigmentation.[126] Unfortunately, there are limited studies regarding the effect of phytocannabinoids, such as CBD, on melanogenesis. Hwang and colleagues demonstrated that CBD stimulated both melanin content and tyrosinase activity, mediated by the CB1 receptors in human epidermal melanocytes. The melanogenic effects of CBD occur primarily through MITF upregulation, which is mediated by the activation of p42/44 MAPK and p38 MAPK signaling.[127]

Involvement of ECS pathways in melanocytes is very complex and unclear, thus requiring additional research with various in vitro and in vivo models. Although endocannabinoids are potential mediators for healthy and diseased skin, it is believed to be premature to target pigmentation disorders using cannabinoids.[124]

## Potential Applications in Oral Care

There is little published about the use of CBD in oral care. In the 1950s, the topical preparations from *C. sativa* were found to contain antiseptic properties against several oral cavities and skin lesions.[128,129] In 2012, Ali et al studied the effect of *C. sativa* seed oil, and petroleum ether and methanol extracts of the whole plant, on two Gram-positive bacteria (*B. subtilis, S. aureus*), two Gram-negative bacteria (*Escherichia coli and Pseudomonas aeruginosa*) and two fungi (*Aspergillus and Candida albicans*). The seed oil exhibited pronounced antibacterial activity against the Gram-positive bacteria, moderate to high activity against Gram-negative bacteria, but was ineffective against the fungi.[130] Rashid et al tested ethanol and methanol extracts of cannabis leaves and stem against different microorganisms. A significant inhibitory effect was observed in the ethanol leaf extracts of *C. sativa*, with 13.8 and 21.33 mm zones of inhibition against *S. aureus and K. pneumoniae*, respectively.[131] At 4 μg/mL and 10 μg/mL concentrations, the aqueous and acetone extracts of *C. sativa* cannabinoids demonstrated a high antimicrobial activity by showing clear zones of inhibition against the bacteria *Pseudomonas aeruginosa* (3–8 mm),

and *Vibrio cholerae* (4–10 mm) and the fungi *Cryptococcus neoformans* (4–10 mm), and *Candida albicans* (4–12 mm).[132] It must be noted that hemp seeds and stalks barely contain CBD content, whereas other parts of the hemp plant contain significant amounts of CBD and other cannabinoids.

Dental plaque is associated with several dental diseases and should be regularly removed using mechanical (toothbrushes, floss) and chemical (mouthwashes) oral regimens. Dental plaque is the complex biofilm that acts as a reservoir of several microbes adhering to the tooth surface and gum line. An antimicrobial treatment can be used as an effective aid for plaque control and to improve the inflamed tissues of gums and bones.[130] Microorganisms forming the biofilm of the dental plaque are Gram-positive bacteria, such as *Streptococcus mutans*, Gram-negative bacteria, and several other anaerobes such as *Fusobacterium* and *Actinobacteria*. In 2019, Stahl et al assessed the efficacy of cannabinoids (BGA, cannabigerolic acid; CBN, cannabinol; CBG, cannabigerol; CBD; and CBC, cannabichromene) in comparison to commercial oral care products. Cannabinoids were more effective in reducing the bacterial content of the dental plaque compared to the commercially available synthetic oral care products. Therefore, natural cannabinoids may have the potential to be used as an effective treatment to remove dental plaque associated oral bacteria and provide a safer alternative to synthetic antibiotics.[129]

## Other Skin Disorders
### Skin Infections

CBD and CBG have been reported to have potent activity against a variety of Gram-positive Methicillin-resistant *Staphylococcus aureus* (MRSA) strains.[133] Likewise, an antimicrobial effect of CBD against *Listeria monocytogenes*, *Enterococcus faecalis* and Methicillin-resistant *Staphylococcus epidermidis* (MRSE) was reported with Minimum Inhibitory Concentration (MIC) values of 4 $\mu$g/mL for MRSA and *L. monocytogenes* and 8 $\mu$g/mL for *E. faecalis* and MRSE.[134] This study also characterized CBD as a helper compound that potentiates the effect of Bacitracin (BAC), a skin antibiotic. The MIC value of BAC was remarkably reduced to at least a 64-fold reduction for MRSA, MRSE and *E. faecalis*, when combined with ½ MIC of CBD as compared to MIC of BAC alone.

Furthermore, to assess the potentiating and synergistic effect against MRSA, growth curve and time kill assay results showed the combined activity of CBD and BAC reduced bacterial viability by 6-$\log_{10}$ cfu/mL as compared to CBD or BAC alone. Interestingly, CBD was able to potentiate the effects of BAC against MRSA (*S. aureus* USA300) and other Gram-positive bacteria. The spectrum of use of CBD and BAC on growth of Gram-negative bacteria, including *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Klebsiella pneumoniae*, and *Escherichia coli*, was also measured. The results obtained from the combined effect of CBD and BAC against these Gram-negative bacteria concluded that the combined activity of CBD and BAC

**Table 1** Examples of Phytochemicals Targeting the ECS with Phytocannabinoid-Like Activity

| Ingredient | Chemical Classification | Plant Source(s) | Mechanism of Actions | Potential Therapeutic Actions |
|---|---|---|---|---|
| Limonene | Terpene | Citrus fruits | Glutathione upregulation[143] | Antioxidant, antitumor activity[143] |
| β-Carophyllene (BCP) | Sesquiterpene | Hops, Copaiba, black pepper, rosemary, hemp essential oil[144] | CB2 receptor agonism[145,146] | Anxiolytic, antinociceptive[144,146–148] |
| Echinacea | Alkylamides | Echinacea, Sichuan pepper | CB2 receptor agonism[149–151] | Anti-inflammatory[152], antimicrobial[153], antioxidant[154] |
| Turmeric | Curcuminoids | Turmeric | CB1 receptor agonism[155] | Anti-inflammatory and antinociceptive properties[156] |
| Boswellic acids | Triterpenes | Frankincense | Inhibition of PGE2 (Prostaglandin E2) synthase[157] | Anti-inflammatory[157] |
| Magnolia | Polyphenols | Magnolia bark | CB2 receptor agonism[158] | Antioxidant, anti-inflammatory[159] |
| Ashwagandha | Lactones and steroidal alkaloids | Withania somnifera | Potential GABA mimetic action[160] | Immuno-modulatory, stress reduction[160] |

was considered ineffective against Gram-negative bacteria. Due to potent antibacterial properties against Gram-positive bacteria, cannabinoids can be used as an effective helper compound when combined with known antimicrobial actives to fight antibiotic resistant Gram-positive bacteria which cause skin disorders and other infections.[134]

### Psoriatic Plaques

Some anecdotal information suggests the use of CBD for treating psoriatic plaques which are characterized by keratinocyte hyperproliferation and chronic inflammation. NF-kB plays a significant role in skin inflammatory conditions like psoriasis, and its expression is strongly induced by TNF-α.[135] Sangiovanni et al demonstrated that CBD and *C. sativa* extract (CSE, standardized to 5% CBD) inhibited TNF-α induced NF-kB transcription in a dose-dependent manner in HaCaT cells.[97] However, in HDF cells, only CSE exhibited NF-kB inhibitory effects. In other cell types, CBD has been reported to have the ability to impair the NF-kB pathway both in-vitro and in-vivo.[136,137] Though CBD has shown to have anti-inflammatory properties, its role in keratinocyte differentiation and proliferation is not clear. Some in vitro studies have shown that CBD inhibits differentiation in immortalized HaCaT cells[138] and also exerts antiproliferative actions on transformed human keratinocytes (HPV16).[139] On the contrary, a study by Casares et al indicated that the role of CBD in treating psoriasis should be approached with caution due to its proliferative effects for keratins 16 and 17.[42] Thus, more robust experimentation is needed to determine the use of treatment for psoriatic lesions.

### Cutaneous Malignancies

The therapeutic potential of targeting the ECS for cutaneous malignancies such as melanoma and non-melanoma skin tumors is described at length in an excellent review article by Toth et al and is beyond the scope of this article.[4] Cannabinoids such as $\Delta^9$-THC and AEA have better scientific research for this application. Though some preclinical studies have shown that CBD inhibits transporter proteins involved in breast cancer[140] the application of CBD for treating cutaneous malignancies has yet to be explored in detail.

## Open Questions and Future Research

The significance of the ECS in maintaining skin homeostasis and the resulting dermatological conditions from its imbalance has garnered scientific attention. Despite promising research on the topical therapeutic potential targeting the ECS, much remains unknown on the complexity of interactions of cannabinoids with other systems of the human body. A good example of this is the unintended interaction of BIA 10–2474 (a FAAH inhibitor intended for treating pain and anxiety) with the lipid network in human cortical neurons resulting in metabolic dysregulation of the nervous system.[141,142] Though the outcomes of this study are stemming from oral treatment at higher doses, it does have sound advice to treat any topical application of cannabinoids with due diligence. While many topical CBD products appear to be relatively well tolerated, topical safety studies are underway, and the evidence is still emerging.

The authors conclude that while the therapeutic potential of CBD for acne, seborrhea, eczema/dermatitis, and skin barrier function is promising, more robust studies are needed to fully validate its efficacy. The therapeutic potential of CBD should also be balanced with largely unknown/contrasting early studies in modulating pigmentation and hair growth. Thus, there is an underlying need for intense fundamental scientific research as any speculative science could lead to unwanted effects like hair growth/loss or hyper/hypopigmentation issues. Looking beyond the horizon of the buzzword CBD, the therapeutic benefits of hemp phytocannabinoids and other botanicals with phytocannabinoid-like activity (Table 1), will most likely be the focus of future research.

## Disclosure

All the authors are employees of Amway Corporation which has commercial offerings in the wellness space. The authors report no other potential conflicts of interest for this work.

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