
# Cannabinoids as Anti-Acne Agents

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The United States Food and Drug Administration currently prohibits the addition of CBD to food and dietary supplement products

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## Executive Summary

Acne vulgaris is a highly prevalent inflammatory skin condition that affects over 9% of the world's population, making it the eighth most common condition worldwide. Global spending on prescription acne therapies and anti-acne cosmetics respectively exceeded $4.1B USD in 2017 and $2B USD in 2018. Acne presents in over 30% of adolescent and adult populations as non-inflammatory comedones and inflammatory lesions characterized as papules, pustules, nodules, and cystic lesions. Generally speaking, comedones form as a result of sebum overproduction and keratinocyte hyperproliferation, while colonization of virulent strains of *Propionibacterium acnes* within the hair follicle exacerbates the immune response and inflammatory state of this condition. While not considered life threatening, acne vulgaris is known to deleteriously impact patients' quality of life and mental health. Treatment is complicated by the diverse etiology and multi-faceted pathogenesis of this condition. Firstline treatment options for moderate to severe acne feature retinoids due to their anti-inflammatory and comedolytic properties, antibiotics which inhibit *P. acnes* growth and reduce inflammation, or androgen-regulating hormones which target normalization of sebum production. However, the use of these treatment options, and other over-the-counter remedies, are often limited by their irritation potential or risk of treatment resistance.

The effects of cannabinoids at non-cytotoxic concentrations on sebum production, gram-positive bacteria, and immune response can direct the development of novel skin therapies with targeted effects for a variety of skin conditions. In the context of acne, current in-vitro evidence suggests that non-cytotoxic concentrations of THCV and CBD are capable of normalizing sebum production and reducing inflammation associated with acne vulgaris. Furthermore, CBD was shown to upregulate expression of the antimicrobial peptide LL-37 cathelicidin, suggesting a potential for antibacterial action against *Propionibacterium acnes.* Cannabinoids have also demonstrated antibacterial activity against other gram-positive bacteria, which brings into question the potential activity cannabinoids may have on gram-positive *P. acnes* in the prevention or management of acne vulgaris.

These findings also suggest that the utility of cannabinoids may extend beyond acne vulgaris to other skin-related conditions. Most notably, non-cytotoxic concentrations of CBG and CBGV reportedly increased lipid synthesis and prevented inflammatory cytokine release, which may be beneficial for therapies targeting conditions associated with dry skin and impaired barrier function, such as xerosis, eczema, and anti-aging applications. As such, cannabinoids may offer solutions for these conditions as stand-alone treatments, or as combination therapies that enhance the efficacy of existing treatment options. However, further in-vivo work is required to validate the safety and efficacy of cannabinoids when administered as topical or oral therapies in clinical settings.

At the forefront of cannabinoid cellular agriculture, LAVVAN utilizes yeast fermentation technology to produce high-quality, reliably sourced, natural cannabinoid ingredients. LAVVAN will provide cannabinoids with unparalleled purity, consistency, potency, and sustainability at a scale capable of serving a range of industries including health, beauty, food and beverage, and pharmaceuticals. LAVVAN's cannabinoids are identical to those found in nature and produced in a cGMP facility in accordance with the most stringent standards, including being devoid of pesticides, mold, bacteria, and other contaminants often found in traditional cannabis agriculture. In addition to providing high purity cannabinoid ingredients, LAVVAN will leverage its cannabinoid formulation expertise to support its industry partners with integrating cannabinoids into formulations for various end products that require specific utility.

## Summary of Scientific Evidence

- Non-cytotoxic doses of CBD and THCV displayed multi-faceted anti-acne effects in in-vitro cell line experiments, including the normalization of excessive sebaceous lipid production and reduction of inflammatory gene expression
- CBD was effective in reducing lipid production in a translational ex-vivo model

### Sebocyte Lipid Synthesis – Basal Conditions

- 10 µM THCV and CBC decreased SZ95 sebocyte lipid synthesis, while 1-10 µM CBD had no effect
- 10 µM CBG and CBGV increased sebocyte lipid synthesis, suggesting applications as therapies for dry skin conditions such as xerosis, eczema, and aging

### Sebocyte Lipid Synthesis – Induced Lipogenesis with Pro-Acne Agents

- 1-10 µM CBD and 10 µM THCV displayed a universal lipostatic effect by inhibiting excessive SZ95 sebocyte lipid synthesis induced by various pro-acne lipogenic agents
- CBC, CBDV, CBG, and CBGV were less effective than CBD and THCV at reducing lipogenesis

### Anti-inflammation

- 10 µM CBD and 0.1 µM of THCV were shown to prevent the elevation of the pro-inflammatory cytokines following lipopolysaccharide-induced inflammation
- 0.1 µM of CBG, CBGV, CBC, and CBDV supressed the release of pro-inflammatory cytokines induced by lipopolysaccharide treatment, but to a lesser extent than THCV and CBD

### Mechanisms of Action

- The lipostatic activity of CBD may be mediated by activation of the TRPV4 ion channels
- THCV may follow the same mechanism of lipostatic action given its affinity for TRPV4 ion channels
- The anti-inflammatory activity of CBD may be mediated by activation of the G protein coupled receptor A2a

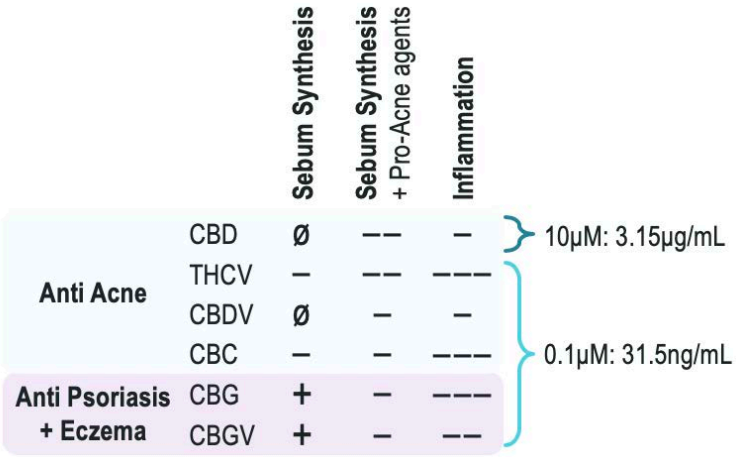


**Figure 1:** Summary of phytocannabinoid effects on three aspects of pathological skin conditions: sebum synthesis under basal conditions, sebum synthesis following irritation with acne-promoting molecules, and production of inflammatory cytokines induced by bacterial components. All cannabinoids exerted anti-acne effects under inflammatory conditions, while exerting differential effects under normal conditions. These findings suggest applications of CBD-derived treatments for “standard” skin, THCV and CBC-based treatments for oily skin, and CBG-derived treatments for dry skin. The magnitude of a reduction (-) or increase (+) in sebum synthesis and inflammation is indicated as mild (one symbol), moderate (two symbols), or high (three symbols), while Ø indicates no change.

## Acne Vulgaris – A Complex Condition

Acne vulgaris is the eighth most prevalent condition worldwide affecting over 9% of the world's population[1]. While prevalence rates vary across geographical regions, acne vulgaris most commonly presents in 30% to 95% of adolescents, often at the onset of puberty due to hormonal changes that result in increased sebum production, with severity increasing throughout pubertal maturation[2,3]. Acne vulgaris may also continue during adulthood, with prevalence rates dropping to 64% and 43% in the 20's and 30's, respectively[3]. Global spending on prescription acne therapies exceeded $4.1B USD in 2017 with the United States comprising the largest regional market, while Europe comprised the largest sector of the global anti-acne cosmetics market which exceeded $2B USD in 2018[4-6].

Acne vulgaris involves deregulation of hair follicle homeostasis and the subsequent development of non-inflammatory comedones and inflammatory lesions[1-3].In all populations, this condition may result in scarring and hyperpigmentation of the affected areas[1,7]. While not considered life threatening, acne vulgaris has been shown to lead to the development of depression, anxiety, suicidal ideation, and may also impact patients' social self-esteem and quality of life[3,7,8].

Diagnosing the etiology of acne vulgaris is complicated by the compounding effect of various internal and external factors which are often unique to each patient. Internal factors include hormones and genetics, while external factors involve diet and colonisation by different strains of the bacterium *Propionibacterium acnes (P. acnes)*[1,3,8]. Acne vulgaris most commonly occurs on the face, chest, and back, and presents as heterogenous follicular lesions that are broadly classified as non-inflammatory comedones or inflammatory papules, pustules, nodules, or cystic lesions[7,9,10]. Comedones are described as open (black heads) or closed (white heads), while papules, pustules, nodules, and cystic lesions are delineated based on the presence of a pus-like substance and their presentation above or below the skin's surface. Non-inflammatory acne can be further characterized as mild, while inflammatory acne is considered moderate or severe depending on the type and number of lesions present.

The pathogenesis of acne vulgaris is characterized by three factors (Figure 2): increased sebum production (known as sebocyte lipogenesis), follicular de-regulation characterized by excess production of the protein keratin (hyperkeratinization), and overgrowth of *P. acnes* which may lead to activation of tissue resident immune cells followed by recruitment of infiltrating immune cells that drive localized inflammation and accelerate the formation of nodular lesions[2,11-13]. Generally speaking, the formation of non-inflammatory comedones is primarily associated with follicular congestion caused by excess sebum and keratin production, while inflammatory lesions are a consequence of augmented inflammation caused by the overgrowth of virulent *P. acnes* strains.

Sebum is a heterogenous lipid substance secreted by sebaceous glands that supports the skin microbiome and forms a protective barrier that prevents water loss from the skin[14]. While an underproduction of sebum is associated with dry skin, an overproduction results in skin that appears oily and often results in the formation of comedones associated with acne[11]. Sebum triglycerides are known to nourish gram-positive *P. acnes*, while serum wax esters together with keratin and dead skin cells form semi-solid plugs that trap comedone content within the hair follicle and accentuate inflammatory processes[12,15,16]. While *P. acnes* is equally prevalent in healthy and acne-affected skin, only certain virulent strains are genetically capable of secreting pro-inflammatory molecules called porphyrins that further entrench the condition[12,13,16,]. The proliferating bacteria combined with the cellular secretion contribute to the formation of physically constrained inflammatory nodules that feature recruitment of inflammatory antigen-presenting and effector immune cells.

Most treatment options target one of these factors, striving for either normalization or reduction of sebocyte lipid synthesis, suppression of hyperkeratinization, inhibition of *P. acnes* growth, or reduction in inflammation. Prescription treatment options include oral or topical formulations containing retinoid derivatives, antibiotics, or androgen-blocking drugs to regulate sebum production and prevent *P. acnes* colonization and inflammation[17]. Over-the-counter therapies provide further antibacterial or exfoliation activity aimed at preventing pore congestion and comedone formation.

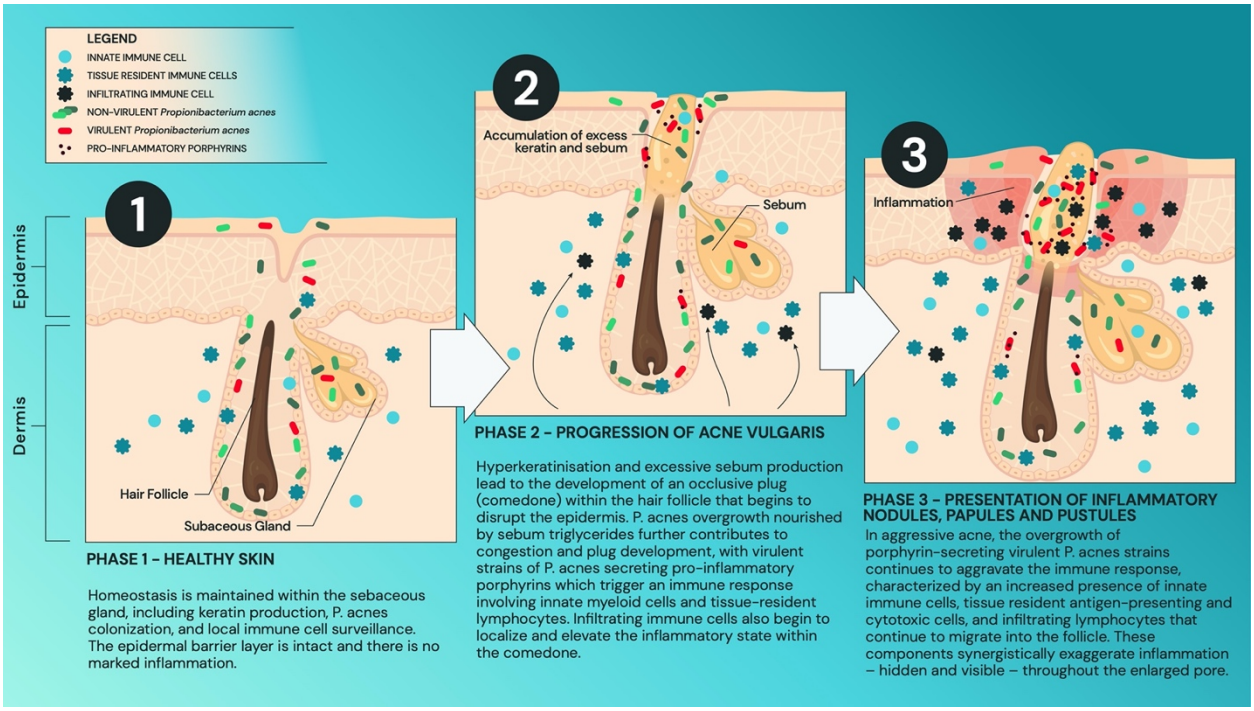


**Figure 2:** The pathogenesis of acne vulgaris.

## Prescription and Over-the-Counter Treatment Options

Retinoids and their derivatives are considered to be among the most effective topical treatment options for moderate to severe acne due to their comedolytic and anti-inflammatory properties[18,19]. Among the current suite of retinoid-type actives, the first generation tretinoin and third generation adapalene are commonly employed as acne and anti-aging treatments. However, their use in topical formulations is often associated with side effects that include irritation, redness, peeling, and photosensitivity. Isotretinoin, another effective first generation retinoid, was originally available as an oral treatment under the brand name Accutane but became highly scrutinized and temporarily removed from the market in 2009 due to severe side effects, namely birth defects in pregnant women, and psychiatric disorders including depression, psychosis, mood disturbances, and suicidal ideation. Today, oral isotretinoin is marketed under stringent risk management programs in both Canada and the United States[20,21].

Other treatment options include tetracycline or macrolide antibiotics which are prescribed in oral or topical formulations to inhibit bacterial growth on the skin and reduce inflammation[17]. In an effort to curtail the growing resistance to these antibiotics, it is recommended that the duration of antibiotic use is limited, and that a combination approach involving topical non-antibiotic therapies is employed[22,23]. Additional prescription therapies include hormone-regulating drugs, such as androgen-receptor blockers which

inhibit the stimulating effect of androgens on sebaceous activity, as well as oral contraceptives which regulate ovarian androgen production[17,24,25].

Alternatively, benzoyl peroxide, salicylic acid, and sulfur with our without resorcinol are often used in over-the-counter topical treatments[17,26]. These actives possess a range of antimicrobial effects against *P. acnes*, as well as keratolytic activity that induces cellular exfoliation to remove sebum and dead skin cells from pores to prevent the formation of new comedones. While considered effective for mild acne, these actives are known to cause skin irritation in the form of localized redness, itching, peeling, or flaking. Although these side effects resolve with discontinued use, they are detrimental to the skin's barrier function, cosmetically unappealing, and often limit the use of these treatment options to short-term use.

There is thus a clear need for anti-acne treatments that are safe and effective for long term use. Ideally, these treatments should be restorative in nature rather than destructive, and capable of maintaining or rehabilitating the skin's natural protective barrier function.

## Cannabinoids as Anti-Acne Agents

The endocannabinoid system plays an important role in the homeostasis of sebocytes, which express cannabinoid receptors and secrete the endocannabinoids Anandamide (AEA) and 2-Arachidonoylglycerol (2-AG), as well as their derivative Arachidonic acid (AA)[27]. These secreted lipids form part of the sebum, a heterogenous lipid substance that functions as a protective moisture-retaining barrier for the skin. In-vitro results obtained using SZ95 sebocyte cell lines suggest that the non-psychoactive phytocannabinoids cannabidiol (CBD), delta-9-tetrahydrocannabivarin (THCV), cannabigerol (CBG),cannabichromene (CBC), cannabigerovarin (CBGV), and cannabidivarin (CBDV) exert varying actions on human sebocyte cells which position these compounds as potential novel topical therapies – not only for the management of acne vulgaris, but also for conditions associated with dry or compromised skin and keratinocyte hyperproliferation, such as xerosis, eczema, psoriasis, and general aging.

## Cannabinoid Cytotoxicity

Results obtained from an in-vitro human SZ95 sebocyte cell line model suggest that CBD, CBC, CBDV, CBG, CBGV, and THCV do not impact sebocyte cell viability at $\leq$10 µM after 24 or 48 hours of treatment[28,29]. However, these cannabinoids were found to be cytotoxic after 24 hours at concentrations $\geq$50 µM, with the mechanism of cell death identified as apoptosis. These results suggest that cannabinoids have a broad therapeutic window wherein efficacy may be observed without affecting the health of skin cells.

## Normalization of Sebum Lipogenesis

The overproduction of sebum, otherwise referred to as sebum lipogenesis, is a fundamental step in the pathogenesis of acne vulgaris. While an underproduction of sebum is associated with dry skin and an impaired barrier function, an overproduction results in the formation of comedones associated with acne. Therefore, lipostatic agents capable of reducing or normalizing sebocyte lipogenesis are desirable acne therapies.

Results obtained using an in-vitro human SZ95 sebocyte cell line model suggest that cannabinoids exert a range of effects on basal sebocyte lipid synthesis (Figure 3)[28, 29]. Following 48 hours of treatment with 10 µM concentrations, CBD and CBDV exerted no effect on sebocyte lipogenesis, while THCV and CBC

reduced lipogenesis. In contrast, CBG and CBGV increased sebocyte lipogenesis, which is desirable for treatments targeting aging and dry skin conditions.

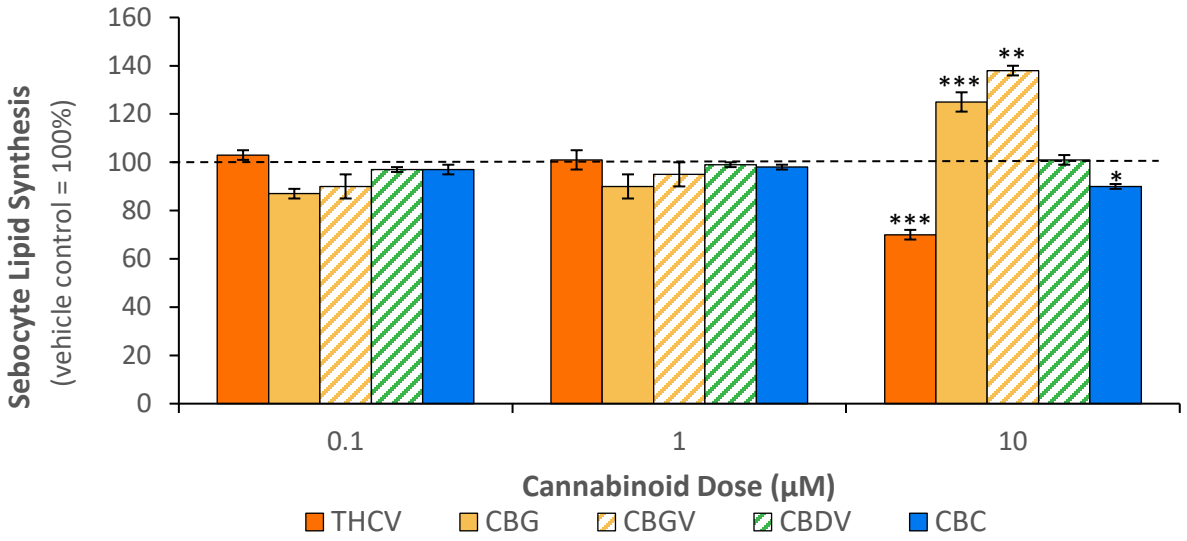


**Figure 3:** The effect of cannabinoids on basal sebaceous lipid synthesis of human immortalized SZ95 sebocytes assessed using Nile Red staining after 48 hours of treatment[28, 29]. Results are expressed in the percentage of the vehicle control (100%, dashed line) as mean ± SEM of four independent determinations. Two additional experiments yielded similar results. Significance against the control is denoted as * ($P < 0.05$), ** ($P < 0.01$) and *** ($P < 0.001$).

The lipostatic effect of each cannabinoid was also evaluated under excessive lipogenesis induced by various pro-acne agents, including AEA, AA, and linoleic acid combined with testosterone (Table 1)[28, 29]. 10 µM CBD was shown to inhibit excessive lipogenesis induced by each of these lipids, while demonstrating a dose-dependent response against AEA. 10 µM THCV reduced AA-induced lipogenesis in a manner comparable to CBD. 10 µM CBC and 10 µM CBDV reduced AA-induced lipogenesis to a lesser extent than CBD and THCV, while 20 µM CBG and 20 µM CBGV supressed AEA-induced lipogenesis.

| Pro-Acne Treatment | CBD | THCV | CBG | CBGV | CBDV | CBC |
|---|---|---|---|---|---|---|
| **AEA 30 µM** | Not tested | 10 µM | 10 µM | 20 µM | Not tested | Not tested |
| **AA 50 µM** | 10 µM | 10 µM | Not tested | Not tested | 10 µM | 10 µM |

**Table 1:** Minimum cannabinoid concentration required to reduce lipogenesis induced by pro-acne agents Anandamide (AEA) and Arachidonic Acid (AA)[28,29]. Sebaceous lipid production was determined by Nile Red staining after 48 hours of treatment. Missing data points are due to incongruencies in dose selection and study design. Significance against the vehicle control is marked by dark yellow ($P < 0.001$) and light yellow ($P < 0.01$).

The researchers explored the mechanism by which CBD mediates these properties by reducing the expression ("knocking down") of multiple genes suspected of playing a role[29]. These experiments implicated the ion channel receptor TRPV4, whose homolog TRPV2 has previously been shown to engage with CBD, as well as the nuclear receptor partner NRIP-1 (important for triglyceride storage) and

the G-protein coupled receptor A2a (which can activate the NF- κβ anti-inflammatory pathway). Further experiments are necessary to determine how these receptors and pathways interact in-vivo.

While the mechanism of action has not been established for THCV, it has been suggested that THCV may follow the same modality due to its affinity for TRPV4 ion channels[28]. Additionally, THCV is known to be an agonist of TRPV1, TRPV2, and TRPV3 ion channels, which are further implicated in the inhibition of sebocyte lipogenesis[28].

## Reduction of Inflammation

The inflammation of lesions characteristic to acne vulgaris is primarily associated with the overgrowth of virulent strains of the bacterium *P. acnes*, which colonize in sebaceous glands and hair follicles. *P. acnes* prosper in high sebum environments, explaining why the onset of puberty often correlates with the onset of acne vulgaris. Additionally, virulent *P. acnes* strains can release inflammatory molecules called porphyrins, which promote the release of pro-inflammatory cytokines by immune cells.

In one study, the gram-negative bacterial antigen lipopolysaccharide (LPS) was applied to an in-vitro human SZ95 sebocyte model and the effect of cannabinoids on genes coding for pro-inflammatory cytokines was measured[29]. 10 μM CBD was shown to prevent the elevation of pro-inflammatory cytokines TNF-α, IL-6, and IL-8 following LPS-induced inflammation, which is consistent with previous studies demonstrating the anti-inflammatory effects of CBD on macrophages during wound healing (Figure 4)[30]. It was proposed that CBD's mechanism of anti-inflammatory action involves activation of the G protein coupled receptor A2a which initiates a cascade effect involving intracellular cAMP elevation, followed by upregulation of tribbles homolog 3 (TRIB3) and inhibition of the NF- κβ anti-inflammatory pathway.

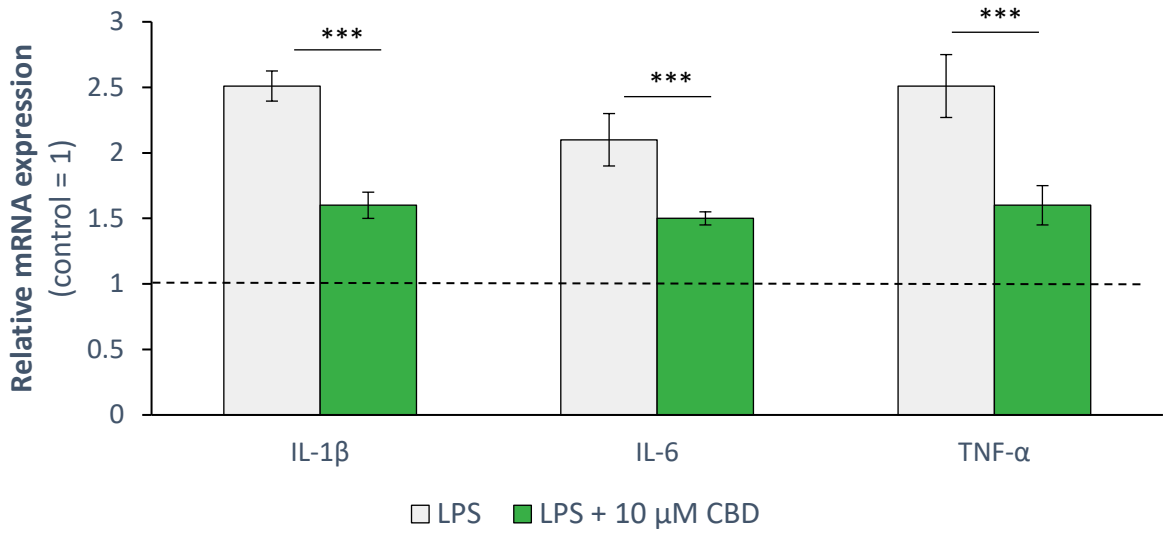


**Figure 4:** The anti-inflammatory effect of CBD determined by expression of inflammatory markers IL-1β, IL-6, and TNF-α expression following 24-hour lipopolysaccharide (LPS) treatment with and without 10 μM CBD[29]. Results are expressed as the mean ± SD of 3 independent determinations. Normalized mRNA expression of the vehicle control is set as 1 (dashed line). Significant differences between treatments with and without CBD are marked as * ($P < 0.05$), ** ($P < 0.01$), and *** ($P < 0.001$).

Similarly, 0.1 µM of THCV also prevented the release of pro-inflammatory cytokines IL-1α, IL-1β, IL-6, IL-8, and TNF-α following LPS-induced inflammation (Figure 5)[28]. 0.1 µM of CBG, CBGV, CBC, and CBDV were also shown to suppress the release of pro-inflammatory cytokines induced by LPS treatment, but to a lesser extent than THCV[28]. CBD, THCV, and the other cannabinoids appear to have anti-inflammatory effects.

Collectively, these results suggest that cannabinoids display an anti-inflammatory class effect. However, discrepancies in experimental design between these two studies coupled with a limited understanding of each cannabinoid's mechanism of action hinders any attempt to interpret this data for the purposes of identifying which cannabinoid is most suited for reducing inflammation associated with acne vulgaris. Direct comparison studies, perhaps involving a first line anti-inflammatory agent as a benchmark, would aid in this effort.

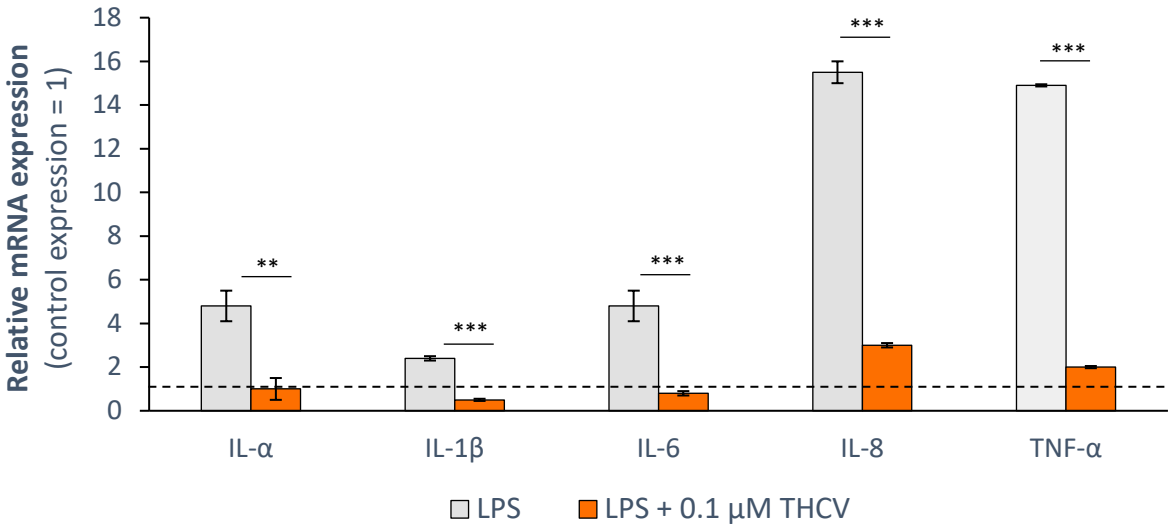


**Figure 5:** The anti- inflammatory effects of THCV determined by expression of inflammatory markers IL-α, IL-1β, IL-6, IL-8, and TNF-α expression following 3-hour lipopolysaccharide (LPS) treatment with and without 0.1 µM THCV[28]. Results are expressed as the mean ± SD of 2-3 independent determinations. Normalized mRNA expression of the vehicle control is set as 1 (dashed line). Significant differences between treatments with and without cannabinoids are marked as * ($P < 0.05$), ** ($P < 0.01$), and *** ($P < 0.001$).

## Cannabinoids as Antibacterial Agents

Novel therapies that selectively target virulent strains of *P. acnes* would be advantageous compared to the oral or topical antibiotics currently employed to inhibit bacterial growth and reduce inflammation given the risk of antibiotic resistance. Interestingly, it was recently shown that CBD, CBG, CBC, CBN, and THC display antibacterial activity at non-cytotoxic concentrations against a range of gram-positive pathogens, including *Staphylococcus aureus* and *Streptococcus spp*[31-35]. These pathogens are often implicated in the development of primary skin infections, such as impetigo, cellulitis, and bacterial folliculitis[36,37].

Given the gram-positive classification of *P. acnes*, it is likely that phytocannabinoids may act directly on *P. acnes*. Furthermore, 10 µM CBD was found to upregulate expression of the antimicrobial peptide LL-37 cathelicidin, suggesting additional avenues for antibacterial action. Further work is required to determine if

CBD and other cannabinoids would be effective treatment options against these bacterial skin conditions, and in the context of acne vulgaris, if these cannabinoids exert antibacterial activity against *P. acnes* in a manner that prevents or manages the clinical development of acne vulgaris.

## In-Vitro to Ex-Vivo Translational Study: CBD

Translational studies have begun to explore these phenomena in more physiological settings. In an ex-vivo study of full-thickness human skin cells obtained from biopsies of scalp and arm skin from four women, 10 μM CBD decreased basal lipogenesis and completely suppressed AEA-induced lipogenesis. Despite these preliminary findings, further in-vivo work is required to validate the safety and clinical utility of cannabinoids for the treatment of acne vuglaris and other skin-related conditions.

## LAVVAN's Cannabinoid Solutions

At the forefront of cannabinoid cellular agriculture, LAVVAN utilizes yeast fermentation technology to produce high-quality, reliably sourced, natural cannabinoid ingredients[38]. LAVVAN will provide cannabinoids with unparalleled purity, consistency, potency, and sustainability at a scale capable of serving a range of industries including health, beauty, food and beverage, and pharmaceuticals. LAVVAN's cannabinoids are identical to those found in nature and produced in a cGMP facility in accordance with the most stringent standards, including being devoid of pesticides, mold, bacteria, and other contaminants often found in traditional cannabis agriculture. In addition to providing high purity cannabinoid ingredients, LAVVAN will leverage its cannabinoid formulations expertise to support its industry partners with integrating cannabinoids into formulations for various end products that require specific utility.

## Conclusion

Acne vulgaris remains one of the most prevalent conditions worldwide despite the availability of numerous topical and oral therapies. Treatment is complicated by the multifaceted pathogenesis of this disease, as well as the variety of internal and external factors that are associated with its development and progression. Existing treatment options are limited by their narrow modality of action, restricted duration of use due to their side effects and, in the case of antibiotics, due to the development of treatment resistance.

In this context, the effects of cannabinoids at non-cytotoxic concentrations on sebum production, gram-positive bacteria, and immune response can direct the development of novel skin therapies with targeted effects for a variety of skin conditions. For instance, acne patients with naturally oily skin may benefit from treatments containing THCV or CBC given the sebum-reducing capabilities of these two cannabinoids. In contrast, treatments containing CBG or CBGV may be better suited for acne patients with dry skin, or for those who suffer from other conditions associated with dry skin and impaired barrier function, such as xerosis, eczema, and psoriasis.

Additionally, these cannabinoids may possess desirable activity against *P. acnes*. Optimal therapies would involve cannabinoid formulations that maintain appropriate levels of *P. acnes* or target virulent strains of this gram-positive bacterium and confer long-term efficacy without the risk of bacterial resistance developing. Such activity would also inhibit the immune response triggered by *P. acnes* and

further compound the anti-inflammatory effect of cannabinoids, which is a highly desirable treatment outcome for inflammatory skin conditions.

While these preliminary findings hold promise for the development of novel acne treatments, further work is required to elucidate the in-vivo mechanistic action of THCV and CBD as anti-acne agents, and to evaluate their safety and efficacy when administered as topical or oral therapies in clinical settings. Similarly, a deeper dive into the lipogenic modality of CBG and CBGV and clinical evaluations may render new treatment options for conditions associated with dry or compromised skin. As such, cannabinoids may offer novel solutions for these conditions as stand-alone treatments, or as combination therapies that enhance the efficacy of existing treatment options.

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