Anti-*Cutibacterium acnes* properties of *Cannabis sativa*

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Abstract

The antimicrobial potential of various cannabis compounds against *Cutibacterium acnes* (*C. acnes*) remains a subject of significant interest in dermatological research. This review aims to elucidate the mechanisms underlying the antibacterial activity of major cannabis compounds, including cannabidiolic acid (CBDA), cannabidiol (CBD), cannabinodiol (CBND), tetrahydrocannabinolic acid (THCA), Δ9-trans-tetrahydrocannabinol (Δ9-THC), Δ8-trans-tetrahydrocannabinol (Δ8-THC), cannabigerol (CBG), and cannabigerolic acid (CBGA). Many cannabis compounds showed antibacterial activity against several Gram-positive bacteria, including *Staphylococcus aureus* (*S. aureus*), *Staphylococcus epidermidis* (*S. epidermidis*), methicillin-resistant *S. aureus* (MRSA), and *C. acnes*, by acting as detergents and permeabilizing bacterial cell membranes by disrupting bacterial biofilms and membrane integrity. Some compounds, such as THCA, the precursor to THC, and THC derivatives, have shown inhibitory effects against staphylococci and streptococci bacteria, but their specific impact on *C. acnes* requires further investigation. In conclusion, while several cannabis compounds show promising antibacterial activity against various pathogens, including *C. acnes*, further research

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is warranted to elucidate their precise mechanisms of action and therapeutic potential in dermatological applications. These findings underscore the importance of investigating cannabis-derived compounds as potential agents for combating bacterial infections, including those affecting the skin. These findings underscore the importance of investigating cannabis-derived compounds as potential agents for combating bacterial infections, including those affecting the skin.

Keyword Cannabis, Acne vulgaris, Phytochemical, Anti-bacteria, dermatology

1 Introduction

Cannabis, an adaptable plant with a rich history of medicinal and recreational use, has gathered significant attention in recent years for its potential therapeutic applications. Beyond its substance contains well-known psychoactive compound, delta-9-tetrahydrocannabinol (THC), and its non-intoxicating counterpart, cannabidiol (CBD), and a diverse array of phytochemicals (Cooper & Haney, 2009). Cannabidiol, the second most prevalent active ingredient in cannabis, a complex plant containing over 100 different cannabinoids, terpenes, and flavonoids, has been traditionally employed for various medicinal purposes. (Cavalli & Dutra, 2021). Cannabinoids have reported reduction of vomiting, appetite stimulation and chemotherapy-induced nausea, and treatment chronic pain treatment, depression, anxiety disorder, psychosis, sleep disorder, glaucoma and has anti-inflammation, anti-bacterial properties and neuroprotective agent (Cavalli & Dutra, 2021). Recent studies have revealed the presence of photochemical compounds in cannabis, such as cannabinoids (e.g., THC and CBD), terpenes (e.g., β-caryophyllene and limonene), and flavonoids (e.g., quercetin and kaempferol), which exhibit diverse pharmacological properties, including antimicrobial activity (Stasiłowicz-Krzemień et al., 2024; Sandulovici et al., 2024). Antimicrobial potential of CBD and other derivatives, reveal against various pathogens such as *Staphylococcus aureus* (*S. aureus*), *Staphylococcus epidermidis* (*S. epidermidis*), *Streptococcus pyogenes* (*S. pyogenes*), *Cutibacterium acnes* (*C. acnes*), *Listeria innocua* (*L. innocua*), *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Escherichia coli* (*E. coli*) (Scott et al., 2022). Among these, the inhibitory effects of cannabis-derived photochemicals on *C. acnes* have piqued the interest of researchers and clinicians alike.

Acne vulgaris, a prevalent skin disorder affecting people worldwide, is characterized by the formation of comedones, papules, pustules, and in severe cases, nodules and cysts. *C. acnes*, a Gram-positive anaerobic bacterium residing on human skin, plays a pivotal role in the pathogenesis of acne. Its proliferation within hair follicles triggers an inflammatory response contributing to the formation of acne lesions (Mayslich et al., 2021). Its overgrowth and colonization within the pilosebaceous ducts are pivotal in the development of acne lesions, triggering inflammation and immune responses that contribute to the clinical manifestations of the disease (Spittaels et al., 2020).

Preliminary studies suggested that certain cannabinoids possess antibacterial properties that may inhibit the growth of *C. acnes*, presenting a novel avenue for acne treatment (Mahmud et al., 2021; Sionov et al., 2022). Understanding the potential mechanisms by which cannabis phytochemicals interact with *C. acnes* holds significant implications for the development of innovative skincare products and therapeutic strategies. In this review, we delved into the evolving landscape of research that investigated the inhibitory effects of cannabis-derived phytochemicals on *C. acnes*. By examining the scientific literature and emerging findings, we aimed to unravel the intricate relationship between these compounds and the bacterium responsible for acne, shedding light on the promising role of cannabis in the development of new and effective treatments for acne-related skin conditions.

2. Potential of cannabinoid on Acne vulgaris

In recent years, there has been growing interest in the potential of cannabinoids, particularly cannabidiol (CBD), found in cannabis, for acne treatment (Yoo & Lee, 2023). Acne begins with hormonal triggers that stimulate the sebaceous glands to produce excess sebum. The excess sebum combines with dead skin cells, forming plugs within hair follicles. *C. acnes* multiply within these blocked follicles, leading to inflammation (Zouboulis, 2004). The immune response causes redness, swelling, and the formation of various acne lesions, including pimples, papules, pustules, nodules, and cysts. *C. acnes* generate several enzymes and natural active molecules to induce immune cells to excrete proinflammatory cytokines. The immune cell can response to *C. acnes*, but not the bacteria itself, has a key major role in the pathogenesis of acne. The pathogenesis factor of acnes includes in muti-factor such as hormonal changes, surplus oil production (sebaceous glands overactive lead to the accumulation of sebum within hair follicles), infection of *C. acnes*, inflammation factor, and family history and genetics (Zouboulis, 2004).

2.1 Cannabinoids and Acne Reduction

Cannabis contains various compounds, with CBD being a notable cannabinoid believed to relieve acne symptoms. CBD exhibited anti-inflammatory properties, reducing the redness and swelling associated with acne lesions (Ferreira et al., 2024). Moreover, CBD regulates sebum production, preventing excessive oil buildup and decreasing the likelihood of clogged pores. More comprehensive studies need to investigate the related mechanisms to support the therapeutic potential of cannabinoids in acne treatment Cannabinoids, particularly CBD, derived from cannabis, offer promising avenues for acne management due to their anti-inflammatory and sebostatic properties. The precise mechanisms and optimal dosages, the potential of cannabinoids in acne treatment represented a significant area of interest (Oláh et al., 2014), offering hope for individuals seeking effective and innovative solutions for managing this common skin disorder (Kurokawa et al., 2009).

2.2 Cannabis compounds and their role in acne treatment

Cannabis contains over 100 different compounds, known as cannabinoids, each with unique properties. Among these, cannabidiol (CBD) and tetrahydrocannabinol (THC) are the most well-known and extensively studied cannabinoids (Atakan, 2012). While THC is psychoactive and not commonly used in medicinal applications, CBD has gained attention for its potential therapeutic benefits, including its role in acne management (Baswan et al., 2020).

2.2.1 Anti-inflammatory Properties of CBD

CBD interacts with the body's endocannabinoid system (ECS), which plays a crucial role in regulating various physiological processes, including inflammation. CBD extracts suppress the levels of the pro-inflammatory cytokines such as TNF-α, IL-6 and IFN-γ while increasing the level of anti-inflammatory cytokine IL-10 in primary human-derived neutrophils and T cells (Aswad M., 2022) CBD modulates the ECS receptors which are believed to control immune functions and play a key role in immune homeostasis, particularly CB2 receptors found in immune cells and skin such as B cells, NK cells, monocytes, polymorphonuclear neutrophils, CD8 lymphocytes, and CD4 lymphocytes. By doing so, it reduces the production of pro-inflammatory cytokines and chemokines, decreasing the inflammatory response associated with acne (Tóth et al., 2019). Inflamed acne lesions, characterized by redness and swelling, can be alleviated through the anti-inflammatory action of CBD, promoting faster healing and reducing the risk of scarring (Filipiuc et al., 2023).

2.2.2 Sebum Regulation by CBD

One of the primary factors contributing to acne is excess sebum production. Sebaceous glands possess receptors for cannabinoids, including CBD. When CBD interacts with these receptors, it helps regulate sebum production. By inhibiting the overactivity of sebaceous glands, CBD prevents the excessive accumulation of sebum within hair follicles (Baswan et al., 2020). This regulatory effect on sebum production reduces the chances of pores becoming clogged, decreasing the formation of new acne lesions.

2.2.3 Antibacterial Effects of CBD

CBD exhibits antimicrobial properties, including activity against the *C. acnes* bacteria prevalent in acne-prone skin. By targeting and inhibiting the growth of these bacteria, CBD reduces the accumulated bacteria within clogged pores. By diminishing the presence of *C. acnes*, CBD contributes to the resolution of existing acne lesions and helps prevent the formation of new ones, particularly inflammatory papules and pustules (Jiang et al., 2022).

2.2.4 Anti-oxidative Effects

CBD possesses antioxidant properties, meaning it can neutralize harmful free radicals that contribute to skin aging and inflammation. By reducing oxidative stress, CBD promotes overall skin health and resilience. In the context of acne, oxidative stress can exacerbate inflammation and impede the healing process (Atalay et al., 2019). CBD's antioxidant effects contribute to a healthier skin environment, supporting the body's natural ability to combat acne-related inflammation (Atalay et al., 2021). The existing evidence highlights its potential as a valuable therapeutic option in addressing the multifaceted nature of acne vulgaris.

3. Role of each major cannabis compound targeting on various bacteria

3.1 Cannabidiolic acid (CBDA)

Cannabidiolic acid (CBDA) is a naturally occurring compound found in the cannabis plant. It is the acidic precursor to CBD (cannabidiol) and is often present in raw cannabis plants (Tahir et al., 2021). Antibacterial property of CBDA, CBDA has no effects on Gram-negative *E. coli* or *P. aeruginosa* but in Gram-positive, *S. aureus* and *S. epidermidis* it was able to act as a detergent and permeabilise the bacterial cell membrane. Target mechanism of CBDA has n-pentyl groups functioning as modulators for lipophilicity which effect on bacterial membrane permeability. However, there is no report to reveal the target mechanism about cannabidiolic acid compound directly effect on *C. acnes* (Scott et al., 2022).

3.2 Cannabidiol (CBD)

Cannabidiol (CBD) a naturally occurring compound found in cannabis plants, including hemp and marijuana, it could also attain when the plant material is heated, dried, or aged as CBDA is converted into CBD through a process called decarboxylation, where the acidic carboxyl group (COOH) is removed (Hilderbrand, 2018). CBD as an antibacterial can be used against Gram-positive bacteria, including the highly resistant *S. aureus*, *Streptococcus pneumoniae* (*S. pneumoniae*), *Clostridioides difficile* (*C. difficile*) and *C. acnes* by disruption in bacterial cytoplasmic membranes leading in membrane permeability in Gram-positive bacteria (Blaskovich et al., 2021). The MIC rang in CBD to inhibit these bacteria are approximately 1-50 ug/ml. Additionally, it can also selectively kill a subset of Gram-negative bacteria, including *Neisseria gonorrhoeae* (*N. gonorrhoeae*). The mechanism of action of cannabidiol has excellent activity against gram-positive bacterial biofilms by preventing the bacteria-mediated depletion in pH values that correlated with bacterial growth inhibition leading biofilm reduction and membrane disruption (Kosgodage et al., 2019).

3.3 Cannabinodiol (CBND)

CBND is the compound that present in *Cannabis sativa*, which is the aromatized derivative of cannabidiol (CBD). CBND is also low concentrations product presented from photochemical conversion of cannabinol. (Kosgodage et al., 2019; Stasiłowicz et al., 2021). Nowadays there is no research focusing on the effect of CBND as anti-bacterial activity.

3.4 Tetrahydrocannabinolic acid (THCA) and Δ9-trans-tetrahydrocannabinol (Δ9-THC)

THCA is the precursor to delta-9-tetrahydrocannabinol (Δ9-THC), which is the primary psychoactive compound in cannabis. THCA itself does not have psychoactive effects. When cannabis plants are harvested and dried, THCA undergoes a process called decarboxylation, in which it loses a carboxyl group (COOH) and is converted into THC (Das et al., 2022). THCA can inhibit Staphylococci and Streptococci bacteria group in low level concentration but Δ9-THC derivatives can also have antibacterial activities against *Bacillus* spp. (Van Klingeren, B., & Ten Ham, M., 1976). However, there is not substantial research specifically demonstrating the effects of THCA on *C. acnes*.

3.5 Δ8-trans-tetrahidrocannabinol (Δ8-THC)

Δ8 THC is an isomer of Δ9-THC with similar pharmacological activity profile and slightly lower psychoactive potency because this compound has minor constituent of cannabis (Tagen & Klumpers, 2022). Some studies demonstrated that the oxygenated derivatives of Δ9-THC and Δ8-THC have been showed antibacterial activity and anticancer effect. Nevertheless, the anti-bacterial activity of Δ8-THC on *C. acnes* still need to further investigate.

3.6 Cannabigerol (CBG)

Cannabigerol (CBG) has a structure that can be described as a molecule made up of a chain of 21 carbon atoms with hydrogen atoms attached to them. This chain creates a backbone, where each carbon atom is connected to two hydrogen atoms except for the ends, which are connected to three hydrogen atoms (Jastrząb et al., 2022). CBG has been found to have properties, against *Streptococcus mutans* (*S. mutans)* a bacterium commonly associated with cavities (Aqawi et al., 2021). CBG effectively inhibited the growth of *S. mutans* causing cells to undergo changes in their shape and membrane structure resulting in swollen cells (Aqawi et al., 2021). Furthermore, CBG treatment leaded to the accumulation of membrane structures within the bacteria, and disrupted their membrane properties causing hyperpolarization and decreased fluidity. This increased permeability of the membrane maked them more vulnerable to damage. Additionally, CBG helped prevent the pH drop typically seen with *S. mutans* infections, which plays a role in tooth decay by

contributing to an environment in the mouth (Aqawi et al., 2022). Hence, CBG has proved to have antibacterial properties specifically against *S. mutans*, however not against *C. acnes*.

3.7 Cannabigerolic acid (CBGA)

CBGA is a precursor to the three major cannabinoid lines found in the cannabis plant: tetrahydrocannabinolic acid (THCA), cannabidiolic acid (CBDA), and cannabichromenic acid (CBCA). CBGA is often referred to as the "stem cell" or "mother cannabinoid" because enzymes in the plant can convert it into different cannabinoids depending on specific conditions (Kim et al., 2022). CBCA the chemical precursor of CBC, has been reported as an antibacterial activity to inhibit MRSA (Galletta et al., 2020) which is demonstrated *in vitro* study faster and more potent bactericidal activity than vancomycin. The target of CBCA can exert antibacterial effects by directly attack the bacterial lipid membrane degrading and altering the bacterial nucleic acid (Galletta et al., 2020). For *C. acnes,* there is no study effect of this compound on target bacterial structure.

4. Conclusion

The investigation into the antibacterial properties of cannabis-derived compounds against many skin-pathogens highlighted the potential of cannabinoids as therapeutic agents in dermatology. Cannabidiol (CBD), in particular, demonstrated broad-spectrum antibacterial activity, including efficacy against highly resistant strains such as MRSA and *C. acnes*. Its mechanism of action involves disrupting bacterial biofilms and compromising membrane integrity, offering promising prospects for the treatment of acne and other bacterial skin infections. While cannabidiolic acid (CBDA), the precursor to CBD, exhibits antibacterial effects against Gram-positive bacteria by permeabilizing cell membranes, its direct impact on *C. acnes* remains unclear. Other cannabinoids, such as tetrahydrocannabinolic acid (THCA) and Δ9-trans-tetrahydrocanna binol (THC), show inhibitory effects against certain bacterial strains, although their specific actions on *C. acnes* require further elucidation. The lesser-studied cannabinodiol (CBND) and Δ8-trans-tetrahydrocannabinol (Δ8-THC) demonstrate antibacterial activity, with potential applications in dermatology pending further investigation. Cannabigerol (CBG) and cannabigerolic acid (CBGA) also exhibit antibacterial properties, albeit not extensively studied against *C. acnes*.

Overall, the research underscores the importance of exploring cannabis-derived compounds as potential alternatives or adjuncts to existing antimicrobial agents in dermatological practice. Further studies are warranted to delineate the precise mechanisms of action, optimize formulations, and assess clinical efficacy and safety profiles. By leveraging the therapeutic potential of cannabinoids, novel treatments for acne and other bacterial skin infections may be developed, addressing unmet medical needs and offering new avenues for patient care.

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