

REVIEW ARTICLE

Cannabidiol As A Novel Therapeutic Strategy For Oral Inflammatory Diseases: A Review Of Current Knowledge And Future Perspectives

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ABSTRACT

The high frequency and painful profile of inflammatory oral lesions and the lack of an effective drug protocol for their management stimulate the search for pharmacological alternatives for the treatment of these conditions. Cannabidiol is the major non-psychotropic constituent of *Cannabis sativa*, receiving lately scientific interest because of its potential in the treatment of inflammatory disorders such as asthma, colitis and arthritis. There is little published

in the current literature about the use of cannabidiol in oral health. Among its many protective functions, the ability to attenuate inflammation through the modulation of cytokines and its antiedema and analgesic effects may be important features in the treatment of oral lesions. In this review, we suggest that cannabidiol can be useful in the management of oral inflammatory disorders. (*Altern Ther Health Med.* 2020;26(S1):12-16.)

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INTRODUCTION

Inflammatory lesions affect the oral tissues with high frequency. These injuries may have traumatic, autoimmune, neoplastic or infectious etiologies and are often capable of causing a break in the mucosal barrier.¹⁻⁴ Rupture of the epithelial structure induces the development of an inflammatory response and becomes a potential source of infection, resulting in pain and discomfort.⁴ Thus, restoring the integrity of mucosal tissue is essential to re-establish oral function.

Wound healing is a complex series of events involving well-defined phases of hemostasis, inflammation, proliferation, and remodeling.^{5,6} This dynamic process is coordinated by several mediators including inflammatory

cells, cytokines and growth factors.⁶ Modulation of the inflammatory response during the healing process of oral lesions is a key factor for tissue repair to occur properly and in a shorter time. This may be especially necessary when considering chronic wounds, which may be induced by conditions such as diabetes and local infection.^{7,8}

The management of oral mucosal lesions is mainly supportive and often consists in relieving pain and symptoms besides attempts to accelerate tissue repair. Despite the variety of medications available, there is no consensus on the ideal treatment modality. Currently, pharmacological approaches include topical and systemic corticosteroids, antibiotics, local anesthetics, antiseptics, immunomodulatory and non-steroidal antiinflammatory agents.^{4,9} Among the strategies to induce and modulate oral healing, the use of phytotherapeutic agents or natural compounds has shown potential.¹⁰⁻¹⁵

Cannabidiol (CBD) is the major non-psychoactive component of *Cannabis sativa*. The therapeutic properties of CBD have been widely studied, and antiinflammatory, analgesic, antioxidant and immunomodulatory effects have been identified.¹⁶⁻¹⁸ In recent years, CBD has demonstrated effectiveness in treating a number of conditions involving both inflammation and oxidative stress, such as rheumatoid arthritis,¹⁹ inflammatory bowel disease,²⁰ diabetes,²¹ and neurodegenerative disorders.²² Furthermore, it is considered well tolerated, without significant side effects when chronically administered.^{23,24}

Despite the vast literature addressing the therapeutic effects of CBD in various pathologies, there are still few studies in oral medicine evaluating its health benefits. CBD has antiinflammatory properties in the treatment of periodontitis,²⁵ and recently, a review indicated CBD as a promising therapeutic agent in the management of chemo- and radio-induced oral mucositis.²⁶ A variety of mechanisms appear to be involved in the beneficial effects of CBD. One in particular is its ability to modulate the production of inflammatory mediators, which are also involved in the oral healing process, allowing its use in oral medicine.²⁵⁻²⁷ In addition, its analgesic and antiedema properties¹⁷ may aid to the management of different oral conditions.

The purpose of this study was to review the literature on the effect of CBD in oral disorders and the therapeutic viability of its use in the repair of oral lesions, considering the scientific evidences and its main characteristics. Accordingly, the authors surveyed the literature related to this subject in the PubMed database, using as search criterion complete articles published in English. Selection involved current studies covering the physiology of wound healing and CBD effects in inflammatory diseases.

CANNABIDIOL

In history, *Cannabis sativa* (marijuana) have been used for medical purpose for centuries. Among its numerous constituents, this plant contains more than 100 active components termed cannabinoids. The 2 most important phytocannabinoids are Δ9-tetrahydrocannabinol (THC) and CBD.^{28,29} These substances are capable of interacting with specific cannabinoid receptors CB₁ and CB₂. While CB₁ receptors are primarily expressed in the central and peripheral nervous system and can modulate excitatory and inhibitory neurotransmission, CB₂ receptors are localized on immune cells, acting as immunomodulators.^{16,30-32}

THC is the most abundant phytocannabinoid in marijuana and has good affinity for CB₁ and CB₂ receptors. However, its undesirable psychoactivity limits the therapeutic use of this substance.¹⁶ CBD, first isolated in 1940, is the main non-psychoactive constituent of *Cannabis sativa*.^{16,18,21} Its use has been recognized in the treatment of several pathologies like Alzheimer's Disease,¹⁶ sepsis,²³ inflammatory bowel diseases²⁰ and also some types of cancer.²¹ The exact mechanism of action of CBD has not been fully elucidated, but appears to include functions independently of CB receptors.²¹ Its beneficial effects such as immune and inflammatory modulation,¹⁶ antioxidation¹⁸ and analgesia,^{17,33} combined with its lack of psychoactive, good safety and a tolerability profile, encourage the use of CBD for numerous therapeutic applications.

CBD AND ORAL MEDICINE

Although widely explored in several pathologies and showing promising effects regarding different organs, few studies have evaluated CBD properties in oral tissues. In the area of oral medicine, we found only two scientific

Table 1. Effects of CBD Treatment in Oral Diseases

Disorder	Results	Reference
Periodontitis	In this experimental study in rats, CBD treatment decreased alveolar bone loss, reduced the expression of receptor activator of nuclear factor-κB ligand RANKL/RANK and decreased neutrophil migration and IL-1β and TNF-α production.	Napimoga et al ²⁵
Oral Mucositis	This literature review concluded that CBD may have a potential antimucositis effect, both in the control of oxidative stress and suppression of the inflammatory response	Cuba et al ²⁶

Abbreviations: CBD, Cannabidiol; IL1-β, interleukin-1 beta; TNF-α, tumor necrosis factor-alpha.

publications regarding the effects of CBD for oral diseases (Table 1). These studies indicated that CBD may be promising in the treatment of periodontitis,²⁵ and chemo- and radioinduced oral mucositis.²⁶

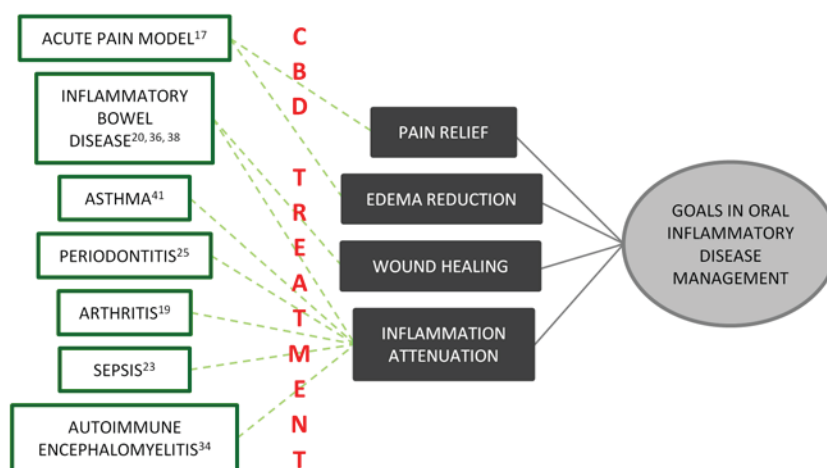
Napimoga et al²⁵ conducted an experimental study with induced periodontitis in rats and found that animals treated with daily intraperitoneal injection of 5 mg/kg CBD for 30 days exhibited decreased alveolar bone loss and a lower expression of RANKL/RANK. Furthermore, in gingival tissue, CBD administration decreased neutrophil migration and reduced interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) production. The authors concluded that these antiinflammatory effects of CBD could be useful in controlling the development of periodontitis.

Marijuana components have already been used in oncology patients due to their benefits in relieving symptoms such as nausea and also controlling appetite, sleep and anxiety problems. Recently, a literature review evaluated the therapeutic viability of CBD in managing oral mucositis induced by anticancer treatment.²⁶ On the basis of its mechanism of action, besides its analgesic and antioxidant effects, authors have proposed that CBD may be used in the treatment of oral mucositis, a serious condition that affects the quality of life of cancer patients.

THERAPEUTIC POTENTIAL OF CBD IN INFLAMMATORY ORAL LESIONS

CBD therapy has been explored in the management of various inflammatory conditions.¹⁶ Its positive effects in chronic conditions, such as autoimmune encephalomyelitis, have been observed even when administered topically.³⁴ Previous studies found that the antiinflammatory effect of CBD frequently occurs in a dose-dependent manner, resulting in a bell-shaped curve.^{19,35} Although the mechanism of action of CBD is still not fully elucidated, its effect on inflammatory diseases may be explained by various biological systems, involving both cellular and molecular events.¹⁶

Figure 1. Why CBD Can Be Considered A Therapeutic Strategy For Inflammatory Oral Lesions? Many beneficial effects of CBD when tested in different disorders indicate its potential in treating a number of inflammatory oral diseases.



Considering the pathogenesis of inflammatory oral lesions, several CBD mechanisms of action could be related to an improvement of tissue repair in oral wounds.^{16,36} Previous publications point to various CBD properties in different diseases that may enhance its potential use in the management of various oral conditions (Figure 1). Each mechanism will be explained individually below.

Modulation of Neutrophil Infiltration

Neutrophils play a critical role in tissue repair, acting mainly in the early stages of the wound healing process.^{5,6} They are responsible for initiating an inflammatory cascade, attracting fibroblasts and macrophages to the injured region. In the late inflammation period, macrophages and lymphocytes are the main cells at the ulcer site, by increasing the production of cytokines and growth factors.^{5,8}

Neutrophil infiltration may contribute to the pathogenesis of various diseases, acting on the amplification and progression of inflammation. It is known that prolonged inflammation may delay wound healing, since excess edema, proinflammatory cytokines and toxic free radicals can be damaging to tissues and slow the progression of tissue repair.^{7,37} The literature suggests that CBD has the ability to act on neutrophil proliferation and chemotaxis.³⁶ *In vivo* studies demonstrated that CBD was able to influence neutrophil infiltration when used in the treatment of periodontitis,²⁵ Crohn's Disease³⁵ and also when administered topically for encephalomyelitis.³⁴

Pain and Edema Reduction

Pain and edema are common complaints of patients with inflammatory oral lesions.^{4,13} According to the literature, CBD may be effective in controlling both symptoms.¹⁷ In rats with induced colitis, daily CBD at 5 mg/kg for 6 days reduced the signs of colon injury, decreasing edema in the intestinal mucosa and submucosa and helping with tissue regeneration.³⁸ This would agree with the data reported by Costa et al¹⁷ who

determined CBD effects in a model of carrageenan-induced acute rat paw inflammation. These authors found a substantial reduction in hyperalgesia and edema after daily oral administration of CBD for 3 days. The effects were dose-dependent and evident within a few hours after a single application of the medication.

Another study observed that CBD had antihyperalgesic properties also in rats with chronic inflammatory pain.³³ Daily oral treatment with CBD reduced chronic pain in a dose-dependent manner, which was associated with a reduction of proinflammatory mediators.

Modulation of The Release of Proinflammatory Cytokines

Some conditions or genetic and clinical variables, such as diabetes, smoking, and inflammatory/immunological pathologies, interfere in wound healing and may delay tissue repair.^{8,27} Previous literature shows that deficient tissue repair of ulcerated oral mucosal lesions can be observed in diabetic rats, and this may be associated with increased inflammatory response and cytokine expression.⁷ Diabetes causes a prolonged inflammatory phase of healing, observed by an increase in polymorphonuclear neutrophil infiltration and higher expression levels of IL-1 β and TNF- α in oral ulcers of these animals. Therefore, the use of drugs that modulate inflammatory response can be effective when adequate tissue repair of oral lesions is desired, especially if conditions that impair oral healing are present.

Malfait et al¹⁹ reported one of the first studies to evaluate the potential of CBD as an antiinflammatory agent. Using a murine model of collagen-induced arthritis, CBD exerted a potent immunosuppressive effect both *in vivo* and *in vitro*, in a dose-dependent manner. The authors suggested that CBD has an immunosuppressive and antiinflammatory action, reducing IFN (interferon)- γ release and suppressing the proliferation of lymphocytes.

In agreement with this study, different inflammatory markers were associated with the antiinflammatory effect of

CBD. In cisplatin-induced nephrotoxicity in mice³⁹ and in rat experimental periodontitis,²⁵ treatment with CBD attenuated inflammation by modulating TNF- α and IL-1 β levels. Similarly, in mice with induced acute lung injury, a single dose of 20 mg/kg CBD modulated neutrophil, macrophage and lymphocyte migration and also decreased TNF and IL-6 production.⁴⁰

Thus, in different inflammatory pathologies, CBD appears to modulate a variety of markers and cytokines. Even in a topical formulation, it was able to attenuate IL-1 β , TNF- α , IL-6, IFN- γ and transforming growth factor-beta (TGF- β) expression in experimental autoimmune encephalomyelitis.³⁴ Additionally, in a model of asthma,⁴¹ CBD treatment reduced levels of IL-4, IL-5, IL-13, IL-6, and TNF- α .

CBD as an Antioxidant

Some studies have pointed out that CBD can be considered promising in the treatment of various conditions due to its ability to influence the immune system and oxidative stress.^{17,18,23} Its antioxidant activity was reported to be effective in treating cisplatin-induced nephrotoxicity³⁹ and inflammatory bowel disease.³⁸ Considering that substances with antioxidant potential are known to improve wound healing and protect tissues from oxidative damage,¹⁰ CBD may have a regenerative effect in the treatment of oral ulcers, including oral mucositis.²⁶

Modulation of MMPs

Matrix metalloproteinases (MMPs) are a group of enzymes responsible for the degradation of extracellular matrix proteins and which participate in inflammation and repair processes. The overexpression of these molecules in inflammatory diseases and other pathological conditions may result in unwanted tissue destruction. Previous studies have found that MMP-2 may be associated with delayed healing and increased inflammation in the pathogenesis of oral diseases such as lichen planus,⁴² periodontitis⁴³ and mucositis.⁴⁴

Rawal et al,⁴⁵ encouraged by gingival enlargement seen in marijuana users, assessed the effects of CBD on human gingival fibroblast metabolism. These authors showed that CBD was not cytotoxic to fibroblasts and, depending on the dose, exerted a biphasic effect on the production of TGF- β and MMP in these cells. Lower CBD concentrations increased TGF- β , MMP-1 and MMP-2 production, but higher CBD concentrations decreased TGF- β and MMP levels and lowered MMP-2 activity. It was suggested that altered inflammatory responses caused by CBD may contribute to drug-induced gingival overgrowth. Thus, the ability of CBD to modulate the production and activity of these enzymes supports the use of this drug in the treatment of inflammatory oral diseases.

CONCLUSION

Although still sparse, available studies of CBD effects on the oral cavity have shown promising results. To date, CBD pharmacodynamics is yet to be defined, and further studies

are required to elucidate the mechanisms of action and potential adverse effects of CBD. This review may be useful in providing awareness of the importance of this theme and highlights the potential use of CBD as a safe pharmacological approach for the treatment of oral inflammatory lesions. CBD may be a starting point for the development of new drugs in oral medicine.

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