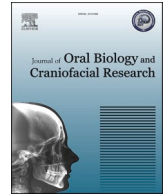




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Unleashing the therapeutic role of cannabidiol in dentistry

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ABSTRACT

Cannabidiol (CBD) found in *Cannabis sativa* is a non-psychoactive compound which is capable of binding to CB1 and CB2 receptors. CBD has recently gained interest in dentistry although it has not been explored sufficiently yet. The therapeutic effects of CBD include anti-inflammatory, analgesic, antioxidant, biological and osteoinductive properties. The aim of this review is to highlight these effects with respect to various oral conditions and shed light on the current limitations and prospects for the use of CBD in maintaining oral health.

1. Introduction

Cannabinoids are molecules that occur naturally in mammals produced by the endocannabinoid system and are known to interact with substances which are endogenous (e.g., 2-arachidonoylglycerol as well as anandamide),^{1,2} phytocannabinoids (e.g., tetrahydrocannabinol and cannabidiol), or other cannabinoid analogues which are synthetic in nature.³ Cannabidiol (CBD) is a non-psychoactive compound procured from the plant named *Cannabis sativa*.⁴

Cannabinoids have the ability to bind to two receptors namely, cannabidiol-1 (CB1) and cannabidiol-2 (CB2); routinely encountered in plasmalemma (cytoplasmic/plasma/cell membrane), axon (nerve fibres) (CB1) and cells of the tissue (CB2).¹ Receptors belonging to CB1 are presynaptic when the brain is concerned and are also instrumental in the regulation of mood, memory, appetite, sleep, and pain by their ability to release neurotransmitters. Small quantities of CB1 receptors are also encountered in peripheral tissues such as the heart, testicles, muscles, liver, pancreas, and adipose tissues. CB2 receptors that wring out in the hematopoietic cells and spleen, are thought to be in charge of the cannabidiols' anti-inflammatory and immunomodulatory effects.²

Several studies and literature reviews have suggested that the therapeutic spectrum of CBD includes its use as an anti-inflammatory,⁵ anti-oxidant,² analgesic,⁶ bone cell differentiation,^{3,7–9} antiepileptic, neuroprotection, anti-cancer and anxiolytic agent. It also holds the

potential to be used for stress relaxation, relief, and sleep improvement.¹⁰ The expression of cannabidiol receptors in various structures present in the oral cavity such as dental pulp stem cells as well as the periodontium opens the portal for its use as a medicinal agent.^{11–13} The purpose of this article is to gauge the myriads of applications of CBD in dentistry while also exploring the probable mechanism of action as well as the current limitations in its use. The review will also help the lacunae associated with the use of CBD and allow the researchers as well as clinicians to adapt CBD as a routinely used therapeutic agent in the dental field.

2. Mechanism of action and pharmacology behind cannabidiol

They function by the stimulation of CB1 and CB2 receptors which are within the endocannabinoid system. This is a complex network of organs presents throughout the body aiding in the expression of CB receptors who play a vital role in homeostasis.¹⁴ The endocannabinoid system is involved in functions such as pain¹⁵, memory,¹⁶ movement,¹⁷ appetite,¹⁸ metabolism,¹⁹ lacrimation, salivation,²⁰ immunity as well as cardiopulmonary functions.²¹ It is worth noting that the vast majority of the effects of cannabinoids, including psychotropics, are caused by CB1 activation, with CB2 playing a more important role in immune and inflammatory functions (Fig. 1).

Endogenous endocannabinoids act as neuro-regulatory modulators,

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facilitating retrograde neurotransmission. A post-synaptic neuron releases endocannabinoids, which primarily bind to CB1 receptors on the presynaptic neuron. This binding inhibits presynaptic calcium channel activation and subsequent neurotransmitter release. If the presynaptic neurotransmitters are primarily inhibitory, such as GABA, the overall effect is excitatory, and vice versa. Cannabinoids, particularly Δ-9-tetrahydrocannabinol (THC), have different psychotropic properties depending on where they bind to the central nervous system (Table 1).²²

3. Routes of administration of cannabidiol

The route of administration for cannabinoids varies. Medical cannabinoids are typically administered orally as capsules or liquid suspensions. Dronabinol is available in capsules with strengths of 2.5 mg, 5 mg, and 10 mg, as well as an oral 5 mg/mL formulation. The medication is typically taken twice daily, 1 h before meals, with titration from the initial dose done gradually based on tolerance and response.²³ Nabilone is available as a 1 mg capsule that can be taken twice or three times per day, depending on the provider and patient’s preferences. Finally, cannabidiol is available as a 100 mg/mL oral solution that can be taken twice daily, beginning with 2.5 mg/kg/day and titrated based on patient response and tolerance.

Cannabinoids can also be administered via the oral route by incorporating them in food products such as infused teas or oils, or inhaled by smoking cannabis or marijuana.²³ Products containing THC are almost always illegal, classified as Schedule I by the US Drug Enforcement Agency (DEA), and thus only available on black markets. However, CBD has gained popularity in recent years and is now available over the counter. Although smoking cannabis has traditionally been the most common method of cannabinoid administration, vaporization with e-cigarettes is becoming more popular, providing a faster, less carcinogenic way of delivering cannabinoids from the lungs into the bloodstream.²⁴ Finally, although sublingual, rectal, ocular, transdermal, and aerosol deliveries have seen research, there is a paucity of literature on

Table 1
Different areas and end-effects of cannabidiol.

Area	End-effect
Hippocampus	Short-term memory impairment
Neocortex	Judgement and sensation impairment
Basal ganglia	Reaction time and movement alteration
Hypothalamus	Increased appetite
Nucleus accumbens	Euphoria
Amygdala	Panic and paranoia
Cerebellum	Ataxia
Brainstem	Anti-emesis
Spinal cord	analgesia
Peripheral nervous system	Dry mouth, conjunctivitis, tachycardia, hypotension and bradypnea

their use.

4. Role of cannabidiol in periodontal therapy

CB1 and CB2 receptors are both expressed in periodontal tissues, but their distribution varies depending on the tissue’s condition.¹² In healthy periodontal tissues, CB1s are abundantly expressed in the periodontal ligament (PDL) and bounteously active in the epithelium than in the PDL.^{25,26} CB2 receptor expression increases when bacteria are present, whereas in a sterile inflammatory condition, both the receptors are expressed in PDL in high quantities but not in the cementum or the alveolar bone.²⁷ So, it appears that the two receptors’ distinct expression patterns are related to various aspects of cellular function, including differentiation and proliferation, inflammatory regulation, and wound healing.²⁸ Numerous investigations have substantiated the involvement of CB2 in the healing of periodontal tissue, specifically in regulating the adhesion and migration of periodontal cells in reaction to signals from the mitogen-activated protein kinase (MAPK) systems and focal adhesion kinase (FAK).^{26,28–30}

Via the CB2 receptor, the CBD analogue HU-308 regulates the degree

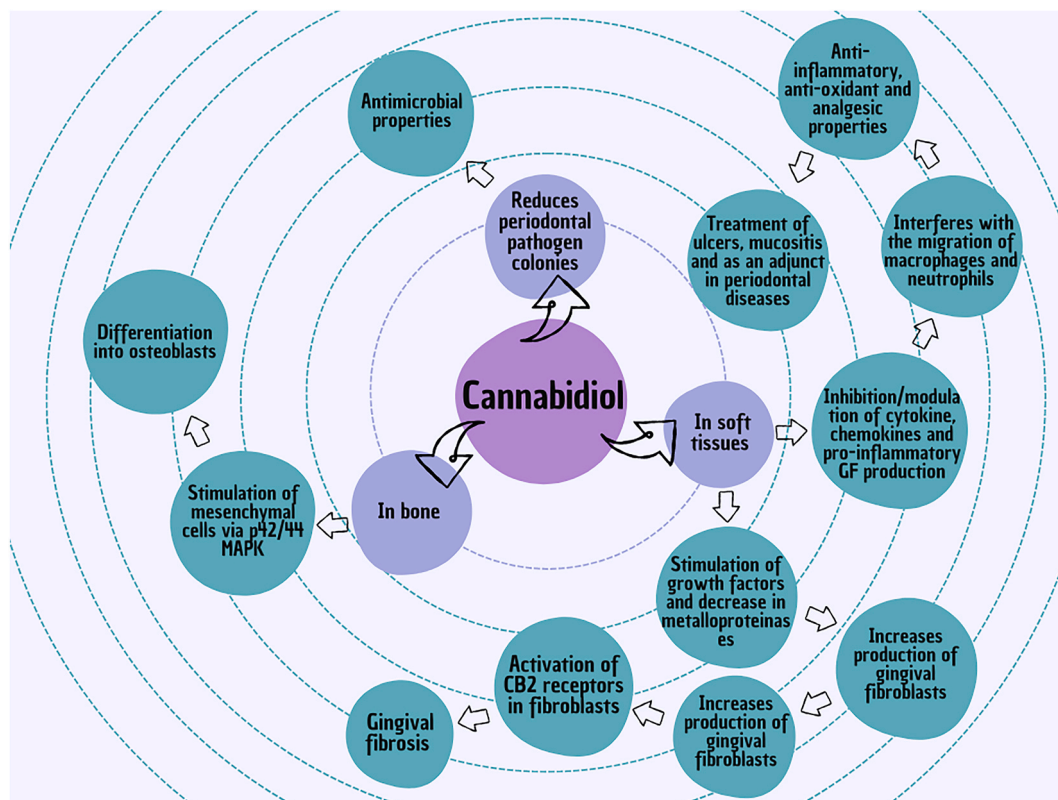


Fig. 1. Main applications of cannabidiol and its synthetic analogues in dentistry.

of periodontal disease and its effects on gingival tissue, alveolar bone, and salivary function. Because CBD suppresses the RANK/RANKL system and reduces pro-inflammatory cytokine levels, it possesses anti-inflammatory and anti-bone resorption characteristics.³¹ An alternate strategy for periodontal therapy could use CBD-mediated inhibition of metalloproteinases and/or activation of gingival fibroblasts with healing growth factors.^{32,33} Due to its antimicrobial activity, CBD has been known to diminish the inflammatory periodontal diseases caused by various bacterial species.^{34,35} Because CBD speeds up the healing process of common ulcers, it is also a viable pharmaceutical alternative in the treatment of oral mucositis due to its anti-inflammatory qualities, which help to reduce the severity and extent of the lesion.^{9,36} It has also demonstrated efficacious effects in decreasing the bacterial charge in tooth plaque.²⁵ CBD is also biocompatible and osteoinductive,^{28,37} as it has been demonstrated to aid in the healing of fractures by triggering the p42/44 pathway in mesenchymal cells, which then undergo osteoblast differentiation at the site of the injury.³⁸

As was previously mentioned, CBD has anti-inflammatory qualities and can lessen the loss of alveolar bone in periodontitis that is produced.^{33,35} Pharmacologically, CBD can have therapeutic, analgesic, or anti-inflammatory effects by selectively activating CB2 receptors, which avoids the side effects brought on by activating CB1 receptors.⁵ The way these anti-inflammatory qualities behaved looked to be comparable to other endogenous cannabinoids, such as anandamide. Specifically, it has been demonstrated that anandamide is present, regulated along the course of periodontal disease, and has a role in the inhibition of pro-inflammatory mediators. Additionally, it might have a role in the physiological defense of periodontal tissues against severe inflammation.³² Moreover, it can decrease the synthesis of inflammatory mediators like interleukins and block NT-kB, a regulator of the immunological and inflammatory response that is typically triggered by endotoxins made from bacterial lipopolysaccharides.⁵ It has also been demonstrated to lessen oxidative and nitrosative stress, interfere with neutrophil and macrophage migration, and block or regulate the synthesis of cytokines, chemokines, and pro-inflammatory growth factors.² Similar to endocannabinoids, CBD has been shown to exhibit anti-inflammatory properties at cannabinoid receptors, either directly or indirectly. This finding may have intriguing therapeutic ramifications. According to a different study, CBD may exacerbate gingival fibrosis by raising the synthesis of fibronectin, transforming growth factor- β , and gingival fibroblasts while lowering the activity and production of matrix metalloproteinase. It has been demonstrated that, within 24 h, low amounts of CBD can raise transforming growth factor β levels by as much as 40 %, suggesting that CBD may inadvertently encourage fibrosis. Additionally, CBD may raise anandamide levels, which through CB1 or other receptors may encourage fibrosis.³²

5. Role of cannabidiol in oral medicine

The oral mucous membrane is the main tissue of the oral cavity that interacts with CBD. Oral mucosal epithelial cells have been shown to exhibit CB1 and CB2 receptors. Human epithelial keratinocytes proliferate and differentiate more when exposed to CB2 receptors than when exposed to CB1 receptors.³⁹

There are CB1 and CB2 receptors found all the way down to the lamina propria's connective tissue. They also indicate their presence in the tongue's taste buds and epithelial cells, which are primarily controlled by the physiological and pathological circumstances of the tongue.⁴⁰ When burning mouth syndrome is present, CB1 receptor expression is downregulated and CB2 expression is upregulated. Furthermore, as both CB1 and CB2 receptor expression has been demonstrated to be elevated, it appears that ECS activation is involved in oncological disorders like mobile tongue squamous cell carcinoma.^{41,42}

The existence of CB1 and CB2 receptors in dental pulp is poorly understood, yet they are identified in nerve fibers which are sympathetic

in nature as well as on the surface of pulp tissue where they border dentin.⁴³ Human odontoblasts also contain CB1s, and these cells may react to immunological stimuli.^{44,45} In fact, TRPV1-mediated extracellular Ca^{2+} ion passage (TRPV1) via extrusion $\text{Na}^{+}\text{-Ca}^{2+}$ exchangers (NCXs) are made possible by activation of these receptors and the cyclic adenosine monophosphate (cAMP) signaling that follows.⁴⁶ This promotes the formation of a dentin bridge secondary in nature as a response to stimuli generated through the odontoblasts. The salivary glands include different locations for CB1 and CB2 receptors. The main salivary glands' striatal duct cells produce CB1, while the cells which are acinar cells—specifically, the myoepithelial cells—express CB2, which is involved in saliva secretion.^{47,48} It is interesting to note that food type and quantity appear to govern the residence and dispersal of CB1s in salivary glands,⁴⁹ and both CB1 and CB2 receptors influence salivary secretions.^{50–52}

CBD has dose-responsive analgesic and anti-inflammatory effects; however, optimal dosages for potential antioxidant and anti-inflammatory effects have not yet been determined.^{9,38,53} The synthesis of mediators of pro-inflammation that cause diseases such as oral mucositis may be altered by CBD's powerful anti-inflammatory, antioxidant, and analgesic effects compared to conventional antioxidants.⁹ Due to the favorable epithelial alterations that CBD produced in ulcer lesions *in vivo*, it may one day be employed as a therapeutic to treat the symptoms of mucositis. One crucial factor that could affect this tissue response is CBD's potential capacity to affect keratinocytes without having any negative side effects. The anti-inflammatory qualities of CBD did not hasten the healing of wounds.³⁶

In an *in-vivo* study, the synthetic analogue HU-308 decreased gingival tissues' loss of alveolar bone and mediators of inflammation, which are elevated when lipopolysaccharide-induced periodontitis cases without therapy are considered. The primary localized impact is a result of CB2 receptor activation, which decreases osteoclastogenesis and promotes osteoblast cell differentiation. According to this, CB2 receptor signaling acts directly on bone cells to stop bone loss while also preventing pro-reabsorption cytokines from being expressed.³¹

Research has demonstrated that CBD possesses potent antibacterial qualities, effectively diminishing bacterial strain colonies in the oral cavity along with two biofilms. Higher concentrations of this drug prevent *Porphyromonas gingivalis* and *Filifactor alocis* from growing, two crucial members of the subgingival microbiota.³⁴ Tooth plaque is a steady, biofilm with an organized structure housing plethora of microorganisms responsible for periodontitis, gingivitis, and tooth cavities. Since Gram-positive bacteria make up most of the pathogens found in dental or oral biofilms, they may be more susceptible to the effects of CBD, which has been shown to reduce bacterial colonies more in comparison to other oral hygiene methods. Although, due to the microbial diversity of dental biofilms, the effectiveness of CBD may vary from person to person.³⁵

6. Role of cannabidiol in trauma and surgery

Due to its biological and osteoinductive characteristics, CBD, either by itself or in conjunction with other medications, has been shown to reliably and efficiently enhance microglial cell migration and bone differentiation via the ECS.³³ Bone cells and skeletal sympathetic nerves both include the ECS, and cannabinoids are crucial for maintaining bone mass homeostasis.⁵⁴ In this case, it appears that CBD increases the expression of the PLOD1 gene, which leads to rise in the maturation of collagen, expression of bone protein, along with mineralization.^{7,38} Because of the potential for better bone tissue biomechanical qualities and neobone development, CBD is a fitting therapeutic subordinate for loss of bone resulting from trauma or surgery.

7. Role of cannabidiol in odontalgia (toothache)

Odontalgia, or toothache, is a debilitating condition that is

frequently the primary complaint of patients who visit the dentist. Although many non-opioid-based preparations, such as nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and others, are prescribed, their role and effectiveness in relieving odontogenic pain are limited.⁵⁵ To combat this, Chrepa et al. conducted a randomized clinical trial and found that oral CBD can be an effective analgesic medication for odontalgia.⁵⁶ Murphy and Hayes demonstrated that the pure CBD drug "Epidiolex" can effectively treat acute dental pain.⁵⁵ However, it is imperative to note that CBD would only serve as temporary bridges until definitive dental care, such as endodontic therapy or exodontia, could be performed. It is also crucial to note that, like any other drug, CBD can cause side effects that patients should be aware of beforehand. These include sedation, abdominal pain, diarrhoea, and elevated liver enzyme levels.⁵⁷

8. Role of cannabidiol in endodontic therapy (direct hooding)

In order to prevent pulpitis, odontalgia, and necrosis in cases of traumas and/or deep caries, it is imperative to encourage odontogenesis.⁵⁸ Since the dental pulp expresses CBD receptors, CBD have the ability to induce odontogenic or osteogenic differentiation. This process stimulates the migration, proliferation, as well as dental pulp stem cells differentiation, increasing the mineralization and synthesis of collagen and having a protective effect on pulp vitality.^{44,59,60} Moreover, TNF-alpha is inhibited by CBD, which also prevents stem cell differentiation. TNF-alpha, interleukin (IL)-1beta, and IL-6 are pro-inflammatory cytokines that are reduced by CBD,⁵⁴ and CBD activates CB1 receptors in odontoblasts to promote extracellular Ca²⁺ entry and the production of reparative dentin.^{61,62}

RUNX family transcription factor 2 (RUNX2), Osteopontin (OPN), intercellular adhesion molecule 1 (ICAM-1), Vascular Endothelial Growth Factor-Based angiostatics (VEGFR1), dentinal matrix acid phosphoprotein 1 (DMP-1), dentin sialophosphoprotein (DSPP), and alkaline phosphatase (ALP) are among the angiogenic and odontogenic genes whose expression is increased by CBD.^{59,63,64}

9. Role of cannabidiol in constitutional conditions involving the oral cavity

Oral mucositis is one of the most horrifying and excruciating side effects of radiation and chemotherapy. Owing to its antioxidant qualities, CBD might lessen oxidative stress, which is connected to oral mucositis.⁶⁵ Additionally, nausea and vomiting are common in cancer patients, and these symptoms can change the oral microbiota by causing inflammation of the oral mucosa and enamel erosion from the acidity of gastric secretions. It has been demonstrated that CBD lessen this negative effect of cancer treatments.^{66,67} In preclinical research, CBD have also been shown to lessen arthritis-related pain and inflammation, which is advantageous if the temporomandibular joint (TMJ) is affected.⁶⁸ For instance, CBD suppresses T-cell proliferation, which stops the generation of interferon (IFN) along with tumor necrosis factor (TNF) as well as the onset of autoimmune rheumatoid arthritis mediated by Th1.⁶⁹

Owing to its profound properties of antioxidation and anti-inflammation, CBD encompasses several positive impacts when it comes to hyperglycemia. It's interesting to note that chronic ECS over-activation has been connected to both type 2 diabetes and obesity,^{70,71} suggesting that CBD may have therapeutic applications in the treatment of type 2 diabetes. In fact, oral health is greatly impacted by this pathological condition, especially when it comes to diabetes-related oral infections.⁶⁶ Lastly, randomized, placebo-controlled trials proves CBD to be effective in treating epilepsy, with a notable decrease in the frequency of seizures.^{72,73} CBD may improve dental health because it reduces the risk of damage and injury to the tissues of the oral cavity as well as lips, which are frequent during epileptic seizures.⁷⁴

10. Present limitations in the use of cannabidiol in dentistry

The lack of a defined legal framework governing CBD quality could lead to a variety of production methods and uneven CBD preparation efficacy.⁷⁵ The components of natural goods obtained from plants vary widely due to the variability of conditions seen in the environment; therefore, the standard and amount of these products extracted naturally depend on various factors such vegetation, geographic location, as well as the circumstances present during extraction.⁷⁶ As a result, different substances that affect therapeutic action may be present in a natural formulation. When it comes to the analytical methods employed to describe the products, there is no set procedure. Thus, in terms of product value and therapeutic effects, it is important to take into account the fluctuation associated with the jurisdiction of the source, condition of storage as well as devising or manufacture of these materials while also considering the potential contaminations.⁷⁷

11. Future prospects

Researching the behavior, dosage, and mode of action of CBD is crucial, especially when it comes to dental applications. Standardized techniques for extracting CBD are unquestionably necessary, as is the standardization of in-vitro and in-vivo testing. It is necessary to assess the cytocompatibility and biocompatibility of CBD side by side. Finally, in order to assess this substance, clinical and laboratory trials ought to be conducted. It is also important to assess if patients find CBD to be acceptable.¹⁰

12. Conclusion

CBD are potent non-psychoactive drug which when used in appropriate proportions under proper guidelines hold the potential to drastically change the current state of dental sciences. However, future researches are imperative focusing on the nature, mechanism, formulations as well as modes of administration to understand this drug thoroughly. Nonetheless, due to its properties such as anti-inflammation, antioxidation, biological nature, analgesia as well as osteoinduction; it is a drug with promising future in dentistry.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Patient/participant declaration of consent statement

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Patient/parent/guardian's consent

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