



GRADUATION PROJECT

Degree in Dentistry

Exploring the cannabinoid-based therapies for oral diseases: Therapeutical potential and implications in Dentistry

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RESUMEN

Introducción: Enfermedades orales, como periodontitis y cáncer oral, siguen siendo un importante problema de salud pública a nivel mundial, y suelen implicar inflamación, destrucción de tejidos y dolor. Las terapias basadas en cannabinoides, en particular el cannabidiol (CBD), han despertado un creciente interés por sus propiedades antiinflamatorias, analgésicas y potencialmente antitumorales en el contexto de la salud bucal.

Objetivos: Este estudio tuvo como objetivo explorar si las terapias basadas en cannabinoides pueden mejorar resultados como la reducción de la inflamación, la regeneración tisular y la supresión tumoral en periodontitis y cáncer oral.

Métodos: Se realizó una revisión bibliográfica utilizando bases de datos como PubMed, Medline y bases de datos fuente Dentistry & Oral Sciences Source. Los criterios de selección se centraron en estudios in vitro, in vivo y clínicos relacionados con el uso de CBD en el manejo de la inflamación oral, cáncer oral y el dolor dental.

Resultados: De los 205 artículos inicialmente seleccionados, 10 cumplieron con los criterios de inclusión. Los hallazgos respaldan el papel del CBD en la reducción de marcadores inflamatorios y en la promoción de la cicatrización de los tejidos orales. Los estudios preclínicos también sugieren efectos antitumorales selectivos en el carcinoma oral de células escamosas, mientras que ensayos clínicos indican un potencial analgésico prometedor.

Conclusiones: Terapias basadas en cannabinoides representan un enfoque complementario prometedor en medicina oral. Sin embargo, se requieren más ensayos clínicos para confirmar su seguridad, eficacia y posible integración en los protocolos.

PALABRAS CLAVE

Odontología, cannabinoides, periodontitis, cáncer oral, dolor.

ABSTRACT

Introduction: Oral diseases such as periodontitis and oral cancer remain a major global health concern, often involving inflammation, tissue destruction, and pain. Cannabinoid-based therapies, particularly cannabidiol (CBD), have gained attention for their anti-inflammatory, analgesic, and potential anti-tumor properties in oral health contexts.

Objectives: This study aimed to explore whether cannabinoid-based therapies can improve outcomes such as inflammation reduction, tissue regeneration, and tumor suppression in periodontitis and oral cancer.

Methods: A literature review was conducted using databases such as Medline, PUBMED, and Dentistry & Oral Sciences Source data bases. Diffelection criteria focused on in vitro, in vivo, and clinical studies related to CBD use in managing oral inflammation, mucosal healing, oral cancer, and also dental pain.

Results: Out of 205 articles initially selected, 10 met the inclusion criteria. Findings support CBD's role in reducing inflammatory markers and promoting healing in oral tissues. Preclinical studies also suggest selective anti-tumor effects in oral squamous cell carcinoma, while clinical trials indicate promising analgesic potential.

Conclusions: Cannabinoid-based therapies offer a promising complementary approach in oral medicine through their ability to modulate inflammatory processes. Further clinical trials are required to confirm their safety, effectiveness, and integration into dental care protocols,.

KEYWORDS

Dentistry, cannabinoids, periodontitis, oral cancer, pain.

GLOSSARY OF ABBREVIATIONS

- **CBD** – Cannabidiol
- **CBDV** – Cannabidivarin
- **CBG** – Cannabigerol
- **CB1** – Cannabinoid Receptor Type 1
- **CB2** – Cannabinoid Receptor Type 2
- **CLL** – Chronic Lymphocytic Leukemia
- **DNA** – Deoxyribonucleic Acid
- **ECS** – Endocannabinoid System
- **HGF** – Human Gingival Fibroblast
- **GABA** – Gamma-Aminobutyric Acid
- **IL** – Interleukin (e.g., IL-1 β , IL-6, IL-10, IL-12)
- **INF- γ** – Interferon gamma
- **LPS** – Lipopolysaccharide
- **NSAIDs** – Non-Steroidal Anti-Inflammatory Drugs
- **OSCC** – Oral Squamous Cell Carcinoma
- **PPAR γ** – Peroxisome Proliferator-Activated Receptor Gamma
- **PGE₂** – Prostaglandin E2
- **THC** – Tetrahydrocannabinol
- **TMJ** – Temporomandibular Joint
- **TNF- α** – Tumor Necrosis Factor alpha
- **TRPV1** – Transient Receptor Potential Vanilloid 1

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1. INTRODUCTION

1.1. Cannabinoids: From Stigma to Scientific Promise.

Cannabinoids, long stigmatized as controversial drugs, are now emerging in a new light : that of a potential remedy. Between taboo and therapeutic hope, this plant raises critical questions, capturing the interest of researchers and patients alike in search of effective, natural solutions, revealing a potential that goes far beyond stereotypes (1) .

Cannabinoids are naturally occurring compounds primarily found in the cannabis plant, *Cannabis sativa*, with over 100 unique types identified (1) . Among them two have been most widely studied, including THC (tetrahydrocannabinol) known for its psychoactive properties and CBD (cannabidiol) valued for its non-psychoactive (2) .

Cannabinoids interact with the body primarily through the endocannabinoid system (ECS), a complex network that helps maintain balance in our bodily functions (3) .

The ECS consists of CB1 and CB2 receptors, found in areas like the brain, immune cells, and other organs, along with endocannabinoids molecules produced naturally by the body, and enzymes that create and break down these molecules (2). When cannabinoids connect with these receptors, they can impact key functions such as pain perception, immune response, mood regulation, and appetite. Essentially, cannabinoids mimic our own endocannabinoids, engaging these natural pathways to produce specific effects. This interaction highlights why cannabinoids hold such promise in treating conditions like chronic pain, epilepsy, and inflammatory disorders, positioning cannabinoid research as a crucial area in advancing modern medicine (1) .

1.1.1. Growing interest in alternative, more targeted therapeutic approaches, including cannabinoids.

Along with the morphine, all cannabinoids has been one of the most utilized cures given that the dawn of your time. This, and the spectacular advances in this unique area of science over recent decades more specifically with the big discovery of the endocannabinoid system in the 1990s (1) .

More recently, there has been a distinct growth in interest among other, more targeted therapeutic options, notably, the use of cannabinoids (1) . Cannabinoids are being positioned as potential adjunct or alternative therapies because traditional treatments for cancer, epilepsy, chronic pain and other chronic and complex disorders are limited by

intolerable side effects or lack of efficacy (4) . From the cannabis plant, cannabinoids act on the endocannabinoid system in our bodies, which is vital for managing pain and inflammation, and for nervous system functions (5) .

Such a distinct mechanism provides a potential avenue for symptom modulation that can be more symptom-specific and possibly efficacy with less off-target side effects than currently available therapeutics (6) . In addition, the continued investigation of synthetic cannabinoids and exact dosing methods will increase the capacity to personalize cannabinoid treatment for individual patients, increasing effectiveness (7) .

Consequently, the medical field is diving into the use of cannabinoids in the pursuit of another emerging approach of medicine known as precision medicine, which aims for effective care as well as striving towards precise to the biology of each unique patient (7) .

1.1.2. Transition from recreational use to medical applications

With legalization taking place for CBD this time, the cannabis transition from recreational to medicinal use represents a particularly big step in societal perception and view. Traditionally only regarded as an illicit drug providing recreational properties, cannabis and its medical properties have recently found their way into the medical spotlight to help treat patients with pain management, anxiety reduction, chronic conditions like epilepsy or multiple sclerosis (8) . Moreover, limited evidence indicates that cannabis legalization does not substantially impact the total amount of opioids prescribed or mortality overall but may help decrease deaths from synthetic opioid-based drugs, also showing potential public health benefits linked to more accessible cannabis. These changes reflect a deeper cultural and policy shift, balancing the interests of public health with the medical benefits of cannabis (9) .

1.2. Cannabinoids CB1 and CB2 receptors in oral disease: Inflammation and pain modulation.

Within the endocannabinoid system, cannabinoids work by activating two receptors: cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2) (1) . This system is a sophisticated organ network that expresses cannabinoid receptors and maintains homeostasis throughout the body (6) .

Pain, memory, mobility, hunger, metabolism, lacrimation/salivation, immunity, and even cardiovascular function are among the several roles played by the endocannabinoid system (10) . It is worth noting that CB1 activation accounts for the great majority of

cannabis side effects, including psychotropics, whereas CB2 plays more significant roles in inflammatory and immunological responses (2) . Endocannabinoids are endogenous neuro-regulatory modulators that oversee retrograde neurotransmission. Here, endocannabinoids released by a post-synaptic neuron mostly bind to CB1 receptors on the presynaptic neuron (2) . Because of this binding, presynaptic calcium channel activity is prevented, which in turn causes the release of presynaptic neurotransmitters. The overall impact is excitatory if the presynaptic neurotransmitters, such GABA, are mostly inhibitory, and vice versa (2) .

1.2.1. Current applications of cannabinoids in managing pain, inflammation, and other conditions.

Cannabinoids are currently being used in medicine-wide for the treatment of various diseases, mainly because of their anti-inflammatory and analgesic properties through central and peripheral pathways, as well as for neurological conditions (5) . There is research backing their effectiveness in chronic pain control, both cancer and non-cancer related as an opioid alternative (11) .

In this case, moderate improvements in pain severity and sleep quality, balanced with some mild adverse effects like dizziness or nausea (12) . They also showed that cannabinoids help relieve both spasticity and neuropathic pain in multiple sclerosis, thereby contributing to improved quality of life and well-functioning for patients (11) .

Cannabinoids are also being researched for their anti-inflammatory properties, which may help patients with autoimmune conditions. And some of the early research indicates that they may also be helpful in treating anxiety and sleep disorders, but we need larger clinical trials to really validate these results (13) .

This emerging literature underscores the increasing therapeutic indications for cannabinoids while highlighting the need for patient-centered, evidence-based care.

1.2.2. Overview of common oral diseases: Periodontitis, Orofacial pain, Oral cancer lesions.

Cannabinoids may be a novel therapeutic treatment for common oral diseases such as periodontitis, orofacial pain and oral cancer lesions (10,13) . Periodontitis, a chronic inflammatory disease of the supporting structures around teeth, is associated with periodontal pain, tooth loss associated with gingival recession. Cannabinoids, and

especially CBD, have been shown in recent research to relieve inflammation and assist healing in periodontitis (13) .

They may have the role of an adjunctive treatment for periodontitis due to their anti-inflammatory and analgesic effects, especially in patients who might be unable to tolerate conventional non-steroidal anti-inflammatory drugs (NSAIDs) because of side effects (11) .

Besides tooth loss due to periodontitis, orofacial pain comprises a wide range of disorders, including temporomandibular joint (TMJ) dysfunction, trigeminal neuralgia and post-surgical pain that can also be treated with cannabinoids (14) . Abstract cannabinoids, the major psychoactive constituents in cannabis, particularly THC and CBD exerted substantial analgesic effects that are correlated with reduced pain intensity in patients who suffered from chronic orofacial pain (15) .

This helps especially those people who have not responded to the usual pain relief methods like opioids or corticosteroids. In addition, cannabinoids have been studied for their ability to help treat oral cancer lesions by decreasing pain and tumor growth (12) . Cannabinoids have been suggested to act as analgesic agents, as well as anti-cancer agents and studies show that they inhibit progression of oral cancers via inducing apoptosis (10) .

1.2.3. Cannabinoids and Periodontitis.

Cannabinoids inhibit inflammation by lowering levels of pro-inflammatory cytokines such as IL-1 β , IL-6 and TNF- α while at the same time increasing anti-inflammatory mediators like IL-10 (a) (16) . This serves to counteract the chronic inflammation that is typical of periodontitis and reduces tissue injury and progression of disease.

It can be expected that CBD will help regulate the immune-inflammatory response in periodontal tissue, reduce damage to soft tissues and support metabolism of alveolar bones (17) . Encouraging as these findings may be, however, further research is needed before we can truly understand how CBD operates as an anti-inflammatory agent and its potential for periodontitis therapy. Bone resorption is a major concern in periodontitis. Cannabinoids such as HU-308 can inhibit osteoclast activity and prevent alveolar bone loss. This osteoprotective effect is important for the integrity of the periodontium (13) .

Cannabinoids have antibacterial properties that may be helpful in controlling bacterial infections associated with periodontal disease. This leads to a healthier oral

environment as well as lessening the damage caused by microbial biofilms (16) . Cannabinoids may also help tissue heal themselves by stimulating the activity of gingival fibroblasts, which are important for the regeneration of periodontal tissues (16) . This being one of their many nice properties, confirmatory studies should be performed before any clinical benefits can become generally valid.

1.2.4. Cannabinoids and oral cancer.

The potential of cannabinoids in oral cancers, including oral squamous cell carcinoma (OSCC), has been particularly encouraging (10) . This ability could be result from how they change processes in cancer cells, such as apoptosis (programed cell death) as well as autophagy and cycle regulation (10) . For example, cannabinoids could downregulate pathways directly linked to the progression of cancer, including those within the PI3K-Akt signaling axis, which are critical for cell growth and survival.

In vitro and in vivo research shows that cannabinoids can inhibit both the formation of new blood vessels needed by tumors, angiogenesis, as well as metastasis (13) .

While at the same time promoting apoptosis in cancer cells. Moreover, they have properties that are anti-inflammatory, a definite advantage considering the chronic inflammation that tends to accompany oral cancer development (29) . They can also change the tumor microenvironment, potentially reducing cancer cell invasion and spread (6) .Cannabinoids have wide-ranging beneficial effects for some types of chemotherapy (12) . Their ability to offset pain, nausea and anxiety, all common side effects of the procedure, makes them ideal drugs to use alongside cancer therapy (10) . Nevertheless, although these findings are encouraging, more detailed research is necessary to hammer out such specifics as correct dosages and methods of administration, along with longer-term safety in using cannabinoids to treat oral cancers.

1.2.5. Cannabinoids and orofacial pain

Orofacial pain encompasses a wide range of conditions affecting the face and oral cavity, including neuropathic, inflammatory, and musculoskeletal origins. It poses a significant clinical challenge due to its complex pathophysiology, varied presentation, and the limitations of conventional therapies (15) . Traditional pharmacological approaches, such as nonsteroidal anti-inflammatory drugs, antidepressants, and opioids, often yield suboptimal outcomes or lead to considerable side effects, especially in chronic cases (6) . In recent years, attention has increasingly turned toward the endocannabinoid system as a potential target for pain modulation. Research has

shown that cannabinoid compounds, particularly cannabidiol, may influence both peripheral and central pain pathways (11) . Emerging literature, on the role of cannabidiol in chronic neuropathic orofacial pain, the broader functions of the cannabinoid system in pain control, and the therapeutic potential of cannabis-derived pharmaceuticals, has laid the groundwork for considering cannabinoids as promising agents in the management of acute and chronic pain (15) . Cannabinoids help relieve pain mainly by interacting with CB1 and CB2 receptors, which can reduce inflammation and slow down pain signal transmission. Some compounds like CBD also affect other targets, such as Transient Receptor Potential Vanilloid 1 (TRPV1), key players in pain perception, further contributing to their analgesic effects (11) . These insights have opened new avenues for investigation in the field of oral medicine and dentistry, particularly in relation to the management of persistent or treatment-resistant orofacial pain conditions (6,11,15) .

Despite these encouraging findings, the precise mechanisms by which cannabinoids exert their effects on orofacial pain remain only partially understood. Variables such as dosage, route of administration, and the specific type of cannabinoid compound used may influence both efficacy and safety outcomes (6) . This highlights the need for deeper investigation into the therapeutic potential of cannabinoids, with particular attention to their role in modulating pain pathways associated with common orofacial conditions such as periodontitis, and oral cancer (19) . Exploring these avenues could open the way for the development of novel, evidence-based strategies for pain management in oral health care.

1.3. Justification

The exploration of cannabinoid-based therapies for oral diseases holds transformative potential for the field of dentistry. Oral diseases, such as periodontal disease and oral cancers, represent significant health burdens that affect patients' overall well-being and quality of life. Current treatments for these conditions often have limitations, including side effects, incomplete efficacy, and challenges in managing chronic inflammation and tissue repair. Cannabinoids, with their unique combination of anti-inflammatory, analgesic, antibacterial, and tissue-regenerative properties, provide an innovative avenue for addressing these challenges.

In the context of periodontal disease, cannabinoids could help reduce inflammation, modulate the immune response, and support bone and tissue regeneration, potentially reversing disease progression. For oral cancers, cannabinoids offer the promise of anti-

tumor effects by inhibiting cancer cell growth and metastasis while simultaneously alleviating the side effects of conventional therapies, such as chemotherapy-induced pain and nausea. Furthermore, the integration of cannabinoid-based therapies into dental practice could enhance personalized care by providing alternative or adjunctive treatments that improve patient outcomes and satisfaction.

Null hypothesis (H0) : Cannabinoid-based therapies do not have beneficial effects on oral diseases like periodontitis and oral cancer and do not mitigate inflammation, support tissue regeneration, or reduce cancer cell progression.

Hypothesis: Cannabinoid-based therapies may have beneficial effects on oral diseases like periodontitis and oral cancer by mitigating inflammation, supporting tissue regeneration, and reducing cancer cell progression, making them a promising strategy in Dentistry.

2. OBJECTIVE

2.1. Primary objective

To examine the potential therapeutic effects of cannabinoid-based treatments on oral diseases such as periodontitis and oral cancer, with a focus on their role in inflammation control, tissue regeneration, and cancer progression

3. MATERIAL AND METHODS

3.1. Inclusion criteria

Inclusion criteria of the publications were defined as follows: (a) publications dates of the last 10 years (2014-2024); (b) male and/or female sex, in vitro studies and research based on animals experiments were studied; (c) the populations studied were human beings of at least 18 years of age; (d) the language of the publication had to be English; (e) at least one of the following key words had to be included in the publication : cannabidiol, periodontitis, oral diseases; (f) whether the publication was either an article or a journal; (g) full text available documents; (h) all manuscripts had to demonstrate at least one of the following factors :

- **Specific cannabinoid compounds:** The studies must evaluate the effects of specific cannabinoids, such as cannabidiol (CBD) or tetrahydrocannabinol (THC), in the context of oral diseases.
- **Targeted oral diseases:** The articles should focus on periodontitis, oral cancer lesions, or other related oral pathologies, ensuring relevance to your thesis topic.
- **Therapeutic outcomes:** The studies must assess the therapeutic potential, including anti-inflammatory, analgesic, anti-tumor, or tissue-regenerative effects of cannabinoids.

3.2. Exclusion criteria

Exclusion criteria were as follows: (a) publication outside of the last 10 years (2014–2024); (b) study not including either men or women, in vitro studies or animals; (c) studied sample did not consist of individuals with at least 18 years of age; (d) publication language other than English; (e) publication that did not include any of the following keywords: cannabidiol, periodontitis, oral lesions; (f) publication type other than article or journal; (g) nonfull-text articles; (h) papers that did not describe one or more of the following variables:

- Specific cannabinoid compounds: The studies must evaluate the effects of specific cannabinoids, such as cannabidiol (CBD) or tetrahydrocannabinol (THC), in the context of oral diseases.
- Targeted oral diseases: The articles should focus on periodontitis, oral cancer lesions, or other related oral pathologies, ensuring relevance to your thesis topic.
- Therapeutic outcomes: The studies must assess the therapeutic potential, including anti-inflammatory, analgesic, anti-tumor, or tissue-regenerative effects of cannabinoids.

Medline, PUBMED, and Dentistry & Oral Sciences Source databases were used to conduct this systematic review. The use of the Boolean equation; AND and OR, to be the key operators, will used it, to help broaden as well as narrow the scope of the search; to ensure that a comprehensive and detailed search is being conducted, and indeed covered the relativity and the specificity of the topic. Keywords such as “Cannabinoids” and “Cannabidiol” as well as “Periodontitis” and “Oral Cancer,” were chosen and were consistently used during the search process to search for relevant studies.

3.3. Boolean equation.

((periodontitis) OR (pain) OR (oral cancer)) AND (Cannabinoid or Cannabidiol or Tetrahydrocannabinol)

3.4. PICO Format:

The PICO research question (participants, intervention, comparison, and outcomes) formulated to help answer the objective is the following:

In patients with oral diseases such as periodontitis and oral cancer lesions (P), does the use of specific cannabinoid-based therapies, such as cannabidiol (I), compared to conventional treatments or no cannabinoid intervention (C), improve therapeutic outcomes, including inflammation reduction, tissue regeneration, and tumor suppression (O).

By delineating those elements, a precise selection and analysis of relevant literature can be done contributing to a deeper understanding of the topic.

Table 1. Working table with preliminary search terms.

P	I	C	O
Population: patients with oral diseases such as periodontitis or oral cancer lesions.	Intervention: use of specific cannabinoid therapies such cannabidiol	Comparison: conventional treatments or no cannabinoid treatment.	Outcome: inflammation reduction, tissue regeneration and tumor suppression.

4. RESULTS

All the studies analyzed in this review were identified through searches conducted on PubMed, Medline, and Dentistry & Oral Sciences Source databases, using predefined keywords along with specific inclusion and exclusion criteria. Initially, 205 articles were retrieved. After going through several selection stages upon reviewing each title 10 full-text articles were selected.

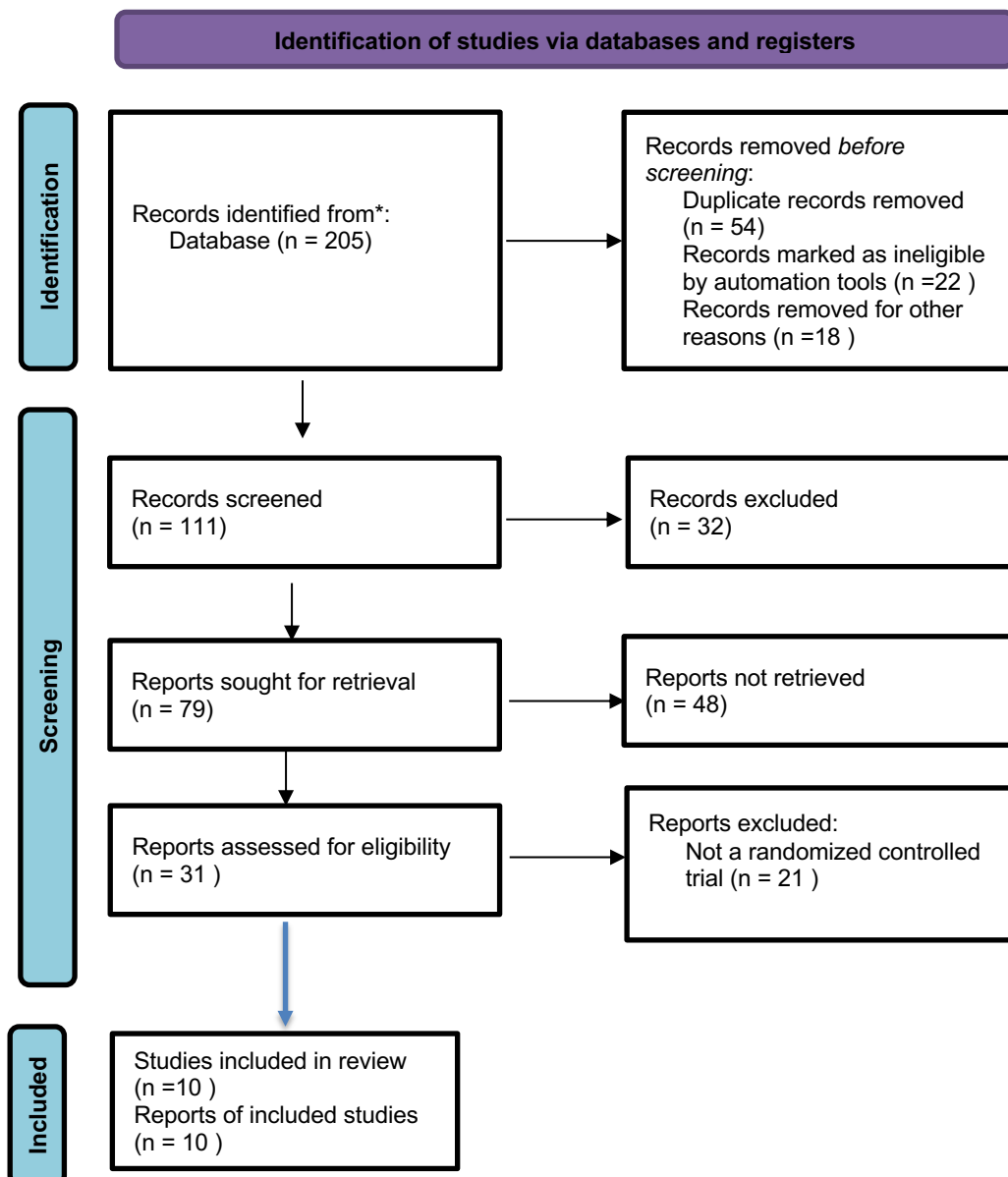


Figure 1. Prisma flowchart with data extraction (20)

Table 2. Therapeutic outcomes and interpretations of cannabinoids applications in oral health

Title	Year and Author	Study type	Study samples	Summary and Comments
Phytocannabinoids regulate inflammation in IL-1 β -stimulated human gingival fibroblasts	2022, Ammaar H. Abidi, Vrush ali Abyankar	In vitro	CBVN, CBG, and CBD inhibit inflammation in IL-1 β -stimulated human gingival fibroblasts. CBVN and CBG decreased PGE ₂ (40%), TNF- α , IL-2, and INF- γ (30–50%), whereas CBD and CBVN diminished IL-4 and IL-13.	These results suggest phytocannabinoids may have therapeutic potential for periodontal disease, but their mixed effects require careful evaluation.
Phytocannabinoids Reduce Inflammation of Primed Macrophages and Enteric Glial Cells: An In Vitro Study	2023, Gal Cohen, Ofer Gover, Betty Schwartz	In vitro	THC (0.05–0.1 μ g/mL) decreased the secretion of TNF- α by ~40%. Furthermore, S100B protein levels in enteric glial cells were also reduced by ~35% (30).	These findings create evidence that low doses of THC may indeed have a targeted therapeutic effect in reducing inflammation that can be traced to macrophages and enteric glial cells.

Cannabis Use and Head and Neck Cancer	2024, Tyler J. Gallagher, Ryan S. Chung	Cohort study	In the study, the 0.285% head and neck cancer occurrence was found in the cannabis group and 0.091% in the non-cannabis group.	These results indicate that prolonged use of cannabis is an important and potentially modifiable risk factor for these cancers, and further investigation into its carcinogenic properties is warranted.
Phytocannabinoids and gingival inflammation: Preclinical findings and a placebo-controlled double-blind randomized clinical trial with cannabidiol	2023, Petr Jirasek Alexandr Jusku, Jana Frankova	In vitro, double-blind clinical trial.	After 56 days of 1% CBD gel application (n = 90), suppression P. gingivalis (MIC: 1.5 µg/mL), and improvement of gingival indices. No adverse effects reported.	The study found that Cannabidiol (CBD) application significantly reduced gingival inflammation and impeded the growth of specific periodontal pathogens.

Reasons for cannabidiol use: a crosssectional study of CBD users, focusing on self-perceived stress, anxiety, and sleep problems	2021, Julie Moltke and Chandni Hindocha	Cross-sectionnal study	Daily doses of <50 mg CBD were reported by 54% of respondents, and 72.6% used the sublingual route for administration.	It highlights that the effects CBD may have on mental health and sleep quality are promising, yet need more validation.
DNA damage and cell death in human oral squamous cell carcinoma cells: The potential biological effects of cannabidiol	2024, Monia Billi, Stefano Pagano, Gian Luca Pancrazi	Experimental study	CBD greatly diminished OSCC (viability, reducing OSCC viability by 64%, 96%, and 99% at 25, 50, and 100 μ M, respectively, after 72 hours of treatment. CBD additionally triggered G0-G1 cell cycle arrest, enhanced apoptosis ($p < 0.001$), and resulted in DNA damage.	The study shows that CBD has a potent cytotoxic effect on OSCC ,causing dose-dependent reductions in cell viability, apoptosis induction, and DNA damage. These could have important implications for OSCC treatment.

The anticancer potential of tetrahydrocurcumin-phytosomes against oral carcinoma progression	2024, Nehal Raouf, Zeinab Elsayed Darwish	Preclinical in vitro study	THC or cisplatin raised apoptosis (29.7%). They induced cell cycle arrest, decreased colony formation to 0.29%, and almost completely inhibited cell migration.	These results suggest that THC-phytosomes are a potential anticancer therapeutic agent against oral squamous cell carcinoma. With enhanced bioavailability, killing cancer cells with little or no damage to healthy oral cells.
Cannabidiol as an Alternative Analgesic for Acute Dental Pain	2024, Chrepa et al.	Double-blind, placebo-controlled clinical trial	A single dose of CBD (10 or 20 mg/kg) reduced dental pain by up to 73% after 3 hours, with onset starting as early as 15 minutes in the higher dose group.	This study provides the first clinical evidence supporting the efficacy and safety of oral CBD as an analgesic for acute dental pain. The rapid onset and substantial pain reduction observed suggest that CBD could serve as a viable non-opioid alternative for managing dental pain.

CBD Promotes Oral Ulcer Healing via Inhibiting CMPK2-Mediated Inflammasome	2022 Qi et al.,	Preclinical in vivo study	Topical CBD lowered IL-1 β , caspase-1, and CMPK2 levels, with effects mainly mediated through PPAR γ . Healing was faster and more complete compared to control.	This study shows that CBD promotes oral mucosal repair by targeting inflammation pathways. The findings support its potential for treating painful inflammatory oral lesions.
Clinical effects of a single dose of cannabinoids to patients with chronic lymphocytic leukemia	2022, Mélen et al.	Clinical trial	A temporary 11% reduction in leukemic B cells was observed, lasting up to 6 hours. No apoptosis or long-term effect occurred. Mild side effects (dry mouth, dizziness) were reported in 91% of patients. Effects wore off after 24 hours.	The study showed limited, short-term immune effects of cannabinoids in chronic lymphocytic leukemia without inducing cancer cell death. It highlights the need for caution and reinforces that cannabinoid efficacy may vary depending on cancer type.

5. DISCUSSION

Cannabinoids have recently become a subject of growing investigation in periodontal research, as their multifaceted biological effects raise questions regarding potential benefits in clinical application (21) . The data suggest that cannabinoid-based therapies, particularly those involving cannabidiol (CBD), have significant potential in modulating inflammatory responses within the oral cavity. Across both in vitro and clinical models, CBD demonstrated the ability to reduce the expression of pro-inflammatory cytokines, to inhibit inflammasome activation, and to promote a tissue environment that conduces to healing. These effects were observed in gingival fibroblasts, ulcerative lesions, and immune cell models, supporting the central hypothesis that CBD may enhance therapeutic outcomes such as inflammation control and possibly tissue repair in patients suffering from oral inflammatory conditions (21–23) . In agreement with the research hypothesis, the study by Abidi *et al.* (2022) provides convincing data that particular phytocannabinoids, more specifically cannabidiol (CBD) and cannabigerol (CBG), can modulate important inflammatory signals in human gingival fibroblasts (HGFs) stimulated with IL-1 β , a pro-inflammatory cytokine that is frequently elevated in periodontitis (24) .

This response speaks to the research question directly in that it provides preliminary evidence that cannabinoid-based therapies, such as the one used in the study, can mitigate inflammatory response of oral tissues compared to those inflammatory conditions that remain untreated. Low concentrations of CBDV and CBG significantly decreased the production of prostaglandin E2 (PGE2), tumor necrosis factor (TNF- α), and interferon-gamma (IFN- γ), with no cell viability loss observed. Since PGE2 and TNF- α are highly regarded in tissue destruction and disease progression during periodontal inflammation, this is most relevant to the hypothesis (24) . The rise in both interleukins, IL-10 and IL-12 levels suggests a differential immunomodulatory role of cannabinoids as opposed to a general suppression of immune activity . This is consistent with the hypothesis that rebalancing the host immune response, instead of blunt inhibition, may be a better approach in chronic oral inflammatory diseases (24) . The lack of CB1 activation and the selective activity on CB2 receptors further argue for an anti-inflammatory action without psychoactive side effects which adds clinical relevance to these observations. So although the research was conducted in a laboratory by testing just one type of cell, it does suggest that phytocannabinoids can act on major steps of the inflammatory process in our body. Results suggest a potential biological basis for the

hypothesis that cannabinoids beneficially influence oral diseases through reduction of inflammation (24) .

Jirasek *et al.* (2024) provide compelling evidence supporting the hypothesis that CBD enhances therapeutic outcomes in patients with oral diseases by reducing inflammation in gingival tissue. In this placebo-controlled, double-blind study, nine female participants with gingival inflammation were instructed to apply a gel containing a CBD formulation over a period of 56 days (23) . Those using CBD demonstrated significantly better outcomes across several clinical markers, including markedly less bleeding on probing and lower gingival index scores compared to both the placebo and chlorhexidine groups. These results indicate that CBD possesses a measurable anti-inflammatory effect in a real-world clinical context, as opposed to solely in laboratory settings (23) . Additionally, the study examined the molecular effects of CBD on cellular processes. It found that CBD reduced the expression of pro-inflammatory cytokines, such as IL-6 and IL-8, and activated the Nrf2 antioxidant pathway, which protects tissues from the damaging effects of oxidative stress. These mechanisms not only elucidate the observed improvements in inflammation but also provide a biological basis for the positive clinical outcomes (23) .

Some studies beyond the oral field provide additional mechanistic parallels. Cohen *et al.* in 2023, showed that CBD, CBG, and CBDV reduced IL-1 β and TNF- α in LPS-stimulated enteric glial cells and macrophages (21) . Although conducted outside the oral cavity, this study supports the hypothesis of a cross-tissue immunomodulatory profile via CB2 and PPAR γ activation. These cross-references indicate that the anti-inflammatory effects of cannabinoids are not restricted to oral tissues but may follow a conserved immunological mechanism applicable to various chronic inflammatory settings (21) .

Qi *et al.* (2022) further expands on this by demonstrating that CBD accelerated oral ulcer healing through inhibition of CMPK2-mediated inflammasome activation, a mechanism that overlaps with those involved in periodontal inflammation (22) . Although the tissue type is different, the fundamental processes of mitochondrial oxidative stress, inflammasome signaling, and cytokine suppression are similar, further supporting the biological plausibility that cannabinoids would be beneficial in a range of oral diseases that have an inflammatory component (22) . Chrepa *et al.* (2024) provide evidence supporting part of the research hypothesis by demonstrating that CBD can effectively relieve

acute dental pain following third molar extraction. Although pain relief was the main goal of the study, the results could be indirectly related to the anti-inflammatory effects of CBD (25) . CBD may be acting on both the pain and underlying inflammatory process, as it has been shown to inhibit the release of pro-inflammatory cytokines such as IL-6 and TNF- α inflammation being one of the main causes of post-operative dental pain. This may reinforce the hypothesis that cannabinoid-based therapies have the potential to promote better therapeutic outcomes in oral health, including inflammation, pain, and possibly tissue repair (25) .

All of the studies together suggest that CBD and similar cannabinoids might help lower inflammation in the mouth by using biological processes that work in the same way across different types of tissues (23) . However, variations between study designs, cell types, cannabinoid concentrations, and delivery modes complicate direct comparisons. While the overall trend supports the hypothesis, these inconsistencies emphasize the need for further research, particularly standardized human trials, to fully assess the therapeutic potential of cannabinoid-based interventions in oral inflammatory disease management (21–25).

In addition to its anti-inflammatory and immunomodulatory effects, cannabidiol has also shown promising anticancer activity (26,27) . The study by Billi *et al.* helps answer the research question by showing that cannabidiol may help slow down the development of oral cancer. In this study, human oral squamous cell carcinoma cells were treated with CBD. The researchers found that CBD caused damage to the cancer cells and triggered their death through a natural process called apoptosis (29) . These effects were proven by detecting specific markers related to DNA damage and cell death. Another good sign is that CBD acted only on the cancer cells, while leaving healthy cells unharmed, which may make it a safe candidate for further research. Indeed, with the study investigating effects on oral cancer cells, it could be even more correlated to their central hypothesis of utilizing cannabinoid-based therapies to enhance treatment in oral disorders by enhancing the therapeutic response following the tumor suppression. The study by Raouf *et al.* (2024) examining tetrahydrocurcumin-phytosomes (THC-phytosomes) on OSCC cells demonstrated significant decreases in cell viability and migration, and increases in apoptosis. While THC is a curcuminoid and not a cannabinoid, its bioactivity profile overlaps partially with that of CBD, especially regarding oxidative stress modulation and anti-metastatic properties. Notably, although both CBD-

and THC-phytosomes elicit cancer cell apoptosis, the mechanisms involved are distinct. CBD works through endocannabinoid system and inflammasome pathways, while THC acts primarily through modulation of antioxidant defenses and caspase cascades. This diversity reveals the potential for further combination of these agents or improved formulations based on mechanistic synergies (27) . What makes these findings particularly relevant is the selectivity observed. THC-phytosomes were cytotoxic to cancer cells while having minimal impact on normal oral cells. This selective action is crucial in cancer treatment, where preserving healthy tissue is a major therapeutic goal, its shared antioxidant and anti-inflammatory properties make it a useful reference point in the context of natural, non-toxic oral therapies (27) .

A clinical study by Mélen *et al.* (2022) used cannabinoids (THC/CBD) given as a single oromucosal dose over a period of time, performed short-term analyses of the cannabinoid dosing on patients with chronic lymphocytic leukemia (CLL). This caused a transient decrease of leukemic B cells in the culture but with no induction of apoptosis or sustained cytotoxic effect (28) . Cell levels returned to baseline within 24 hours, and no clinical benefit was seen. While these findings validated the ability of cannabinoids to modulate immune cells, they also revealed that such effects may be too attenuated to provide therapeutic benefit in hematological malignancies (26) .

This is in sharp contrast to the well-established preclinical data on the effects of CBD in OSCC, where the profibrotic effects of CBD are overshadowed by evidence that it is capable of inducing apoptosis and oxidative stress in tumor cells. These variances indicated that the anticancer properties of cannabinoids may be tumor specific and context dependent. Blood cancers like CLL seem less susceptible to single-dose cannabinoid agents, while solid tumors such as OSCC may respond more aggressively due to factors including CB2 receptor expression and local inflammation (26,27) . CB2 receptors are involved in the inflammatory and neoplastic processes in the oral mucosa, which could provide an understanding of a stronger response in transformation of tumor tissues in OSCC with cannabinoids (26) . The low and transient response noted with CLL in contrast implies that either systemic or blood cancers are relatively insensitive to cannabinoid-induced cytotoxicity or that repeated dosing and combinatory therapies would need to be tested before any benefit would be seen . All of this highlights the need for cancer-specific research. The promising results obtained in OSCC models should warrant further exploration, but they should not be generalized to all cancer types unless there is sufficiently supportive data (26,27,29) .

Furthermore, there is very limited information from in vivo models as well as clinical trials in oral cancer to evaluate their long-term efficacy or safety in humans (30). Recent studies have provided comparative evidence that cannabinoid-based therapies present a unique avenue for treatment of chronic oral conditions where immune regulation is required, for both local and systemic immune responses. The results align with emerging theories regarding host modulation therapy in periodontitis, which suggest that modulating the patient's inflammatory response may be a better strategy than solely targeting bacterial pathogens. Cannabinoids like CBD, could play an adjunct role or enhance existing protocols for this purpose, especially in patients who continue to experience inflammation after mechanical debridement or antiseptic use (23,28,29).

This review presents certain limitations that should be acknowledged. Firstly, the search was conducted using a limited number of databases, which may have restricted the breadth of potentially relevant studies included. Expanding the search to additional databases could have increased the comprehensiveness of the results. Secondly, the inclusion and exclusion criteria, although defined to ensure a focused analysis, might have unintentionally excluded studies that could provide valuable insights. A broader set of criteria or a more flexible approach might have captured a wider range of data and perspectives. Moreover, the relatively small number of studies identified reflects the limited existing literature on the topic, which inherently constrains the depth of analysis. Finally, as with any systematic approach, the interpretation of data and results may be influenced by the subjective judgment of the reviewer during the selection and analysis process, despite efforts to maintain objectivity.

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judgment of the reviewer during the selection and analysis process, despite efforts to maintain objectivity and consistency throughout the review.

Also, the bulk of studies were either conducted in the lab or among very small populations of patients, making it difficult to know whether the findings would hold true in real-life clinical settings. In addition, the way in which cannabinoids are administered, the dose, how they are given and in what form is not consistent from one study to another, making comparisons difficult. In the case of oral cancer, the data is particularly uneven (27,29,30). Laboratory studies indicate that CBD may help murder cancer cells, but some large human studies suggest a potential association between cannabis use and an increased risk of head and neck cancers (30). But those studies are difficult to interpret because many cannabis users also smoke or drink alcohol, the true culprit. This means we must exercise caution in making conclusions, especially about how lab results compare to the real world (30).

Another problem is that most studies now only focus on single types of cells, such as fibroblasts or keratinocytes, without considering the full complexity of the mouth, including factors like blood flow, bacteria or other illnesses the patient may have (21,27). Moreover, in many countries regulations related to using cannabinoid-based substances as therapeutic drugs still remain wildly unclear or restrictive, limiting their use in dental practice (23). In order to advance, we require robust clinical studies that test cannabinoids in larger and more heterogeneous patient populations. And it also would make sense to test standardized products, such as gels or mouth rinses, especially for common issues like gum disease, ulcers or pain after dental procedures (22). We also need to know more about the long-term effects of cannabinoids and whether it is safe to use them regularly (25). That said, so far the most promising results appear to be in inflammation. Indeed, several studies indicate that cannabinoids particularly CBD reduce inflammatory markers in oral cells and tissues. These effects have been observed both in lab experiments and in initial clinical trials, leading researchers to hope that cannabinoids might be effective in treating chronic gum diseases or accelerating healing after oral injuries (21–24).

6. CONCLUSIONS

1. Cannabinoid-based therapies show promising potential in the management of oral diseases such as periodontitis and oral cancer. Through their ability to modulate inflammatory processes, reduce oxidative stress, and support tissue regeneration, cannabinoids may help restore immune balance and promote healing in chronically inflamed oral tissues. By influencing cytokine profiles, they help modulate excessive immune responses without fully suppressing host defenses. Their action appears selective, with minimal cytotoxicity observed in healthy oral cells, which supports their safety profile in therapeutic contexts. Moreover, their selective action on key pathways involved in cancer progression suggests a possible therapeutic role in oral oncology. While current evidence remains preliminary and context-dependent, these findings underscore the need for further investigation into the clinical applications and long-term efficacy of cannabinoids in oral medicine.

7. SUSTAINABILITY

Exploring cannabinoid-based therapies in oral medicine opens new clinical perspectives while supporting a more sustainable model of healthcare, in line with several UN Sustainable Development Goals (SDGs).

Economically (SDG 3 & 9), these treatments—especially in topical forms like gels or mouthwashes—may reduce long-term costs by limiting reliance on systemic drugs, repeated prescriptions, and invasive procedures. Their integration could optimize resources in managing chronic conditions like periodontitis.

Environmentally (SDG 12 & 13), cannabinoids derived from renewable plants such as hemp present a lower ecological footprint than many synthetic drugs. Biodegradable packaging and minimal processing may further reduce the environmental impact of outpatient oral care.

Socially (SDG 3 & 10), cannabinoid therapies meet growing patient demand for natural, non-invasive, and personalized treatments. Their good tolerance profile and accessibility could improve equity in oral healthcare, especially for those sensitive to conventional drugs or with limited access to specialized care.

By addressing these three pillars, economic viability, environmental responsibility, and social equity, cannabinoid integration into oral medicine supports a more holistic and sustainable approach to 21st-century healthcare.

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