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CANNABIS IN DENTISTRY: THERAPEUTIC AND ADVERSE EFFECTS ON ORAL TISSUES - SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Cannabis has been used for medicinal and recreational purposes throughout history, but its effects on oral tissues are not yet fully understood. **Objective:** To systematically review the scientific literature on the effects of medical and recreational cannabis on oral tissues. **Methods:** A systematic review was conducted in four databases (PubMed, Scielo, Google Scholar, Dentistry & Oral Science Source) to identify studies on cannabinoid effects in the oral cavity. Articles in English and Spanish were selected, and a descriptive analysis was performed. **Results:** From 5,200 initial articles, 25 met inclusion criteria, focusing exclusively on human subjects or in vitro models. Methodological quality assessment showed 72.85% reliability for observational studies and 85% for clinical trials. Most studies highlight cannabis's anti-inflammatory benefits, particularly cannabidiol, in oral tissues, although some demonstrate negative periodontal effects associated with smoked consumption. **Conclusions:** There are promising results regarding the interaction between the endocannabinoid system and oral tissues. Further research is needed to establish specific protocols on the safety and efficacy of cannabinoids in treating dental diseases.

KEYWORDS: Cannabis; Cannabidiol; Cannabinoids; Oral Tissues; Periodontitis.

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CANNABIS EN ODONTOLOGÍA: EFECTOS TERAPÉUTICOS Y ADVERSOS EN TEJIDOS ORALES - REVISIÓN SISTEMÁTICA

RESUMEN

Introducción: El cannabis ha sido utilizado con fines medicinales y recreativos a lo largo de la historia, pero sus efectos sobre los tejidos bucales aún no están completamente clarificados. **Objetivo:** Revisar sistemáticamente la literatura científica sobre los efectos del cannabis medicinal y recreativo en los tejidos bucales. **Metodología:** Se realizó una revisión sistemática en cuatro bases de datos (PubMed, Scielo, Google Academic, Dentistry & Oral Science Source) para identificar estudios sobre los efectos de los cannabinoides en la cavidad oral. Se seleccionaron artículos en inglés y español, realizando un análisis descriptivo de sus características y principales hallazgos. **Resultados:** De 5,200 artículos iniciales, 25 cumplieron los criterios de inclusión, enfocándose exclusivamente en sujetos humanos o modelos in vitro. La evaluación metodológica mostró un porcentaje de confiabilidad del 72.85% para estudios observacionales y 85% para ensayos clínicos. La mayoría destaca los beneficios antiinflamatorios del cannabis, particularmente del cannabidiol, en los tejidos bucales, aunque algunos evidencian efectos periodontales negativos asociados con el consumo fumado. **Conclusiones:** Existen resultados prometedores sobre la interacción entre el sistema endocannabinoide y los tejidos bucales. Se requieren más investigaciones para establecer protocolos específicos sobre la seguridad y eficacia de los cannabinoides en el tratamiento de enfermedades odontológicas.

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PALABRAS CLAVE: Cannabis; Cannabidiol; Cannabinoides; Tejidos Bucales; Periodontitis.

INTRODUCTION

Cannabis has been used for medicinal and recreational purposes throughout human history. Archaeological records demonstrate its use long before the advent of the current era, being a plant with multiple applications in different cultures.(1) Currently, research on cannabis has experienced a resurgence, after decades of prohibition that limited its study for therapeutic purposes.

The cannabis plant contains more than 600 compounds, the most studied being cannabinol (CBN), cannabidiol (CBD), and tetrahydrocannabinol (THC). These phytocannabinoids interact with the human endocannabinoid system, composed of CB1 and CB2 receptors distributed throughout the body, including oral tissues.(2) While THC is primarily responsible for psychoactive effects, CBD has gained attention for its anti-inflammatory, analgesic, and therapeutic properties without associated psychoactive effects.(3)

In dentistry, there is growing interest in understanding how cannabinoids affect oral tissues and whether they can offer therapeutic alternatives for conditions such as periodontal disease, orofacial pain, and inflammatory processes.(4) However, it is also necessary to consider

potential adverse effects, particularly associated with smoked cannabis consumption.(5)

The present study reviews systematically the scientific literature on the effects of cannabis on oral tissues, analyzing both therapeutic benefits and possible adverse effects.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

A systematic search was conducted in four electronic databases: PubMed, Scielo, Google Scholar, and Dentistry & Oral Science Source (EBSCO-Host). The search strategy employed the following keywords: Cannabis, Dronabinol, Cannabidiol, Cannabinoids, Buccal Mucosa, Cell Survival, Toxicity, and Pain. Boolean operators "AND" and "OR" were used to combine these terms for a comprehensive search.

The inclusion criteria were: (1) articles published in English and Spanish without publication date restriction; (2) in vitro studies involving oral tissues or cells; (3) clinical studies focused on oral health outcomes; and (4) case-control studies examining medicinal and recreational cannabis use and its effects on oral tissues. Exclusion criteria were established as: (1) studies that did not mention cannabis and living tissues; (2) studies in children; and (3) animal studies, which were initially included but later excluded from the final analysis to focus exclusively on human and in vitro research.

Data Extraction and Quality Assessment

For information collection, the guidelines established in the PRISMA declaration were followed.(6) Two independent reviewers screened titles and abstracts for relevance, and full texts of potentially eligible studies were retrieved for detailed evaluation. Disagreements between reviewers were resolved through discussion or by consulting a third reviewer.

The methodological quality of each study was evaluated using the AXIS scale for observational studies (7) and the CONSORT declaration for clinical trials. The quality assessment was performed independently by two reviewers, and any discrepancies were resolved through consensus.

The information extracted from each article included: author, year of publication, title, objective, type of study, results, clinical parameters evaluated, form of consumption/administration, effects detected, and main conclusions. All data were compiled in standardized tables for systematic comparison and analysis.

Data Analysis

A descriptive analysis was performed, focusing on the characteristics of the studies and their primary findings. Due to the heterogeneity of the study designs, populations, interventions, and outcomes, a meta-analysis was not conducted. Instead, a narrative synthesis approach

was used to present and discuss the results, organized by thematic categories.

RESULTS

Study Selection and Characteristics

From the 5,200 articles initially identified, 25 met the inclusion criteria after removing duplicates and excluding studies that used animal models. These 25 studies focused exclusively on human subjects or in vitro models. The methodological quality assessment showed a total reliability percentage of 72.85% for observational studies and an 85% verification for clinical trials.

Table 1 presents a comprehensive overview of the 25 human and in vitro studies included in this systematic review, highlighting their methodological characteristics and main findings related to the effects of cannabinoids on oral tissues. The studies are categorized into: Endocannabinoid System Studies (6 studies), Clinical Periodontal Studies (6 studies), In Vitro CBD Studies (4 studies), Antimicrobial Studies (5 studies), and Clinical Applications Studies (4 studies).

Table 1. Key Human and In Vitro Studies on Cannabis Effects on Oral Tissues

Author (Year)	Study Design	Population/Model	Main Findings	Quality
Endocannabinoid System Studies				
Konermann et al. (8)	Laboratory study	Human periodontal tissue	Differential receptor expression: healthy tissue	Moderate

			has more CB1 (13.5%) than CB2 (7.1%); during bacterial inflammation CB1 decreases (9.7%) while CB2 increases (14.7%)	
Nakajima et al. (9)	In vitro & clinical	Human gingival fibroblasts and crevicular fluid	Anandamide detected in crevicular fluid reduces LPS-induced inflammatory mediators through CB1/CB2 receptors	Moderate
Kozono et al. (10)	Clinical	Human patients with periodontitis	Increased anandamide levels in gingival crevicular fluid after periodontal surgery	Moderate
Zhang et al. (11)	In vitro	Human periodontal ligament cells	Methanandamide inhibits LPS-induced production of IL-6, IL-8, and MCP-1 at 10 μM without affecting cell viability	Moderate
Özdemir et al. (12)	In vitro	Human periodontal ligament cells	AEA (10 μM) with LPS inhibits IL-6, IL-8, and MCP-1 production; 2-AG (10 μM) with LPS increases these cytokines	Moderate
Abidi et al. (13)	In vitro	Human periodontal ligament fibroblasts	CB2 receptor ligands inhibit production of IL-6 and MCP-1 stimulated by various inflammatory factors	High
Clinical Periodontal Studies				
López et al. (14)	Cross-sectional	1,015 adolescents	No association between cannabis use and periodontal diseases	Moderate

Thomson et al. (5)	Cohort study	903 young adults	Positive association between cannabis smoking and periodontal disease (RR: 1.6-3.1)	High
Kayal et al. (15)	Cross-sectional	Adult drug users	More severe periodontitis in cocaine and heroin users	Low
Esquivel-Pedraza et al. (16)	Cross-sectional	54 subjects in prison	Higher frequency of oral pigmented lesions among marijuana users (p = 0.03)	Low
Arias (17)	Cross-sectional	People in rehabilitation	Mild to moderate clinical attachment level, gingival bleeding	Low
Shariff et al. (18)	Cross-sectional	1,938 US adults (NHANES)	Cannabis users show greater probing depth, more clinical attachment loss, and higher odds of severe periodontitis (OR: 1.7)	High
In Vitro CBD Studies				
Sacerdote et al. (19)	In vitro	Human macrophages	CBD modulates chemotaxis and IL-10/IL-12 production	High
Molina-Holgado et al. (20)	In vitro	Glial and neuronal cultures	Cannabinoids induce IL-1ra release, showing neuroprotective effects	High
Libro et al. (21)	In vitro	Human gingival mesenchymal stem cells	CBD inhibits NALP3 inflammasome activation and suppresses IL-18 expression	High
Rawal et al. (22)	In vitro	Human gingival fibroblasts	CBD increases TGF-β production up to 40% and fibronectin production up to 100% at low concentrations	Moderate
Antimicrobial				

Studies				
Ali et al. (23)	In vitro	Bacterial cultures	Cannabis extracts show pronounced antibacterial activity, especially against *B. subtilis* and *S. aureus*	Moderate
Khan et al. (24)	In vitro	Bacterial and fungal cultures	Greater bacterial inhibition against Gram-negative strains	Moderate
Frassinetti et al. (25)	In vitro	Bacterial cultures	Hemp seed extract selectively inhibits *S. aureus* growth and biofilm formation without affecting probiotic bacteria	High
Iseppi et al. (26)	In vitro	Bacterial cultures	Hemp essential oils show good antibacterial activity against Gram-positive bacteria	Moderate
Gu et al. (27)	In vitro	Bacterial cultures and monocytes	High doses (10 µg/ml) of phytocannabinoids inhibit growth of *P. gingivalis* and *F. alocis*	High
Clinical Applications Studies				
Crippa et al. (28)	Clinical trial	Anxiety disorder patients	CBD shows anxiolytic effects	High
Poli et al. (29)	Clinical trial	Chronic pain patients	Medical cannabis reduces pain intensity and disability	Moderate
Vigil et al. (30)	Clinical study	Human patients	Hemp oil shows significant pain relief effects	High
Aizikovich (31)	In vitro	Human cancer cells	New cannabinoids show anticancer effects	Moderate

Baram et al. (32)	In vitro	Human cancer cell lines	Cannabis extracts show heterogeneous antitumor effects — High

*Quality: High (≥80% of criteria met), Moderate (50-79% of criteria met), Low (<50% of criteria met) according to AXIS/CONSORT scales

Endocannabinoid System and its Effects on Periodontal Tissues

The studies included in Table 1 revealed important findings about the endocannabinoid system in periodontal tissues. Konermann et al.(8) demonstrated that CB1 receptor expression is significantly higher in healthy periodontal ligament structures compared to CB2. However, during bacterial inflammation, this relationship is reversed, with CB1 decreasing and CB2 increasing, suggesting a crucial role of the endocannabinoid system in regulating the periodontal inflammatory response.

Nakajima et al.(9) found detectable levels of anandamide (AEA) in gingival crevicular fluid, observing that this endocannabinoid significantly reduces the production of proinflammatory mediators (IL-6, IL-8, and MCP-1) induced by Porphyromonas gingivalis lipopolysaccharides in human gingival fibroblasts. These effects were attenuated by selective CB1 and CB2 antagonists, confirming the mediation of these receptors in the anti-inflammatory response.

Kozono et al.(10) observed an increase in anandamide levels in gingival crevicular

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fluid after periodontal surgery in human patients with periodontitis, suggesting involvement of the endocannabinoid system in periodontal healing processes. Additionally, Zhang et al.(11) demonstrated that methanandamide inhibits the LPS-induced production of proinflammatory cytokines in human periodontal ligament cells, further supporting the anti-inflammatory potential of cannabinoids in periodontal tissues.

Studies by Özdemir et al.(12) revealed differential effects of endocannabinoids on cytokine production in periodontal ligament cells. While anandamide (10 μM) inhibited LPS-induced production of IL-6, IL-8, and MCP-1, 2-araquidonilglicerol (2-AG) increased these cytokines, highlighting the complex interactions between different components of the endocannabinoid system in periodontal inflammation.

Effects of CBD and Smoked Cannabis on Oral Tissues

Libro et al.(21) demonstrated that CBD modulates the immunophenotype and inhibits the activation of the inflammasome in human gingival mesenchymal stem cells, showing potential anti-inflammatory mechanisms at the cellular level. The study highlighted CBD's ability to suppress NALP3, CASP1, and IL18 expression, suggesting a protective role against excessive inflammatory responses. These findings are consistent with those of Sacerdote et al.(19), who showed that CBD modulates

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chemotaxis and alters the production of inflammatory cytokines in macrophages.

On the other hand, Thomson et al.(5) and Shariff et al.(18) found significant associations between smoked cannabis consumption and periodontal disease in human population studies. Shariff et al.(18) reported greater probing depth, more clinical attachment loss, and higher odds of severe periodontitis (OR: 1.7; 95% CI: 1.3-2.4) in frequent recreational cannabis users, based on data from 1,938 adults in the NHANES 2011-2012 survey.

López et al.(14) found no association between cannabis use and periodontal diseases in a cross-sectional study of 1,015 adolescents, suggesting that age, duration of use, or other factors may influence the relationship between cannabis consumption and periodontal health. Kayal et al.(15) examined the periodontal health status of illicit drug users, finding that cannabis consumption, especially when combined with other drugs, negatively affects periodontal health.

Esquivel-Pedraza et al.(16) documented a higher frequency of oral pigmented lesions among marijuana users ($p = 0.03$) in a prison population, while Arias(17) observed mild to moderate clinical attachment loss and gingival bleeding in individuals recovering from marijuana addiction, highlighting additional oral manifestations beyond periodontal effects.

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Antimicrobial Properties and Effects on Extracellular Matrix

Several studies have demonstrated antimicrobial properties of Cannabis sativa extracts against various pathogens. Frassinetti et al.(25) found that hemp seed extract exerts selective antibacterial activity against pathogenic strains without affecting the growth of probiotic bacteria, in addition to inhibiting biofilm formation by *Staphylococcus aureus*. Similar findings were reported by Iseppi et al.(26), who evaluated the antibacterial activity of essential oils from hemp, finding good efficacy against Gram-positive bacteria.

Gu et al.(27) observed that high doses of phytocannabinoids inhibit the growth of *Porphyromonas gingivalis* and *Filifactor alocis*, but not *Treponema denticola*, suggesting a potential role in modulating oral microbiota. Additionally, Ali et al.(23) demonstrated pronounced antibacterial activity of cannabis extracts against various strains, with different extracts showing varying degrees of efficacy depending on the bacterial species. Khan et al.(24) further reported that Cannabis sativa extracts exhibit greater inhibition against Gram-negative compared to Gram-positive bacteria.

Rawal et al.(22) investigated the effects of CBD on extracellular matrix metabolism in human gingival fibroblasts. They found that CBD increases transforming growth factor β production by up to 40% and fibronectin production by approximately 100%, while decreasing matrix metalloproteinase production and

activity. These results suggest that CBD could promote fibrotic gingival enlargement, which poses both possible therapeutic applications and precautions in its clinical use.

Other potential applications of cannabinoids in dentistry might be derived from studies like Poli et al.(29), who reported significant reduction in pain intensity and disability in patients with chronic pain treated with medical cannabis, suggesting possible benefits for managing orofacial pain. Similarly, Vigil et al.(30) documented significant antialodynic effects of hemp oil in a pain model, while Crippa et al.(28) reported anxiolytic effects of CBD, which could benefit anxious dental patients.

DISCUSSION

This systematic review demonstrates the complex interaction between cannabinoids and oral tissues. As can be observed in Table 1, there is a temporal and methodological diversity in studies conducted on this topic, with a notable increase in research during the last decade. This increase reflects the growing scientific interest in the potential therapeutic applications of cannabis in dentistry, driven in part by changes in legislation and social perception regarding the medicinal use of this plant.(1,4,35) The discovery of the endocannabinoid system in periodontal tissues has opened new perspectives for understanding the mechanisms of periodontal inflammation regulation and potential therapeutic approaches.(2,8,9,36)

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The results show a duality in the effects of cannabis on oral health, as evidenced in the findings. On one hand, beneficial properties are observed, mainly anti-inflammatory and antimicrobial, associated with cannabinoids such as CBD.(3,19,25,37) These effects appear to be mediated through various mechanisms, including modulation of inflammatory cytokine production, inhibition of the NALP3 inflammasome, and regulation of the NF-kappaB pathway.(9,20,21,38) On the other hand, smoked cannabis consumption is associated with adverse periodontal effects,(5,18,39) although it is important to consider that many cannabis consumers are also tobacco smokers, which could be enhancing these negative effects.(33,40)

The evidence on the anti-inflammatory properties of CBD in human cell models is particularly promising, suggesting a potential therapeutic role in the management of oral inflammatory diseases.(19,20,21,35) Studies by Libro et al.(21) demonstrated CBD's ability to inhibit inflammasome activation in human gingival mesenchymal stem cells, consistent with the general anti-inflammatory effects of CBD described in the literature.(34,36) Additionally, Molina-Holgado et al.(20) reported that cannabinoids induce the release of the endogenous interleukin-1 receptor antagonist, which may contribute to their anti-inflammatory and neuroprotective effects, a finding supported by subsequent research on neuroinflammatory conditions.(35,37)

The antimicrobial properties of cannabis extracts against oral pathogens suggest another possible application in dentistry, particularly in dental biofilm control.(23,24,25,26,27,38) Frassinetti et al.(25) showed how hemp seed extract selectively inhibits S. aureus growth without affecting probiotic bacteria, which could be valuable for maintaining oral microbiome balance while targeting pathogenic species. This selective antimicrobial activity distinguishes cannabis-derived compounds from conventional antibiotics, potentially offering advantages in terms of microbiome preservation as highlighted in recent microbiological research.(27,38)

The effects of CBD on gingival fibroblasts reveal a potential mechanism for the treatment of oral wounds,(22,39) although they also suggest caution regarding possible gingival enlargement effects.(22,40) This duality reflects the complexity of the interaction between cannabinoids and oral tissues, underlining the need for specific protocols for different oral conditions. Moreover, findings by Aizikovich(31) and Baram et al.(32) on the heterogeneous effects of different cannabis extracts on cancer cells highlight the importance of standardization in cannabis-based preparations for therapeutic use, as emphasized in pharmacological studies.(35,36)

The differential expression patterns of CB1 and CB2 receptors in periodontal tissues in different states (healthy, bacterial inflammation, sterile inflammation), suggest a regulatory role

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of the endocannabinoid system in the periodontal inflammatory response.(8,37) This is consistent with the regulatory function of this system in other tissues of the organism, as demonstrated by Mackie(2) and further explored in comprehensive reviews of cannabinoid receptor distribution and function.(35,36)

Studies exploring the effects of cannabis on the central nervous system may also have implications for dentistry. Crippa et al.(28) reported anxiolytic effects in patients with social anxiety disorder, findings that align with broader research on cannabinoid applications in anxiety management.(38,39) These findings suggest potential applications in managing dental anxiety and improving patient comfort during dental procedures, although specific studies in dental settings are still needed as noted in recent clinical guidelines.(36,40)

An important limitation in the current literature is the scarcity of controlled clinical studies specifically designed to evaluate the effects of cannabinoids on oral pathologies. Many of the analyzed studies come from in vitro studies,(13,19,20,21,22,23,24,25,26,27,31,32,37) which limits direct extrapolation to clinical practice. Additionally, there is heterogeneity in the formulations, concentrations, and routes of administration used, making direct comparisons between studies difficult, as observed in pharmacological analyses.(35,38) The few clinical studies available, such as those by Thomson et al.(5), Shariff et al.(18), and López et al.(14), focus primarily on the effects of

recreational cannabis use rather than controlled therapeutic applications, a limitation also noted in systematic reviews of cannabinoid clinical applications.(36,39)

Further research should account for the genetic and epigenetic factors that may influence individual responses to cannabinoids, as suggested by immunopharmacological studies.(37,40) Recent developments in cannabinoid delivery systems, including oral applications specifically designed for the buccal environment, also warrant investigation for dental applications.(35,38) The potential interaction between cannabinoids and conventional dental treatments, including possible effects on anesthesia efficacy and postoperative healing, represents another important avenue for future research.(36,39)

Future research should prioritize well-designed clinical trials evaluating standardized cannabis-based formulations for specific oral conditions. Particular attention should be given to dosage, administration routes, and potential interactions with conventional dental treatments. Additionally, long-term effects and safety profiles should be thoroughly investigated to establish evidence-based protocols for dental practice, especially considering the varying legal status of cannabis products across different jurisdictions.(35,40)

CONCLUSION

The endocannabinoid system plays a significant role in oral tissue homeostasis.

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Cannabinoids exhibit anti-inflammatory, antimicrobial, and matrix-modulating properties potentially beneficial for various conditions. Future research should focus on developing specific oral formulations that maximize benefits while minimizing adverse outcomes.

Smoked cannabis appears associated with adverse periodontal effects, although these findings should consider confounding factors such as concurrent tobacco use. Clinical protocols addressing both therapeutic applications and potential risks are needed, particularly considering the increasing cannabis legalization worldwide.

Dental professionals must stay informed about cannabis effects on oral tissues to provide comprehensive patient care. This emerging field offers promising opportunities for novel therapeutic approaches including periodontal inflammation management, antimicrobial strategies, and pain control applications.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTION STATEMENT

Conceptualization and Design: E.C.M., A.M.D.; Literature Review: E.C.M., A.M.D.; Methodology and Validation:

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