

CANNABIS USE AND ITS ORAL EFFECTS ON ORAL CAVITY – A LITERATURE REVIEW

Dentistry

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ABSTRACT

Cannabis is a complex plant with a rich array of compounds including cannabinoids like delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which have contrasting effects on human body. The discover of these compounds in cannabis has led to researchers to uncover the endocannabinoid system (ECS), an intricate network of receptors and enzymes. The ECS plays a crucial role in regulating various physiological processes, including mood, memory, appetite, pain sensation, and immune function.

KEYWORDS

INTRODUCTION:

One notable trend in recent years has been the consistent increase in cannabis potency worldwide. This rise in potency, particularly concerning THC levels, has raised concerns among health professionals and policymakers due to its potential impact on public health. Abidi et al (2022) describes that use of cannabis as a therapeutic agent and its use as a medicinal purpose has changed greatly over the period of years. Higher potency cannabis products may pose increased risks of adverse effects, including addiction, cognitive impairment, psychiatric disorders, and respiratory issues. Moreover, the changing landscape of cannabis legalization and commercialization has introduced new challenges in regulating potency, quality control, and public health education. As cannabis becomes more accessible and culturally accepted, it's imperative to balance the potential benefits of its medicinal use with the risks associated with misuse and abuse, especially in populations vulnerable to its adverse effects, such as adolescents and individuals with mental health disorders.

"Marijuana refers to the dried leaves, flowers, stems, and seeds from the Cannabis sativa or Cannabis indica plant". This plant contains the mind-altering chemical called THC (tetrahydrocannabinol), which is responsible for the psychoactive effects commonly associated with marijuana use. Historically, smoking has been the predominant method of cannabis ("marijuana") consumption, but vaping cannabis and the availability of various cannabis-infused products, including edibles, beverages, oils, concentrates, and topical ointments, have become increasingly common. Keboa et al (2020) found that there is less association of smoking cannabis and oral diseases, although there are different studies which states cannabis smoking as a risk factor for oral diseases. Research suggests that a considerable proportion of marijuana users may develop marijuana use disorder, which can have significant negative consequences for individuals' health, relationships, and overall well-being. Le and Palamar (2018) stated that cannabis is third commonly used drug in US after alcohol and tobacco in older adults.

The push for cannabis legalization and medical marijuana laws in various states across the United States has indeed been a significant trend in recent years. Proponents of medical marijuana argue that cannabis can offer therapeutic benefits for a range of medical conditions, including chronic pain, epilepsy, multiple sclerosis, and side effects of cancer treatment such as nausea and appetite loss. Decriminalization and legalization measures aim to mitigate these harms by shifting focus from punitive measures to public health and harm reduction strategies. Legalizing cannabis allows for regulation and taxation of the industry, potentially generating revenue for states and local governments while ensuring product safety and quality control. This approach also aims to undermine illegal cannabis markets and associated criminal activities.

However, it's important to note that there are also concerns and criticisms associated with cannabis legalization and medical marijuana law in USA:

- **Lack of FDA Approval:** While some studies suggest potential medical benefits of cannabis, the FDA has not approved cannabis for the treatment of specific medical conditions. The lack of regulatory oversight and standardized dosing protocols raises concerns about the safety, efficacy, and consistency of medical marijuana products.
- **Potential Health Risks:** Despite its perceived medicinal properties, cannabis use carries certain health risks, including addiction, cognitive impairment, respiratory issues, and potential psychiatric effects, especially in vulnerable populations such as adolescents and individuals with mental health disorders.

Cannabis smoking is also linked with oral health complications such as periodontal issues, dry mouth, leukoplakia, and a potential elevated risk of mouth and neck cancer. The surge in cannabis usage, largely due to the expanding legalization for medical and recreational purposes in numerous U.S. states, despite federal prohibition, suggests that dental professionals are likely to encounter more patients experiencing diverse side effects from cannabis use. With the wider availability and consumption of cannabis and its derivatives, dental practitioners can anticipate encountering a broader spectrum of oral health issues associated with cannabis use. Additionally, cannabis-infused edibles may contribute to dental cavities and other oral health concerns, especially if they contain high levels of sugars. Moreover, the systemic effects of cannabis use can indirectly impact oral health by affecting immune function and inflammation, potentially exacerbating periodontal disease and oral infections.

Biological Effects of Cannabinoids via Receptors

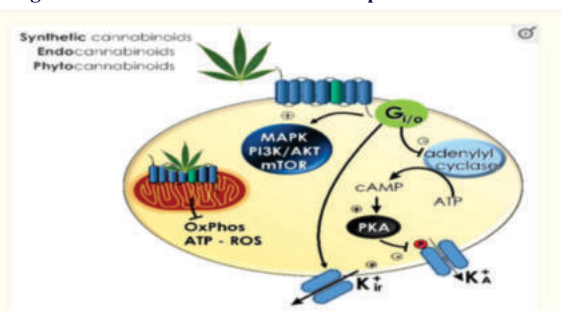


Figure 1 (Bellocchio L et al. 2021)

Cannabinoids exert their physiological and pathophysiological effects primarily by binding to a variety of cannabinoid receptors and initiating diverse signaling pathways (see Figure 1). Bellocchio L et al. (2021) reports that among these receptors, CB1 is the most extensively studied. The primary mode of action of CB1 involves inhibiting adenylyl cyclase, a second messenger system, in a dose-dependent manner via Gi/o proteins. This inhibition leads to a decrease in intracellular cyclic adenosine monophosphate (cAMP) levels. Consequently, the activity of cAMP-dependent protein kinase (PKA)

is downregulated, affecting downstream signaling pathways such as ion channels and cellular electrical properties.

Moreover, Bellocchio L et al. (2021) states that recent research indicates that beyond their conventional localization and signaling at the plasma membrane, CB1 receptors are also linked to mitochondrial membranes in various cell types. Activation of these subcellular receptor pools profoundly affects cellular bioenergetic status, leading to significant behavioral and physiological changes.

Cannabinoid orofacial Receptors:

Tongue:

Bellocchio L et al. (2021) reported that number of researchers found both CB1 and CB2 cannabinoid receptors on human tongue. CB1 and CB2 are found mainly in the epithelial cells of tongue and also found in circumvallate and fungiform papillae. CB2 and transient receptor potential vanilloid type 1 (TRPV₁) are also present in epithelial cells adjacent to taste buds and in basal layer of tongue.

Salivary Glands:

The salivary glands express both CB1 and CB2 receptors, each with specific localization patterns and functions:

CB1 Receptors:

- These are detected in the major salivary glands, specifically localized in the striated duct cells near the apical membrane.
- Their expression is not observed in acinous cells.
- In the submandibular gland, CB1 receptors are primarily expressed in the basolateral membranes of ductal cells. However, they are also found in the serous cells of mixed acini depending on dietary status.

CB2 Receptors:

- CB2 receptors are mainly visualized in myoepithelial cells surrounding the acini, where saliva production and release occur.
- They are also present in neurons of ganglia from the secretory ducts.

Regulation of Cannabinoid Receptor Expression:

- Cannabinoid receptor expression in salivary glands is influenced by various factors, including food quantity and quality, as well as noradrenergic tone.

Functional Impact:

- Activation of both CB1 and CB2 receptors negatively regulates saliva secretion.
- This negative action may explain the dry mouth sensation commonly experienced by heavy cannabis users.

Research Findings

- Studies from the Elverdin lab suggest the negative impact of CB1 and CB2 receptor activation on saliva secretion.
- Anandamide, an endogenous cannabinoid, activates CB1 receptors in rat parotid glands, leading to cAMP accumulation, amylase release, Na⁺-K⁺-ATPase inhibition, and impacts upon salivary gland functions.

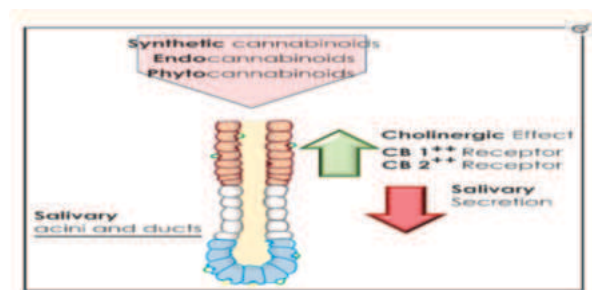


Figure 2 (Bellocchio L et al. 2021)

Pulp Tissue:

In dental pulp tissues, while CB1 receptor expression has been detected in limited reports, cannabinoids show promise for therapeutic applications in this oral tissue:

CB1 Receptor Expression:

- CB1 receptors have been found at the pulp-dentin border,

particularly located on nerve terminals within the dental pulp tissue

- This pattern of expression persists in nerve fibers of symptomatic painful dental pulp

Therapeutic Potential:

- Given the role of neurotransmitter suppressors in inhibiting various types of transmission, combined with the presence of CB1 receptors on these nerve terminals, cannabinoids emerge as potential therapeutic targets for dental pain conditions
- Cannabinoid-based medicines could offer relief from dental pain by modulating neurotransmitter release through CB1 receptor activation

Dentin Repair and Regeneration:

- Cannabinoid treatment of rat odontoblasts has been demonstrated to stimulate the formation of "reparative dentin" by regulating extracellular calcium entry
- This mechanism of CB1-mediated dental pulp tissue repair involves the activation of matrix metalloproteinase-2 in dental pulp cells

Overall, cannabinoids hold promise for therapeutic interventions in dental pulp tissues, offering potential benefits in pain management and dentin repair/regeneration. Further research in this area could lead to the development of cannabinoid-based treatments for dental conditions.

Periodontal Tissue:

In periodontal tissues, both CB1 and CB2 receptors are implicated in various pathological conditions, including inflammation and wound healing:

- CB1 receptors are expressed at significantly higher levels than CB2 receptors in both the epithelium and periodontal ligaments (PDL) of healthy subjects.
- Following bacterial inflammation, there is a switch in receptor expression, with downregulation of CB1 and overexpression of CB2 receptors within the PDL.

Bellocchio L et al. (2021) states that the research findings, such as done by Liu et al. and Nakajima et al., provide evidence for the therapeutic potential of cannabinoid compounds in periodontal regeneration, wound healing, and inflammation management. Further investigation into the mechanisms underlying cannabinoid receptor signaling in periodontal tissues could lead to the development of novel therapeutic strategies for periodontal diseases.

Technical Work:

Cannabinoid Drugs used to treat Dry mouth: Total of studies included to study the effect of cannabinoid on dry mouth. Darling et al. included one cross sectional study done on 300 patients who used cannabinoid in the form of smoking. Study found a higher incidence of leukoedema and dry mouth in subjects who are regular users of cannabis then control group. Other studies were done on animals like rats and pigs. Out of this two were done rats and one was done on pigs. Pririno et al. showed that after the dietary administration in 32 pigs there was endocannabinoid activity in salivary gland ducts.

Cannabinoids and Dental Caries:

Three studies were included on the topic of cannabinoids and dental caries, comprising both clinical and in vitro research:

Case report by Grafton et al.: This study reported a case of low compliance in a marijuana smoker who underwent a tooth extraction procedure, which resulted in a high incidence of dental caries.

Retrospective Cohort Trial by Ditmyer et al.: This retrospective cohort study included 66,941 subjects and found an increase in the prevalence and severity of dental caries in patients who reported administration of tobacco and marijuana.

In Vitro Study: Liu et al. conducted an in vitro study where they reported that delta-9-tetrahydrocannabinol (THC), a compound found in marijuana, promoted periodontal cell adhesion and migration in wound tissue healing.

These studies collectively suggest a potential association between marijuana use and dental caries. The clinical studies indicate a higher incidence of dental caries in individuals who smoke marijuana, while

the in vitro study provides insight into the potential mechanisms by which cannabinoids, specifically THC, may influence periodontal tissue healing. Further research is warranted to elucidate the exact relationship between cannabinoids and dental caries and to explore potential preventive and therapeutic strategies.

Cannabinoid and Periodontal diseases:

The included articles on cannabinoids and periodontal diseases encompass various types of research, including clinical studies, in vitro experiments, and animal studies:

Clinical Studies:

- Thomson et al.: Reported that cannabis smoking may be an independent risk factor for periodontal disease in patients with periodontitis, regardless of tobacco use.
- Shariff et al.: Demonstrated a correlation between cannabis smoking and deeper probing depths, increased clinical attachment loss, and higher risk for severe periodontitis.

Animal Studies:

- Nogueira-Filho et al.: Showed in rat models that cannabis smoke exposure could lead to increased alveolar bone loss, indicating a negative impact on periodontal health.

In vitro and In vivo Studies:

- Several studies investigated the effects of synthetic cannabinoid-derived molecules, such as anandamide (AEA), 2-arachidonoylglycerol (2-AG), AM251, AM630, and HU-308, on periodontal tissues.
- These studies indicated increased activity and proliferation of human gingival fibroblasts, inhibition of RANK/RANKL expression leading to lower bone loss, and anti-inflammatory as well as osteoprotective effects on oral tissues in vivo

In Vitro Studies:

- Studies conducted on human periodontal fibroblasts (HPLF) and human gingival fibroblasts demonstrated a strong inhibition of pro-inflammatory molecules such as lipopolysaccharide (LPS), tumor necrosis factor-alpha (TNF- α), and interleukin-1 beta (IL-1 β) expression by cannabinoids.

These findings collectively suggest a complex relationship between cannabinoids and periodontal diseases, with evidence indicating both detrimental effects associated with cannabis smoking and potential therapeutic benefits of cannabinoid-derived molecules on periodontal health. Further research is needed to fully understand the mechanisms involved and to explore the potential of cannabinoids as therapeutic agents for periodontal diseases

Cannabis consumption and Oral Health:



Figure 3 (Bellocchio Let al. 2021)

Cannabis abuse has long been associated with negative effects on oral health. Several factors contribute to the increased risk of oral health problems among cannabis users:

- Cannabis use can lead to decreased saliva production, resulting in dry mouth. This condition can increase the risk of dental caries, as saliva helps to neutralize acids and remineralize tooth enamel.
- Cannabis users may have a higher incidence of dental caries due to factors such as dry mouth, poor oral hygiene, and increased consumption of sugary snacks, which are common side effects of cannabis use.
- Irritation from cannabis smoke and decreased immune function associated with cannabis use can contribute to soft tissue diseases such as oral candidiasis (thrush) and leukoplakia.

- Cannabis use may be associated with neglect of oral hygiene practices such as brushing and flossing, leading to plaque accumulation, gingivitis, and periodontal disease.
- Cannabis use has been linked to an increased risk of periodontal disease due to factors such as decreased saliva flow, inflammation, and compromised immune function.
- While the direct link between cannabis use and oral cancer is still debated, some studies suggest that long-term cannabis smoking may increase the risk of developing oral cancer, especially when combined with other risk factors such as tobacco use.

Despite these negative effects, cannabis may have potential benefits in dental anesthesia and post-operative pain management. Cannabis-derived compounds, such as cannabinoids, have been investigated for their analgesic properties and could potentially offer an alternative or adjunctive treatment for pain control in dental procedures. Overall, while cannabis abuse poses risks to oral health, further research is needed to fully understand the relationship between cannabis use and oral health outcomes, as well as to explore the potential therapeutic applications of cannabis-derived compounds in dentistry.

CONCLUSION:

Svrakic et al (2012) reported that as cannabis legalization continues to progress, dental professionals should be prepared to address the oral health implications of cannabis use with their patients. This may involve educating patients about the risks associated with different consumption methods, promoting preventive measures like regular dental check-ups and good oral hygiene, and providing appropriate treatment for any resulting oral health issues. Bellocchio L et al. (2021) further reports that his knowledge is crucial for healthcare providers, particularly oral healthcare professionals and dentists, given the increasing prevalence of legalized cannabinoid consumption and its potential impact on oral health. Marijuana smoking, the most common method of cannabis consumption, is associated with various direct and indirect adverse effects on oral health. However, the evidence linking cannabis to oral/dental diseases remains contradictory and limited, partly due to different personal risk factors and insufficient details on marijuana usage. Further well-designed research controlling for confounding factors is necessary. More basic and clinical research is required to elucidate the mechanisms of action of cannabis, enabling the development of synthetic agonists, antagonists, and modulators of the endocannabinoid system. This focused research approach will facilitate the precise targeting of systemic and oral effects, leading to the development of new therapeutic approaches with increased efficacy and reduced side effects. Ultimately, this will benefit patients by expanding treatment options and improving overall healthcare outcomes.

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