UNIVERSITY OF CAXIAS DO SUL

AREA OF KNOWLEDGE AND SCIENCE OF LIFE

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IS CANNABIS A RISK FACTOR FOR PERIODONTAL DISEASE? : A BIBLIOGRAPHIC REVIEW

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Course Completion Work presented as a requirement for obtaining the title of Bachelor of Dentistry at the University of Caxias do Sul, Area of Knowledge Life Sciences.

Advisor: Prof. Dr. Lucianna Benfica Abrão

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LIST OF ABBREVIATIONS

BA	Bone Area
BD	Bone Density
BL	Bone Loss
CAL	Combined Attachment Loss
CBD	Cannabidiol
CBN	Cannabinol
FRC	Frequent recreational Use
MSI	Marijuana Smoked Inhalation
THC	Delta-9-Tetrahydrocannabinol

ABSTRACT

Tobacco smoking has long been considered a risk factor for periodontal disease development owing to the components of tobacco such as nicotine. However cannabis has been shown in recent years to play comparable functions in the development of disease. With marijuana use increasing across all sociodemographic categories, periodontal complications may pose a significant and growing oral health concern. Although cannabis is classed as a non-addictive substance with a danger level comparable to coffee or cigarettes, current research indicates that long-term use can result in harmful side effects such as interfering with the pathophysiology of bone and perhaps possessing immunosuppressive qualities. Therefore, the purpose of this study was to conduct a bibliographic review providing available evidence to investigate the recreational use of cannabis as a risk factor for periodontal disease. The study also included an analysis of the drug's probable mechanism of action, its effect on periodontal tissues, and the age range most affected by the drug's usage. This study used publications containing relevant information in languages such as English , Portuguese and Spanish published over the last 15 years as well as researches conducted on people and animals . Databases searched were PubMed, Google Scholar, Scielo, and Scopus. In the end, the study indicated that recreational cannabis use may soon be linked to periodontal disease, alongside cigarette use. This is because the drug's mechanism may impact the immune response and reduce periodontal tissue's ability to heal following disease activity, and this may be dosage dependant. It is also thought to aggravate the condition by causing alveolar bone loss and disrupting the microbial dysbiosis. Due to the drug's short-term exposure, these traits are likely to be exhibited in adults and elders.

Key words: *Cannabis sativa*, marijuana, periodontal disease and periodontal tissues

SUMMARY

INTRODUCTION

The term periodontal disease refers to the pathological inflammatory conditions that affect the periodontal tissues, in particular the gingiva, supporting bone and conjunctive tissue surrounding the teeth (1). Periodontal disease is one of the significant causes of tooth loss in adults (2) being considered the sixth most prevalent chronic disease in the world and affecting approximately 11.2 percent of the world's population (3). It features a complex multifactorial aetiology, in which an accumulation of bacteria predominately anaerobes gram negative in the subgingival region of the teeth induces an inflammatory process that stimulates tissue destruction mediated by the host itself (4). Without treatment, this progressive destruction of the periodontal ligament e alveolar bone can lead to formation of periodontal pockets and gingival retraction (5).

In accordance with Highfield, 2009, the diagnostic of periodontal disease requires a firm knowledge of what equivalents to healthy periodontium (6). Periodontal health is characterised by an integral periodontium with no insertion loss, probing depth up to 3 mm, no bleeding on probing and no radiographic bone loss (7). The most prevalent categories of periodontal disease are gingivitis and periodontitis. Gingivitis is characterised by inflammation of the gingiva without evidence of insertion loss. In contrast to the irreversible form, periodontitis is characterised by gingival inflammation that progresses beyond the gingiva, resulting in the irreversible breakdown of connective tissue attachment to the root and resorption of alveolar bone in a susceptible individual (8). In the oral cavity, more than 700 bacteria can be identified, the bulk of which are anaerobic and aerobic. A rise in periodontal pocket formation is linked to the growth of an anaerobic subgingival microbiota consisting of anaerobes and microaerophilic gram-negative bacilli in the presence of chronic inflammation (9). It was concluded that *Porphyromonas gingivalis (P. gengivalis*), *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*), and *Tannerella forsythia* (*T. forsythia*) are periodontal pathogens when they are present in sufficient numbers and in susceptible hosts (10).

Various factors can contribute to the risk of periodontal diseases. These factors, both modifiable and non-modifiable, play a major role in periodontal disease clinical manifestations (11). Among the risk factors are smoking, diabetes, obesity, overweight and genetic factors (12). According to Nazir, 2017, smoking is one of the major deteriorating factors of periodontal disease. Cigarette, weed, and pipe smokers are more

likely to have advanced periodontal disorder than non-smokers(13). Cannabis is the generic term for preparations such as marijuana, hashish and hash oil derived from the plant *Cannabis sativa* (14). Smoking marijuana is the most common and efficient way of using Cannabis due to its ease in preparation and its effects are fast (15). The Cannabis sativa plant contains over 421 chemical compounds, including more than 60 active compounds known as cannabinoids(16–18), which function through an endogenous cannabinoid receptor system in the human body to generate their impact (15). Delta-9-tetrahydrocannabinol or THC is mostly responsible for the psychoactive properties that cannabis users seek. Following this, cannabidiol or CBD, then cannabinol CBN, a naturally occurring THC catabolic item. The latter two are non- psychoactive but are known to have therapeutic benefits such as anticonvulsant and anti-inflammatory properties (12).

According to the world drug report, 2020, cannabis is the world´s most used drugs with an estimated 192 million past-year users in 2018, corresponding to 3.9 per cent of the global population aged 15–64 (19). The Americas continues to see the largest annual rate of cannabis consumption with 8.8 percent of people aged 15 to 64. Cannabis use has been steadily growing in the United States since 2007, especially among young adults aged 18–25 and older adults aged 26 and older (19). Based on the statements of Fischer *et al*, 2019, recent epidemiological statistics for Brazil are small, but it is estimated that 2 to 3 percent of the adult population and approximately 5 to 14 of high school and post-secondary students currently consume marijuana (20). North America along with some other countries, has seen an increase in the use of cannabis due to the growing interest in jurisdictions to legalise and adopt a more public health-oriented policy, decriminalizing also the non-medical use of the drug (20).

For many years, tobacco use has been recognised as a behavioural risk factor for periodontal disease through its systemic effects. However, in recent times, several studies have concluded that cannabis independent of tobacco use may also result in the onset of the disease leading to early periodontal tissue loss at an early age in young adults (21). In a study by Noguiero-Filho *et al*., 2011, they proved that Cannabis sativa (marijuana) can interfere in bone pathophysiology because of its effect on osteoblastic and osteoclastic activity but could not prove its impact on other periodontal tissues. While in a more recent study done by Zhen Ju., 2019, it was proven that cannabinoids may have cytotoxic and immunosuppressive properties on human monocytes and epithelial cells exposed orally

in the presence of oral pathogens. Therefore, this research aims to summarizing all the evidence available, linking the use of cannabis as a significant risk factor for periodontal disease.

2. OBJECTIVES

2.1 GENERAL

The use of Cannabis as a risk factor for periodontal disease was investigated.

2.2 SPECIFIC OBJECTIVES

- The available evidence of the association of Cannabis Sativa in periodontal disease was reviewed.
- The mechanism of action of the derivatives cannabidiol, cannabinol and delta-9-tetrahydrocannabinol from the Cannabis sativa plant on periodontal tissues was analysed.
- The periodontal effects with recreational use of the plant were recognized.
- The age range in which periodontal disease most affects with the use of the drugs was evaluated.

3. METHODOLOGY

A literature review was conducted based on 38 publications in which 18 had specific evidence on the topic. Key words included Cannabis sativa, marijuana, periodontal disease and periodontal tissues. The databases that were used to conduct the search included PubMed, Google Scholar, Scielo and Scopus.

3.1 CRITERIA FOR SELECTION OF WORKS

3.1.1 Inclusion Criteria

The inclusion criteria included any material that addresses the topic in languages such as English, Portuguese and Spanish and studies done in humans and animals done over the last 15 years.

3.1.2 Exclusion Criteria

Any research that was done before the 15 year limit.

4. BIBLIOGRAGHY REVIEW

Periodontal disease is distinguished by the inflammation and persistent loss of periodontal attachment apparatus as a result of a strong inflammatory response to germs. The most common bacterial pathogens of periodontal disorders are gram-negative anaerobic species that express a variety of possible virulence factors via encouraging host immune cells to generate a variety of chemicals and pro-inflammatory factors through protein produced on the membrane target (22)

For the most of the twentieth century, periodontal disease was thought to be a condition that struck people after they were caused solely by tooth plaque and unrelated to lifestyle decisions(23), however, in recent years, it has been suggested that the disease is caused by degenerative changes in the periodontal tissues in addition to long-term exposure to a number of risk factors (24). Marijuana usage for recreational purposes could be considered one of these risk factors. Cannabis is classified as a mild drug that is only as hazardous as coffee or cigarettes, but recent studies have shown that long-term usage can result in negative side effects such as periodontal disease(12). The drug is considered to be the most psychoactive drug, also having anti-inflammatory agents which decrease anti-oxidative activities and production of destructive – inflammatory cytokines and enhancing the induction of apoptosis and T – regulatory cells (25).

4.1 CANNABIS SATIVA AND ITS DERRATIVES

Cannabis is a versatile crop with applications in nutrition, medicine, and textile industry. The crop is said to have originated and been domesticated in Asia about 5000 years ago, and it has been intertwined with human history since then. Cannabis biotypes with high THC levels were extensively utilized for medical and recreational purposes in South Asian countries, forming a strong link to social and religious rites (26). With the increasing acceptability of cannabis use for medicinal and recreational purposes, there

has been a shift in cannabis availability, a reduction in perceived danger, and a broadening of incentives for usage (27) .

The cannabis plant has about 500 chemical components, including hundreds of cannabinoids and non-cannabinoids. In the plant, non-cannabinoids components such as terpenes and flavonoids have been identified as the source of flavour and fragrance. Cannabinoids refer to a diverse set of compounds that act on cannabinoid receptors . They are classified into three categories: endogenous cannabinoids (endocannabinoids), synthetic cannabinoids, and phytocannabinoids (22).The most common cannabinoids are Tetrahydrocannabinol (THC), cannabidiol (CBD), cannabidinol (CBN), cannabigerol (CBG), tetrahydrocannabivarin (THCV), cannabichromene (CBC), and their respective acids. THC is primarily responsible for cannabis' psychotropic effects. It acts as a partial agonist on the cannabinoid receptors CB1 and CB2. The central nervous system (cerebral cortex, hippocampus, basal ganglia, and cerebellum), as well as the lungs, liver, and kidneys, possess CB1 receptors. Immune and hematopoietic cells have the most CB2 receptors. CBD, unlike THC, does not have a direct effect on the CB1 and CB2 receptors, which are responsible for psychoactive effects. CBD is anticonvulsant, analgesic, anti-anxiety, antiemetic, immune-modulating, anti-inflammatory, neuroprotective, and anti-tumorigenic (28). Cannabinol (CBN) is a cannabinoid that is frequently produced during the oxidation of THC.(29) . Cannabinoids seem to attenuate the production of some inflammatory mediators, such as interferon-g, tumour necrosis factor-A, interleukin-1),6 and interleukin-10 (30).

4.2 EFFECTS OF CANNABIS ON PERIODONTAL DISEASE

Tobacco use is a well-known risk factor for periodontitis, owing to the reduction in oxygenation induced by nicotine's vasoconstriction of the tissues . New study, however, has found biological plausibility for a possible relationship between periodontal disease and cannabis use. (3). The tobacco - independent relative risk for marijuana use has been calculated to be between 1.6 and 3.1, depending on the disease severity threshold used, which is comparable to tobacco smoking. The combined risk of tobacco and cannabis is predicted to be 2.5 [1.5-4-5] (31). Still, the concurrent use of cannabis and tobacco, which

is prevalent among users makes it difficult for studies to isolate the effects of cannabis alone (32).

In a study done by Mederos *et al*., 2018, they observed a significant association between Cannabis use and the prevalence of periodontitis where cannabis users had a prevalence of periodontal disease 44 percent higher than that of non- users. While the significance of the endocannabinoid system in gingival health is still unknown, current research has repeatedly shown that marijuana is a significant risk factor for periodontitis in humans. Importantly, it has been demonstrated that destructive periodontal diseases in marijuana users may begin sooner than in the overall periodontitis population, which typically does not develop periodontitis until middle age (33) .

Possible effects of cannabis can begin with the long-term inflammation in individuals who consume cannabis at high temperatures, as well as compounds produced during intake. This is followed by high dosage of the drug having an opposite effect when compared to low CBD concentrations that have anti-inflammatory effect (12). Joshi *et al*., 2008, reported that Cannabis users have periodontal disease which might be linked to the xerostomia effect which is followed by plaque and calculus build up as a result of inadequate plaque management . Saliva has a critical function in the protection of periodontal tissues. Its reduction produced by cannabis-activated inhibitory systems might have negative consequences (32). This in accordance with Fawad *et al*., 2020 where it was proven that marijuana smokers had a considerably lower salivary immunoinflammatory response than heavy cigarette smokers and non-smokers with periodontitis (25).

Periodontitis progresses and is etiopathogenetic in part because of the inflammatory immunological response. Pro inflammatory cytokines increase soft tissue inflammation and marginal bone loss in inflammatory diseases like periodontitis, as evidenced by the number of sites per individual with a probing depth PD and clinical attachment loss of ≥ 4mm, which is significantly higher among frequent marijuana smokers compared to those who do not use recreational drugs. Cannabis induces an anti-inflammatory response, and it's possible that this impact of bone remodelling is overlapping in periodontal tissues, adding to periodontal deterioration, as demonstrated in Nogueira *et al*, 2011 study in which it was shown that when rats with and without teeth with induced - periodontitis were exposed to Cannabis, bone loss was greater in the teeth

with periodontitis; however, no changes were seen in teeth without periodontitis when exposed to Cannabis (34).

Several biological systems have been proposed as potential modulators of the inflammatory process involved in periodontal disease. Cannabinoids are a new class of mediators that may have a role in the management of this disease (22). Innate immune cells express the cannabinoid receptor CB2, but exogenous cannabinoids have been shown to reduce host resistance to certain pathogenic pathogens such as Listeria monocytogenes. A study conducted by GU *et al*, 2019 was the first to report on the effects of three marijuana-derived cannabinoids THC, CBD and CBN on the innate response to three variant oral pathogens, *P. ginvalis*, *F. alocis* and *T.denticola* in monocytes and epithelial cells in vitro and in mice in vivo. The viability of two critical human innate cell types, epithelial cells and monocytes, was impaired at cannabis dosages above those expected to occur in vivo. These innate cells are critical for detecting bacterial infections and initiating and progressing an inflammatory response capable of protecting or clearing the periodontium from the microbial assault. High dosages of CB receptor agonists have been suggested to be cytotoxic to human periodontal ligament fibroblasts, according to current research. If these phenomena exist in humans in situ, cannabis may potentially act as a risk factor for periodontal disease by impairing the barrier function and the body's natural ability to fight infection (33) .

In a 38–year prospective longitudinal study of a representative birth cohort, which its objective was to test the association between cannabis use over twenty years and a variety of physical health indices at early life, it concluded that Cannabis use when compared to tobacco use, for up to 20 years is associated with periodontal disease but is not associated with other physical health problems in early midlife. Periodontal health was the only component of health in the research that revealed a strong negative relationship in analyses of both persistent and joint years of cannabis usage. This was attributed to post-study findings that cannabis users brushed and flossed less than others and were more likely to be alcoholics. However, even after adjusting for tobacco pack years, childhood health, brushing and flossing, and alcohol dependency, the link between cannabis use and poor periodontal health remained significant (35).

4.3 AGE GROUP MOST AFFECTED BY PERIODONTAL DISEASE FROM CANNABIS RECREATIONAL USE

Given that periodontitis is more common among the elderly, and given the global (particularly in industrialized nations) trend of population aging, a rise in periodontitis prevalence is predicted in the near future (3). Marijuana is the most widely used illegal drug among youth and young adults, with rates increasing for both categories since 2008, with young adults having the greatest rate relative to any other category (36). This might be an early warning sign of periodontal disease in young people since, according to the findings of Thomson *et al*., 2008, regular cannabis usage (defined as once a week or more) more than doubled from the ages of 18 to 26 and subsequently decreased somewhat by the ages of 32 (21). Even though this was speculated, it was reported that researches on adults and the elderly have found that Cannabis has a greater influence than studies on teenagers (3). This might imply that long-term cannabis use is harmful to periodontal tissues and that public health initiatives to minimize cannabis use may enhance the population's periodontal health (21).

5. DISCUSSION

The majority of research found cannabis to be a rapidly growing risk factor for periodontal disease, which is particularly concerning given the rise in marijuana usage (12,21,31,35,37) . The findings suggest that cannabis consumers' periodontal health may deteriorate . It is also important to note that information gathered using the Newcastle-Ottawa scale was indicative of the worst gingival or periodontal conditions in cannabis smokers, with increased clinical attachment loss in frequent users being the most concerning. This suggests that the periodontal risk associated with regular cannabis consumption may be dose dependent (37).

Rat model studies by Napimoga et al., 2009, Noguiero Filho et al., 2011 e Gu et al., 2019 respectfully, all showed cannabis and its derivatives having an impact on the function of immune system. Nogueiro et al., 2011 demonstrated that Cannabis sativa more

specifically its derivative Tetrahydrocannabinol interfered with bone physiopathology (osteoblast and osteoclast activity) increasing bone loss (BL) resulting from ligature-induced periodontitis on the first molar tooth in rats when they were exposed to cannabis smoke for 8 minutes per day for a 30 day period . In the study, all ligated teeth from both groups had BL and a lower BA and BD when compared to unligated teeth (P 0.05), demonstrating the induction of periodontal disease and validating the results of the study. When compared to ligated teeth from the control group and when compared to negative control, which is unligated teeth from the control group, the ligated teeth from the MSI group had the highest BL and the lowest BD (P 0.05). In light of the fact that neither the healthy nor the contralateral control sites in the MSI groups showed any changes in bone, the increased bone loss found in the marijuana group in the periodontitis (ligated) sites could be attributed to impaired immune function during the BL process or even the activation of specific receptors that could lead to increased bone loss (30).

The administration of CBD (cannabidiol), a cannabinoid component extracted from the cannabis plant that does not produce psychoactive effects and has anti-inflammatory properties, on the other hand, was shown to significantly reduce BL in rats suffering from experimental periodontitis, according to Napimoga *et a*l., 2009. According to the findings of this study, such an "anti-inflammatory effect" may be related to drug-induced reductions in bone-related molecules such as receptor activator of nuclear factor-kappa B and receptor activator of nuclear factor-kappa B ligand expression, neutrophil infiltration, and cytokine production at gingival tissue (interleukin-1b and tumour necrosis factor-a) (22,30).

On the order hand, Gu *et al*., 2019 reported on three phytocannabinoid subtypes THC, CBD and CBN and their antimicrobial properties, cytotoxic and immunosuppressive influences of an oral bacteria- exposed human monocytes. CBD, CBN, and THC each suppressed P. gingivalis-induced IL-12 p40, IL-6, IL-8, and TNF release while enhancing the anti-inflammatory cytokine, IL-10, from human innate cells. Similar phenomena were observed in F. alocis- and T. denticola-exposed human monocytes and human gingival keratinocytes. Higher phytocannabinoid doses (≥5.0 μg/ml) compromised innate cell viability and inhibited the growth of P. gingivalis and F. alocis, relative to unexposed bacteria. T. denticola, however, was resistant to all cannabinoid doses tested (up to 10.0 μg/ml). Intense cannabis doses harmed the health of two human innate cell types:

epithelial and monocytes. Innate cells detect bacterial infection and start an inflammatory response to protect the periodontium. These data suggest that cannabis use may change oral bacterial makeup. If phytocannabinoids help some bacterial species survive in the human oral cavity, then marijuana may contribute to the microbial dysbiosis associated with periodontitis (33). It should be noted, however, that animals are not natural users of cannabis and that the majority of trials do not accurately reflect the long-term persistence of human cannabis use (37).

In the epidemiologic studies done, cannabis was seen to be a potential risk factor for periodontal disease as those who participated in the frequent smoking of marijuana where reported to have greater combined attachment loss (CAL). The prospective cohort study done by Thomson *et al*., 2008 they showed that after controlling for tobacco smoking and other significant cofounders, regular exposure to cannabis smoke was substantially related with the frequency and incidence of periodontal attachment loss by age 32 years however there could have been and underestimation due to the study using only 3 sites (mesiobucal, buccal and distolingual) per tooth as opposed to the 6 sites to determine periodontal attachment loss (21). Shariff *et al*., 2017 examined the prevalence of periodontitis in a 1938-person sample 974 had "ever used recreational cannabis" and 465 had "frequent recreational cannabis" (FRC). The FRC group had 1.8mm mean attachment loss while the non-FRC group had 1.6mm ($p = 0.004$) therefore agreeing with Thomson *et al*., 2008 . On the contrary, Lopez and Baelum 2009 investigated a random sample of high school students from the Province of Santiago, Chile. 4.5 percent of the study population had CAL 3mm or less. Also, 18.9% had used cannabis once, and 6% had used it regularly. The findings of the multiple logistic regression analysis showed no link between cannabis usage and CAL 3mm, independent of the tobacco-smoking category studied (38).

Comparing, these researches indicated that regular cannabis smoking had a greater detrimental influence on adults and elders. The three explanations for this seems to be: a) the low incidence of periodontitis in young people reduces the statistical power to detect differences; b) because bone loss is associated with periodontitis, the low prevalence of periodontitis in young people may hide the probable effect of cannabis on bone loss (3) and also most young individuals who smoked cannabis had a short term exposure to the drug.

6. CONCLUSION

In conclusion:

- Recreational usage of cannabis may soon be deemed a risk factor for periodontal disease even after the independent use of tobacco.
- This is due to the drug's possible mechanism of affecting the immune response and reducing periodontal tissue's capacity to recover after disease activity which can be dose dependent and frequent use.
- It is also considered to exacerbate the illness in users who already have it by inducing alveolar bone loss and disorganizing the microbial dysbiosis.
- These characteristics are likely to be seen mostly in adults and elder individual due to young adults having short term exposure with the drug.

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