Influence of cannabis use on periodontal disease: a scoping review

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Abstract

Recent publications suggest the possible association between cannabis (Cannabis sativa) and periodontitis. **Objective**: To analyze the possible influence of cannabis use on periodontal disease, highlighting the available evidence and identifying the associated variables in the studies. **Materials and methods**: We conducted a scoping review applying a structured search method in PubMed/MEDLINE, Science Direct, LILACS, SciELO including publications until May 2017. **Results**: In vivo studies showed greater bone loss in animals exposed to cannabis. Clinical cases show that chronic cannabis use may result in gingival enlargement (with clinical features similar to phenytoin induced enlargement) and localized severe chronic periodontitis. Most of the epidemiological studies confirmed the possible association between cannabis and periodontitis. **Conclusions**: The specific mechanism by which cannabis acts in the gingival tissues is unknown.

Keywords: cannabis, periodontal disease.

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Introduction

Periodontitis is one of the most common chronic diseases, with a high prevalence that varies according to each population group[1,2]. It affects approximately 46% of adults in the United States of America[1]. In turn, a recent *global burden* report showed that over 11% of the world's population presents severe forms of the disease[2]. In Latin America, almost 10% of the young population is affected by periodontal disease, and approximately 35% of children have gingivitis, with the highest prevalence rates in Colombia (77%) and Bolivia (73%)[3]. In adults, periodontitis affects up to 62.6% of individuals[4]. In Uruguay, data from the First National Survey of Oral Health showed that among young people (15 to 24), the percentage of individuals with no signs of bleeding, with absence of tartar and probing depth (PD) ≥ 4mm was close to 30%[5]. Similarly, individuals aged between 35 and 44 had a 16.5% prevalence of moderate and 5.9% prevalence of severe periodontal disease respectively[6]. The highest prevalence was found in individuals aged between 65 and 74, where 34.7% had moderate periodontitis and 17% severe periodontitis[6]. These results emphasize the importance of prevention and treatment in oral health programs[7].

Periodontal disease is mainly characterized by gingival inflammation, formation of periodontal pockets and destruction of the supporting tissues (alveolar bone and periodontal ligament)[8]. It is the result of the interaction of microbial biofilm (necessary etiological factor but insufficient in itself), a susceptible host and modulating factors[9]. Several studies have shown the existence of risk factors, among them tobacco[10], diabetes[11–14], obesity/overweight[15,16] and genetic factors[17,18]. These elements modulate the host's susceptibility or resistance with each microbial challenge[9].

Recent publications suggest a possible association between cannabis (*Cannabis sativa*) and periodontitis. However, the use of cannabis components could have positive effects as they might reduce inflammatory processes[23]. If we consider the increase in the prevalence of cannabis use throughout the world (16% in the United States, 11% in France and 9% in Uruguay)[24], it is essential to research the possible effects of cannabis on the oral cavity and periodontal tissues in order to understand its role in the onset of periodontal disease and to develop and lead appropriate public health policies.

Therefore, the aim of this scoping review is to analyze the possible influence of cannabis use on periodontal disease, surveying the available evidence and identifying the associated variables in the studies.

Methodology

Study design: The scoping review involves a systematic search but does not imply an analysis of the methodological quality of the studies. This review presents a summary of the articles available in the literature by providing an overview of the existing content, setting future research paths and pointing to the gaps in the literature[25,26].

Search strategy: We conducted a scoping review applying a structured search method in PubMed/MEDLINE, Science Direct, LILACS, and SciELO including publications until May 2017. We used keywords and controlled terminology (MeSH terms) based on questions structured according to the PICO Model: "What is the possible influence of cannabis use on periodontal disease?" where we defined:

Population: individuals with periodontal disease.

Intervention: cannabis use

Control: individuals who do not use cannabis

Result: Periodontal disease alteration

In this way, the following search strategy was implemented: (periodontal disease OR periodontitis OR gingivitis OR gingival disease) AND (cannabis OR marijuana). All study designs on humans and animals were included.

Study selection and eligibility criteria: Four researchers participated in the paper search (MM, AF, LC and EA) for the review design, and were advised by a librarian. The records were entered into EndNote (Thomson Reuters, Rochester, New York, NY, USA) to eliminate duplicates and create a virtual library. The researchers read and filtered the titles and abstracts for all records that complied with the predefined criteria. No language or year restriction was applied. All original papers were included. Letters to the editor, *in vitro* articles and reviews were not included in this review. Additionally, the references of each paper were traced in order to broaden the search.

Results

A total of 260 records were obtained from the search, of which 65 articles remained after removing duplicates. After reading titles and abstracts, 10 articles were selected to read the full text. Two of these articles were excluded[27,28]. The reasons for exclusion are presented in figure 1. Finally, eight articles met the inclusion criteria and were included in this review (Figure 1).

***In vivo* studies:** Studies on mice evaluated the influence of the inhalation of cannabis and cannabidiol (CBD) on periodontal disease measuring attachment loss and bone density. Increased bone loss and lower bone density were observed in mice exposed to cannabis or cannabidiol, which shows that these substances can negatively influence periodontal tissues.

Clinical cases: Two clinical cases were included in this review[29,30]. These articles show that long-term cannabis consumption may lead to gingival enlargement with clinical features similar to the ones caused by phenytoin,[30] in addition to chronic localized severe periodontitis[29].

Epidemiological studies: four epidemiological studies were retrieved. Table 1 shows the main features of the studies. The methodological design of most studies was cross-sectional[19,20,31], and there was a prospective study from a cohort of births[27]. Fifty percent of the studies were population-based[19,27], while one was conducted with high school students[20] and another with aboriginal communities from Australia. Three of the four studies were conducted on adults[19,27,31], while only one evaluated adolescents[20]. Similarly, Shariff et al. [19] included patients with diabetes and previous periodontal treatment, while Lopez et al. [20] were the only ones that evaluated the patients' oral hygiene habits.

Although cannabis exposure and the classification of periodontal disease have been categorized differently in the studies reviewed, cannabis use is linked to periodontal disease (Table 2). We observed a significant association between cannabis use and prevalence of periodontitis[21,31], where cannabis users had a prevalence of periodontal disease 44% higher than that of non-users[31]. Similarly, population data from the United States National Health and Nutrition Examination Survey showed that the recreational use of cannabis was associated with advanced probing depth and clinical attachment loss[19]. Additionally, a study conducted on Chilean students found a Necrotizing Ulcerative Gingivitis (NUG) odds ratio that was 53% lower in individuals

who had never used cannabis compared to frequent users[20]. The other associations were not statistically significant[20].

Influence of cannabis on periodontal disease: Table 1 shows the impact of cannabis on periodontal disease according to the action of its chemical components. Authors state that the causes of chronic inflammation in patients that use cannabis are the high temperatures and chemicals released during the consumption, followed by the clinical symptoms of xerostomy (as it has parasympatholytic properties), which would enhance the pathological effect[32]. We must remember that cannabis components that are not cannabinoids (products of combustion) are similar to those in tobacco and can have local and systemic effects [21,22,33]. Only low CBD concentrations can have an anti-inflammatory effect, while high doses would have the opposite effect[34].

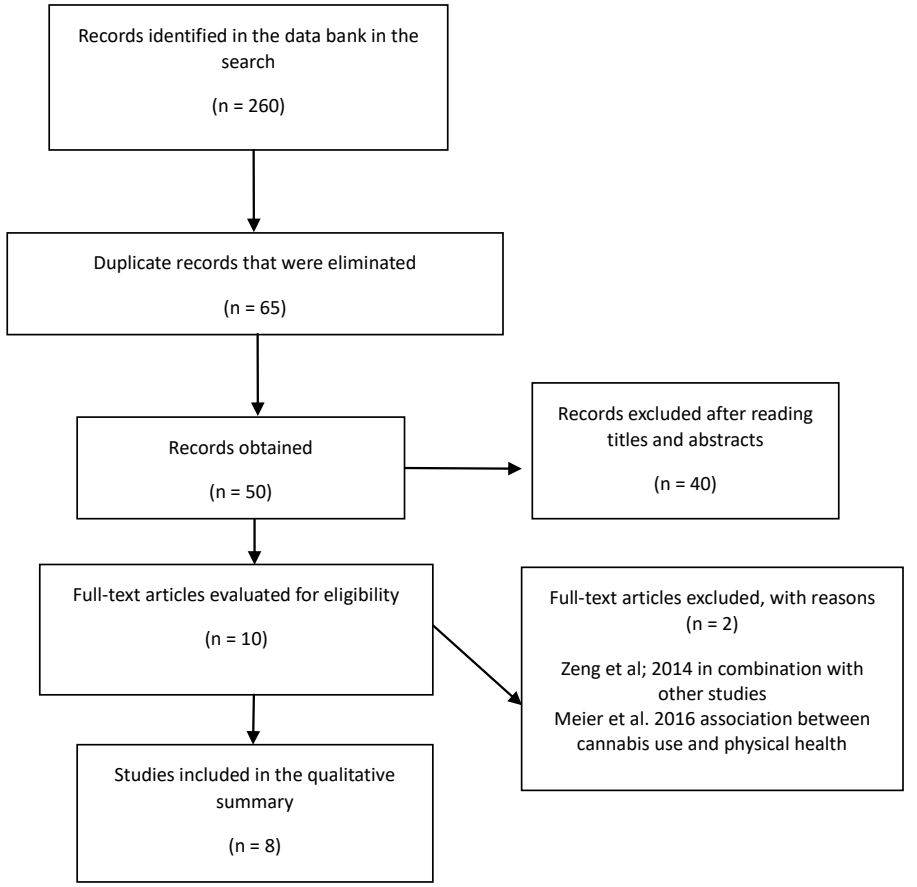

Figure 1: Flow chart showing the articles included.

Table 1. Chart comparing the epidemiological studies conducted to date. Relevant variables are identified to create a standardized research protocol to compare results.

	Thomson et al 2008	López et al 2009	Jamieson et al. 2010	Shariff et al. 2016
Number of patients	903	9203	425	1938
Country	New Zealand	Chile	Australia	United States of America
Study design	Prospective (cohort)	Cross-sectional	Cross-sectional	Cross-sectional
Population	Population-based study	High school students	Aboriginal communities	Population-based study
Age*	Adults aged 26 to 32	Adolescents aged 12-14; 15-17; 18-21	Adults over 18	Adults aged 30 to 49
Probing depth	Si	Si	Si	Si
Gingival recession	Si	Si	Si	Si
Clinical attachment loss	Si	Si	Si	Si
% bleeding	No	No	No	No
Tobacco **	Si	Si	Si	Si
Cannabis **	Si	Si	Si	Si
Diabetes	No	No	No	Si
Previous periodontal treatment	No	No	No	Si
% Plaque	Si	No	No	No
Oral hygiene habits	No	Si	Si	No

***Over 18 years of age. **Frequency, amount, and time elapsed since start of consumption, recreational or medical use.**

Table 2. Summary of clinical studies aiming to prove the association between presence of periodontal disease and cannabis consumption

Author	Cannabis exposure	Periodontal record	Periodontal disease
	Association / Quality of the study		
Thomson 2008	"No exposure", "Moderate exposure", "High exposure"	3 sites / 2 quadrants (26 years old) - Full mouth (32 years old) (except 3rd molars and implants)	CAL ≥ 3mm
	Strong association between cannabis use and prevalence of periodontitis		
López 2009	"Never used cannabis", "Regular use of cannabis"	6 sites/Incisors, 1st and 2nd molars	CAL ≥ 3mm, NUG.
	An association was found only when cannabis had never been used and with a lower NUG prevalence. There was no association for any other case		
Jamieson et al. 2010	"Never used or used only once" "Occasional use" "Frequent use"	2 sites/Full mouth (except 3rd molars and implants)	PD ≥ 5mm and CAL ≥ 4mm (moderate periodontitis)
	Cannabis users had a 44% higher prevalence of periodontal disease that individuals who do not use cannabis.		
Shariff 2016	"Never used" (Non-FRC) "Used every month for a year" (FRC)	6 sites/Full mouth (except 3rd molars and implants)	PD ≥ 4mm and CAL ≥ 3mm (incipient periodontitis)
	A strong association was found for FRC and presence of PD and CAL compared to non-FRC users.		

CCL: Clinical crown lengthening; PD: Probing depth; CAL: Clinical attachment loss; NUG: Necrotizing Ulcerative Gingivitis; FRC: Frequent recreational cannabis. Non-FRC: Non-frequent recreational cannabis.

Chart 1 Graphic description of the possible impact of cannabis on periodontal disease according to the action of its chemical components.

Tobacco	Cannabis
Nicotine (↑ Inflammation)	CBD (↓ Inflammation)
Combustion compounds (↑ Inflammation)	Combustion compounds (↑ Inflammation)

Discussion

This work is the first scoping review that analyzes the connection between periodontal disease and cannabis consumption as it summarizes the evidence available. Eight articles were included, ranging from animal studies and clinical cases to observational (prospective and cross-cutting) studies, and indicating an influence and possible association of individuals who use cannabis and periodontitis. As this is a very important public health issue, health services should raise awareness of the risk that regular and occasional cannabis users run of having this pathology.

Cannabis sativa L. (hemp), has been known for many years for the use of its fibers in the textile industry, for clothing, material constructions and paper[35,36]. It was only in 1930 that isolated compounds called *cannabinoids* were isolated from cannabis. The most abundant ones within the extract are: Delta-9-tetrahydrocannabinol (THC), which has the strongest psychoactive effect, its precursor, cannabidiol, as well as cannabiol, a catabolic THC product formed spontaneously. These last two lack THC's psychoactive effect, but have been found to have anticonvulsant properties[35,37].

Currently, there are different types of cannabinoids according to their origin: 1) phytocannabinoids, derived from the cannabis plant; 2) endogenous cannabinoids (endocannabinoids), produced by the body itself of humans or other animals and 3) synthetic cannabinoids, with an identical chemical composition, but produced in the laboratory[38]. The characterization of these and other derivatives, as well as the receptors they interact with, have improved our understanding of the Endocannabinoid System[35,39].

THC is the major psychoactive constituent and participates as a partial agonist for cannabinoid receptor type I (CB1) and type II (CB2). CBD is not psychoactive and is an antagonist for CB1 and CB2. It acts in multiple other receptors and may be an agonist for some systems[39]. The pharmacological effects of CBD are mediated by G-protein-coupled receptors, CB1 and CB2. When activated, CB1 receptors inhibit sympathetic transmission by acting on voltage-gated calcium and potassium channels, which are known to modulate epileptiform activity and seizures. CB2 receptors are primarily expressed in the immune system and have limited expression in the central nervous system. The effects of CBD are CB2 receptor-independent[40,41]. Thus, cannabis is usually smoked, vaped or consumed orally in the form of foods, teas or capsules[41].

In this way, approximately 3.8% of the world's population consumed cannabis in 2014 (183 million people): Iceland has the highest figure (18.3% of the population over the last 12 months), followed by the United States (16.2%), Chile in the fifth position (11.83%), France in the sixth (11.1%), and Uruguay coming in eleventh with 9.3%[42]. According to the World Drug Report 2011 (annual United Nations Office publication), in 2006, 14.8% of young people in Uruguay had consumed cannabis in the previous year, while only 6% of adults had used it[43]. The Final Report of the 5th National Household Survey on Drug Use of 2011 published by the National Drug Board

in 2016[44] shows that since 2011 Uruguay has had an increase of three percentage points in marijuana consumption. This is the most widely used substance in the population after alcohol, tobacco and sedatives. Twenty-three percent of the people between the ages of 15 and 65 have used marijuana some time in their lives, and 9.3% say they used it in the last 12 months (161,000 people), and 6.5% in the last 30 days. There are 21,355 daily marijuana users in Uruguay.

Although cannabis is considered a "soft" drug which is only as harmful as coffee or tobacco, cannabis use can cause chronic secondary effects, such as periodontal disease[21,32]. The temperature of the combustion smoke is higher than that of cigarettes[30]. The lesions reported are similar to those of tobacco users, but always less severe[30]. Both acute and chronic consumption lead to nicotine stomatitis and uvulitis[30]. This connection between tobacco and cannabis is even closer: a study reports that not all tobacco users smoke cannabis, but 90% of cannabis consumers smoke tobacco[45]. This makes it difficult to independently diagnose the effects of both types of substances in the studies. This is why some reports conduct statistical analyses also with individuals who do not smoke tobacco, and the association with periodontal pathologies remains[19]. As most individuals who smoke cannabis also use tobacco[31], this may enhance the harmful effects of both drugs.

Multiple studies show the association of cannabis with high levels of oral biofilm, dental caries, candida albicans (but not candidiasis)[41], leukoedema, leukoplakia[46] and stomatitis[37,41]. In addition, excessive exposure to cannabis was associated with an increase in respiratory diseases and in the prevalence of cancer of the oropharynx[39]. Reports indicate that 58.3% of women and 47.4% of men reported pulpitis during cannabis consumption. Pulpitis could be added to the list of adverse vascular effects associated with cannabis use already reported (conjunctivitis, tachycardia, hypotension, angina pectoris)[47,48]. Thus, it is important to note that only low concentrations of CBD can have an anti-inflammatory effect and that high doses are harmful[34]. In the case of oral cancer, proinflammatory and carcinogenic compounds have been found in cannabis smoke, similar to the composition found in tobacco smoke, including carbon monoxide[22,33,49,50].

THC and CBD stimulate the release of prostaglandin E2 (PGE2) from synovial cells and inhibit the *in vitro* synthesis of leukotrienes of human nuclear polymorphic cells[51]. Additionally, it has also been reported that CBDs suppress proinflammatory mediators[52–54] such as IFNγ (gamma interferon), FNT-α (tumor necrosis factor-alpha), IL-1b (interleukin 1 beta)[55] and IL-10 (interleukin 10)[56]. In another study, where CBD doses were systemically injected in rats, researchers concluded that they are an emerging class of mediators that might participate in the control of periodontal pathologies as they help reduce inflammation[57]. Contrary to these findings, other authors conducted the same clinical trial, noting increased bone loss in the furcation area of the teeth with induced periodontitis. However, no effect was noted on periodontally healthy sites, which could be related to an alteration of the immune function during the bone resorption process, or even the activation of specific receptors that could increase bone destruction[58]. In this sense, there has been some speculation regarding the endocannabinoid system, which could play a role in the regulation of bone metabolism[59,60].

In addition, we identified specific receptors for this substance in periodontal tissues, which was followed by an increase in the release of anandamide, an agonist for the cannabinoid receptor derived from arachidonic acid[61]. Other studies confirm these data: the relationship between the endocannabinoid system (receptors and mediators produced by our body) and periodontal disease was studied, and researchers detected a proliferation of gingival fibroblasts when the system was activated, suggesting a

new path for periodontal disease therapy[62,63]. A recent study shows how human gingival mesenchymal stem cells that were pre-treated with CBD before the transplant increase their survival rate in the host as they modulate their immune and inflammatory response[41,64].

In turn, in 2012 Rawal et al.[63] described two clinical pictures in patients and consumers. The features that always appeared were inflammation of papillae and gingival margin, with presence of nodular areas, similar to those in patients that consume dilantin (phenytoin), mainly in anterior teeth. Their analysis is very interesting as they find possible coincidences in these clinical pictures, finding similarities in the chemical components of both substances: 1) cannabidiol (CBD) is also used as an anticonvulsant, 2) CBD may increase the effects of phenytoin and phenobarbital, 3) CBD and phenytoin have a similar structure, displaying rings in the same pattern. The authors conclude that both comply with the stoichiometric requirements suggested for the action of an anticonvulsant, deducing that inflammation may be caused by the same mechanism[63].

In 2016, Momen-Heravi et al. reported the case of a 23-year-old female patient diagnosed with periodontal disease. The patient reported daily use of cannabis for three years. The author recounts inflammation of papillae and gingival margins, mainly at the anterior region of the mandible, where the cannabis cigarette was placed. The X-ray showed loss of alveolar bone in that area[29]. Regarding the treatment, the authors recommend behavior modification and non-surgical and surgical therapy for the successful management of cannabis-related periodontitis[29].

In this context, the first epidemiological study that analyzed the relationship between cannabis use and periodontal disease was conducted in 2008 by Thomson et al.[21] in New Zealand. The population was made up of adults born in a hospital in the country in 1972 and 1973. The periodontal clinical examination was performed on two occasions, at ages 26 and 32. The recording system included two quadrants on three sites per tooth, examining Gingival Recession (GR), Probing Depth (PD) and Clinical Attachment Loss (CAL). Cannabis exposure was assessed applying a self-report methodology. From this information, three groups were obtained: 1) no exposure 2) low exposure (1-40 times in the previous year) and 3) high exposure (over 41 exposures in the previous year). The study also enquired about socioeconomic status, tobacco use, sex, reason for attending the dental clinic, and biofilm accumulation[21]. Of the patients, 32.3% had not consumed cannabis in the previous year, and 47.4% and 20.2% had done so at low and high exposure rates respectively. Most consumers were men, of low socioeconomic status and who rarely sought dental care, with significant levels of bacterial plaque[21]. This confirms the previous findings that show these individuals tend not to worry about their health, which in turn can be linked to oral pathologies[32]. Of the patients, 33% were tobacco smokers and 17% ex-smokers. This is consistent with Fairman[45] in that frequent cannabis consumers were also tobacco users, and as age increased, tobacco consumption increased too[32].

The reported results show that cannabis use was strongly associated with the prevalence of periodontitis, with the greatest differences found in PD $\geq$ 5mm. However, no association was found between the consumption of both substances at the same time and periodontal disease. According to Thomson, the use of cannabis may be a risk factor for periodontal disease when used independently from tobacco, and as age increases so do prevalence and incidence[21].

The association with Necrotizing Ulcerative Gingivitis (NUG) was also researched on a sample of adolescents. In this case, six sites were measured and observed in the incisors and second molars, and the NUG diagnosis was made[20]. Like Thomson et al., they found that it was a limitation not to know the dose and

length of cannabis use, as the questionnaire included "never consumed" or "regular consumption" with 18.9% and 6% respectively. Of the regular consumers, only 16.3% were smokers, contrary to what Thomson et al. and Fairman found. The NUG diagnosis did not consider pain or bleeding, hence its high prevalence compared to other studies; no association with cannabis consumption was found[20,21,45].

In turn, in 2016, Shariff observed the same in adults in the United States, where 26.6% were frequent cannabis users. From that group, 29.2% had PD ≥ 4mm, 24.8% PD ≥ 6 mm and 24.5% PD ≥ 8mm, comparing these data to that of non-frequent users: 22.3%, 19.2% and 18.9%. They concluded that frequent cannabis use is associated with increased probing depth and gingival recession, as well as higher likelihood of severe periodontitis[19].

Although the studies have varying methodologies, *in vivo* studies, clinical cases and epidemiological studies seem to indicate an association between cannabis use and periodontal disease; this may increase bone loss, exacerbating or initiating periodontitis. These authors recommend including the variables there presented (Table 1) to achieve a standardized research protocol, non-existent so far, to be able to compare the results of different studies conducted in the future. The authors recommend that further epidemiological studies, preferably prospective or case-control studies, be conducted, since clinical trials would be ethically unacceptable. In addition, it is important that future research include statistical analyses, checking if individuals are tobacco users in order to reduce any potential bias. The results of this review should be interpreted with caution since they are based on studies that apply very different methodologies.

Conclusions

The specific mechanism by which cannabis acts on gingival tissues is unknown due to the insufficient number of studies conducted so far and the differences in methodologies and in the populations studied. However, cannabis consumption seems to make periodontal disease worse. This is why health services should take action to raise awareness of the strong likelihood of regular cannabis users having this pathology.

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