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Review Article

Endocannabinoid system and periodontitis: mechanisms and therapeutic implications

Sistema endocanabinoide e periodontite: mecanismos e implicações terapêuticas

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Resumo

Introdução: A periodontite é um importante problema de saúde pública. Embora o princípio da terapia da periodontite esteja focado principalmente na remoção do biofilme dental e dos fatores associados, sua fisiopatologia registra diferentes eventos moleculares e inflamatórios relacionados ao sistema imunológico do hospedeiro, como a participação do sistema endocanabinoide. **Objetivo:** Esta revisão teve como objetivo explorar e elucidar os mecanismos e papéis do sistema endocanabinoide na fisiopatologia da periodontite e suas possibilidades para futuras terapias relacionadas. **Material e método**: Realizou-se uma busca eletrônica na plataforma PubMed por estudos envolvendo a ação do sistema endocanabinoide sobre a periodontite. **Resultado**: Dezenove estudos clínicos e pré-clínicos foram incluídos nesta revisão narrativa. **Conclusão:** Os receptores canabinoides tipo 1 e 2 são componentes integrais do sistema endocanabinoide e manifestam-se de várias formas nos tecidos periodontais. As ações e mecanismos através dos quais os receptores canabinoides são ativados em locais saudáveis ou inflamados continuam a ser o foco de investigações em curso. Além disso, os fitocanabinoides e canabinoides sintéticos apresentam potencial como tratamentos, com estudos pré-clínicos indicando benefícios na redução da inflamação e na facilitação da reparação dos tecidos.

Descritores: Canabinoides; receptor CB1 de canabinoide; receptor CB2 de canabinoide; inflamação; periodontite.

Abstract

Introduction: Periodontitis is a major public health problem. Although the principle of periodontitis therapy is mainly focused on removing dental biofilm and associated factors, its physiopathology enrolls different molecular and inflammatory events related to the host immune system, as the participation of the endocannabinoid system. **Objective:** This review aimed to explore and elucidate the mechanisms and roles of the endocannabinoid system on periodontitis physiopathology and its possibilities for future related therapies. **Material and method**: An electronic search was carried out on the PubMed platform for studies involving the action of the endocannabinoid system on periodontitis. **Result**: Nineteen clinical and preclinical studies were included in this narrative review. **Conclusion:** Cannabinoid receptors type 1 and 2 are integral components of the endocannabinoid system, manifesting in various forms in the periodontal tissues. The actions and mechanisms through which cannabinoid receptors are activated in healthy or inflamed sites remain the focus of ongoing investigations. Moreover, phytocannabinoids and synthetic cannabinoids show therapeutic potential, with pre-clinical studies indicating benefits in reducing inflammation and facilitating tissue repair.

Descriptors: Cannabinoids; CB1 receptor; CB2 receptor; inflammation; periodontitis.

INTRODUCTION

Periodontitis (PD) is a chronic inflammatory multifactorial disease associated with the presence of a dysbiotic biofilm[1,2]. Characterized by progressive destruction of the tooth-supporting apparatus, if untreated, PD may lead to tooth loss, although it is treatable and preventable in most cases[3-5]. Furthermore, its importance is highlighted as a major public health problem, being the most common chronic inflammatory non-communicable disease of humans[3,6].

Although the principle of PD therapy mainly focuses on removing dental biofilm and associated factors, its physiopathology enrolls different molecular and inflammatory events related to the host immune system[7,8]. The activation of innate immune mechanisms by different receptors, such as Toll-like receptors (TLRs), are not only capable of recognizing pathogen-associated molecular patterns (PAMPs) but also modulating downstream signaling cascades, resulting in the activation of different transcription factors, such as nuclear factor-kappa B (NF-κB)[7,9,10]. Finally, these events are signaled by cytokine networks and different molecular mediators that dictate disease progression. These characteristics and events of PD highlight the importance of mechanisms related to the inflammatory response and its modulation for new insights and therapies[11,12].

Recently, much has been discussed about the role of the endocannabinoid system (ECS) and the action of the phytocannabinoids in human health and inflammatory processes[13-15]. The ECS comprises endocannabinoids, cannabinoid receptors (CBs) type 1 (CB1) and type 2 (CB2), and enzymes governing endocannabinoid metabolism, offering a finely tuned regulatory apparatus[13,16]. Endocannabinoids are lipidic mediators deriving from arachidonic acid, synthesized in a stimulus-dependent manner, engaging cannabinoid receptors, expressed on immune cells and pertinent cell populations[17,18]. This interaction can elicit the regulation of proinflammatory cytokines production and immune cell activation, with potential interest in new investigations on PD inflammatory processes and new therapies focused on host immune modulation[19-21].

This review aims to explore and elucidate the mechanisms and roles of the ECS on PD physiopathology and its possibilities for future related therapies.

LITERATURE REVIEW

Cannabinoid Receptors and Periodontitis

Cannabinoid receptors, CB1 and CB2, are integral components of the ECS and are present in the periodontal tissues[19]. Belonging to the family of G protein-coupled receptors (GPCR) on the surface of cell membranes, they are found in inactive and active functional states. Once activated, these receptors modulate the release of pro-inflammatory cytokines[22,23].

CB1 receptors, although also present in periodontal tissues, are primarily concentrated in the central nervous system[22]. When activated by endocannabinoids or exogenous ligands like tetrahydrocannabinol (THC), CB1 receptors interact with Gαi/o proteins, leading to the inhibition of adenylyl cyclase and subsequent reduction in cyclic AMP (cAMP) levels[24]. This action results in the dampening of intracellular signaling pathways, influencing neurotransmitter release and synaptic transmission[25]. The Gαi/o protein coupling also activates mitogen-activated protein kinases (MAPK) and protein kinase B (Akt) pathways, contributing to the regulation of not only synaptic plasticity and neuronal function but also participating of immune response and inflammation processes by the triggered pathways[26].

CB2 receptors, however, are primarily found on immune cells and in peripheral tissues that interact with Gαi proteins to modulate various immune responses and inflammatory processes[27,28]. It is reported that the activation of CB2 receptors is also capable of inhibiting adenylyl cyclase activity, reducing cAMP levels, but leading to a decrease in protein kinase A (PKA) activation, contributing to the dampening of immune cell activation and cytokine release[29].

Confirming previous findings in the literature, Liu et al.[30], reports that CB1 receptors are located sparsely in the periodontal tissues of healthy mice, with more concentration in perivascular cells and some infiltrated cells in the gingival epithelium. CB2 distribution, in turn, is widely expressed in the periodontal tissues at more abundant levels, from the junctional epithelium, gingival connective tissue, and PDL until the alveolar bone surface. These characteristics and distributions of CBs are aligned with the information that CB1 is more present in the central nervous system, and CB2 in peripheral tissues[22,27,28].

Moreover, it is demonstrated that CB2 activation on human periodontal ligament fibroblasts (hPDLF) is also related to other downstream transcriptional and signaling effectors, such as NF-κB, jun N-terminal kinase (JNK), c-Jun (activator protein-1, AP-1), extracellular signal-regulated kinase (ERK), p38, and cAMP response element-binding protein (CREB)[31-33]. The interaction of CB2 receptors with G-proteins plays a crucial role in regulating the immune system, positioning it as a potential therapeutic target for inflammatory conditions such as PD[21,34].

Two recent clinical cross-sectional studies have described the presence and activation of CB1 and CB2 receptors in gingival biopsies of periodontitis patients[21,34]. According to, Ataei et al.[34], gene expression analyses by real-time quantitative polymerase chain reaction (RT-qPCR) resulted in significantly lower expression of CB2 receptors in periodontitis patients' biopsies compared with healthy patients. Besides, the expression of CB1 was not significantly different in both groups of patients in this study.

Conversely, Pellegrini et al.[21] reported by immunohistochemistry analyses that the number of CB1 and CB2 receptors in inflamed sites of recurrent periodontitis patients were significantly higher than in those with non-recurrent disease and in healthy subjects. Results from the autoradiography for G-protein detection of activated CBs, however, reported that inflamed sites of recurrent periodontitis patients had significantly lower CBs receptor activation than those of healthy subjects.

Combined, these results indicate that the activation of CB receptors might provide a protective effect on periodontal tissues since they were more expressed in healthy individuals, mostly CB2, and dysregulated in periodontitis patients[21,34]. Furthermore, according to the authors, the increased CB expression in recurrent PD patients might indicate a higher susceptibility of the tissues to activate the protective cellular/molecular mechanisms against inflammatory stimuli, but ineffectively[21].

Conversely, Konermann et al.[35] describe more immunohistochemical staining of CB1 than CB2 receptors in PDL cells of healthy individuals. In periodontitis patients, while there is no variation in CB1 levels, CB2 receptors are more expressed than in healthy individuals. Furthermore, Alves et al.[36] reported that external stimuli, like electroacupuncture, could reduce bone loss in the furcation of experimental periodontitis animals by enhancing CB2 activity.

These pre-clinical and clinical findings and inconsistencies highlight the importance of new investigations on the presence and activation of CBs in inflammatory sites of periodontitis. While remains ambiguous about the number, type, and activation of CBs in healthy or periodontitis sites, their better understanding might help in the future detection of inflammatory processes initiation and susceptibility to PD recurrence, such as in the treatment of the disease itself by administration of local or systemically cannabinoids[21,34]. Furthermore, little is still known about the action of the ECS in the osseointegration process of dental implants or peri-implantitis.

Cannabinoids and Periodontitis

Cannabinoids are considered a broader category of compounds that include those found in the cannabis plant (phytocannabinoids) and those produced synthetically[13]. Endocannabinoids, in turn, are a specific type of cannabinoids produced endogenously within the body and represent a class of lipid signaling molecules that serve as central components of the ECS[16,18]. These endogenous compounds play a crucial role modulating a diverse array of physiological processes,

with a complex signaling network that relies on the interactions between endocannabinoids and specific cannabinoid receptors (CB1 and CB2)[13]. Two primary endocannabinoids, AEA and 2-AG, also present in periodontal tissues, have been extensively characterized (Table 1)[19,20,39].

Table 1. Included studies on ECS and PD

Reference (Year)	Study design	CB receptor	Cell line	Animal model	CB agonist / test drug	Main findings
Nakajima et al.[19] (2006)	*In vitro*	CB1 and CB2	HGF	-	AEA	AEA significantly reduced the production of IL-6, IL-8, and MCP-1 induced by P. gingivalis LPS in HGFs, attenuated by AM251 and SR144528. AEA blocked LPS-triggered NF-kB activation.
Kozono et al.[20] (2010)	*In vitro*, *In vivo* and Clinical cross-sectional	CB1 and CB2	HGF	Oral wounds / rats	AEA; CP55940; 2-AG	Upregulation of the expression of CB1/CB2 receptors in wound-healing model. Proliferation of HGFs by AEA were attenuated by AM251 and AM630. CP55940 induced phosphorylation of ERK 1/2, p38MAPK, and Akt in HGFs. Wound closure by CP55940 in an *in-vitro* scratch assay was significantly suppressed by inhibitors of MEK, p38MAPK, and PI3-K. Increase in AEA levels in the gingival crevicular fluid after periodontal surgery in human patients with periodontitis.
Qian et al.[27] (2010)	*In vitro*	CB2	hPDL	-	HU-308	HU-308 enhanced the mRNA levels of osteogenic genes. Expression of the OPG was up-regulated, whereas RANKL expression was downregulated. Accelerated mineralization was observed in hPDL cells with HU-308.
Ossola et al.[37] (2012)	*In vivo*	CB1	-	LPS-induced periodontitis / rats	Meth-AEA	Topical Meth-AEA significantly diminished alveolar bone loss. Reduction of biological mediators of periodontal disease augmented by LPS.
Rettori et al.[38] (2012)	*In vivo*	CB1 and CB2	-	Ligature-induced periodontitis + immobilization stress / rats	AEA	Local injection of AEA decreased corticosterone plasma levels and the content of the cytokines TNF-α and IL-1β in gingival tissue in periodontitis-stress groups. AEA-induced inhibitions were mediated by CB1 and CB2.
Özdemir et al.[39] (2014)	*In vitro*	CB1 and CB2	hPDL	-	AEA; 2-AG	hPDL viability was significantly increased by AEA in the presence of P. gingivalis LPS. In P.gingivalis LPS stimulated hPDL, AEA down-regulated gene-expression and protein production of IL-6, IL-8, and MCP-1.
Ossola et al.[40] (2016)	*In vivo*	CB2	-	LPS-induced periodontitis / rats	HU-308	HU-308 attenuated alveolar bone loss resulted by LPS-induced periodontitis, and reduction of inflammatory mediators augmented in LPS-injected rats (iNOS, TNF-α, and PGE2).

Table 1. Continued...

Reference (Year)	Study design	CB receptor	Cell line	Animal model	CB agonist / test drug	Main findings
Konermann et al.[35] (2017)	*In vitro*, *In vivo* and Clinical cross-sectional	CB1 and CB2	hPDL	Mechanically-induced root resorptions	-	CB1 expression was significantly higher in healthy PDL structures compared to CB2. Bacterial inflammation affected a decrease in CB1, but an increase in CB2.
Abidi et al.[31] (2018)	*In vitro*	CB2	hPDLF	-	AEA, HU-308	LPS, TNF-α, and IL-1β increased IL-6 and MCP-1 production, which were inhibited by AEA, SMM-189, and HU-308. AEA alone significantly increased IL-6, but not MCP-1 levels.
Alves et al.[36] (2019)	*In vivo*	CB1 and CB2	-	Ligature-induced periodontitis / rats	Electroacupuncture	Increased bone loss in the furcation of experimental periodontitis (EP) and experimental periodontitis-electroacupuncture (EA) - sham groups. Enhanced CB2 immunolabeling was observed in the periodontal tissues in the EP-EA group when compared to the EP and EP-EA-sham groups.
Gu et al.[24] (2019)	*In vitro* and *In vivo*	CB2	TIGK; CD14+ human monocytes	Gavage Infection Model / knockout $CB2^{-/-}$ mice	CBD; CBN; THC	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.
Liu et al.[30] (2019)	*In vitro* and *in vivo*	CB1 and CB2	hPDLF	Periodontal tissue biopsies / mice	THC	Both CB1 and CB2 were expressed in periodontal tissues but with different expression patterns. THC promoted periodontal cell wound healing by inducing hPDLF cell adhesion and migration. The effect of cannabinoids on periodontal fibroblast cell adhesion and migration was mainly dependent on the CB2.
Yan et al.[41] (2019)	*In vitro*	CB1	PDLSC	-	R-1 Meth	CB1 overexpression or R-1 Meth promoted the osteo/dentinogenic differentiation of PDLSCs. Deletion of CB1 or the application of AM251 repressed the osteo/dentinogenic differentiation of PDLSCs. The activation of CB1 enhanced the TNF-α- and INF-γ-impaired osteo/dentinogenic differentiation potential in PDLSCs. CB1 activated p38 MAPK and JNK signaling and repressed PPAR-γ and Erk1/2 signaling.
Abidi et al.[32] (2020)	*In vitro*	CB2	hPDLF	-	AEA, HU-308	AEA exhibited pro-inflammatory and anti-inflammatory effects. CB2R ligands attenuated p-p38 and p-NFκB, but a late rise in p-38 was seen with HU-308.

Table 1. Continued...

Reference (Year)	Study design	CB receptor	Cell line	Animal model	CB agonist / test drug	Main findings
						As p-ERK levels declined, a significant increase in p-ERK was observed later in the time course by synthetic CB2R ligands. P-JNK was significantly affected by SMM-189 only, while p-CREB was elevated significantly by CB2R ligands. HU-308 affected both cAMP and β-arrestin pathway. SMM-189 only stimulated cAMP.
Ossola et al.[42] (2020)	*In vivo*	CB2	-	LPS-induced periodontitis / rats	HU-308	Rats subjected to experimental periodontitis showed higher bone resorption areas, number of osteoclasts and gingival content of prostaglandin E2 than controls, while HU 308 prevented, the deleterious effects.
Zhang et al.[43] (2020)	*In vitro*	CB1 and CB2	hPDL	-	Meth-AEA	Meth-AEA significantly inhibited P. gingivalis LPS-induced production of IL-6, IL-8, and MCP-1.
Abidi et al.[33] (2022)	*In vitro*	CB1 and CB2	HGF	-	CBVN; CBG; CBD	In IL-1β-stimulated HGFs, PGE2 production was significantly suppressed by CBG and CBVN. CBD and CBG elevated PGE2. IL-β-stimulated HGF with pCBs significantly reduced INF-ɣ, TNF-α, and IL-2. Suppression of IL-4 was seen with CBD and CBVN, while only CBVN exerted suppression of IL-13. pCBs significantly increased IL-6, IL-10, and IL-12 levels, while none of the pCBs reduced the expression of IL-8 in IL-1β-stimulated HGF.
Ataei et al.[34] (2022)	Clinical cross-sectional	CB1 and CB2	-	-	-	Expression of CB2 in periodontitis patients was significantly lower than in healthy patients. Expression of CB1 was not significantly different in periodontitis or healthy patients.
Pellegrini et al.[21] (2023)	Clinical cross-sectional	CB1 and CB2	-	-	-	The number of CBs in inflamed sites of recurrent periodontitis was significantly higher than in those with non-recurrent disease and in healthy subjects, but less activated. Levels of AEA in inflamed sites of non-recurrent patients were higher than in inflamed recurrent sites and in healthy sites. After periodontal therapy, levels of AEA were significantly lower in both periodontal groups. In recurrent sites, AEA was lower than in non-recurrent and healthy subjects.

2-arachidonylglycerol (2-AG); Anandamide (AEA); Cannabidiol (CBD); Cannabidivarin (CBVN); Cannabigerol (CBG); Cannabinol (CBN); Cannabinoid receptor type 1 (CB1); Cannabinoid receptor type 2 (CB2); Embryonic stem cell-derived microglia cells (ESdM); Human gingival fibroblasts (HGF); Human PDL cells (hPDL); Human periodontal ligament fibroblasts (hPDLF); Human telomerase-immortalized gingival keratinocytes (TIGK); Methanandamide (Meth-AEA); Palmitoylethanolamide (PEA); Periodontal ligament stem cells (PDLSC); Phytocannabinoids (pCBs); R-1 methanandamide (R-1 Meth); Selective agonist of CB2 (HU-308); Selective antagonist of CB1 (AM251); Selective antagonist of CB2 (SR144528); Selective CB2 cannabinoid antagonist/inverse agonist (AM630); Selective CB2 inverse agonist (SMM-189); Synthetic cannabinoid agonist (CP55940); Tetrahydrocannabinol (THC).

AEA is an endocannabinoid derived from arachidonic acid. Acting as a partial agonist for CB1 receptors, it is expressed mainly in the central nervous system[44]. On periodontal tissues, although AEA is mainly linked to CB1 activation, studies have shown that it might also regulate periodontal inflammation via receptors CB1 and CB2 in inflamed gingival tissue biopsies and human gingival fibroblast (HGF)[19,20]. By reducing proinflammatory cytokines, such as TNF-α, IL-1β, IL-6, IL-8, and MCP-1, AEA inhibits NF-κB transcription, reducing corticosterone plasma levels[19,20,38,39]. Moreover, it was also reported the AEA capability of promoting HGF proliferation and epithelial formation at wound healing sites via ERK1/2 with CB1 and CB2 activation in animal models[20]. Lastly, it is also reported that the presence and quantification of endogenous AEA in periodontal tissues might indicate inflammatory disease activity[20,21]. Thus, according to Pellegrini et al.[21], from a clinical perspective, low levels of AEA may indicate a predisposition for the reactivation of the disease in periodontitis patients under a periodontal maintenance program.

In contrast to AEA, 2-AG interacts with both CB1 and CB2 in different tissues as a full agonist[45]. Its interaction with CB2 receptors is essential in various events of cytokines release, cell migration, and tissue homeostasis[17]. Moreover, 2-AG appears to promote detrimentally inflammatory processes and has been reported in higher concentrations in the gingival crevicular fluid (GCF) of periodontitis patients compared to healthy subjects[39]. Conversely, 2-AG appears not to interfere or vary pre-surgically and post-surgically at periodontal wounds[20].

The selective activation of these cannabinoid receptors by endocannabinoids is a critical aspect of the ECS, as it allows for context-specific regulation of various physiological functions[15,34]. The presence of both AEA and 2-AG, as other endocannabinoids, with their distinct affinities and receptor interactions, enables the ECS to finely tune cellular responses to maintain homeostasis and adapt to external challenges[13].

The use of phytocannabinoids or synthetic cannabinoids is also a therapeutic possibility in PD treatment under investigation[24,27,30,32,33,37,40-43]. Pre-clinical studies have demonstrated that systemic or local application of different cannabinoids (Table 1) might mimic endocannabinoids action and interact with both CB1 and CB2 in periodontitis models *in vitro* and *in vivo*[24,33]. The main findings related to their use in periodontitis models are upregulation expression of osteogenic genes during repair of diseased sites[27], attenuation of alveolar bone loss[37,40,42], suppression of proinflammatory cytokines[24,27,33,37,43], and inhibition of periodontal pathogens growth[24] (Table 1).

In summary, this body of evidence under construction underscores the potential therapeutic value of cannabinoids in the treatment of PD. Future investigations in the area may provide a better understanding of the role of CBs and their modulation by endocannabinoids, or drugs that mimic their action, in treating PD as other diseases.

CONCLUSION

a. CB1 and CB2 are integral components of the ECS and manifest in various forms within periodontal tissues.

b. The actions and mechanisms through which CBs are activated in healthy or inflamed sites remain the focus of ongoing investigations.

c. Phytocannabinoids and synthetic cannabinoids show therapeutic potential, with pre-clinical studies indicating benefits in reducing inflammation and facilitating tissue repair.

d. Additional research is necessary to comprehend their mechanisms and clinical applications in periodontitis management.

AUTHOR CONTRIBUTIONS

Lélio Fernando Ferreira Soares: Conceptualization, research, methodology, writing of the original manuscript. Luan Viana Faria: Conceptualization, methodology, writing of the original manuscript. Joni Augusto Cirelli:

Conceptualization, methodology, project management, supervision, validation of data and experiments, proofreading and editing.

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REFERENCES

1. Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Periodontol. 2018 Jun;89(Suppl 1):S173-82. http://dx.doi.org/10.1002/JPER.17-0721. PMid:29926951.

2. Chapple ILC, Mealey BL, Van Dyke TE, Bartold PM, Dommisch H, Eickholz P, et al. Periodontal health and gingival diseases and conditions on an intact and a reduced periodontium: Consensus report of workgroup 1 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Periodontol. 2018 Jun;89(Suppl 1):S74-84. http://dx.doi.org/10.1002/JPER.17-0719. PMid:29926944.

3. Sanz M, Herrera D, Kebschull M, Chapple I, Jepsen S, Berglundh T, et al. Treatment of stage I-III periodontitis-The EFP S3 level clinical practice guideline. J Clin Periodontol. 2020 Jul;47(Suppl 22):4-60. http://dx.doi.org/10.1111/jcpe.13290. PMid:32383274.

4. Chapple IL, Van der Weijden F, Doerfer C, Herrera D, Shapira L, Polak D, et al. Primary prevention of periodontitis: managing gingivitis. J Clin Periodontol. 2015 Apr;42(Suppl 16):S71-6. http://dx.doi.org/10.1111/jcpe.12366. PMid:25639826.

5. Herrera D, Sanz M, Kebschull M, Jepsen S, Sculean A, Berglundh T, et al. Treatment of stage IV periodontitis: the EFP S3 level clinical practice guideline. J Clin Periodontol. 2022 Jun;49(Suppl 24):4-71. http://dx.doi.org/10.1111/jcpe.13639. PMid:35688447.

6. Billings M, Holtfreter B, Papapanou PN, Mitnik GL, Kocher T, Dye BA. Age-dependent distribution of periodontitis in two countries: findings from NHANES 2009 to 2014 and SHIP-TREND 2008 to 2012. J Clin Periodontol. 2018 Jun;45(Suppl 20):S130-48. http://dx.doi.org/10.1111/jcpe.12944. PMid:29926501.

7. Pan W, Wang Q, Chen Q. The cytokine network involved in the host immune response to periodontitis. Int J Oral Sci. 2019 Nov;11(3):30. http://dx.doi.org/10.1038/s41368-019-0064-z. PMid:31685798.

8. Sanz M, Bäumer A, Buduneli N, Dommisch H, Farina R, Kononen E, et al. Effect of professional mechanical plaque removal on secondary prevention of periodontitis and the complications of gingival and periodontal preventive measures: consensus report of group 4 of the 11th European Workshop on Periodontology on effective prevention of periodontal and peri-implant diseases. J Clin Periodontol. 2015 Apr;42(Suppl 16):S214-20. http://dx.doi.org/10.1111/jcpe.12367. PMid:25626357.

9. Meyle J, Dommisch H, Groeger S, Giacaman RA, Costalonga M, Herzberg M. The innate host response in caries and periodontitis. J Clin Periodontol. 2017 Dec;44(12):1215-25. http://dx.doi.org/10.1111/jcpe.12781. PMid:28727164.

10. AlQranei MS, Chellaiah MA. Osteoclastogenesis in periodontal diseases: possible mediators and mechanisms. J Oral Biosci. 2020 Jun;62(2):123-30. http://dx.doi.org/10.1016/j.job.2020.02.002. PMid:32081710.

11. Souza JA, Rossa C Jr, Garlet GP, Nogueira AV, Cirelli JA. Modulation of host cell signaling pathways as a therapeutic approach in periodontal disease. J Appl Oral Sci. 2012 Mar-Apr;20(2):128-38. http://dx.doi.org/10.1590/S1678-77572012000200002. PMid:22666826.

12. Sedghi LM, Bacino M, Kapila YL. Periodontal disease: the good, the bad, and the unknown. Front Cell Infect Microbiol. 2021 Dec;11:766944. http://dx.doi.org/10.3389/fcimb.2021.766944. PMid:34950607.

13. Klein TW, Newton C, Larsen K, Lu L, Perkins I, Nong L, et al. The cannabinoid system and immune modulation. J Leukoc Biol. 2003 Oct;74(4):486-96. http://dx.doi.org/10.1189/jlb.0303101. PMid:12960289.

14. Bellocchio L, Inchingolo AD, Inchingolo AM, Lorusso F, Malcangi G, Santacroce L, et al. Cannabinoids drugs and oral health-from recreational side-effects to medicinal purposes: a systematic review. Int J Mol Sci. 2021 Aug;22(15):8329. http://dx.doi.org/10.3390/ijms22158329. PMid:34361095.

15. Jirasek P, Jusku A, Simanek V, Frankova J, Storch J, Vacek J. Cannabidiol and periodontal inflammatory disease: a critical assessment. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2022 May;166(2):155-60. http://dx.doi.org/10.5507/bp.2022.012. PMid:35332345.

16. Klein TW, Newton CA, Friedman H. Cannabinoids and the immune system. Pain Res Manag. 2001;6(2):95-101. http://dx.doi.org/10.1155/2001/326867. PMid:11854771.

17. Guindon J, Hohmann AG. Cannabinoid CB2 receptors: a therapeutic target for the treatment of inflammatory and neuropathic pain. Br J Pharmacol. 2008 Jan;153(2):319-34. http://dx.doi.org/10.1038/sj.bjp.0707531. PMid:17994113.

18. Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem Pharmacol. 1995 Jun;50(1):83-90. http://dx.doi.org/10.1016/0006-2952(95)00109-D. PMid:7605349.

19. Nakajima Y, Furuichi Y, Biswas KK, Hashiguchi T, Kawahara K, Yamaji K, et al. Endocannabinoid, anandamide in gingival tissue regulates the periodontal inflammation through NF-kappaB pathway inhibition. FEBS Lett. 2006 Jan;580(2):613-9. http://dx.doi.org/10.1016/j.febslet.2005.12.079. PMid:16406050.

20. Kozono S, Matsuyama T, Biwasa KK, Kawahara K, Nakajima Y, Yoshimoto T, et al. Involvement of the endocannabinoid system in periodontal healing. Biochem Biophys Res Commun. 2010 Apr;394(4):928-33. http://dx.doi.org/10.1016/j.bbrc.2010.03.080. PMid:20233580.

21. Pellegrini G, Carmagnola D, Toma M, Rasperini G, Orioli M, Dellavia C. Involvement of the endocannabinoid system in current and recurrent periodontitis: a human study. J Periodontal Res. 2023 Apr;58(2):422-32. http://dx.doi.org/10.1111/jre.13103. PMid:36727611.

22. Gullapalli S, Amrutkar D, Gupta S, Kandadi MR, Kumar H, Gandhi M, et al. Characterization of active and inactive states of CB1 receptor and the differential binding state modulation by cannabinoid agonists, antagonists and inverse agonists. Neuropharmacology. 2010 Jun;58(8):1215-9. http://dx.doi.org/10.1016/j.neuropharm.2010.03.001. PMid:20214912.

23. Weis WI, Kobilka BK. The molecular basis of g protein-coupled receptor activation. Annu Rev Biochem. 2018 Jun;87(1):897-919. http://dx.doi.org/10.1146/annurev-biochem-060614-033910. PMid:29925258.

24. Gu Z, Singh S, Niyogi RG, Lamont GJ, Wang H, Lamont RJ, et al. Marijuana-derived cannabinoids trigger a CB2/PI3K axis of suppression of the innate response to oral pathogens. Front Immunol. 2019 Oct;10:2288. http://dx.doi.org/10.3389/fimmu.2019.02288. PMid:31681262.

25. Reich CG, Mihalik GR, Iskander AN, Seckler JC, Weiss MS. Adolescent chronic mild stress alters hippocampal CB1 receptor-mediated excitatory neurotransmission and plasticity. Neuroscience. 2013 Dec;253:444-54. http://dx.doi.org/10.1016/j.neuroscience.2013.08.066. PMid:24035826.

26. Ruehle S, Wager-Miller J, Straiker A, Farnsworth J, Murphy MN, Loch S, et al. Discovery and characterization of two novel CB1 receptor splice variants with modified N-termini in mouse. J Neurochem. 2017 Aug;142(4):521-33. http://dx.doi.org/10.1111/jnc.14099. PMid:28608535.

27. Qian H, Zhao Y, Peng Y, Han C, Li S, Huo N, et al. Activation of cannabinoid receptor CB2 regulates osteogenic and osteoclastogenic gene expression in human periodontal ligament cells. J Periodontal Res. 2010 Aug;45(4):504-11. http://dx.doi.org/10.1111/j.1600-0765.2009.01265.x. PMid:20412420.

28. Napimoga MH, Benatti BB, Lima FO, Alves PM, Campos AC, Pena-Dos-Santos DR, et al. Cannabidiol decreases bone resorption by inhibiting RANK/RANKL expression and pro-inflammatory cytokines during experimental periodontitis in rats. Int Immunopharmacol. 2009 Feb;9(2):216-22. http://dx.doi.org/10.1016/j.intimp.2008.11.010. PMid:19070683.

29. Sharma R, Singh S, Whiting ZM, Molitor M, Vernall AJ, Grimsey NL. Novel Cannabinoid receptor 2 (CB2) low lipophilicity agonists produce distinct cAMP and arrestin signalling kinetics without bias. Int J Mol Sci. 2023 Mar;24(7):6406. http://dx.doi.org/10.3390/ijms24076406. PMid:37047385.

30. Liu C, Qi X, Alhabeil J, Lu H, Zhou Z. Activation of cannabinoid receptors promote periodontal cell adhesion and migration. J Clin Periodontol. 2019 Dec;46(12):1264-72. http://dx.doi.org/10.1111/jcpe.13190. PMid:31461164.

31. Abidi AH, Presley CS, Dabbous M, Tipton DA, Mustafa SM, Moore BM 2nd. Anti-inflammatory activity of cannabinoid receptor 2 ligands in primary hPDL fibroblasts. Arch Oral Biol. 2018 Mar;87:79-85. http://dx.doi.org/10.1016/j.archoralbio.2017.12.005. PMid:29274621.

32. Abidi AH, Alghamdi SS, Dabbous MK, Tipton DA, Mustafa SM, Moore BM. Cannabinoid type-2 receptor agonist, inverse agonist, and anandamide regulation of inflammatory responses in IL-1β stimulated primary human periodontal ligament fibroblasts. J Periodontal Res. 2020 Oct;55(5):762-83. http://dx.doi.org/10.1111/jre.12765. PMid:32562275.

33. Abidi AH, Abhyankar V, Alghamdi SS, Tipton DA, Dabbous M. Phytocannabinoids regulate inflammation in IL-1β-stimulated human gingival fibroblasts. J Periodontal Res. 2022 Dec;57(6):1127-38. http://dx.doi.org/10.1111/jre.13050. PMid:36070347.

34. Ataei A, Rahim Rezaee SA, Moeintaghavi A, Ghanbari H, Azizi M. Evaluation of cannabinoid receptors type 1-2 in periodontitis patients. Clin Exp Dent Res. 2022 Oct;8(5):1040-4. http://dx.doi.org/10.1002/cre2.608. PMid:35719011.

35. Konermann A, Jäger A, Held SAE, Brossart P, Schmöle A. *In vivo* and *in vitro* identification of endocannabinoid signaling in periodontal tissues and their potential role in local pathophysiology. Cell Mol Neurobiol. 2017 Nov;37(8):1511-20. http://dx.doi.org/10.1007/s10571-017-0482-4. PMid:28289947.

36. Alves LCV, Lisboa MRP, da Silveira HF, de Sousa LM, Gusmão JNFM, Dias DBS, et al. Electroacupuncture increases immunoexpression of CB1 and CB2 receptors in experimental model of inflammatory bone loss. Bone. 2019 Oct;127:59-66. http://dx.doi.org/10.1016/j.bone.2019.05.015. PMid:31121356.

37. Ossola CA, Surkin PN, Pugnaloni A, Mohn CE, Elverdin JC, Fernandez-Solari J. Long-term treatment with methanandamide attenuates LPS-induced periodontitis in rats. Inflamm Res. 2012 Sep;61(9):941-8. http://dx.doi.org/10.1007/s00011-012-0485-z. PMid:22581275.

38. Rettori E, De Laurentiis A, Zorrilla Zubilete M, Rettori V, Elverdin JC. Anti-inflammatory effect of the endocannabinoid anandamide in experimental periodontitis and stress in the rat. Neuroimmunomodulation. 2012;19(5):293-303. http://dx.doi.org/10.1159/000339113. PMid:22777139.

39. Özdemir B, Shi B, Bantleon HP, Moritz A, Rausch-Fan X, Andrukhov O. Endocannabinoids and inflammatory response in periodontal ligament cells. PLoS One. 2014 Sep;9(9):e107407. http://dx.doi.org/10.1371/journal.pone.0107407. PMid:25226300.

40. Ossola CA, Surkin PN, Mohn CE, Elverdin JC, Fernández-Solari J. Anti-inflammatory and osteoprotective effects of Cannabinoid-2 receptor agonist HU-308 in a rat model of lipopolysaccharide-induced periodontitis. J Periodontol. 2016 Jun;87(6):725-34. http://dx.doi.org/10.1902/jop.2016.150612. PMid:26846967.

41. Yan W, Cao Y, Yang H, Han N, Zhu X, Fan Z, et al. CB1 enhanced the osteo/dentinogenic differentiation ability of periodontal ligament stem cells via p38 MAPK and JNK in an inflammatory environment. Cell Prolif. 2019 Nov;52(6):e12691. http://dx.doi.org/10.1111/cpr.12691. PMid:31599069.

42. Ossola CA, Rodas JA, Balcarcel NB, Astrauskas JI, Elverdin JC, Fernández-Solari J. Signs of alveolar bone damage in early stages of periodontitis and its prevention by stimulation of cannabinoid receptor 2. Model in rats. Acta Odontol Latinoam. 2020 Sep;33(2):143-52. http://dx.doi.org/10.54589/aol.33/2/143. PMid:32920617.

43. Zhang F, Özdemir B, Nguyen PQ, Andrukhov O, Rausch-Fan X. Methanandamide diminish the Porphyromonas gingivalis lipopolysaccharide induced response in human periodontal ligament cells. BMC Oral Health. 2020 Apr;20(1):107. http://dx.doi.org/10.1186/s12903-020-01087-6. PMid:32295577.

44. Wang Y, Liu Y, Sarker KP, Nakashima M, Serizawa T, Kishida A, et al. Polymyxin B binds to anandamide and inhibits its cytotoxic effect. FEBS Lett. 2000 Mar;470(2):151-5. http://dx.doi.org/10.1016/S0014-5793(00)01313-2. PMid:10734225.

45. Kreitzer FR, Stella N. The therapeutic potential of novel cannabinoid receptors. Pharmacol Ther. 2009 May;122(2):83-96. http://dx.doi.org/10.1016/j.pharmthera.2009.01.005. PMid:19248809.

CONFLICTS OF INTERESTS

The authors declare no conflicts of interest.

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