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The immunomodulatory role of phytocannabinoids in an *in vitro* peri-implantitis model

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Abstract

The present study aimed to identify the immunomodulatory effects of phytocannabinoids and their potential to reduce the inflammatory burden in peri-implantitis and periodontitis. Human gingival fibroblasts (HGFs) were obtained from the American Type Culture Collection (ATCC) and cultured as per the manufacturer's recommendations. Cellular viability was assessed by measuring the effects of phytocannabinoids on cellular dehydrogenase activity using the Cell Counting Kit-8 (CCK-8) assay. Interleukin-1β (IL-1β) alone (1 ng/ml), titanium particles alone (Ti), and in combination were added an hour before the addition of cannabinoid ligands. After 24 hours, the conditioned medium was transferred to a Mesoscale Discovery (MSD) Human Pro-Inflammatory kit and analyzed using the MSD Sector 2,400 machine or Cisbio human metalloproteinase 2 (MMP2) & Tissue Inhibitor of Metallo Proteinases 1 (TIMP1) kits using a BioTek Synergy 2 Multidetection Microplate Reader. The data were analyzed using GraphPad Prism 6.0. The results showing the effects of cannabidiol (CBD), cannabidivarin (CBVN), and cannabigerol (CBG) on interleukin (IL)-1β-stimulated production of cytokines in primary HGFs were assessed, determining the levels of interferon-gamma (IFN-γ), IL-10, IL-13, IL-4, IL-6, and tumor necrosis factor-alpha (TNF-α) with/without Ti. All cytokines were significantly elevated with the IL-1β treatment, while the expression of IFN-γ, IL-6, and TNF-α was decreased with CBG and CBVN with/without Ti. CBD did not significantly affect IFN-γ or TNF-α but significantly suppressed IL-6 both with/without Ti. IL-13 and IL-4 levels induced by IL-1β were suppressed by all three

phytocannabinoids, but only CBVN significantly suppressed IL-4 in IL-1β+Ti. CBD exhibited a significant rise in IL-10 levels, while the other cannabinoids did not. All phytocannabinoids reduced MMP2 levels, with CBG having the highest inhibitory effect. None of the phytocannabinoids had a significant effect on TIMP1 expression. In conclusion, the effective inhibition of cytokines and MMP2 by phytocannabinoids in HGFs suggests that targeting the endocannabinoid system may lead to the development of novel drugs for periodontal and peri-implant therapy, which will aid in strategies to improve oral health.

Keywords: Implant, Peri-implantitis, Cannabinoid, Endocannabinoid