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Cannabinoids reduce extracellular vesicle release from HIV-1 infected myeloid cells and inhibit viral transcription

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37.9 million individuals are infected with human immunodeficiency virus type 1 (HIV-1) globally, with approximately 50% exhibiting HIV-associated neurocognitive disorders (HAND). HIV-1 viral RNAs, such as Trans-activating Response (TAR) RNA, have been shown to be incorporated into extracellular vesicles (EVs) which incite an inflammatory response from recipient cells. The primary cannabinoids in cannabis, Cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC), have been shown to reduce inflammation. Furthermore, it has been shown that cannabis use in people living with HIV-1 is associated with a lower viral load, lower circulating CD16+ monocytes, and high CD4+ T-cell count, suggesting a potential therapeutic application. To assess the effects of CBD and THC in HIV-1 infection, HIV-1 infected U1 monocytes and primary macrophages were treated with CBD or THC. The EV concentrations from these cells were then analyzed using nano-tracking analysis, and the cellular and extracellular RNA and proteins were analyzed via reverse transcription-quantitative polymerase chain reaction (RT-qPCR) and Western blot analysis respectively. We have utilized biotin-labeled CBD for pull-down experiments and found many interacting proteins from both undifferentiated and differentiated infected macrophages that clearly show a connection with various stages of autophagy. Our data suggests a significant decrease in the number of EVs released from infected cells potentially due to a reduction in viral transcription and the activation of autophagy. Overall, these studies are significant in that cannabinoids, particularly CBD, may provide a protective effect by alleviating the pathogenic effects of EVs in HIV-1 and CNS-related infections.