CBD and Low THC as an Alternative Therapeutic Aid in Pain Relief

The Central Asian native plant, Cannabis Sativa, is a shrub consumed by an estimated 200-300 million people all around the world as teas, smoke, pills, suppositories, eye drops, oral buccal sprays, and other forms for therapeutic benefits (Gonçalves, J., Rosado, T., Soares, S., Simão, A., Caramelo, D., Luís, A., Fernández, N., Barroso, M., Gallardo, E., and Duarte, A., 2019). Cannabidiol (CBD) is a cannabis derivative without psychotropic effects and has been shown to have a role to play in reducing pro-inflammatory proteins in the brain, such as *TNFA*, *S100B*, and *IL-1B* (Esposito, G., Scuderi, C., Valenza, M., Togna, G., Latina, V., et al., 2011). CBD is a therapeutic being used in research to treat Alzheimer’s disease (AD) and has shown in rats that it stimulates neuronal growth (Esposito, et al., 2011). CBD is also found to have no side effects as an anti-tumor cancer drug in brain tumor gliomas that inhibits the many proteins involved in tumor cell division and spreading from the malignant tumor to healthy brain tissue (Solinas, M., Massi, P., Cinquina, V., Valenti, M., Bolognini, D., et al., 2013). CBD has also been shown to restore gut homeostasis in irritable bowel diseases such as ulcerative colitis (UC) by lowering production of the inflammatory protein S100B and protecting the intestinal wall (De Filippis, D., Esposito, G., Cirillo, C., Cipriano, M., and De Winter, B., et al., 2011).

Tetrahydrocannabinol (THC) is a psychoactive cannabinoid that can cause anxiety, hallucinations, euphoria, and paranoia but when used in varying limited ratios with CBD can have beneficial self-reported effects of helping neuropathic pain, insomnia, anorexia, post-traumatic stress disorder (PTSD), depression, nausea, and spasticity (Casarett, D., Beliveau, J., and Arbus, M., 2019). The treatment of Parkinson disease (PD), fibromyalgia, cancer pain, epilepsy, AD, and Multiple Sclerosis (MS) have shown some instances of benefits to using CBD in combination with THC to manage pain and other symptoms of those diseases (Goncalves, et al., 2019). Users of THC and CBD together in a high THC to CBD ratio have been shown to have higher affinity towards negative psychotherapeutic effects by impairing memory and leading to psychosis (Swift, W., Wong, A., Li, K., Arnold, J., and McGregor, I., 2013).

THC is more lipophilic or fat-loving, therefore it is absorbed more readily than CBD and stores longer in the fat layers of the body. As a topical application for either of these cannabinoids, the CBD version is able to cross the skin barrier better than THC (Gonçalves, et al., 2019). The CB1 and CB2 receptors make up the endocannabinoid system of the body and THC is the only one that directly effects either receptor, particularly the CB2 receptor with its mixed psycho-therapeutic effects (Goncalves, et al., 2019). The CB2 receptors are found in the hematopoietic cells and the immune system of the leukocytes, spleen, and tonsils (Goncalves, et al., 2019). The CB1 receptor is found in the central nervous system (CNS), peripheral nervous system (PNS), some organs like the heart, spleen, digestive tract, urinary tract, reproductive tract, and in the leukocytes and endocrine glands (Goncalves, et al., 2019). CBD does not affect either endocannabinoid receptor but does indirectly affect the CB1 receptor by binding to the in-active sites that the cell membrane channels use to mediate physiological responses like sight, pain, pressure, temperature, and taste (Goncalves, et al., 2019).

Cannabis is still considered a Schedule I drug but has been legalized in many US states and Canada but is authorized to treat medical conditions and for scientific research by international law (Goncalves, et al., 2019).

Using a study from GEO, GSE57571, samples were used to explore genes that summaries obtained from the gene data of the National Center for Bioinformatics Information (NCBI) at www.ncbi.nlm.nih.gov/gene to extract information about inflammation cytokines, receptors for cannabinoids, estrogen and other hormonal genes, and tumor growth and suppressor or apoptosis genes. In an exploratory data analysis of this data set. There were limited cell culture and simulated human sebum growth cultures used to assess the effects of the CBD cannabinoid on the hair follicles and arm hair follicles of sebum in three females that tested a control group in culture and the effects of a separate culture of that same sample 24 hours after applying CBD oil to the biological matter. There is a total of five microarray samples in this data. The first sample is the original cell culture of sebum biological matter at the initialization of the experiment or the first hour of the 24 hours the study was done and ends in ‘Rep1.’ From this sample two other samples were derived to make similar copies for comparing control and CBD treated. Those samples end in ‘Rep2’ where the second ‘Rep2’ is a lab technical repeat. The other two samples are the values obtained 24 hours later from the control and separately from the CBD treated sample. They have sample names ending in either ‘CTRL’ or ‘CBD’ to identify which sample is which (Oláh, Tóth, Borbíró, Sugawara, Szöllõsi, Czifra, Pál, Ambrus, Kloepper, Camera, Ludovici, Picardo, Voets, Zouboulis, Paus, and Bíró, 2014).

In R software the dplyr package was used to add fields that could take the differential expression (DE) of the final CBD treated sample of sebum minus the control or non-treated sebum sample, a magnitude field for the absolute value in the change from the CBD treated compared to the non-treated control group, and a fold change of the ratio of the CBD treated to control sample values after 24 hours. These fields were added to the end of this data on the sebum genes involved in inflammation, cell death or proliferation, tumor suppression or initialization, and cannabinoid receptors if the genes were in the data labeled as those genes obtained from NCBI. This final data set was uploaded to a personal online repository and can be obtained from <https://github.com/JanJanJan2018/CBD_pain_relief/DE_sebum_order.csv>.

In that data set, it is clear that some genes had a 50-90 per cent decrease in gene expression and some had more than 100% increase in expression in CBD treated sebum compared to non-treated sebum samples after 24 hours. The following table, Table 1, shows the highlighted genes as red that are more than 50 per cent increased or decreased in the CBD treated versus the non-treated sample of sebum. There are four genes having a greater than 50 per cent increase in expression after being treated with CBD. Those genes having an increase are *TRIB3, TRAF1, ESR1,* and *IL1B.* These genes are summarized from NCBI in this same data set. *TRIB* ortribbles pseudokinase 3and *TRAF1* or TNF receptor associated factor 1 are involved in the process of tumor cell death. *ESR1* or estrogen receptor 1 encodes an estrogen receptor that is used for hormonal and DNA binding as well as the transcription factor in the nucleus. *IL1B* or interleukin 1 beta is a mediator in the inflammation process and can cause pain hypersensitivity when it mediates the production of cyclooxygenase-2 (*PTGS2*) in the central nervous system. That gene, *PTGS2*, is increased by 22 per cent in CBD treated sebum. The three genes that are more than 50 per cent decreased in CBD treated sebum compared to non-treated sebum after 24 hours are *CNB1, AR*, and *NRIP1*. *CNB1* is the cannabinoid receptor 1 and this lowering effect of the *CNB1* gene in CBD treated samples of sebum probably indicates that the cannabinoid CBD does not use the receptor for CNS induced effects as previously discussed in other research (Goncalves, et al., 2019). The *AR* or androgen receptor gene behaves as a steroid-hormone activated transcription factor and is an androgen receptor gene. The *NRIP1* gene is nuclear receptor interacting protein 1 and is responsible for modulating estrogen receptor transcription activity.

Table 1: CBD Treated Sebum Differential Expression Values

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| --- | --- | --- | --- |
| **Gene** | **GSM1385016.CTRL** | **GSM1385017.CBD** | **DE\_CBD\_mns\_CTRL** |
| TRIB3 | 7.6472 | 9.103322 | 1.456122 |
| TRAF1 | 6.866 | 7.707344 | 0.841344 |
| ESR1 | 2.9373 | 3.679091 | 0.741791 |
| IL1B | 11.4589 | 12.080408 | 0.621508 |
| ICAM1 | 9.5599 | 10.037292 | 0.477392 |
| TNF | 3.6411 | 4.022212 | 0.381112 |
| TGFB1 | 7.3283 | 7.653875 | 0.325575 |
| TRPV2 | 4.9487 | 5.252485 | 0.303785 |
| CNRIP1 | 3.0299 | 3.313889 | 0.283989 |
| IL10 | 3.4231 | 3.679091 | 0.255991 |
| PTGS2 | 4.5165 | 4.738671 | 0.222171 |
| IFNG | 3.366 | 3.490365 | 0.124365 |
| S100B | 2.9891 | 3.102988 | 0.113888 |
| SHBG | 4.0035 | 4.073103 | 0.069603 |
| CNR2 | 4.1808 | 4.245898 | 0.065098 |
| NFKB1 | 10.1001 | 10.148697 | 0.048597 |
| IL17A | 3.8998 | 3.890546 | -0.009254 |
| IL6 | 11.0788 | 10.929585 | -0.149215 |
| TNFSF10 | 5.31 | 4.921954 | -0.388046 |
| CNR1 | 3.0299 | 2.482512 | -0.547388 |
| AR | 4.4262 | 3.61357 | -0.81263 |
| NRIP1 | 8.184 | 7.253319 | -0.930681 |

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