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 greater than 10 per cent decrease in gene expression and some had more than 10 per cent 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 10 per cent increased or decreased in the CBD treated versus the non-treated sample of sebum. There are four genes having a greater than 10 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 4.9 per cent in CBD treated sebum. The three genes that are more than 10 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

![A screenshot of a cell phone

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generated](data:image/jpeg;base64,/9j/4AAQSkZJRgABAQEAYABgAAD/4VxARXhpZgAATU0AKgAAAAgABgALAAIAAAAmAAAIYgESAAMAAAABAAEAAAExAAIAAAAmAAAIiAEyAAIAAAAUAAAIrodpAAQAAAABAAAIwuocAAcAAAgMAAAAVgAAEUYc6gAAAAgAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAFdpbmRvd3MgUGhvdG8gRWRpdG9yIDEwLjAuMTAwMTEuMTYzODQAV2luZG93cyBQaG90byBFZGl0b3IgMTAuMC4xMDAxMS4xNjM4NAAyMDE5OjA4OjIzIDExOjQ4OjUxAAAGkAMAAgAAABQAABEckAQAAgAAABQAABEwkpEAAgAAAAMwMAAAkpIAAgAAAAMwMAAAoAEAAwAAAAEAAQAA6hwABwAACAwAAAkQAAAAABzqAAAACAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA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The next figure, Figure 1, shows those specific genes with more than 50 per cent change in CBD treated to non-treated sebum in differential expression values with the red scatter points for the down-regulated genes in CBD treated, and blue for up-regulated genes in CBD treated sebum.

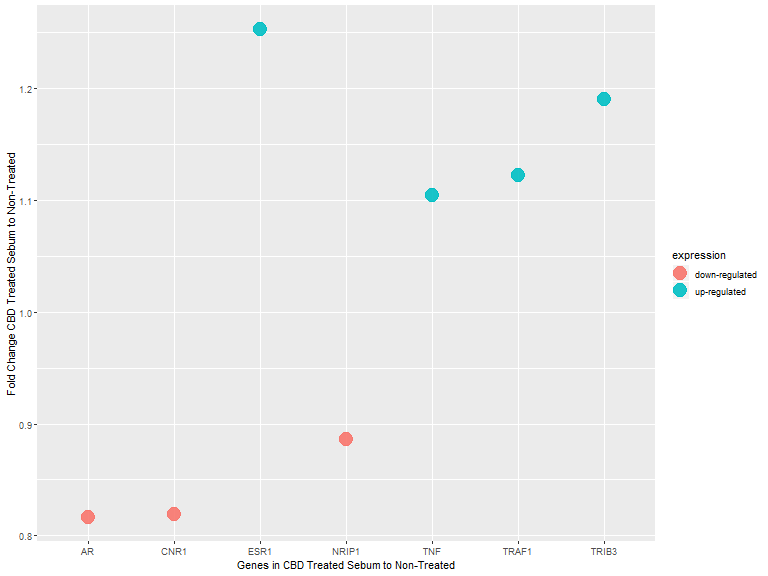


Figure 1: Differential expression values of those genes having more than 50 per cent change in up or down regulation CBD treated sebum compared to non-treated sebum.

There was also a GEO data set on glioma treated CBD from three samples comparing three control groups to their CBD treated gene expression values GEO Series GSE57988 (Singer, E., Judkins, J., Salomonis, N., Matlaf, L., Soteropoulos, P., McAllister, S., and Soroceanu, L. , 2015). In that study, the researchers analyzed the effects of glioma stem cells in culture and found that while treating the cells with CBD and also expressing a gene known to have antioxidant benefits (*SLC7A11-*solute carrier family member 7) resulted in anti-tumor properties that involved noticeable in culture drops in cell division and spreading in glioma stem cells (Singer, et al., 2015).

The data this study donated to the NCBI was used to study the gene expression levels of the same genes used in the above analysis on CBD treated sebum. The fold change and differential expression values were added to this data to get the amount of change in up and down regulation of CBD treated glioma stem cells. This table of data is shown in Table 2 that follows with those genes having greater than 5 per cent change in up or down regulation shown in red. Those genes are *TNFSF10* and *S100B* for greater than 5 per cent up regulation in CBD treated glioma stem cells compared to non-treated. As well as genes *IL6, PTGS2,* and *TRIB3* for the greater than 5 per cent change in down regulated genes are also in Table 2. *TRIB3*, a tumor cell death gene, was also shown in the sebum samples as having greater than 5 per cent change in up-regulation, but in this case it is one of the genes down-regulated in glioma stem cell treated CBD samples. The up-regulated genes *S100B* and *TNFSF10* are summarized in normal tissue to be involved in cell cycle differentiation and proliferation as well as cell death signaling in tumor cells respectively (NCBI, 2019). While the down-regulated genes *IL6* and *PTGS2* are shown in normal human tissue to be an inducer of inflammation at acute or chronic location and involvement in prostanoid biosynthesis inflammation respectively. Since *PTGS2* acts to intensify pain when up regulated with *IL1B*, this could indicate the down regulation of this gene can show less pain in glioma patients being treated with CBD oil.

Table 2: CBD Treated Glioma Stem Cell Gene Expression Data

![A screenshot of a cell phone

Description automatically generated](data:image/jpeg;base64,/9j/4AAQSkZJRgABAQEAYABgAAD/4U66RXhpZgAATU0AKgAAAAgABgALAAIAAAAmAAAIYgESAAMAAAABAAEAAAExAAIAAAAmAAAIiAEyAAIAAAAUAAAIrodpAAQAAAABAAAIwuocAAcAAAgMAAAAVgAAEUYc6gAAAAgAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAFdpbmRvd3MgUGhvdG8gRWRpdG9yIDEwLjAuMTAwMTEuMTYzODQAV2luZG93cyBQaG90byBFZGl0b3IgMTAuMC4xMDAxMS4xNjM4NAAyMDE5OjA4OjIzIDExOjQxOjQ1AAAGkAMAAgAAABQAABEckAQAAgAAABQAABEwkpEAAgAAAAMwMAAAkpIAAgAAAAMwMAAAoAEAAwAAAAEAAQAA6hwABwAACAwAAAkQAAAAABzqAAAACAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA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The data from Table 2 was used to show how the genes with greater than 5 per cent gene expression changes compare similarly for up and down regulated genes. Figure 2 shows the side by side comparison of those genes in up regulation as blue scatter points and down regulated as red scatter points. You can see how *TNFSF10* and *PTGS2* have almost the same opposing changes in the CBD treated glioma cells, with *TNFSF10* being increased and *PTGS2* decreased. This could mean the *PTGS2* is being secreted less because it causes pain, and the tumor cell death cycle gene *TNFSF10* is being secreted more to regulate the tumor cells for better health. Interestingly, TRIB3 and TRAF1, were down regulated in CBD treated glioma tumors but up regulated in sebum samples. This could be because they are not involved in sebum type inflammation tumors created by glioma cells but a different tumor cell death gene TNFSF10 was up regulated in glioma treated with CBD oil. The gene *S100B* is also up regulated about the same amount as the gene *IL6* changes in down regulation. Which could mean how S100B regulates the many cell cycles it mediates is needed more in CBD treated samples but also while less of the cytokine IL6 that causes acute inflammation and immune cell proliferation is needed less.

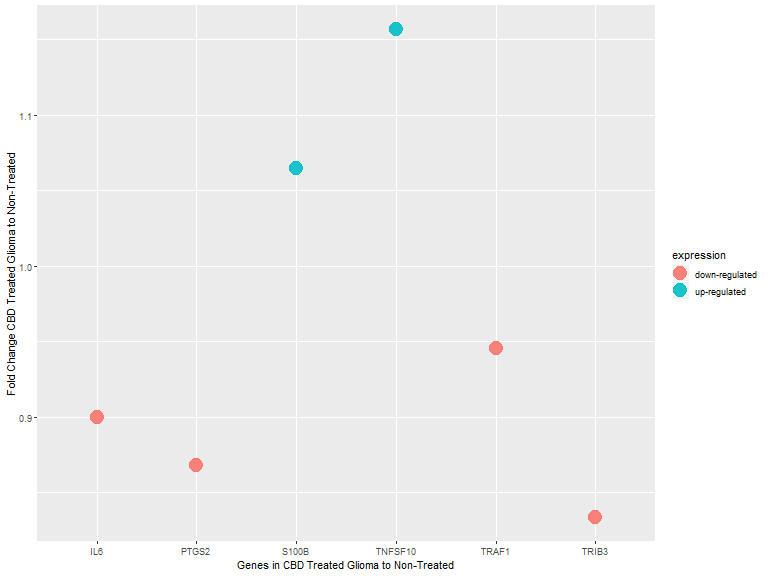


Figure 2. CBD Treated Glioma Stem Cell Genes Having Greater than 50 Per Cent Change

CBD as a cannabinoid alternative pain-relieving therapeutic treatment for sebum in acne patient samples, seems to also show the effects that CBD potentially has on genes that regulate inflammation, hormones, pain, and tumor regulation. Ongoing research is still being done on CBD and THC cannabinoids, but given the current literature, it is safe to say that CBD is not toxic in most cases, and safe to use as a therapeutic for pain relief though it may take a while to be effective. It shows results as soon as one day for improving tumor regulation by up regulating those genes that help immune pathways to kill tumor cells and stop tumor cell proliferation in both glioma and sebum samples treated with CBD oil. But different cytokines and tumor regulating genes were expressed differently in the two different studies. CBD can also reduce hormonal activity as shown with the down regulated genes responsible for hormone mediation and expression. As far as THC goes in combination with CBD, it appears to help those with fibromyalgia, AD, PD, epilepsy, anorexia, PTSD, anxiety, pain, and more. But finding the right combination of THC with CBD is still being investigated to maximize therapeutics while keeping the side effects of THC like the psychosis, upset digestion, memory functions, and others at a minimal.

See if your local physicians or research institutions at world class or private institutions are recruiting for CBD research studies and if you qualify if interested. The limits in this state of California for THC is less than 1 percent at 0.003 or 0.03% THC with CBD. There seems to be a difficulty in assessing the correct doses and effects cross studies and cross cannabinoid due to the difference in potency of plants and the amount of fat and history of use that many patients who use CBD and THC products have. This is one area that is broad for more research in regulation and possible withdrawals and side effects from cannabinoid use.

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