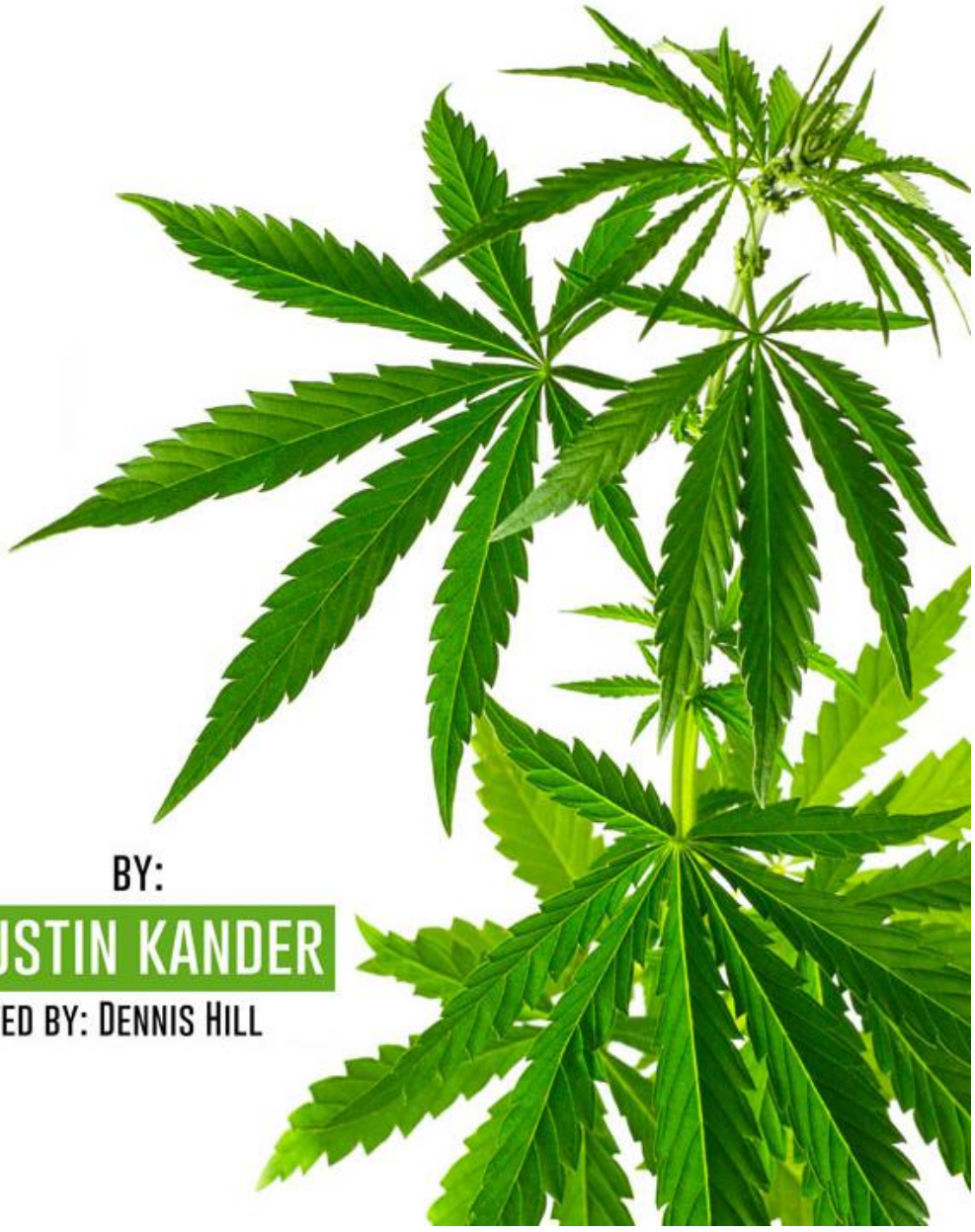
CANNABIS FOR THE TREATMENT OF CANCER

THE ANTICANCER ACTIVITY OF PHYTOCANNABINOIDS AND ENDOCANNABINOIDS



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Millions of people around the world die from cancer every year. Despite advances in oncological science, many types of cancer are virtually incurable. Furthermore, even when conventional options are effective, they often cause long-term or permanent damage along with immense short-term pain and discomfort. Due to these circumstances, there is a desperate need for new, safe, and powerful treatments.

Phytocannabinoids derived from the cannabis plant appear to be the biologically ideal solution to cancer. They exert anti-cancer activity against both common and lesser known cancers in cell and animal models, and their generalized therapeutic effects indicate they may fight all cancers at some level. Of course, it is more than likely that some specific types of cancers or some patient populations will be resistant to phytocannabinoid treatment. However, it is clear that cannabis extracts can fight many cancers in humans, and research is critically needed to determine the full extent of these effects. The existing scientific and anecdotal evidence is a useful guide for future research.

The sections of this book are as follows:

I. The Protective Role of the Endocannabinoid System Against Cancer
II. The Anti-Cancer Activity of Phytocannabinoids
III. Human Case Results

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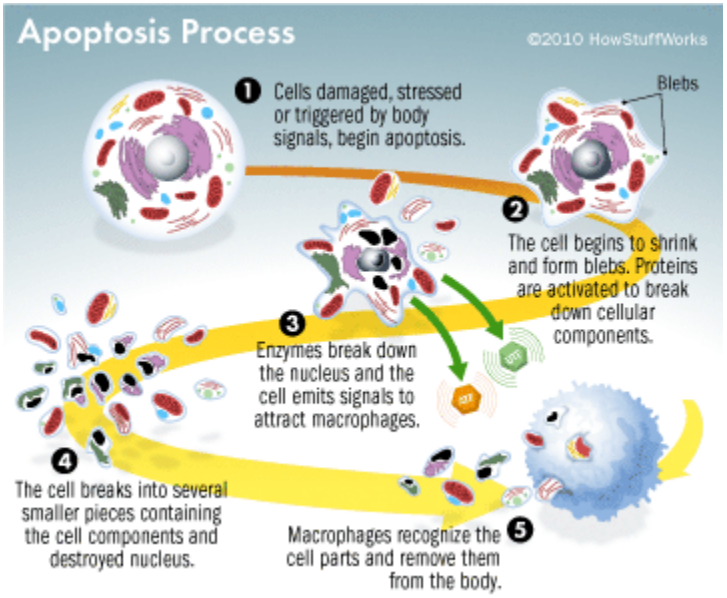
I. The Protective Role of the Endocannabinoid System Against Cancer

The endocannabinoid system (ECS) is a network of cannabinoid receptors-, endogenous cannabinoids (endocannabinoids), and enzymes that function to maintain homeostasis in organisms. As environmental factors change, the ECS works to stabilize numerous health metrics. Part of the system's homeostatic role is conferring protection against a wide variety of internal and external threats. For example, endocannabinoids increase in the brain after head trauma as an attempt to protect cells (Pacher, Bátkai, and Kunos). Significant evidence suggests the ECS plays a protective role against cancer as well.

Both endocannabinoids and phytocannabinoids inhibit cancers through several mechanisms. The most potent method is induction of apoptosis, or programmed cell death. All cells contain the machinery to destroy themselves when they become too old or damaged. However, cancer cells grow abnormally and cease to initiate apoptosis. Cannabinoids restore the ability of cancer cells to undergo programmed cell death, thus killing them. Through the complex modulation of biological processes, cannabinoids also slow cancer cell reproduction, prevent tumors from forming their own blood vessels, and inhibit the spread of cancer within local tissue and to other tissues. These functions are respectively known as anti-proliferative, anti-angiogenic, anti-invasive, and anti-metastatic properties. Other unique modes of action that do not fall under these categories are explained later.



(Edmonds)

Endocannabinoids have been shown to kill numerous types of cancer cells. Anandamide, the first endocannabinoid discovered, is predominantly responsible for the ECS's anti-cancer activity. Several studies have implicated anandamide and related compounds as anti-cancer agents. In

addition to discussing results, the following analyses will include information on relevant concepts and compounds. As such, the earliest portions of the following section contain a significant amount of basic biology information, which is necessary for complete understanding. The need to explain concepts and compounds progressively diminishes throughout the book.

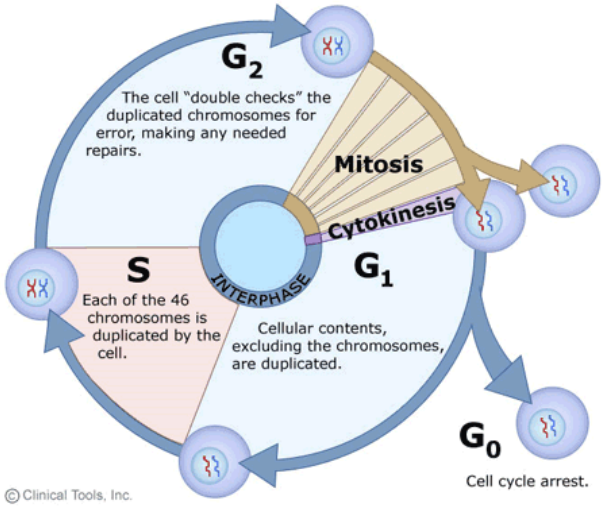
Studies

A June 2003 study in *Prostate* reported that anandamide induced apoptosis in the prostate cancer cell lines LNCaP, DU145, and PC3 (Mimeault et al.). Cancer cell lines are standardized collections of cells with the same genetic makeup. In this case, the cell lines above are different types of prostate cancer with different levels of metastatic potential. LNCaP has low potential, DU145 has moderate potential, and PC3 has high potential (Pulukuri et al.). Therefore, PC3 theoretically represents the most potentially fatal form of prostate cancer, as the true danger of cancer stems from its ability to travel throughout the body.

Anandamide inhibited proliferation and induced apoptosis in the above cell lines by activating CB_1 receptors on the cancer cells' surface (Mimeault et al.). This caused a decrease in epidermal growth factor receptor (EGFR) expression and less epidermal growth factor (EGF)-stimulated growth. EGF is a growth factor protein that increases cell proliferation through binding with EGFR (Herbst). By reducing EGFR, anandamide cut off a significant source of fuel for the cancer cells.

In addition to affecting EGFR, CB_1 activation increased cellular ceramide production. Ceramide is a lipid molecule that comprises part of cell membrane structures. It is also involved in a variety of cellular functions and signaling. When the amount of ceramide rises to a certain point, it can interfere with the cell cycle.

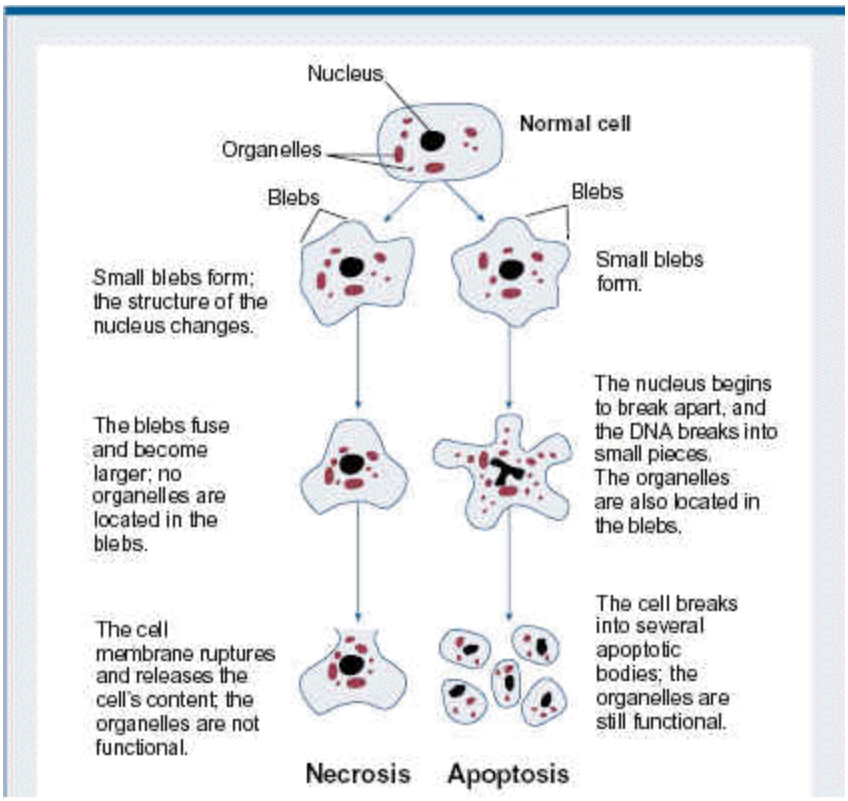
The cell cycle is the process by which a cell divides into two daughter cells ("The Cell Cycle"). It consists of four stages – Gap 1 (G_1), Synthesis (S), Gap 2 (G_2), and Mitosis (M). The gaps, which are essentially checkpoints to prevent errors (among other functions), prepare the cell for DNA replication (S stage) and cellular division (M stage). The Gap 0 (G_0) stage is a resting, quiescent state. An increase in ceramide has been linked to cell cycle arrest in the G_1 stage (Zhu et al.).



("The Cell Cycle, Mitosis")

In the *Prostate* study, the anandamide-mediated ceramide increase led to G_1 arrest and "massive cell death by apoptosis and/or necrosis" in DU145 and PC3 cells. The cytotoxic effects of anandamide were strongest against the DU145 and PC3 lines, with less efficacy against the LNCaP line.

Cannabinoids generally kill cancer cells by initiating apoptosis, but there are instances where necrosis occurs instead. Necrosis usually results from injury by a traumatic stimulus, and is characterized by cell membrane rupture and spillage of cell contents into the extracellular area. This can lead to inflammation and death of adjacent cells (Goodlett and Horn). Most standard chemotherapeutic agents kill cancer via necrosis. Apoptosis is more deliberate and keeps adjacent cells safe. It is better for cancer cells to die via apoptosis than necrosis. In the vast majority of studies, cannabinoids are indicated to cause apoptotic cell death, which is one of their primary advantages.



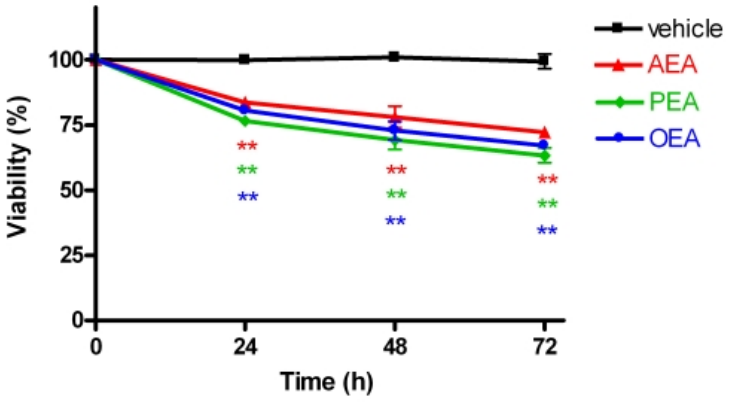
(Goodlett and Horn)

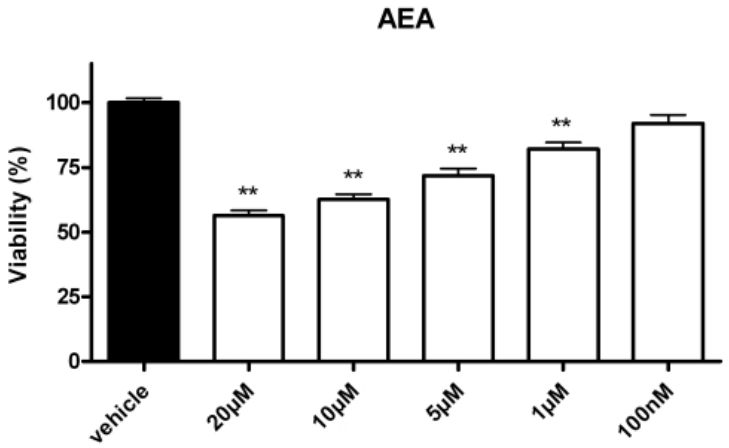
A 2011 study demonstrated anandamide and two other endocannabinoid-like compounds, palmitoylethanolamide (PEA) and oleoylethanolamide (OEA), reduced the viability of N1E-115 neuroblastoma cells (Hamtiaux et al.). Cell viability is a key measure of cell health.

There are several indicators of cell viability, including adenosine triphosphate (ATP) concentration ("Cell Proliferation"). ATP is the chief unit of energy in cells, and it declines rapidly during necrosis or apoptosis. Higher levels generally mean a more viable cell. There are other cell viability assays like membrane leakage assays and mitochondrial assays for situations where measuring metabolic activity via ATP is not possible.

The technique used in the above study and many others is the MTT assay. It measures the activity of mitochondrial enzymes and their ability to convert a specific chemical dye into insoluble crystals.

While reduction in cell viability often leads to apoptosis, the above study found anandamide, PEA, and OEA reduced the number of viable cells without inducing apoptosis (Hamtiaux et al.). The compounds time- and dose-dependently decreased viability, so as more time elapsed and higher concentrations were used, the loss of viability progressively increased.





Results for PEA and OEA were very similar and can be found on Page 11 of the online study.

In addition to impairing viability, anandamide reduced cell proliferation without inducing apoptosis. These effects were enhanced when the compound was combined with a fatty acid amide hydrolase (FAAH) inhibitor. FAAH is the enzyme that breaks down anandamide, so inhibiting it is an indirect way of increasing anandamide concentration.

Since apoptosis was not induced, it was concluded the antiproliferative effects of anandamide and the FAAH inhibitor were due to an arrest of the cell cycle progression. Overall, the results indicated a probable reduced transition from the G_1 to S phase, as well as a "global slow-down of the cell cycle progression that appears to extend to all phases of the cell cycle" (Hamtiaux et al.). In effect, anandamide prevents DNA replication and mitosis of neuroblastoma cells.

To find out the mechanisms by which anandamide inhibited proliferation, the N1E-115 cells were examined for the presence of receptors that respond to cannabinoids. CB_1 (but not CB_2), $TRPV_1$, GPR55, PPAR-alpha (PPAR-α), and PPAR-gamma (PPAR-γ) receptors were all found. Antagonists of these receptors were administered alongside anandamide to determine if they could prevent the antiproliferative effects. Since the addition of the antagonists had no effect, it was shown that anandamide's mechanism of action was not mediated via any of the traditional

receptors. However, there are other cancers where anandamide does induce apoptosis or other effects through CB_1 and $TRPV_1$.

In this case, receptor-independent effects involving cell membrane changes were responsible for anandamide's effects. Using a lipid raft disruptor, it was determined that the antiproliferative effects were lipid raft-mediated. Lipid rafts are components of the cell membrane structure that facilitate membrane fluidity and protein trafficking. Many types of receptors are located within these lipid raft microdomains. Some property of anandamide apparently enables it to interact with lipid rafts independently of receptors to stop cancer cell reproduction.

Lipid rafts were implicated in the anandamide-induced apoptosis of rat C6 glioma cells in a 2005 study in *The Journal of Biological Chemistry* (Bari et al.). The study also suggested that lipid rafts control CB_1 binding and signaling. Indeed, CB_1 receptors are among many G protein-coupled receptors (GPCRs) that function within lipid rafts.

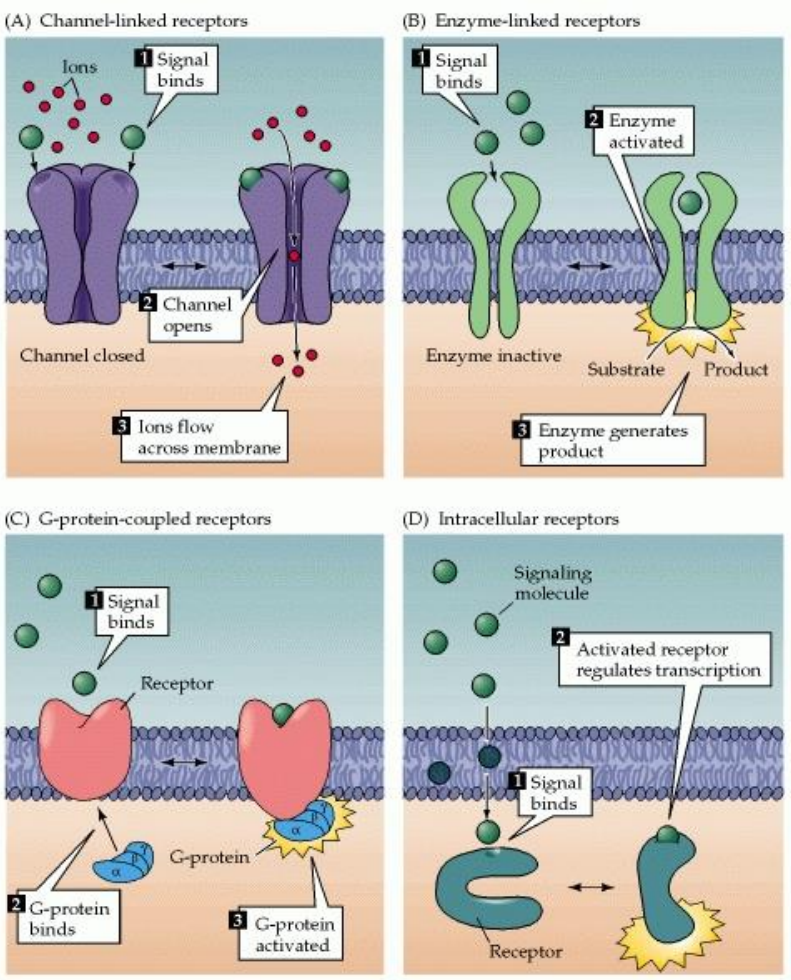
Most receptors are found on the outside of cells, and their activation causes a response inside the cell. Receptors are protein-based and integral to thousands of biological functions. GPCRs are one of four categories of cellular receptors (Purves et al.). They include the traditional cannabinoid receptors CB_1 and CB_2. Orphan GPCRs, so-called because their endogenous ligand is unknown, also interact with cannabinoids. In the future, at least some orphan receptors, like GPR55, will inevitably be reclassified as cannabinoid receptors. Other receptors like $TRPV_1$ and PPAR-γ fall into the categories of channel-linked receptors and intracellular receptors, respectively.

GPCRs pass through the cell membrane seven times and are attached (coupled) to guanine nucleotide-binding proteins. They are also known as heterotrimeric guanosine triphosphate (GTP) binding proteins or simply G proteins. GTP, like ATP, is a nucleoside triphosphate involved in many biological processes. G proteins are classified as heterotrimeric because they consist of three different subunits – alpha, beta, and gamma ("Cell Signalling").

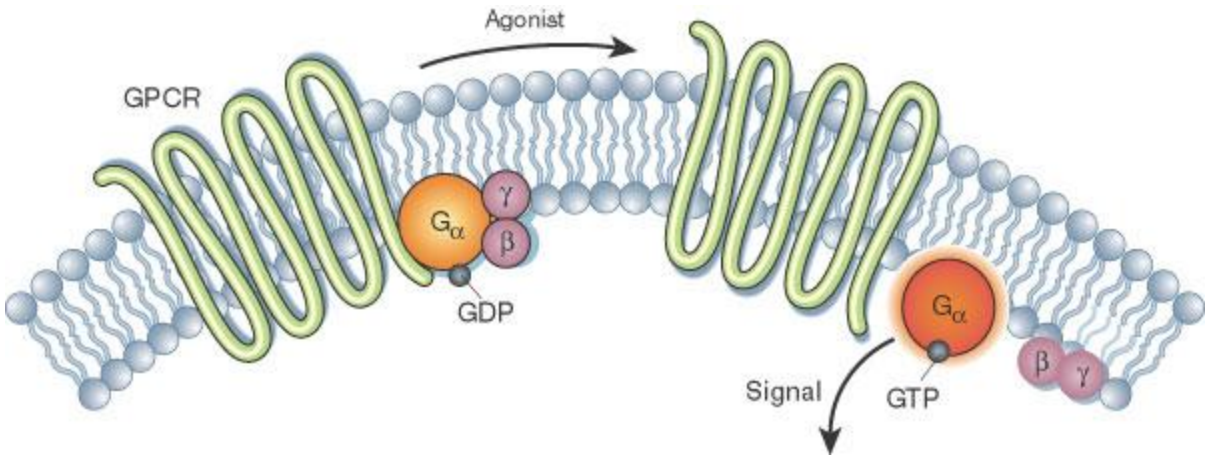
When a ligand binds with a receptor, the receptor's structure changes and the attached G protein is activated. This activation entails an exchange of guanosine diphosphate (GDP) for GTP in the alpha subunit, which allows the G protein to split into an active GTP-bound alpha subunit and beta/gamma complex (a single large molecule composed of the beta and gamma subunits). Until the subunits separate, the G protein is considered inactive. After splitting, the subunits activate distinct effector enzymes or ion channels, which regulate concentrations of secondary messengers ("Cell Signalling"). This process results in a specific cellular response, such as modulating gene expression. The signal terminates when the GTP in the alpha unit is reduced to GDP, which allows the alpha and beta/gamma subunits to recombine and reattach to the receptor ("Guanine Nucleotide").

While the beta/gamma complex is important, the alpha subunit is primarily responsible for the regulation of effectors. G proteins are categorized based on the type of alpha subunit present. For example, a G_s protein stimulates the enzyme adenylyl cyclase, whereas G_i proteins inhibit it. Adenylyl cyclase is a major enzyme with regulatory importance in nearly all cells, as it catalyzes

the conversion of ATP to cyclic AMP (adenosine monophosphate), which is an important second messenger that relays signals from first messengers (extracellular receptor ligands).



(Purves et al.)



("GPCR")

In the previous study, $TRPV_1$ receptors were implicated in the apoptosis-inducing effect of anandamide (Bari et al.). Interestingly, CB_1 receptors were found to have a protective effect in C6 cells, as blocking them with an antagonist increased anandamide-mediated apoptosis. However, lipid raft disruption and CB_1 antagonism had no effect in human CHP100 neuroblastoma cells, as they lacked CB_1 receptor expression. As with C6 cells, apoptosis in CHP100 cells occurred through $TRPV_1$ receptor activation. Not being GPCRs, $TRPV_1$ receptors are not localized within lipid rafts and thus are not affected by raft disruption.

Activation of $TRPV_1$ disrupts mitochondrial integrity and allows cytochrome c to pass through the mitochondrial membrane. Mitochondria are the energy-producing organelles of cells, and their proper function is integral to cell viability. Cytochrome c is a small protein in the mitochondria involved in the electron transport chain, which generates energy in the form of ATP. The protein also plays a role in mediating apoptosis, so its accumulation outside the mitochondria encourages programmed cell death.

$TRPV_1$ receptors are located throughout the entire body, including neuronal and nonneuronal tissues in the brain and peripheral organ systems. They are also located inside cells on structures like smooth endoplasmic reticulum and the Golgi apparatus (Veronesi and Oortgiesen). The receptors are activated by a stunningly wide variety of stimuli, including endogenous ligands like anandamide and inflammatory mediators. High temperatures, low-pH acids, and electrostatic charges can activate $TRPV_1$ channels as well. Activation can result in the release of neuropeptides like Substance P, a compound well known for conveying pain signals. Other cells respond to these neuropeptides by releasing pro-inflammatory cytokines like interleukin-1 beta and tumor necrosis factor-alpha, which promote and sustain inflammation. Ultimately, due to the distribution of $TRPV_1$ receptors and the agents they respond to, they are probably involved with environmental and chemical-associated neurogenic inflammation. For some reason, cannabinoid-mediated $TRPV_1$ activation does not seem to cause inflammatory issues.

A 2010 study from a Chinese institute demonstrated the effects of anandamide on both human L02 liver cells and HepG2 hepatocellular carcinoma cells (Wu et al.). CB_1 receptor expression levels were low in both types of cells; conversely, CB_2 receptor levels were high.

Anandamide was found to induce necrosis in the HepG2 cells, but not the L02 cells, by activating both CB_1 and CB_2 receptors. This is an interesting conclusion, given that anandamide does not bind well with CB_2 receptors and the CB_1 receptor levels on the cancer cells were low.

The necrosis was accompanied by an increase in two important protein classes. The first, p38 mitogen-activated protein kinases (MAPKs), are part of a family of enzymes involved in embryogenesis, stress responses, and the cellular processes of differentiation, proliferation, and apoptosis (Pearson et al.).

The second class, Jun N-terminal kinases, are also a type of MAPK integral to cell proliferation and apoptosis processes. The context (source of stimulation and cell type) of JNK activation influences which action is taken (Dhanasekaran and Reddy). Kinases are enzymes that act as signal transducers by transferring phosphate groups between molecules. The movement of phosphate groups can turn enzymes on or off. Both the p38 MAPK and JNK pathways are involved in many cannabinoid-related apoptosis processes.

A 1998 study conducted in Italy showed that anandamide dose-dependently inhibited proliferation of the breast cancer cell lines MCF-7 and EFM-19 (De Petrocellis et al., "The Endogenous"). The endocannabinoid had no pro-apoptotic effects but reduced the number of cells in the S phase of the cell cycle. 2-arachidonoyl glycerol (2-AG), the other primary endocannabinoid, inhibited EFM-19 proliferation as well. Anandamide also impaired proliferation of the breast cancer cell lines T-47D and BT-474, but was ineffective against other cell types including N18TG2 neuroblastoma, RBL-2H3 leukemia, and H5V endothelioma cells.

Interestingly, anandamide was proposed to exert its anti-proliferative effect through a CB_1-like receptor, but not explicitly the CB_1 receptor itself. Despite the lack of explicit designation, it is likely CB_1 activation was at least partially responsible for anandamide's effect, as it was reversed by the CB_1 antagonist SR141716A.

Many forms of breast cancer fuel their own growth through the production of hormones. Prolactin is one such hormone; it is involved in the production of milk and hundreds of other processes. Most breast cancer cell lines produce significant amounts of prolactin, which subsequently activates prolactin receptors and enhances proliferation through acceleration of the G_1/S transition. Anandamide appears to reduce prolactin receptor synthesis, thus inhibiting prolactin action. The endocannabinoid also downregulated levels of the *brca1* protein, which increases in response to prolactin and is involved in promoting the aforementioned cell cycle transition.

In summary, the process can be described as:

CB_1-like receptor activation -> downregulation of prolactin receptors -> decrease in prolactin activity -> decrease in *brca1* protein expression -> decrease in cancer cell proliferation.

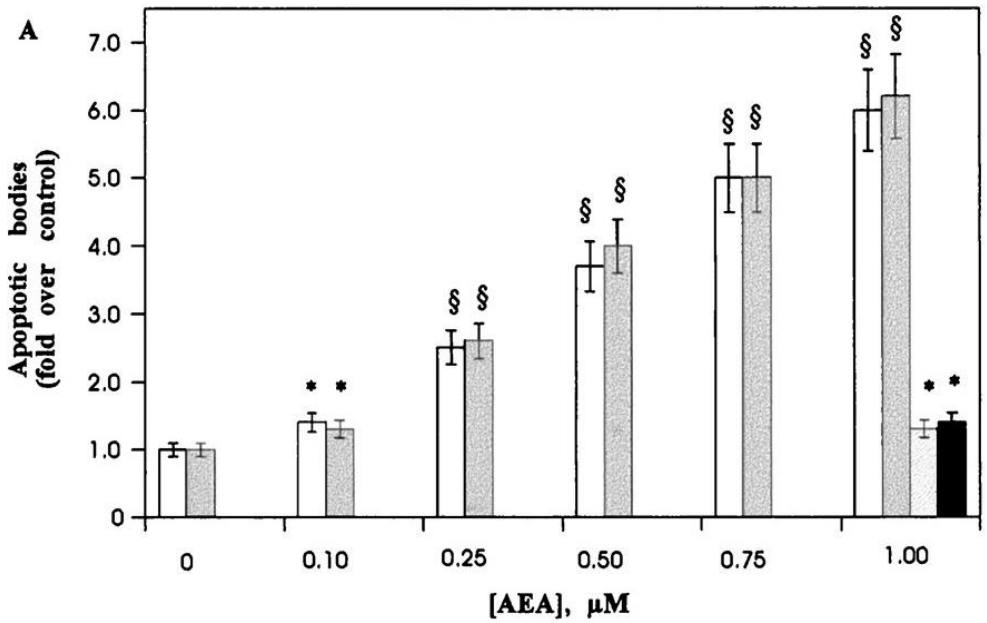
Another publication from Italian researchers reported the efficacy of a metabolically stable analog of anandamide called 2-methyl-2'-F-anandamide (Met-F-AEA) against breast cancer cell adhesion and migration (Grimaldi et al.). Met-F-AEA inhibited adhesion and migration of human and mouse

breast cancer cell lines MDA-MB-231 and TSA-E1 on a Type IV collagen surface through activation of CB_1 receptors. The compound was also found to significantly reduce the number and size of metastatic nodes in an *in vivo* model.

The anti-metastatic effects were proposed to occur via reductions in phosphorylation of focal adhesion kinase (FAK) and Src, two tyrosine kinases involved in migration and adhesion of many cell types. As previously described, kinases help convey signals and activate other enzymes by transferring phosphate groups from high-energy donors like ATP. Tyrosine kinases are simply a subclass of the general kinase family, distinguished by the propensity of phosphate groups to attach to a tyrosine amino acid.

Dysregulation of FAK, Src, and other tyrosine kinases is involved in the proliferation of many cancers, which has led to the development of tyrosine kinase inhibitors as a conventional treatment option. Since CB_1 receptor activation was implicated in the reduced phosphorylation of FAK and Src kinases, CB_1 agonists may potentially reduce kinase activity without the side effects of traditional kinase inhibitors.

A study in *The Journal of Biological Chemistry* illuminated how anandamide induces apoptosis in human neuroblastoma CHP100 and lymphoma U937 cells (Maccarrone et al.). Rat glioma C6 cells and human leukemia DAUDI cells were also susceptible to anandamide. Apoptosis increased in a dose and time-dependent manner. The endocannabinoid and endocannabinoid-like compounds 2-AG, oleoylethanolamide (OEA), and palmitoylethanolamide (PEA) had no effect on the cancers. The graph below depicts the dose-dependent relationship between anandamide and apoptosis. The levels of apoptosis are indicated relative to the apoptosis rates of nontreated cancer cells. The white bars are CHP100 cells and the gray bars are U937 cells.



The apoptotic effects in both cell lines were mediated by $TRPV_1$ receptors. However, in agreement with a previous study, the apoptosis response of C6 cells to anandamide was higher when CB_1 receptors, but not CB_2 receptors, were blocked. Interestingly, the apoptosis response of DAUDI cells to anandamide was higher when the CB_2 receptors, but not CB_1 receptors, were blocked. In these cases, cannabinoid receptors appear to have an anti-apoptotic role whereas $TRPV_1$ receptors seem to have a pro-apoptotic function. Somehow, despite anandamide being able to bind with CB_1 and $TRPV_1$ receptors, it preferentially activates the latter receptor to induce apoptosis, rather than the former receptor to prevent it. It is also possible that anandamide activates both receptors, but the function of $TRPV_1$ overrides that of CB_1.

Researchers also combined anandamide with cannabidiol (CBD), a plant-based cannabinoid. The combination slightly increased the apoptosis rates seen in both C6 and DAUDI cells compared with cells treated solely with anandamide.

Several downstream actions after $TRPV_1$ activation by anandamide were responsible for initiating the apoptosis process. One of these actions was mitochondrial uncoupling, wherein the mitochondria switched from manufacturing energy in the form of ATP to producing it as heat.

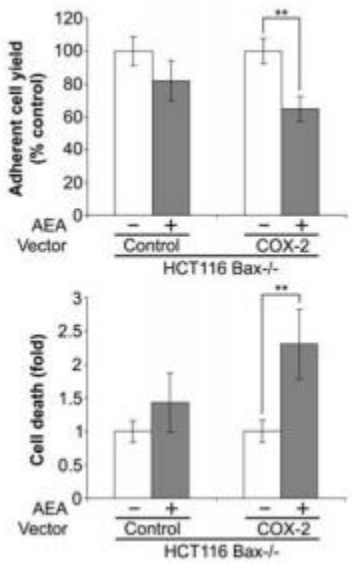
Intracellular calcium levels and cytochrome c levels also increased. Cytochrome c stimulates activity of the apoptotic enzymes caspase-3 and caspase-9. Caspases are integral components of the programmed cell death process. They fall under the category of proteases; enzymes which break down proteins. In effect, the activation of $TRPV_1$ by anandamide increases intracellular calcium levels, which leads to mitochondrial uncoupling, the release of cytochrome c, and subsequent enhancement of caspase activity, ultimately resulting in apoptosis.

Interestingly, while the above study and some others have indicated an apparent protective effect of CB_1 receptors on cancer cells, a 2011 study from the Central Hospital of Wuhan in China showed how anandamide strongly suppressed the proliferation of CaCo-2 colorectal cancer cells through a CB_1 receptor-dependent mechanism (Liao et al.). Anandamide also induced apoptosis in the cancer cells through an apparent receptor-independent interaction with lipid rafts. These effects of anandamide were dose-dependent and increased expression of the pro-apoptotic enzyme caspase-3. An earlier 2008 study in Italy had showed increasing anandamide levels with enzyme or transport inhibitors reduced the development of precancerous colon lesions (Izzo et al.).

Another study conducted in 2010 revealed more about how anandamide induces non-apoptotic cell death in apoptosis-resistant colon cancer cells (Patsos et al.). First, it was shown that cyclooxygenase-2 (COX-2) expression was a determining factor in the sensitivity of cancer cells to anandamide-induced apoptosis. COX-1 and COX-2 are enzymes that help synthesize prostanoids, which are fatty-acid based molecules that promote inflammation. While the specific function of COX-2 in regards to cell death was not explored in the article, its necessity was adequately demonstrated. HCA7 colorectal cancer cells, which highly express COX-2, are sensitive to cell death via anandamide, but blocking COX-2 expression protects cancer cells from death and growth inhibition.

To explore how anandamide affected apoptosis-resistant cancers, the researchers used HCT116 colorectal carcinoma cells which were deficient in Bak and Bax expression. These

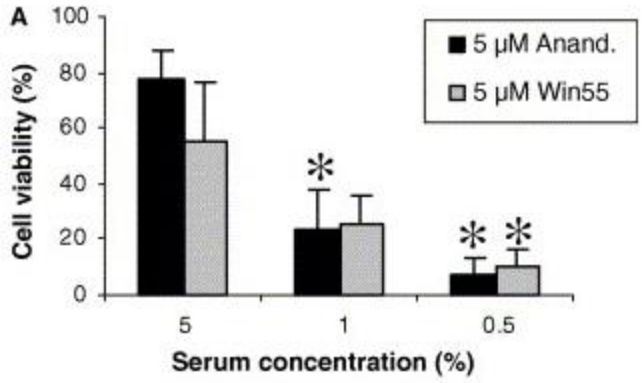
proteins are integral to the apoptosis process, so cells lacking these proteins are apoptosis-resistant. Since HCT116 cells are naturally low in COX-2, they were transfected with the enzyme. Indeed, when COX-2 was present, anandamide was very effective at inducing non-apoptotic cell death in HCT116 cells. Anandamide also induced cell death in unaltered HCT116 cells, but at a lower rate than the COX-2 transfected cells. The process was not mediated by the cannabinoid receptors or reactive oxygen species (ROS) generation.

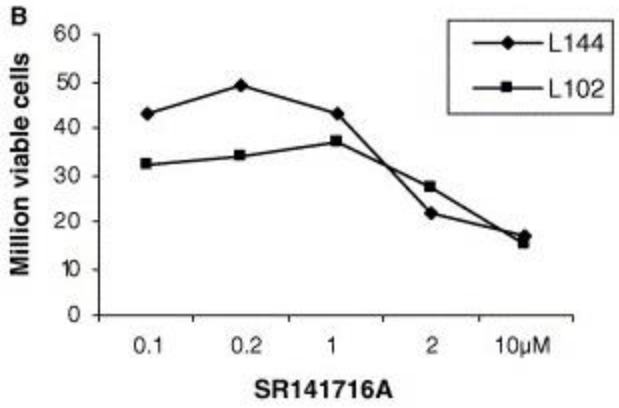


A 2009 study from the University of Tokyo examined the effect of anandamide alone or in combination with the chemotherapeutic agent paclitaxel on human gastric cancer HGC-27 cells (Miyato et al.). At the very low dose of 1 micromole (μM), anandamide stimulated proliferation of cancer cells; at the larger dose of 10μM, it strongly suppressed proliferation and induced apoptosis through an apparent CB_1 receptor-dependent mechanism. A synthetic CB_1 agonist, arachidonyl-2-chloroethylamide, produced similar bimodal effects.

At the 10μM level, but not 1μM, anandamide synergistically enhanced the pro-apoptotic action of paclitaxel, possibly by activating caspase-3, -8, and -9. This supports the idea that cannabinoids do not interfere with traditional chemotherapy, but enhance its effectiveness.

The effects of cannabinoid receptor stimulation and blockade on mantle cell lymphoma (MCL) cell viability were researched in a 2005 Swedish study (Flygare et al.). MCL cells derived from tumor biopsies of fifteen patients were used, along with numerous other cell lines. Interestingly, anandamide and the synthetic cannabinoid Win-55,212-2 (both CB_1/CB_2 agonists) as well as the CB_1 antagonist SR141716A all inhibited viability of biopsy-derived MCL cells. Also of particular interest, in this case a *reverse* dose-dependent relationship was observed with the cannabinoids. Smaller doses caused sharper reductions in cell viability. Conversely, there was a dose-dependent relationship between SR141716A and reduced viability of the cancer cells.





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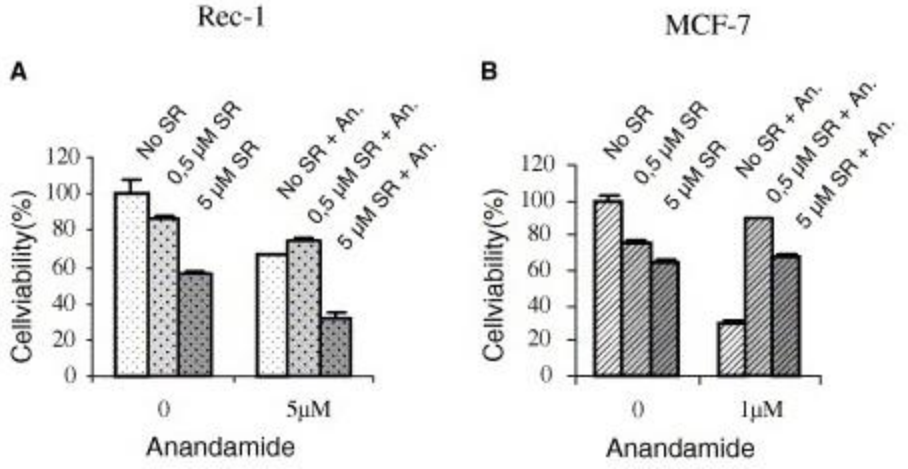
As the study points out, it is curious how CB_1 blockade has been shown to either potentiate or inhibit the anti-cancer effects of anandamide. The relationship was examined further by testing anandamide and SR141716A combinations on the Rec-1 MCL cell line and the MCF-7 breast cancer cell line. A small (1μM) dose of SR141716A inhibited anandamide's ability to reduce viability in the REc-1 line, but a larger dose (5μM) potentiated it. On the contrary, in the MCF-7 line, both doses inhibited anandamide. Interestingly, the smaller dose had a greater inhibitory effect than the larger one.



A further experiment led the authors to conclude that CB_1 receptors mediated the viability-reducing effect of anandamide. Furthermore, although CB_1 antagonism had an anti-cancer effect, CB_1 agonism was shown to exert greater anti-cancer action. This was determined through experiments that compared Win-55,212-2 and SR141716A. While the role of $TRPV_1$ receptors was not explored, it is possible that, as shown in other studies, the concurrent activation of $TRPV_1$ and antagonism of CB_1 creates greater anti-cancer effects. In any case, the ability of both CB_1 activation and blockade to stop cancer warrants more investigation into why this is happening.

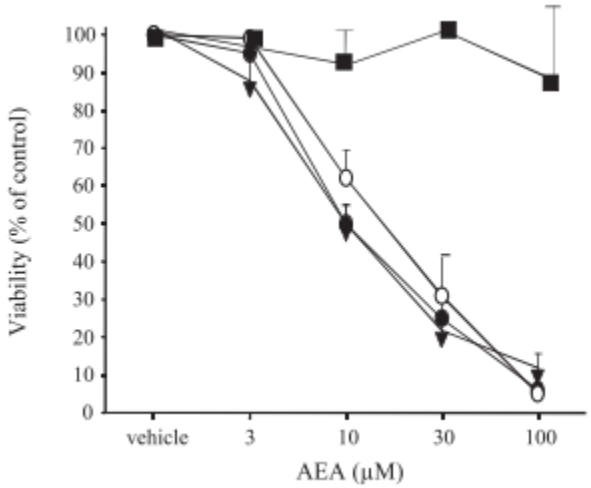
An October 2013 study by researchers at the University of Pisa in Italy described how anandamide induced apoptosis in melanoma A375 cells (Adinolfi et al.). By activating CB_1 receptors, anandamide led to a concentration-dependent decrease in cell viability with a corresponding increase in caspase-3 and caspase-7 activation, which is associated with apoptosis. Lipid rafts and GPR55 were also potentially implicated in the action of anandamide, as the activation of GPR55 with a synthetic agonist reduced cell viability and the destruction of lipid rafts reversed anandamide-induced cytotoxicity.

COX-2 and lipoxygenase (LOX), a family of enzymes involved in catalyzing reactions involving polyunsaturated fatty acids, were also integral to the cytotoxic effect of anandamide. While the precise mechanisms were not explored, it was postulated that COX-2 metabolizes anandamide into cytotoxic prostaglandin E_2-ethanolamides. Additionally, it was theorized that metabolism of anandamide by 15-lipoxygenase into eoxamides contributed to anandamide-mediated cytotoxicity. These theories were based on observations from other studies.

A May 2014 study in *Head & Neck* showed that anandamide, but not 2-AG, inhibited proliferation of human head and neck squamous cell carcinoma (HNSCC) SNU-1041, SNU-1066, and PCI-1 cells (Park et al.). High levels of anandamide killed the cells. Another HNSCC cell line, PCI-13, as well as two noncancerous cell lines (HOK-16B and fibroblast cell lines), were unaffected by anandamide. The anticancer effects were not mediated by cannabinoid or TRPV receptors, but relied on the intracellular transport of anandamide into the cancer cells. Once inside the cells, anandamide caused an increase in reactive oxygen species (ROS) and 8-isoprostanes (prostaglandin-like compounds formed from free-radical catalyzed peroxidation of fatty acids).

Increased ROS levels were largely responsible for the antiproliferative and cell-killing effects of anandamide. Whether the death of cells was apoptotic or necrotic in nature was not explored.

A study by researchers at University Hospital in Switzerland examined anandamide's effects on Caski, HeLa, and C299 cervical carcinoma cells (Contassot et al.). Anandamide administration induced apoptosis in all three cell lines, as indicated by DNA fragmentation and caspase-7 cleavage. The effects were mediated primarily through activation of $TRPV_1$ receptors. Blocking CB_1 or CB_2 receptors enhanced the viability-reducing effect of anandamide, indicating a protective role of cannabinoid receptors for those cells.



(The square box is healthy cells, the others are the three cervical carcinoma cell lines)

Despite some uncertainties at the cellular level, human evidence suggests both CB_1 and CB_2 receptors possess anti-cancer functionality. A study compared dozens of hepatocellular carcinoma patients with either high or low expression levels of CB_1 and CB_2 receptors (Xu et al.). Patients with high expression levels had significantly better disease-free survival than those with low expression levels. This phenomenon may be due to the involvement of CB_1 and CB_2 receptors in suppression of tumor development. Another study in the *Journal of Neurochemistry* lent more support to the notion that endocannabinoids mediate an anticancer effect. It compared the levels of 2-AG and anandamide, among other constituents of the endocannabinoid system, in Grade IV glioblastoma and Grade I meningioma tissues to normal human brain tissue (Petersen et al.). The glioblastoma tissues had far higher levels of anandamide, 17-fold higher than normal tissue, while meningiomas had 20 times more 2-AG than normal tissue. The authors concluded, "The enhanced level of the 2-arachidonoyl glycerol, anandamide and other N-acylethanolamines detected in the two types of tumour tissue may possibly act as endogenous anti-tumour mediators by stimulation of both cannabinoid and non-cannabinoid receptor-mediated mechanisms."

II. The Anti-Cancer Activity of Phytocannabinoids

Given the ability of endocannabinoids to kill and inhibit cancer cells, it makes sense that phytocannabinoids have similar properties. In fact, there is significantly more research related to the anti-cancer activity of phytocannabinoids than endocannabinoids. Before examining the research, it is important to understand the similarity between both types of cannabinoids.

Endocannabinoids are Omega-3- and Omega-6-derived chemicals that function as neurotransmitters in the brain and throughout the body (Ramsden et al.). They activate CB_1 and CB_2 receptors to exert a variety of biological effects, ultimately working to maintain homeostasis. For example, if neurons are firing off neurotransmitters excessively, endocannabinoids stimulate presynaptic CB_1 receptors to inhibit neurotransmission.

Phytocannabinoids are terpenophenolic compounds produced uniquely in the cannabis plant (Galal). Like endocannabinoids, they also activate CB_1 and CB_2 receptors in vertebrate organisms, as well as specific downstream pathways (Laprairie et al.). There is an especially powerful similarity between anandamide and tetrahydrocannabinol (THC). A 2007 study found that anandamide produced THC-like discriminative and neurochemical effects (Solinas et al., "The Endogenous"). Furthermore, all the major cannabinoids, including cannabidiol (CBD), cannabichromene (CBC), cannabigerol (CBG), cannabinol (CBN), and tetrahydrocannabivarin (THCV), influence endocannabinoid synthesizing and degrading enzymes as well as anandamide cellular uptake (De Petrocellis et al., "Effects"). More research will undoubtedly yield further similarities between phytocannabinoid and endocannabinoid activity.

Brain Cancer

The relationship between cannabis and brain cancer is especially strong. Cannabinoids are known to cross the blood-brain barrier, and have been shown to kill numerous types of brain cancer cells. Their high barrier permeability and strong apoptosis-inducing effects make cannabinoids very promising candidates for the treatment of many brain cancers.

A 1998 study by Dr. Manuel Guzmán in Spain showed how THC induced apoptosis in C6.9 glioma cells (Sánchez et al.). THC caused a dose-dependent drop in mitochondrial oxidative metabolism. It also increased ceramide levels by stimulating the breakdown of sphingomyelin, a ceramide-containing lipid found in cell membranes. Researchers posited that ceramide may be the mediator of THC-induced apoptosis. In addition to C6.9 cells, the astrocytoma cell line U373 MG and the neuroblastoma cell line $N_{18}TG_2$ were also susceptible to THC. Non-transformed astrocytes and neurons were not susceptible, indicating the selective ability of THC to specifically target cancerous cells. The pro-apoptotic effect, at least so far as C6.9 cells, was not mediated by CB_1 receptors.

Another 2004 study from Guzmán's team showed that THC helped prevent the formation of new blood vessels (angiogenesis) to tumors (Blázquez et al., "Cannabinoids Inhibit the Vascular"). Through the use of synthetic cannabinoid receptor agonists and antagonists, as well as

anandamide, it was determined the anti-angiogenic effects were conferred through CB_1 and CB_2 receptors. Cannabinoid-induced ceramide biosynthesis was posited to be integral to the decrease in vascular endothelial growth factor (VEGF), which is arguably the most important proangiogenic molecule. The anti-angiogenic effects were seen in C6 glioma cells, U373 MG astrocytoma cells, PDV.C57 skin carcinoma cells, and ECV304 bladder cancer epithelioma cells.

In addition, activation of CB_2 receptors with the synthetic cannabinoid JWH-133 altered the expression of 10 genes related to the VEGF pathway. Several cannabinoids also reduced activation of vascular endothelial growth factor receptor-2 (VEGFR-2) without changing total expression levels of the receptor. JWH-133 administration caused a sharp reduction in the size of mouse gliomas, thus confirming the ability of CB_2 activation to inhibit angiogenesis *in vivo*.

To test whether cannabinoid receptor activation had any functional relevance in humans, researchers locally administered THC directly into the tumors of two patients with glioblastoma multiforme. Biopsies were taken before and after the treatment. In both patients, VEGF and total VEGFR-2 levels decreased, despite the latter effect not being observed in the cells. Therefore, this study provides human evidence that a phytocannabinoid could be clinically useful as an anti-angiogenic agent.

A 2008 study showed that THC reduced matrix metalloproteinase-2, a protein associated with the invasion and progression of tumors (Blázquez et al., "Cannabinoids Inhibit Glioma"). In the glioma cell lines C6.9, SW1088, T98G, U87MG, and U118MG cells, THC reduced MMP-2 expression. The reduction of MMP-2 in U87MG cells in particular was mostly mediated by CB_2 receptor activation, and was associated with reduced invasion of the cancer cells. Increased ceramide levels and subsequent upregulation of the stress-related protein p8 were integral to the anti-invasive effects of THC.

In mice given subcutaneous gliomas with C6.9 glioma cells, THC decreased tumor growth and MMP-2 expression. However, other MMP family members also associated with glioma invasion were unaffected, and mice with gliomas from cannabinoid-resistant C6.4 cells did not respond to THC treatment (tumor growth and MMP-2 expression were unchanged).

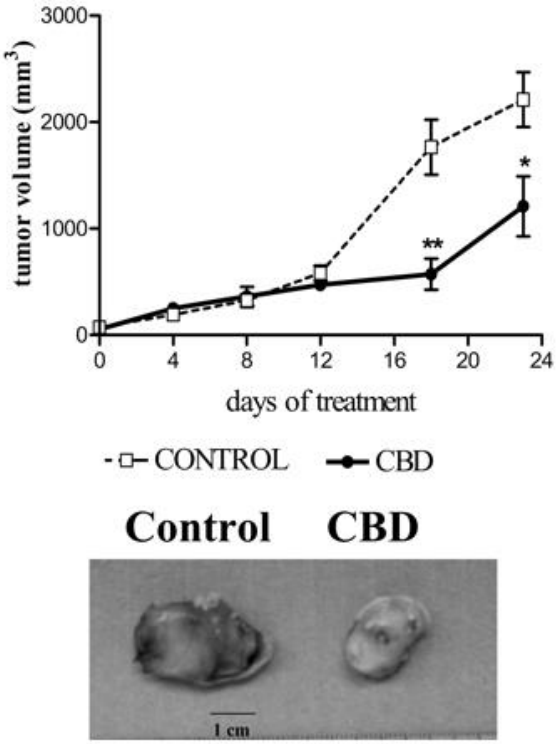
Finally, two human patients with glioblastoma multiforme were administered THC directly into their tumors. Before-and-after biopsies revealed that MMP-2 levels were effectively reduced in both patients.

Like THC, CBD exerts numerous cytotoxic effects on brain cancer cells. A 2004 study from an Italian university explained how CBD reduced viability, inhibited proliferation, and induced apoptosis in the U87 and U373 glioma cell lines (Massi et al.). In a concentration and time-dependent fashion, CBD inhibited mitochondrial oxidative metabolism and caused apoptotic cell death. The effects may have been partially mediated by CB_2 receptors, but a curious observation complicated matters. When CB_2 receptors alone were blocked with an antagonist, CBD's antiproliferative effects were significantly but not completely reduced. However, when CB_1 and $TRPV_1$ receptors were blocked along with CB_2 receptors, its effects were not reduced.

Furthermore, even the antagonistic effect of isolated CB_2 blockade disappeared after four days. Since inactivation of the cannabinoid receptors with pertussis toxin had no influence on

CBD's effects either, it is unlikely that either CB_1 or CB_2 receptors played a major role in this case. While the study did not conclude which receptor mediated CBD's effects, an increase in oxidative stress was implicated as a mechanism of action.

Researchers also induced U87 tumors in mice to determine the *in vivo* effectiveness of CBD. The graph below illustrates the positive results.



In a 2013 study, researchers explored how CBD affects proliferation, viability, and invasion of U87-MG and T98G glioma cells (Solinas et al., "Cannabidiol"). CBD caused a decrease in invasion from 10% to 90% in a concentration-dependent manner. The amount of CBD required to inhibit invasion was much less than what was required to reduce viability. In U87-MG cells, CBD downregulated six proteins involved in malignancy, motility, invasion, and angiogenesis of tumors (MMP-9, TIMP-1, TIMP-4, uPA, SerpinE1-PAI-1, and VEGF). In T98G cells, CBD downregulated nine proteins (MMP-9, TIMP-4, SerpinE1-PAI-1, VEGF, TGF-β1, CXCL-16, PDGF-AA, MCP-1, and Angiogenin).

CBD also reduced phosphorylation (and thus, activation) of two signaling pathways related to cancer cell survival and proliferation; extracellular signal-regulated kinases (ERK1/2) and Akt (sometimes known as protein kinase B). These two pathways are known as pro-survival signaling pathways (Vauzour et al.; Benbrook and Masamha), so inhibiting ERK1/2 and Akt in cancer cells has been linked to pro-apoptotic and antiproliferative effects.

ERK is also known as MAPK, a kinase enzyme discussed earlier (specifically, MAPK1 is also known as ERK2 and MAPK3 is also known as ERK1). MAPK activation regulates MMP activation, so CBD's ability to reduce the MAPK/ERK pathway may be responsible for its effects

on MMP enzymes. Specifically in the U87-MG cells, CBD inhibited hypoxia-inducible factor 1-alpha (HIF1-α), a molecule responsible for inducing cell survival, motility, and angiogenesis under hypoxic (low oxygen) conditions. It was not determined which receptor mediated these effects, although cannabinoid and vanilloid receptors were ruled out.

The researchers also noted that T98G cells have been deemed cannabinoid-resistant due to their insensitivity to THC. However, their work demonstrated the effectiveness of CBD against this cell line.

A brief study in the *British Journal of Pharmacology* showed that CBD inhibited migration of U87 glioma cells in a concentration-dependent manner (Vaccani et al.). Cannabinoid and vanilloid receptors were not responsible for this anti-metastatic effect.

An April 2015 study in the *International Journal of Cancer*, conducted by Italian researchers from several universities, illustrated a unique way by which CBD can fight gliomas (Nabissi et al.). The cannabinoid reduced viability, promoted differentiation, and stimulated autophagy in glioma stem-like cells (GSCs). Evidence suggests glioblastoma tumors are composed of both normal tumor cells and smaller amounts of cancer stem cells (Altaner). GSCs are resistant to chemotherapy and radiation, and may be responsible for the aggressive recurrence rate of glioblastomas. Therefore, the ability to inhibit these types of cells is an especially critical attribute of effective brain tumor drugs.

CBD was found to reduce viability in GSC lines #1, #30, and #83. This effect was mediated by $TRPV_2$ receptors, but not CB_1, CB_2, or $TRPV_1$ receptors. CBD also increased expression of $TRPV_2$ receptors on the GSCs. CBD downregulated phosphorylated Akt; a decrease in the phosphorylated, activated form of Akt is a key signal for autophagy. Activation of autophagy was responsible for the decrease in viability, as well as cell cycle arrest at the G_o/G_1 phase. Interestingly, CBD also modulated the expression of genes involved in the regulation of autophagy and apoptosis.

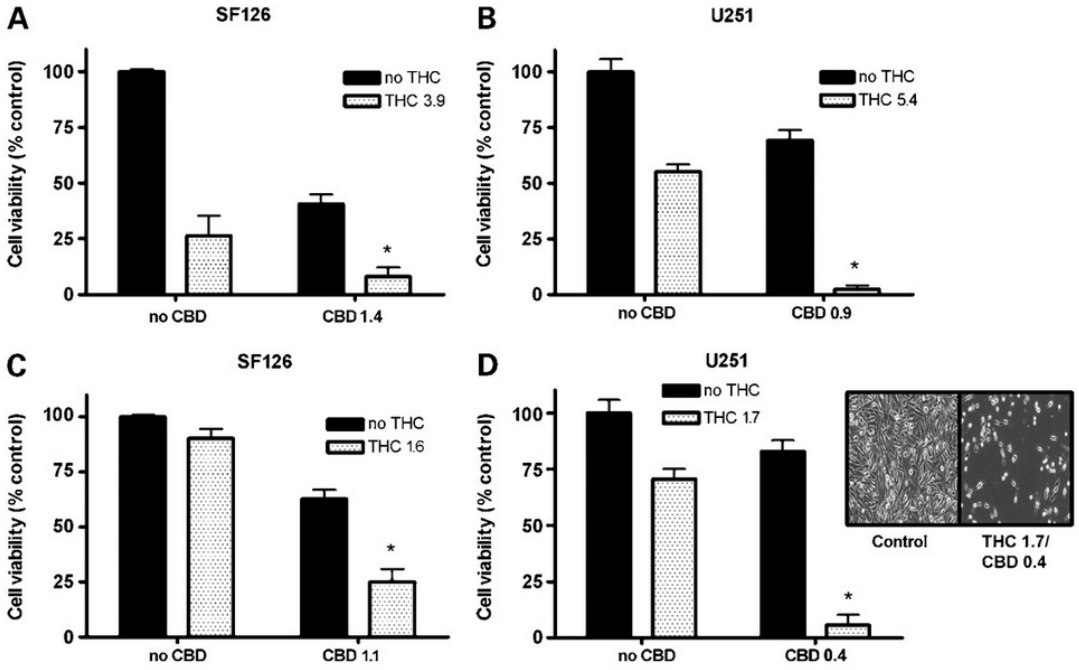
Furthermore, autophagy was necessary for the induction of GSC differentiation. As cells become more differentiated, or specialized towards a certain function, they become easier to treat. That is, poorly differentiated cancer cells are harder to treat than well-differentiated cancer cells, at least partially because they have underdeveloped signaling pathways that are targeted by cancer drugs.

After inducing autophagy, CBD caused reductions in the stem cell markers CD133, Oct-4, SSEA-1, and Nestin, as well as increases in the differentiation markers GFAP and beta-III tubulin. These markers reached levels comparable to those seen in differentiated GSCs. CBD also increased expression of Aml-1a, a transcription factor protein that regulates differentiation; indeed, it promoted differentiation and impaired proliferation in GSCs. Furthermore, Aml-1a was shown to bind to $TRPV_2$ gene promoters, which increased levels of $TRPV_2$ receptors.

By stimulating differentiation, CBD increased the sensitivity of GSCs to carmustine, a chemotherapeutic agent. GSCs were resistant to carmustine treatment alone, but when the drug was combined with CBD, a strong increase in apoptotic cells was observed. However, CBD combined with temozolomide, another chemotherapy drug, was not effective.

Although CBD can inhibit the psychoactive effects of THC, both cannabinoids work synergistically (greater than additively) to fight cancer. A January 2010 study from the California Pacific Medical Center Research Institute demonstrated this synergy in the context of glioblastoma (Marcu et al.). The researchers first tested THC and CBD individually against the glioblastoma cell lines SF126, U251, and U87. Both compounds had strong antiproliferative effects in all cell lines, but CBD was substantially stronger. For example, the antiproliferative IC_{50} value of THC in the U87 line was 3.3μmol/L, whereas it was only 0.6μmol/L for CBD. Therefore, it took 5.5 times more THC to inhibit U87 cell proliferation by 50% (compared to controls) than CBD.

In the SF126 and U251 cell lines, THC and CBD acted synergistically to inhibit cell proliferation. No such effect was observed in the U87 line. Synergy was determined using the combination index technique. Below is a graphical representation of THC and CBD effects alone and in combination.



While THC and CBD acted synergistically to inhibit cell growth, they did not work synergistically to inhibit cell invasion. However, both cannabinoids were significant anti-invasive agents and together produced a small additive effect. Both cannabinoids also caused cell cycle arrest, specifically increasing the number of cells in the G_0/G_1 phase and decreasing those in S phase. In this case, there was a synergistic effect on cell cycle arrest.

Interestingly, in both U251 and SF126 cells, the combination of THC and CBD caused a substantial reduction in phosphorylated ERK (pERK), but not total ERK. This effect was not seen when either THC or CBD were used alone (although high doses of isolated CBD caused a small reduction in pERK; no effect was seen with high doses of isolated THC), potentially indicating that anticancer synergy was created through the activation of a new biological pathway, rather than

increased activation of the pathways THC and CBD individually modified. Given this observation, it makes sense that THC and CBD synergistically increased apoptosis in addition to the other effects. Furthermore, simply increasing the dose of isolated THC treatment was unable to achieve the level of apoptosis seen with combined THC and CBD treatment.

CB_2 activation and an increase in reactive oxygen species (ROS) were additional mechanisms by which THC and CBD induced apoptosis. Since blocking CB_2 receptors did not affect isolated CBD-induced apoptosis, it is likely that THC was primarily responsible for CB_2-mediated apoptosis. However, blocking ROS production inhibited the apoptosis induced by isolated THC, isolated CBD, and combination treatments. An increase in ROS causes cellular stress and can lead to cell death.

Isolated treatment of U251 cells with THC, as well as combined treatment with THC and CBD, led to increased expression of the stress-associated gene p8. There was not much difference between the isolated and combination treatments, and isolated CBD did not have a statistically significant impact on p8 expression, indicating that pathway is unique to THC.

Isolated THC and CBD treatment also had little to no effect on caspase-3, -7, and -9 activation. However, the combination treatment substantially upregulated the activity of those caspases, as well as increased expression of poly (ADP-ribose) polymerase (PARP). PARP refers to a number of specific proteins involved in DNA repair and cell death.

In summary, combining THC and CBD led to the unique downregulation of pERK and upregulation of caspase and PARP activity. This is the likely explanation for why combined THC and CBD treatment synergistically decreased proliferation, enhanced cell cycle arrest, and increased apoptosis of glioblastoma cells.

It is interesting to note that numerous companies have applied to the FDA for orphan drug designation (ODD) status for cannabinoids for the treatment of brain tumors. Orphan drugs are those developed and intended for conditions affecting 200,000 people or less. While obtaining ODD status is only the first step in bringing such a drug to market, the FDA still considers scientific evidence on safety and efficacy when granting this status. Due to the non-specific page titles and convenience of viewing, the direct links are provided below.

AXIUM Pharmaceuticals, CBD and THC designated on 01/08/2018 for treatment of glioblastoma multiforme
(https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=620417)

Insys Development Company, CBD designated on 09/24/2014 for treatment of glioma
(https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=450814)

Insys Development Company, CBD designated on 8/20/2014 for treatment of glioblastoma multiforme
(https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=444814)

GW Research Ltd., CBD and THC designated on 12/3/2015 for treatment of glioma (https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=498215)

Interestingly the FDA has also granted ODD status for CBD and/or THC for the treatment of infantile spasms, Dravet syndrome, Lennox-Gastaut syndrome, tuberous sclerosis complex, Fragile X syndrome, Graft versus Host Disease, pediatric schizophrenia, neonatal hypoxic ischemic encephalopathy, amyotrophic lateral sclerosis, and complex regional pain syndrome. The list can be seen by searching "cannabidiol" on this page - https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm. A unique link does not appear after the search is made.

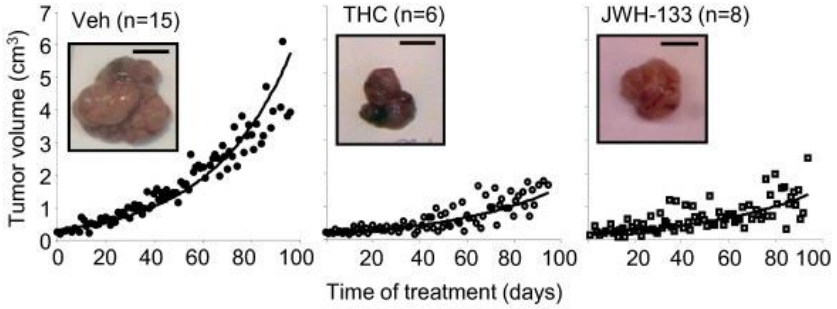
#	Generic Name	Orphan Designation	Designation Date	Designation Status
1	cannabidiol	Treatment of infantile spasms	07/23/2015	Designated
2	cannabidiol	Treatment of Dravet syndrome	07/01/2014	Designated
3	cannabidiol	Treatment of tuberous sclerosis complex.	04/19/2016	Designated
4	cannabidiol	Treatment of Fragile X syndrome	02/23/2016	Designated
5	cannabidiol	Prevention of Graft versus Host Disease (GVHD).	07/14/2015	Designated
6	cannabidiol	Treatment of glioma	09/24/2014	Designated
7	cannabidiol	Treatment of pediatric schizophrenia (pediatrics is defined as 0 through 16 years of age)	11/17/2014	Designated
8	cannabidiol	Treatment of infantile spasms	06/13/2016	Designated
9	cannabidiol	Treatment of Graft versus Host Disease	11/29/2016	Designated
10	cannabidiol	Treatment of glioblastoma multiforme	08/20/2014	Designated
11	cannabidiol	Treatment of Lennox-Gastaut syndrome	06/23/2014	Designated
12	cannabidiol	Treatment of Dravet syndrome.	11/14/2013	Designated
13	cannabidiol	Treatment of neonatal hypoxic ischemic encephalopathy	04/22/2015	Designated
14	cannabidiol	Treatment of Dravet syndrome	12/21/2017	Designated
15	cannabidiol (CBD)	Treatment of Lennox-Gastaut syndrome	10/24/2017	Designated
16	cannabidiol (CBD) and Delta-9-tetrahydrocannabinol (THC)	Treatment of glioblastoma multiforme	01/08/2018	Designated
17	Cannabidiol and delta-9-tetrahydrocannabinol	Treatment of amyotrophic lateral sclerosis	03/15/2018	Designated
18	cannabidiol;	Treatment of Lennox-Gastaut syndrome	02/27/2014	Designated
19	delta-9-tetrahydrocannabinol and cannabidiol	Treatment of complex regional pain syndrome	03/07/2018	Designated
20	delta-9-tetrahydrocannibinol and cannabidiol	Treatment of glioma.	12/03/2015	Designated

Breast Cancer

Breast cancer primarily affects women, but men also have about a .1% chance of developing the disease (U.S. Breast Cancer). Many forms of the disease are highly aggressive, and there is a great need for new treatments.

A 2010 study by Dr. Manuel Guzmán's team illustrated how THC combated HER-2 breast cancer; it also examined the nature of cannabinoid receptor expression in different mammary tissues (Caffarel et al.). Normal, non-transformed tissue had no significant CB_1 or CB_2 expression, while breast cancer cells had low CB_1 expression and high CB_2 expression. ErbB2-positive breast cancer had especially high levels of CB_2 receptors. The ErbB2 tyrosine kinase receptor is a member of the EGF receptor family, and its overexpression in breast cancer cells is associated with very aggressive, highly invasive, highly proliferative, and poorly differentiated cancers.

In mice, THC strongly reduced tumor growth. It also decreased the number of tumors the animals generated throughout treatment. THC-treated animals never developed more than three tumors, whereas 41% of untreated animals developed four or more tumors. The synthetic CB_2 agonist JWH-133 was also effective.



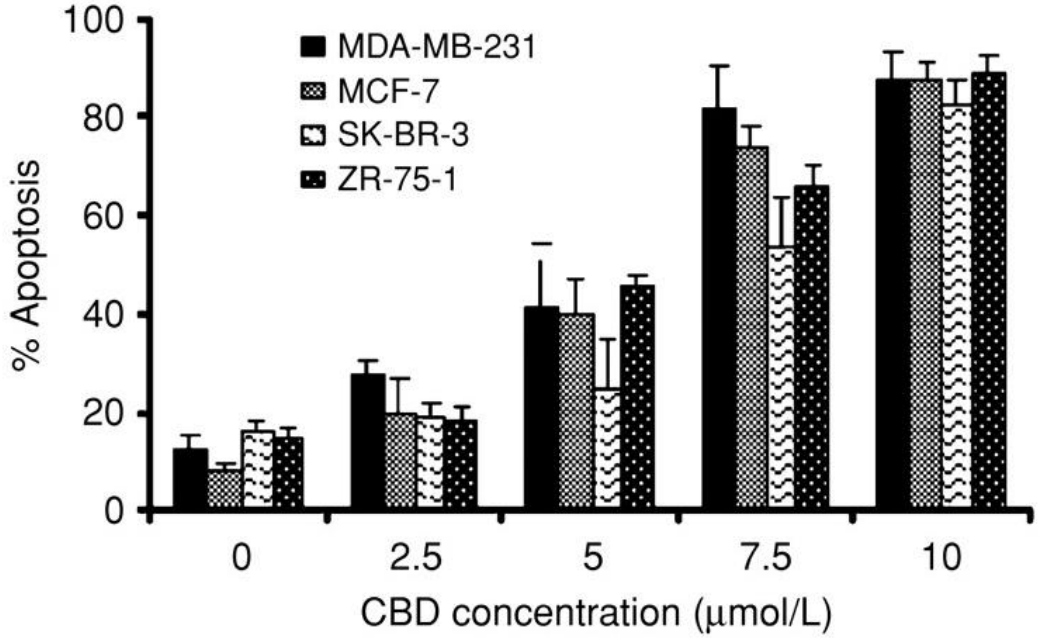
Tumors/ animal	1	2	3	4 or more
Control (n=12)	25%	8%	25%	41%
THC (n=6)	50%	17%	33%	0%
JWH-133 (n=6)	33%	50%	17%	0%

THC affected cancer growth through numerous mechanisms. It induced apoptosis, inhibited angiogenesis, reduced proliferative potential, and decreased lung metastases. A reduction in MMP-2 was associated with the anti-angiogenic action.

Using the N202.1A cell line, the researchers determined THC exerted its effects via CB_2 receptor activation. The cannabinoid diminished levels of phosphorylated S6 ribosomal protein, which is associated with activation of the Akt/mammalian target of rapamycin (mTOR) pathway. Therefore, THC exerted its effects at least in part through downregulation of Akt/mTOR. The

mTOR protein is a kinase that regulates many aspects of cell growth, proliferation, and survival. Indeed, N202.1A proliferation was reduced with THC and JWH-133 administration.

A 2011 study in *Molecular Cancer Therapeutics* described several mechanisms by which CBD reduced viability and caused apoptosis in breast cancer cells (Shrivastava et al.). Both estrogen receptor-positive (MCF-7 and ZR-75-1) and estrogen receptor-negative (MDA-MB-231 and SK-BR-3) breast cancer cells were susceptible to CBD.



Autophagy, a catabolic process in which lysosomes break down cellular components, often precedes or accompanies apoptosis. Depending on the setting, autophagy can protect from apoptosis, act as an alternative pathway to cell death, or act with apoptosis as a combined mechanism for cell death. Indeed, both autophagy and apoptosis increased in a concentration-dependent manner. This effect was mediated through the induction of endoplasmic reticulum (ER) stress, independently of CB_1/CB_2 and $TRPV_1$ receptors. ER stress was quantified by increased phosphorylation of EIF2α kinases, which are activated in response to numerous kinds of stress stimuli.

CBD also decreased phosphorylated Akt, thus downregulating its signaling. The reduction in Akt precedes autophagy and apoptosis, a logical phenomenon given its role as a survival molecule. Other components of the Akt pathway, including mTOR and 4EBP1, had decreased phosphorylation. The proto-oncogenic (a gene with the potential to cause cancer) protein cyclin D1 was also reduced in a concentration-dependent manner.

CBD increased the cleavage of procaspases -3, -7, and -9 into their smaller, active forms; caspases -3, -7, and -9. It also activated capsase-8, which cleaves cytosolic (found in the cytosol)

Bid. Bid is a member of the Bcl-2 protein family, which regulates mitochondrial homeostasis during apoptosis (Lutter, Perkins, and Wang). Cytosolic Bid is cleaved by caspase-8 into its active form, truncated Bid (tBid), where it moves to the mitochondria and increases mitochondrial membrane permeability (a phenomenon also associated with reductions in mitochondrial membrane potential). This leads to the release of cytochrome c, which can promote cell death through further caspase activation. Bax, another member of the Bcl-2 family, was also increased by CBD and contributed to the enhanced mitochondrial membrane permeabilization.

Additionally, Fas-ligand (Fas-L) expression increased; the activation of the cell death receptor Fas by Fas-L leads to caspase-mediated apoptotic cell death (Waring and Müllbacher). Therefore, CBD was posited to initiate mitochondria-mediated apoptosis through both internal (tBid translocation) and external (Fas-L) pathways. CBD also induced cleavage and translocation of beclin-1, an autophagy-regulating protein, to the mitochondria, which yet further enhanced cytochrome c release and apoptosis.

CBD increased ROS generation in the breast cancer cells, an effect which was integral to subsequent autophagy and apoptosis. This step seems to be fairly upstream in the CBD-induced apoptotic pathway, although the exact point of ROS generation was unclear.

Research from the California Pacific Medical Center in California, led by Dr. Sean McAllister, illuminated an incredible method by which CBD reduces breast cancer cell proliferation, invasion, and metastasis (McAllister et al.). The cannabinoid can reduce expression of the Id-1 gene, which codes for the Id-1 protein. This protein enhances proliferation and invasion of breast cancer cells, as well as other types of cancer.

Three days of CBD treatment of human breast cancer MDA-MB-231 cells led to almost complete abolishment of Id-1 expression. Interestingly, CBD also increased expression of the Id-2 gene, a pro-differentiation factor associated with a good prognosis in breast cancer patients. Cancer cells that are more differentiated and closer in structure to normal cells generally grow slower and are less aggressive than poorly differentiated, highly abnormal cells. Decreasing Id-1 and increasing Id-2 expression could be a potent mechanism behind CBD's anticancer effects.

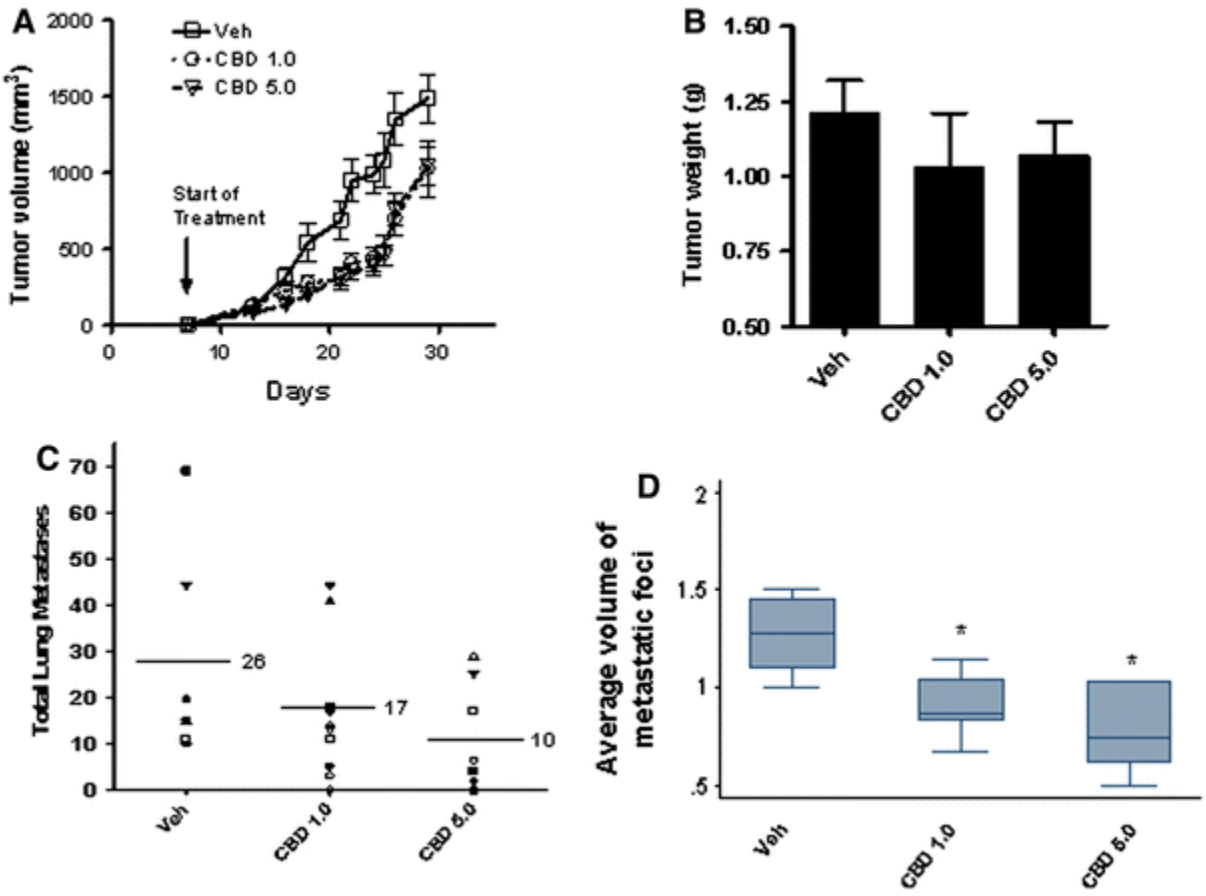
Also of interest, and in contrast to previous studies showing decreased ERK activation after CBD treatment, this study showed CBD-induced downregulation of Id-1 was dependent on upregulation of ERK activity. It was noted that sustained upregulation of ERK leads to inhibition of cell growth, whereas short-term upregulation leads to cell growth.

An increase in ROS was also shown to play a key role in Id-1 downregulation. Co-activation of the independent ERK and ROS pathways seemed to converge and lead to greater Id-1 downregulation.

The researchers used mouse metastatic breast cancer 4T1 cells to determine the effects of CBD on the cell cycle. In both 4T1 and MDA-MB-231 cells, cell cycle arrest was observed; specifically, there was an increase of cells in the G_o/G_1 phase and a decrease of those in the S phase. Downregulation of Id-1 in 4T1 cells inhibited cell invasiveness.

Using an *in vivo* model, it was shown that CBD significantly reduced primary tumor growth, the number of lung metastases, and the volume of metastases, in a largely dose-dependent

manner. The primary tumor developed resistance to the inhibitory properties of CBD by Day 25 of treatment. Although not discussed in the study, such resistance can likely be overcome by using different ratios of THC and CBD, as well as incorporating other cannabinoids and terpenoids with anticancer activity.



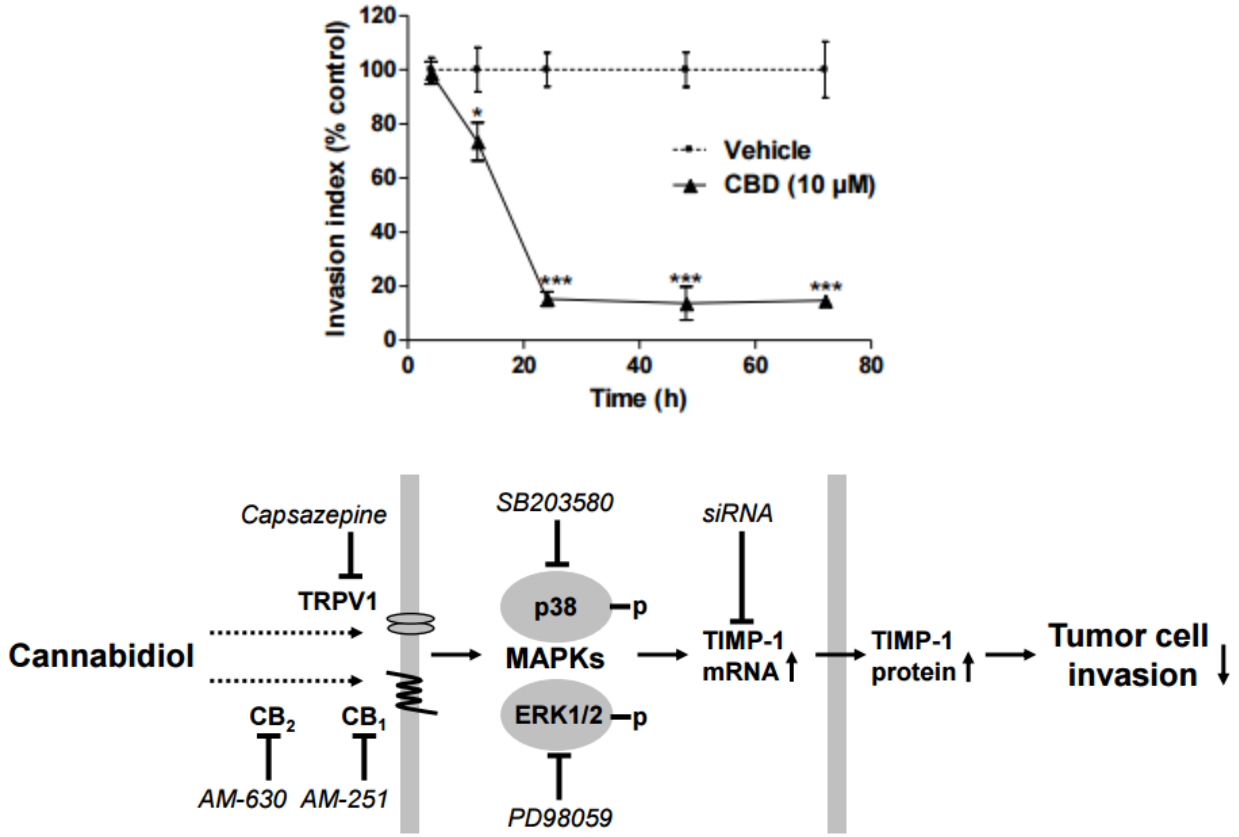
Cervical Cancer

Cervical cancer is one of the most common cancers affecting women. Interestingly, the first cell line ever isolated was from a woman with cervical cancer named Henrietta Lacks in 1951 (Freeman). The line, known as HeLa, went on to become the most commonly used cell line in the world. A 2010 study by German researchers used the HeLa and C33A cervical cancer lines to examine the anticancer impact of CBD (Ramer et al., "Cannabidiol"). At remarkably low concentrations, CBD was able to inhibit invasion of HeLa cells. Under one of the experimental conditions in which smaller numbers of cells were used (2.5×10^5 cells per well vs. 5×10^5 cells per well), CBD also significantly reduced cell viability.

The anti-invasive action was caused by the CBD-induced increase of tissue inhibitor of metalloproteinase-1 (TIMP-1). TIMP-1 is a protein involved in the regulation of cell growth and apoptosis (Egea et al.). The increase in TIMP-1, and the subsequent decrease in invasion, was dependent on activation/phosphorylation of p38 and p42/44 MAPKs. These effects were mediated by CB_1, CB_2, and $TRPV_1$ receptors.

Researchers used A549 lung cancer cells along with the C33A cervical cancer line to test whether the observed effects were not confined to HeLa cells. Indeed, in both A549 and C33A cells, CBD exhibited an anti-invasive effect that was dependent on p38 and p42/44 MAPK activation and TIMP-1 expression. Under the experimental condition using 2.5×10^5 cells per well, CBD significantly reduced viability of both types of cells.

Seeded cell number	Cellular viability (%)					
	HeLa		A549		C33A	
	Vehicle	CBD	Vehicle	CBD	Vehicle	CBD
5.0×10^5	100 ± 8.9	98.3 ± 7.6	100 ± 8.4	90.7 ± 6.3	100 ± 5.2	82.8 ± 4.1*
2.5×10^5	100 ± 2.3	62.5 ± 2.6***	100 ± 4.1	54.8 ± 1.1***	100 ± 6.0	56.2 ± 3.6***
1.0×10^5	100 ± 1.1	2.0 ± 0.2***	100 ± 3.3	1.5 + 0.6***	100 ± 8.4	12.1 ± 2.6***
0.5×10^5	100 ± 6.9	1.8 ± 0.1***	100 ± 1.4	1.5 + 0.7***	100 ± 6.2	11.4 + 0.8***
0.1×10^5	100 ± 4.2	3.3 ± 0.2***	100 ± 17.5	1.0 ± 0.8***	100 ± 1.3	10.6 ± 4.4***



Another study by the same lead author indicated the potential of THC to fight cervical cancer (Ramer and Hinz). THC and an anandamide analog, methanandamide (MA), diminished invasion of HeLa cells in a concentration-dependent manner. The compounds also exhibited progressively greater cytotoxic effects as lower cell densities were used in viability assays, as similarly observed in the above study.

The same pathway identified in the above study applied in this case. THC and MA administration led to increased activation of p38 and p42/44 MAPKs, which caused an increase in TIMP-1 levels. These effects were dependent on CB_1 and CB_2 receptors; in the case of MA, $TRPV_1$ receptors were also involved. Lower MMP-2 levels were also observed, although curiously, these cannabinoid-induced effects were not dependent on CB_1, CB_2, or $TRPV_1$ receptors.

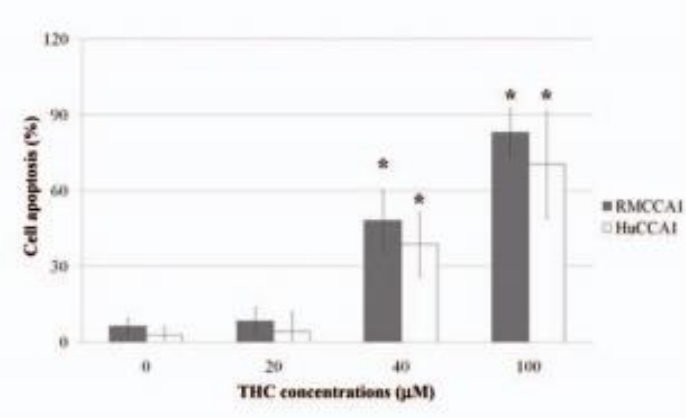
In addition to the HeLa cell line, THC and MA exerted anti-invasive effects against A549 and C33A cells through the same mechanisms.

Cholangiocarcinoma

Cholangiocarcinoma, or bile duct cancer, is an aggressive cancer characterized by rapid growth and metastasis. It is often diagnosed at an advanced stage, and new treatments are urgently required. A 2010 study published in *Cancer Investigation* by Thailand researchers indicated the potential of THC to act as a treatment for this type of cancer (Leelawat et al.).

It was first demonstrated that the human cholangiocarcinoma cell lines RMCCA1 and HuCCA1 expressed both CB_1 and CB_2 receptors. The levels of CB_1 were higher in the cancerous tissue compared to normal tissue. CB_2 levels were relatively similar, with apparent evidence of some upregulation in cancerous tissue.

At low concentrations of 5-20μM (roughly equivalent to a few milligrams), THC had no significant effect on cholangiocarcinoma cell proliferation. However, the 20μM concentration substantially inhibited migration and invasion. Within the 40-100μM (100μM is about 31 milligrams) concentration range, THC inhibited cell proliferation in a dose-dependent manner. At these concentrations, it also induced apoptosis in both cell lines.



Actin is a highly abundant structural protein found in virtually all eukaryotic cells ("Actin"). Actin polymerization is the process by which the monomeric units of actin combine to form actin filaments. Together with motor proteins, these filaments create actin cytoskeletons, which are involved in many cellular functions like cell motility and mechanical signal transduction. Actin is also involved in the generation of pseudopodia, which are protrusive structures coming out of the cell membrane that help with locomotion. The low dose range (5-20μM) of THC effectively decreased actin polymerization and psuedoponia formation. These phenomena explain, at least in part, the anti-invasive effect of THC.

THC also apparently inhibited cell resistance to anoikis, a form of apoptosis that occurs when cells do not receive survival signals from the extracellular matrix. The abrogation of this resistance may stem from THC's ability to reduce phosphorylation of Akt and mitogen-activated

protein kinase kinase 1/2 (MEK1/2). MEK1/2 activates MAPK molecules, so reducing phosphorylation of MEK1/2 ultimately inhibits the MAPK survival pathway.

Colon Cancer

Colon cancer is one of the top causes of cancer-related deaths. While it can often be eliminated when caught early, advanced colon cancer has been virtually incurable. Cannabinoids show great promise in treating this disease.

A November 2011 study in *Anticancer Research* determined that CBD induced apoptosis and inhibited proliferation of SW480 colon cancer cells (Sreevalsan et al.). This was accomplished through CBD-induced phosphatase expression, specifically the molecules *DUSP1*, *DUSP10*, serum ACPP, cellular ACPP and PTPN6. These phosphatases inhibit kinase activation by removing their phosphate groups. While the researchers did not determine which kinases the phosphatases interacted with, previous studies have shown induction of *DUSP1* by cannabinoids resulted in MAPK inactivation. Therefore, it is possible that CBD ultimately induced apoptosis through inhibition of the MAPK pathway. While this is not certain, the researchers conclusively demonstrated that CBD-induced apoptosis was phosphatase-dependent, as blocking phosphatase enzymes reduced apoptosis.

The study also used the synthetic CB_1 agonist WIN 55,212-2, which induced apoptosis through similar phosphatase-dependent mechanisms. A very surprising observation was made when determining the role of cannabinoid receptors. Blocking either CB_1 or CB_2 receptors inhibited CBD-induced apoptosis, but such blockade had no effect on WIN-induced apoptosis. Due to these results, the researchers concluded CBD's effects were cannabinoid receptor-dependent and WIN's effects were receptor-independent. This is interesting, as CBD does not normally directly activate CB_1 or CB_2 receptors, and may even antagonize them (De Mello Schier et al.; Morgan et al.). However, some evidence suggests CBD acts as an inverse agonist at both cannabinoid receptors (Pertwee). CBD may indirectly activate cannabinoid receptors by increasing endocannabinoid activity, as discussed further below.

A 2012 study from the Endocannabinoid Research Group in Italy used CBD and the carcinogenic agent azoxymethane (AOM) to evaluate the chemoprotective (ability to reduce risk of cancer) potential of the cannabinoid (Aviello et al.). As expected, AOM administration in mice caused preneoplastic lesions (known as aberrant crypt foci [ACF]), polyps, and tumor formation, and was associated with upregulation of phosphorylated Akt, inducible nitric oxide synthase (iNOS, an enzyme sometimes associated with tumor development), and COX-2 (an inflammatory enzyme). Downregulation of caspase-3 also occurred. CBD reduced ACF (67% inhibition), polyps (57% inhibition), and tumor formation (66% inhibition) at least partially by countering the AOM-induced Akt and caspase-3 changes, although the cannabinoid had no effect on COX-2 or iNOS. Therefore, the *in vivo* reduction in tumors was likely driven by reduced Akt phosphorylation and restoration of caspase-3 expression. Graphical representation of the results is found below. As shown, the lower dose of CBD (1mg/kg vs. 5mg/kg) was more effective than or generally as effective as the higher dose.

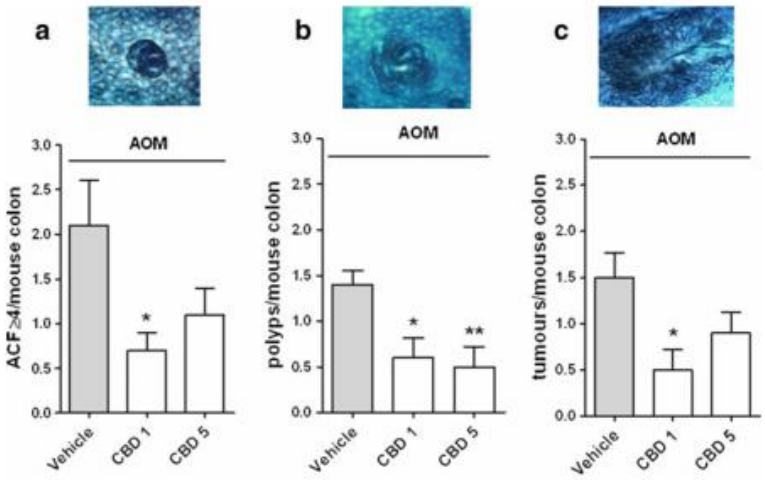


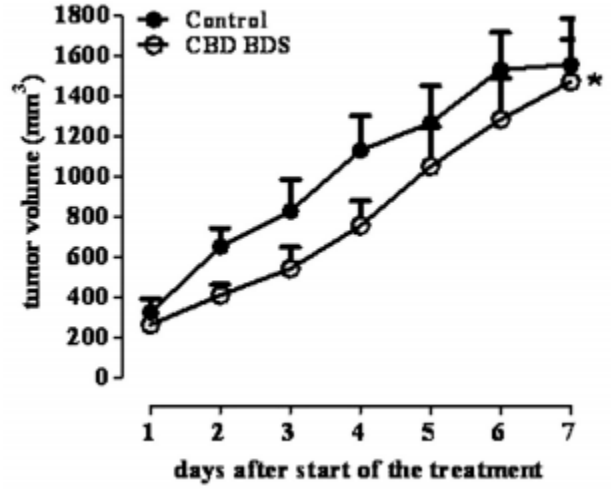
Fig. 1 Aberrant crypt foci with four or more crypts (ACF≥4/mouse) (**a**), polyps (**b**) and tumours (**c**) induced in the mouse colon by AOM: effect of cannabidiol (CBD, non-psychotropic cannabinoid, 1 and 5 mg/kg). AOM (40 mg/kg in total, IP) was administered, at the single dose of 10 mg/kg, at the beginning of the first, second, third and fourth week. CBD was given (IP) three times a week for the whole duration of the experiment starting 1 week before the first administration of AOM. Measurements were performed 3 months after the first injection of AOM. Insets: representative images of an ACF (**a**), polyp (**b**) and tumour (**c**) captured at ×20, ×10 and ×5 magnifications, respectively. Each bar represents the mean±SE mean of 9–11 mice. **P*<0.05 and ***P*<0.01 vs vehicle

Using human Caco-2 and HCT116 cell lines, the researchers determined that CBD could not reduce cell viability at concentrations between 0.01µM and 10µM. However, CBD exerted strong antiproliferative effects at the same concentrations. In the Caco-2 cells, CBD mediated its effects through CB_1, $TRPV_1$, and PPAR-γ receptors, but not CB_2 receptors. Reduced expression of phosphorylated Akt was observed, along with increased levels of 2-AG. Anandamide levels were also higher, although this observation was not statistically significant. This phenomenon could explain the CB_1 and CB_2-dependent nature of many of CBD's effects, as the cannabinoid may indirectly activate the receptors by increasing endocannabinoids.

A later 2014 study from the same research group showed how whole-plant CBD-rich cannabis extract, known as CBD botanical drug substance (CBD BDS), along with pure CBD, reduced proliferation of human DLD-1 and HCT116 colon cancer cells (Romano et al.). Both CBD BDS and pure CBD inhibited proliferation, but not viability, of these cells. Healthy cells were unaffected by either type of CBD treatment. The potency and efficacy of either treatment was identical. The researchers also determined CBD BDS had greater affinity for CB_1 and CB_2 receptors than pure CBD, and the CBD BDS inhibited proliferation via activation of both cannabinoid receptors. On the contrary, pure CBD inhibited proliferation via CB_1, but not CB_2, receptors. It is very likely that the presence of other cannabinoids and terpenoids influences the pharmacodynamics and pharmacokinetics of CBD.

In addition to the cell studies, the effects of CBD BDS in two *in vivo* models were examined. Using AOM, preneoplastic lesions (ACF), polyps, and tumors were induced in mice. CBD BDS at 5mg/kg significantly reduced ACF formation by 86%, polyps by 79%, and tumors by 40% (although statistical significance was not fully achieved in the last measure). In a xenograft model, the substance also slowed tumor growth. However, by Day 7 of treatment there was no difference between the control and CBD BDS groups. The possibility that tumors can develop

resistance even to complex cannabis formulations must be considered, and in practice, there may be a need to modify cannabis extract treatments if resistance is observed.



Although THC and CBD have gotten all the attention so far, cannabigerol (CBG) is another cannabinoid with potent anticancer activity. In fact, CBG is the parent cannabinoid from which all other cannabinoids are derived. It is a weak partial agonist of CB_1 and CB_2 receptors, a potent $TRPA_1$ agonist, a weak $TRPV_1$ and $TRPV_2$ agonist, and a potent $TRPM_8$ and 5-HT1A antagonist. In short, the receptor interactions of CBG are quite complex.

A 2014 study in *Carcinogenesis* showed that CBG reduced viability in Caco-2 and HCT116 cells in a concentration and time-dependent manner (Borrelli et al.). At the concentration used to reduce viability by 50% in the cancer cells, CBG did not affect viability of healthy cells, although at exceptionally high levels it did exhibit a cytotoxic effect.

CBD and cannabidivarin (CBDV), which are also $TRPM_8$ antagonists, inhibited Caco-2 cell viability in a concentration-dependent manner. Cannabichromene (CBC), which does not have activity at $TRMP_8$, also inhibited cell growth but to a lesser degree than the other cannabinoids. Indeed, $TRPM_8$ antagonism was determined to be integral to the anticancer effect of CBG.

Blocking CB_1 receptors had no effect on the action of CBG; interestingly, blocking CB_2 receptors enhanced CBG's inhibitory power. Other TRP channels besides $TRPM_8$ were not involved.

In addition to reducing viability, CBG was a potent inducer of apoptosis in Caco-2 cells. It dramatically increased expression of CCAAT/Enhancer-binding protein homologous protein (CHOP), which activates the apoptosis process. This effect was dependent on $TRPM_8$ antagonism. CBG also significantly increased ROS production, which contributed to its proapoptotic ability.

Using mice, researchers found that CBG inhibited tumor growth by 45.3%. The differences in tumor volumes between the control and treated mice became statistically significant at day 3 of treatment; statistical significance was sustained until the end of the experiment. Therefore, the tumors did not develop resistance to CBG.

As in the previous studies, AOM was used to induce ACF, polyps, and tumors in mice. At 5mg/kg, CBG completely suppressed the formation of ACF and reduced tumors by half. However, it had no significant effect on polyp formation.

Kaposi's Sarcoma

Kaposi's sarcoma (KS) is a cancer characterized by the growth of abnormal tissue under the skin or in the lining of the mouth, nose, or throat ("Kaposi's Sarcoma"). It can also appear in other organs. KS occurs frequently in HIV/AIDS patients due to their weakened immune systems, where it develops very quickly. When KS occurs in otherwise healthy people, it usually progresses more slowly. KS is caused by Kaposi sarcoma-associated herpesvirus (KSHV). KSHV-infected endothelial cells are commonly used to conduct *in vitro* experiments for KS research.

A 2012 study in *Genes & Cancer* explored the effects of CBD on KS (Maor et al.). First, it was shown that CBD had no effect on the infection of primary human dermal microvascular endothelial cells (HMVECs) by KSHV. However, CBD exerted a strong antiproliferative effect against KSHV-infected HMVECs. CBD also reduced proliferation of normal HMVECs, but to a much lesser extent, indicating a predominantly selective mechanism of action against infected cells. This selectivity was further observed in CBD-induced apoptosis; while CBD caused apoptosis in all cells, the effect was more pronounced in KSHV-infected HMVECs, especially at lower concentrations. However, at higher concentrations, apoptosis rates were similar among the healthy and infected cells.

KSHV vGPCR is a unique type of G protein-coupled receptor that promotes KS tumorigenesis by immortalizing endothelial cells and enhancing proliferation. In a dose-dependent fashion, CBD inhibited production of this receptor. It also reduced GRO-α, a protein associated with enhancement of vGPCR activity. CBD had no effect on IL-8, another enhancement-related protein.

CBD significantly reduced levels of VEGFR-3, which promotes KSHV-induced infection, growth, and transformation of endothelial cells. Furthermore, CBD dose-dependently decreased levels of VEGF-C, a ligand of VEGFR-3, suggesting the compound comprehensively inhibits signaling of this pathway to impair proliferation and induce apoptosis in KS cells.

Leukemia & Lymphoma

There are several manifestations of leukemia, but most start in blood-forming tissue like bone marrow ("Leukemia"). The cancer is associated with a significant accumulation of immature white blood cells in the blood. Lymphoma is a similar cancer that affects white blood cells; notably, it also involves the lymph nodes, and thus is a cancer of the lymph system ("Lymphoma"). Hodgkin lymphoma starts directly in the lymph nodes, but other forms like non-Hodgkin lymphoma can originate in white blood cells (specifically T or B cells).

A 2005 study conducted at St. Bartholomew's Hospital in London indicated the potential of THC to inhibit numerous types of leukemia cells (Powles et al.). THC reduced the viability of acute lymphoblastic leukemia CEM, acute promyelocytic leukemia HL60, and erythroleukemia HEL-92 cells. The latter cells were more resistant to THC than the former two, but still susceptible. THC also induced apoptosis in these cell lines, as well as normal peripheral blood mononuclear cells, suggesting non-selective action. However, the authors posited this was potentially tissue-specific, as selectivity was observed in neuronal cells. The cytotoxic effects of THC were not mediated by CB_1 or CB_2 receptors. THC also worked additively, but not synergistically, with the chemotherapeutic agent cisplatin to reduce cell viability.

THC altered the expression of genes influencing the MAPK pathway, ultimately affecting levels of MAPK phosphatase 3 (MKP3) and mitogen-activated protein kinase kinase 2 (MEK2). MEK2 phosphorylates ERK2/MAPK1, whereas MKP3 dephosphorylates ERK2/MAPK1; therefore, the former has an activating role and the latter has an inactivating role. THC significantly suppressed the MAPK pathway by increasing MKP3 and decreasing MEK2, contributing to inactivation of ERK2/MAPK1 through multiple mechanisms. Not surprisingly, THC also decreased phosphorylated ERK expression. These effects underlie at least a significant part of THC's viability-reducing ability. Researchers stated THC was "exceptionally efficacious" at inducing cell death.

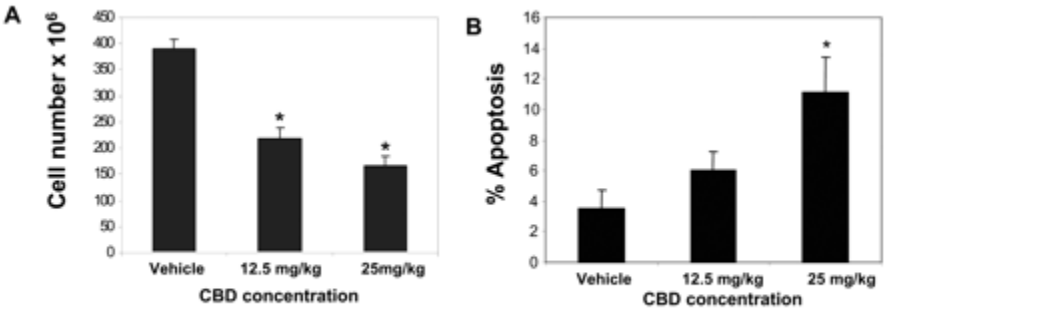
A 2006 study carried out by the University of South Carolina School of Medicine demonstrated how CBD reduced viability and induced apoptosis in both EL-4 murine lymphoma and human Jurkat and MOLT-4 leukemia cell lines (McKallip et al.). The anticancer effects described below were dependent on CB_2 receptor activation, but CB_1 and $TRPV_1$ receptors were not involved.

CBD impaired cell viability through a wide variety of processes. It increased cleavage of caspase-8 and procaspase-2, -9, and -10 into their smaller forms; these steps initiate the apoptotic caspase cascade. CBD-induced cleavage of Bid also occurred. As discussed in the breast cancer section, cytosolic Bid is cleaved into tBid, where it transfers to the mitochondria, reduces mitochondrial membrane potential, and facilitates the release of cytochrome c into the cytosol, promoting apoptosis.

CBD increased expression of two specific subtypes of nicotinamide adenine dinucleotide phosphate-oxidases (NADPH oxidases), the Nox4 and $p22^{phox}$ enzymes. NADPH oxidases produce superoxide and other ROS molecules (Bedard and Krause). One of the primary purposes of ROS

production is defense against invading bacteria, as oxidant molecules are capable of killing organisms. NADPH oxidases are also involved in cellular signaling, regulation of gene expression, and posttranslational protein processing. By increasing Nox4 and $p22^{phox}$, CBD stimulated ROS generation. The increase in ROS led to a reduction in phosphorylated p38 MAPK levels, which contributed at least in part to CBD-induced apoptosis. Levels of phosphorylated ERK and phosphorylated JNK were unaffected.

CBD also reduced the size of EL-4 derived tumors in mice.



Cannabidiol treatment leads to reduced tumor burden and apoptosis in vivo.

A 2006 study conducted by researchers at Virginia Commonwealth University described how THC dose-dependently induced apoptosis in Jurkat leukemia cells (Jia et al.). The effects were mediated by both $CB_1$and CB_2 receptors. Interestingly, Jurkat cells naturally express significant levels of CB_2 and low levels of CB_1, which would seemingly preclude involvement of CB_1 receptors. However, THC significantly increased the expression of both types of cannabinoid receptors, a phenomenon which apparently enhanced the cannabinoid's anticancer properties.

Suppression of the Raf-1/MEK/ERK cytoprotective signaling pathway was the chief mechanism promoting THC-induced apoptosis. First, THC reduced phosphorylation of the Raf-1 protein. The phosphorylation of Raf-1 activates a MAPK cascade, beginning with the phosphorylation of MAP2K1/MEK1 and MAP2K2/MEK2 and subsequently MAPK3/ERK1 and MAPK1/ERK2 ("RAF1"). Indeed, all of these phosphorylated proteins were diminished by THC treatment, although there were no effects on their total levels (their non-phosphorylated forms were still present). Another protein involved in the pathway, p90RSK, also showed reduced phosphorylation. Furthermore, inhibition of ERK1/2 was observed in MOLT-4 leukemia cells, SupT1 lymphoma cells, and Hut78 Sezary Syndrome (an aggressive T-cell lymphoma).

The suppression of the ERK signaling cascade caused dephosphorylation of the protein Bad, which translocated to the mitochondria and interfered with the survival function of the proteins Bcl-2 and Bcl-X_L. In contrast with previously described molecules, dephosphorylation activates Bad while phosphorylation deactivates it. In its latter form, Bad is sequestered in the cytosol, and when dephosphorylated undergoes translocation. Specifically, p90RSK catalyzes the phosphorylation of Bad, an effect which largely underlies p90RSK's prosurvival role. Researchers

confirmed that THC-induced inactivation of ERK and activation of Bad played an integral role in apoptosis.

In summary, the process can be described as:

CB_1 and CB_2 receptor activation -> Decreased sequential phosphorylation of Raf-1, MEK1/MEK2, ERK1/ERK2, and p90RSK -> Dephosphorylation of Bad and subsequent translocation from cytosol to mitochondria -> interference with Bcl-2 and Bcl-X_L survival proteins, leading to cell death.

Another study in *Experimental Cell Research* conducted by Dr. Manuel Guzmán further demonstrated how THC induces apoptosis in Jurkat cells (Herrera et al.). The cannabinoid increased ceramide levels via CB_2 receptor activation. The ceramide then reduced mitochondrial membrane potential, causing release of cytochrome c. Subsequently, there was an increase in caspase-3, -7, and -8 activities. Specifically, cytochrome c led to the activation of caspase-3, which then activated caspase-8, ultimately inducing apoptosis. A feedback loop may exist, given that caspase-8 can also enhance mitochondrial membrane permeabilization through its interaction with Bid.

A 2013 study by Dr. Wai Liu and other researchers at the University of London illuminated the synergistic anticancer properties of numerous nonpsychotropic cannabinoids, including CBD, CBG, cannabigevarin (CBGV), and their respective acid forms, being cannabidiolic acid (CBDA), cannabigerolic acid (CBGA), and cannabigevaric acid (CBGVA) (Scott et al.). In CEM and HL60 leukemia cells, all the cannabinoids were able to arrest cell cycle progression at all phases of the cell cycle (global arrest), leading to reduced cell numbers. CBD induced apoptosis at higher doses.

The cannabinoids generally increased ERK in both cell lines. They also substantially increased $p21^{WAFI}$, a kinase inhibitor that is intimately involved in cell cycle modulation, including arrest, as well as the regulation of cell growth and death.

CBD was combined one at a time with the other cannabinoids to test for synergistic or antagonistic relationships. All combinations tested were either additive or mildly synergistic in nature. The neutral cannabinoids were all more effective than their acidic counterparts, and of those, CBD and CBG were the strongest.

An interesting observation was the benefit of a "recovery phase" for increasing cytotoxicity. The researchers observed that prolonged cannabinoid treatment had an extended cytostatic effect rather than cytotoxic. However, by stopping cannabinoid treatment after several days of administration, the cell cycle resumes and the cells die.

A patent published on December 23, 2004 described the use of CB_2 agonists, including THC, for the treatment of malignancies like leukemia or lymphoma ("Patent US20040259936").

Treatment of neoplasia

US 20040259936 A1

ABSTRACT

A method of treating a patient in need of therapy for an abnormality of cells of the immune system is provided comprising administration of a therapeutically effective dose of a compound having CB2 cannabinoid receptor activity. The abnormality is particularly a malignancy such as a leukemia or lymphoma.

Publication number	US20040259936 A1
Publication type	Application
Application number	US 10/497,911
PCT number	PCT/US2002/039310
Publication date	Dec 23, 2004
Filing date	Dec 9, 2002
Priority date	Dec 7, 2001
Also published as	CA2468794A1, EP1461027A1, EP1461027A4, WO2003049727A1
Inventors	Leonard Nagarkatti, Prakash Nagarkatti, Robert McKallip, Catherine Lombard, Seongho Ryu, Less «
Original Assignee	Nagarkatti Leonard C, Prakash Nagarkatti, Mckallip Robert, Catherine Lombard, Seongho Ryu, Less «
Export Citation	BiBTeX, EndNote, RefMan

Referenced by (7), Classifications (18), Legal Events (1)

External Links: USPTO, USPTO Assignment, Espacenet

Liver Cancer

Liver cancer can be especially debilitating and usually results from scarring (cirrhosis) of the liver. The most common form is hepatocellular carcinoma (HCC) ("Liver Cancer"). HCC is the third leading cause of cancer-related deaths worldwide.

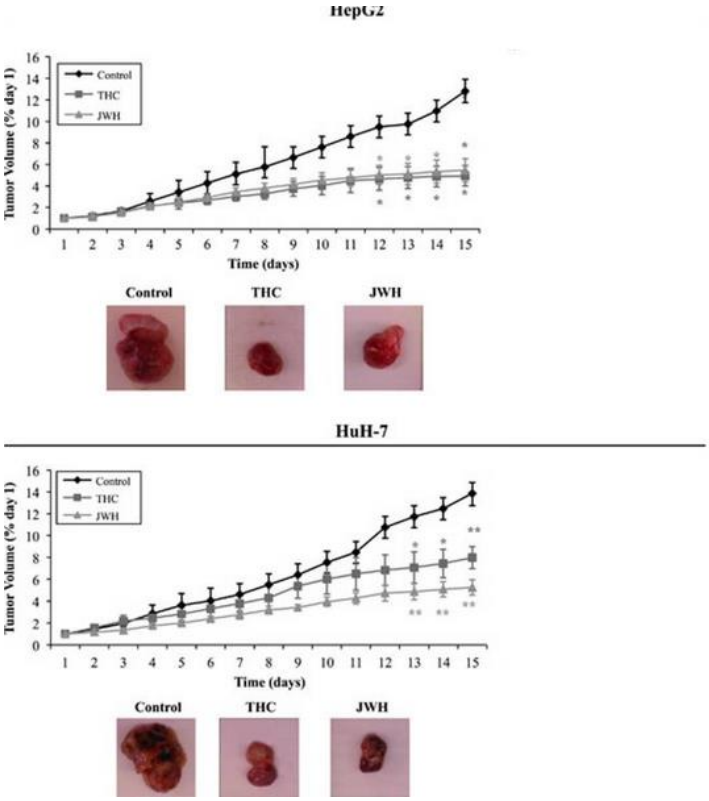
THC is a potent inducer of apoptosis in the human HCC cell lines HepG2 and HuH-7 (Vara et al., "Anti-Tumoral"). The effect was mediated by CB_2, but not CB_1, receptors. THC increased the lipidated form of microtubule-associated protein 1 light chain 3α (LC3), an autophagy-related molecule which attaches to autophagosomes after autophagy becomes stimulated. Autophagosomes are organelles that absorb cellular debris or components ("Lippincott-Schwartz"). They transfer these components to lysosomes via fusion, where they are digested. By influencing this process, THC contributed to dynamic autophagy in both cell lines. It was shown that autophagy induction by cannabinoids occurred before apoptosis and was necessary for full cell death to occur. One of the pathways leading to autophagy was dependent on endoplasmic reticulum (ER) stress. The first step appeared to be an increase in ceramide biosynthesis, which is associated with ER stress. THC increased phosphorylation of eukaryotic translation initiation factor 2 (eIF2α), a protein involved in the ER stress response. It also upregulated the pseudokinase tribbles homolog 3 (TRB3), which inhibits the Akt/mTORC1 pathway (mTOR exists in two complexes, C1 and C2; C1 was overtly implicated in this study). Indeed, in addition to enhancing eIF2α and TRB3, activity of the Akt/mTORC1 pathway was inhibited. Specifically, there was decreased phosphorylation of Akt. Other proteins involved in the pathway, including p70S6 kinase and ribosomal protein S6, also exhibited decreased phosphorylation.

Furthermore, there was increased phosphorylation of adenosine monophosphate-activated protein kinase (AMPK). This kinase is an important intracellular nutrient status sensor and key regulator of autophagy. Its enhanced activation contributed to cannabinoid-induced autophagy and apoptosis; in fact, AMPK contributed heavily to LC3 lipidation (the attachment of LC3 to autophagosomes that stimulates autophagy).

THC appeared to activate AMPK by stimulating activity of calmodulin-activated kinase kinase (CaMKK), which is one of the chief enzymes that phosphorylates AMPK. The other major kinase involved in AMPK phosphorylation, human tumor suppressor liver kinase B1 (LKB1), was not involved.

As demonstrated through pharmacological and genetic blockade experiments, it was shown that inhibition of the Akt/mTORC1 pathway by TRB3 upregulation and stimulation of AMPK occurred through independent mechanisms, although they both contributed to LC3 lipidation and autophagy.

To demonstrate effectiveness *in vivo*, mice were treated daily with 15mg/kg of THC for 15 days. The cannabinoid "almost totally blocked the growth of HepG2 cell-derived tumors." Similar effects were seen in HuH-7 tumors. Increased AMPK phosphorylation and reduced Akt phosphorylation were also observed, indicating the observed cell-level effects transferred to animals.



A later study by most of the same researchers further illuminated the role of the PPAR-γ receptor in THC-induced apoptosis of HepG2 and HuH-7 cells (Vara et al., "Involvement"). PPAR-γ is a receptor found inside cells that helps regulate lipid metabolism and insulin sensitization. Its activation is associated with growth inhibition and apoptosis of numerous tumor cells (Krishnan, Nair, and Pillai).

THC increased PPAR-γ mRNA and protein expression in an AMPK-independent manner, suggesting that AMPK and PPAR-γ are independent pathways activated by cannabinoids. However, TRB3 was found to be integral to the expression of PPAR-γ in both control and cannabinoid-treated cells, indicating TRB3's fundamental importance to PPAR-γ.

Although the interaction between TRB3, autophagosomes, and PPAR-γ is complex, it was concluded that cannabinoids induce autophagy through PPAR-γ activation. The receptor also played a role in cannabinoid-induced apoptosis, contributing to the cleavage of procaspase-3 into caspase-3. While THC is known to directly activate PPAR-γ (O'Sullivan), researchers posited that in this case, the activation was indirect.

Through an experiment with mice, PPAR-γ activation was shown to be critical to the *in vivo* anticancer effect of THC.

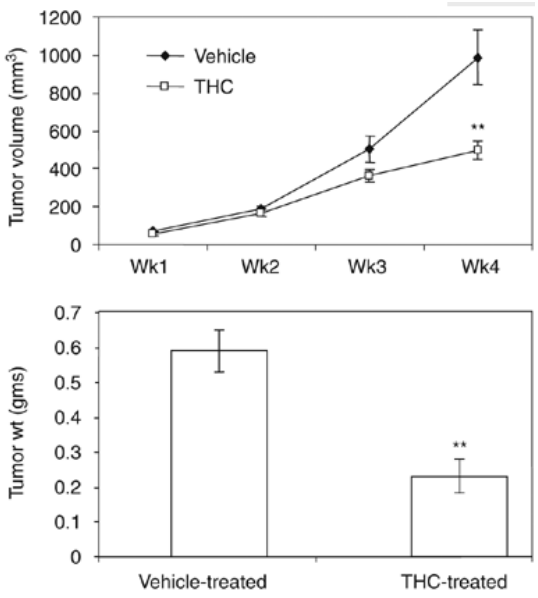
Lung Cancer

The earliest study examining the anticancer potential of cannabis was related to lung cancer. Carried out in 1974 at the University of Virginia, the research showed that THC and cannabinol (CBN), as well as the THC analog delta-8-THC (the primary form is delta-9), inhibited tumor growth and reduced primary tumor size in mice (Munson et al.). Specifically, THC was associated with dose-dependent reduction of tumor growth, whereas delta-8-THC and CBN reduced primary tumor size. All three cannabinoids increased average survival time. Interestingly, CBD had no effect on tumor growth or survival.

A 2008 study in *Oncogene* conducted by researchers at Harvard Medical School further described how THC fights lung cancer (Preet, Ganju, and Groopman). Human non-small cell lung cancer cell lines A549 and SW-1573, which express CB_1 and CB_2 receptors, were employed for the research. THC significantly reduced EGF-stimulated cell migration and invasion in both cell lines. THC also inhibited proliferation and induced apoptosis, although this effect took longer to occur.

EGFR activation by EGF causes a series of events associated with cell proliferation, including MAPK stimulation. THC inhibited EGF-induced ERK1/2 (p44/p42), JNK1/2, and Akt phosphorylation. There was also a reduction in VEGF, which is associated with angiogenesis. However, phosphorylation of focal adhesion kinase (FAK) was increased. Under different circumstances, FAK phosphorylation can contribute to or reduce the migratory potential of cancer cells. Of interest, FAK phosphorylation was inhibited in the animal studies, rather than enhanced as in the cell studies.

Mice treated daily with 5mg/kg for 28 days had significantly reduced surface lung metastases, as well as ~50% reductions in lung weight and ~60% reductions in lesion number. A similar protocol in a different *in vivo* model, although lasting for only 21 days, showed that THC inhibited tumor growth by ~60%. The cannabinoid achieved this at least partially by inhibiting proliferation and angiogenesis. Furthermore, FAK, ERK1/2, and Akt phosphorylation were reduced; total levels of these proteins remained constant.

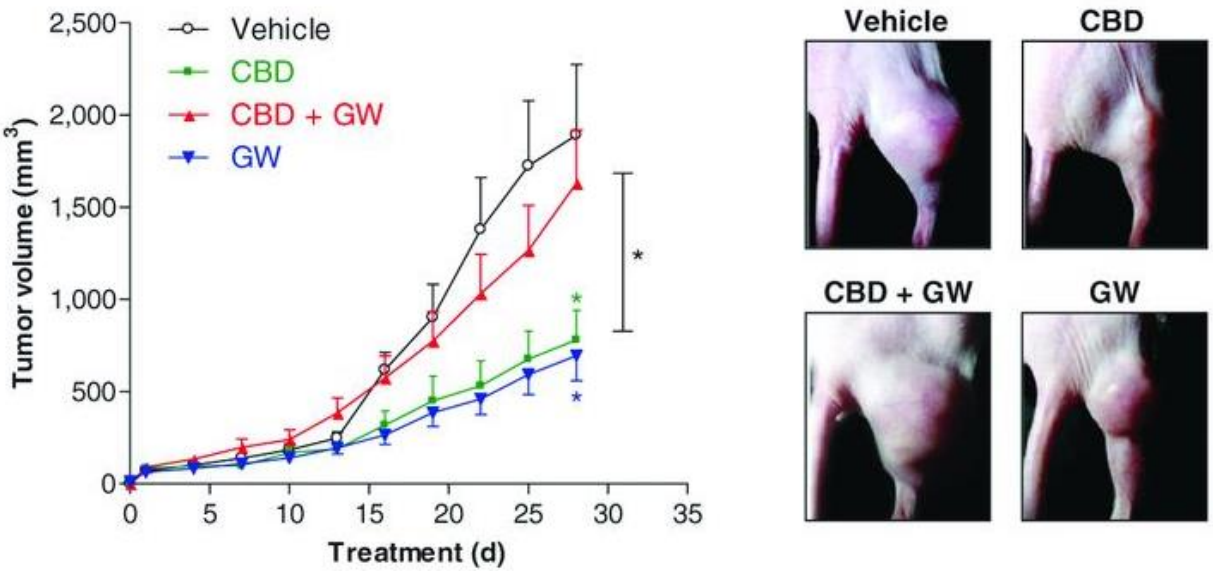


A 2013 study in *Molecular Cancer Therapeutics* from the University of Rostock in Germany illuminated the roles of COX-2 and the PPAR-γ receptor in CBD-induced apoptosis of human A549 and H460 lung cancer cells (Ramer et al., "COX-2"). CBD increased COX-2 and PPAR-γ mRNA and protein expression in a CB_1/CB_2- and $TRPV_1$-independent manner. COX-2 is an enzyme involved in inflammation; specifically, it synthesizes pro-inflammatory lipids such as prostaglandins. Both COX-2 activity and PPAR-γ activation were integral to CBD's anticancer effects.

The COX-2 upregulation led to the subsequent increases in prostaglandin E2 (PGE2), prostaglandin D2 (PGD2), and 15-Deoxy-Delta-12,14-prostaglandin J2 (15d-PGJ2). Of these, PGD2 and 15d-PGJ2 induced apoptosis in both cell lines through PPAR-γ activation. Therefore, CBD may have indirectly killed the cells by increasing COX-2 expression, which enabled the enzyme to synthesize more prostaglandin molecules. In addition, by increasing PPAR-γ expression, CBD appeared to make the cancer cells more susceptible to the cytotoxic effects of the prostaglandins.

In an animal model, CBD significantly reduced tumor volume. In tumor samples, COX-2 and PPAR-γ mRNA and protein expression were elevated. However, since higher COX-2 levels are associated with angiogenesis, researchers checked for the appearance of vascularization markers. Such markers were found to be reduced rather than increased, indicating a potential anti-angiogenic role of CBD as well.

The graph below illustrates results from the animal study. Interestingly, the PPAR-γ antagonist used in the study reduced the effect of CBD when applied concurrently, but it had a virtually identical anticancer effect when used alone. This phenomenon potentially indicates that either PPAR-γ activation or antagonism can have anticancer effects.



A 2014 study from the University of Rostock in Germany described how cannabinoids work with the body's immune system to fight lung cancer (Haustein et al.). First, CBD was shown to induce expression of intercellular adhesion molecule-1 (ICAM-1) in A549 and H460 lung cancer cells, as well as in metastatic cells derived from a lung cancer patient. ICAM-1 is expressed by white blood cells and participates in T-cell mediated host defense (Van de Stolpe and Van der Saag).

By increasing ICAM-1, CBD enhanced the adhesion of cancer cells to lymphokine activated killer (LAK) cells. LAK cells fall into a special category of immune system-based natural killer (NK) cells that are activated by the cytokine interleukin-2 (Fagan and Eddleston). They are capable of lysing (digesting and destroying) tumor cells that regular NK cells are ineffective against; furthermore, LAK cells are selective for cancer cells with little to no activity against healthy cells. Therefore, the ability of CBD to increase ICAM-1 and stimulate lysis by LAK cells is a unique method by which the cannabinoid works to boost anticancer immune function and kill cancer. Not surprisingly, blocking ICAM-1 eliminated CBD-induced tumor cell killing by LAK cells.

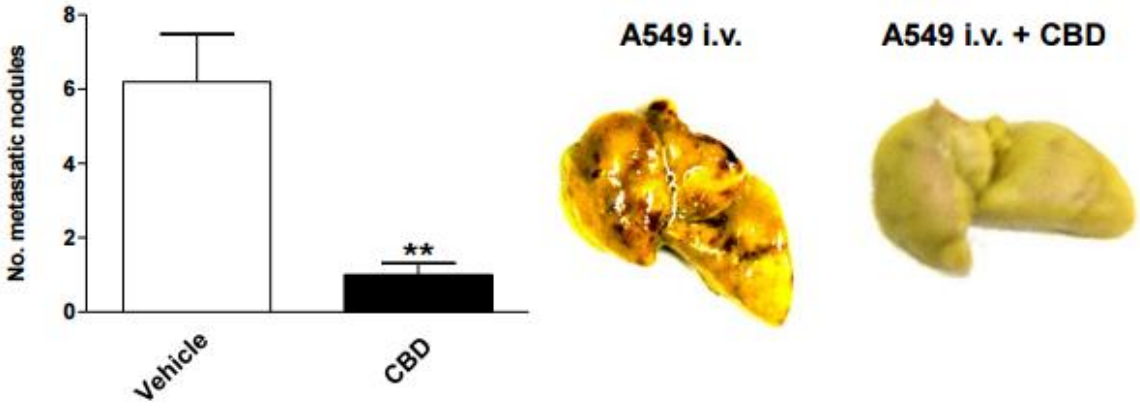
Several receptors were implicated in the effects of CBD. CB_1, CB_2, and $TRPV_1$ receptors were all integral to the initial increase in ICAM-1. The LFA-1 receptor, which interacts with ICAM-1, was subsequently integral to conferring LAK cell-mediated cancer cell death.

THC and an analog of anandamide, methanandamide, also increased ICAM-1 and cancer cell death in a similar manner as CBD. However, CBD appeared to be stronger, inducing larger increases in ICAM-1 than THC or methanandamide.

All three cannabinoids were tested in healthy BEAS-2B bronchial epithelial cells. They had very little to no effect on ICAM-1 expression in these cells, and there was no increase in cytotoxic lysis by LAK cells, indicating the selectivity of cannabinoids against cancer.

A previous study primarily focused on cervical cancer also explored CBD's effects on A549 cells (Ramer et al., "Cannabidiol"). By acting through CB_1, CB_2, and $TRPV_1$ receptors, CBD activated p38 and p42/44 MAPKs and caused an increase in TIMP-1. This led to decreased invasion of A549 cells.

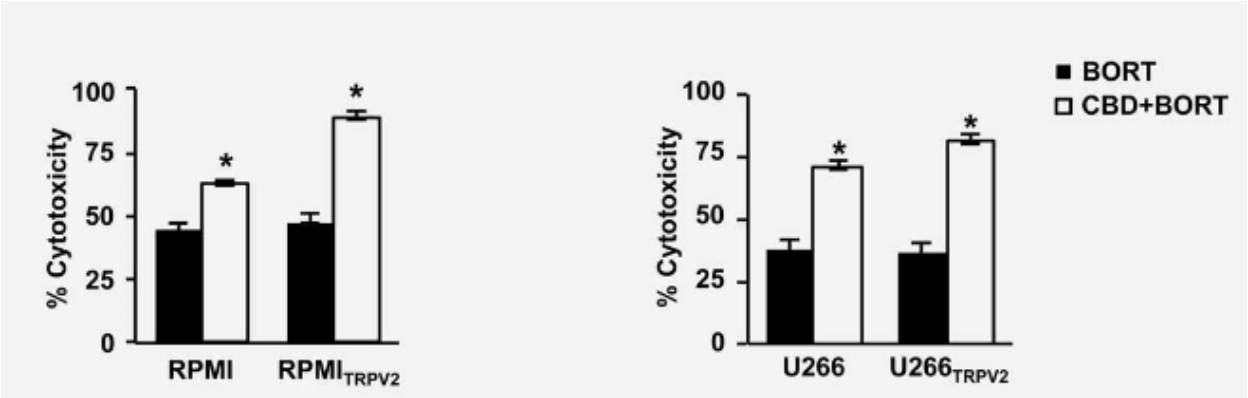
An *in vivo* test using A549 cells injected into mice was carried out to further explore the inhibitory properties of CBD. Vehicle-treated mice had an average of 6 lung metastatic nodules, whereas CBD-treated mice had an average of 1 nodule; overall, there was an 84% inhibition of metastasis.



Multiple Myeloma

Multiple myeloma (MM) is a cancer of plasma cells, which comprise part of the immune system ("Multiple Myeloma"). There is no cure, and the cancer can be especially aggressive. A June 2014 study in the *International Journal of Cancer* demonstrated how CBD kills RPMI8226 and U266 MM cells (Morelli et al.). First, CBD sharply reduced viability in both cell lines. When the lines were transfected with $TRPV_2$ receptors, they responded to CBD even faster. The researchers did this to more accurately represent the *in vivo* manifestation of MM.

CBD worked by itself or synergistically with the chemotherapy drug bortezomib to reduce MM viability and proliferation, as well as arrest the cell cycle at the G_1 phase and induce necrotic cell death. The presence of $TRPV_2$ receptors enhanced all the anticancer properties of CBD. Although CBD exerted effects through $TRPV_2$ receptors when they were present, its effects in both $TRPV_2$-positive and –negative cells were independent of CB_1, CB_2, $TRPV_1$, and PPAR- γ receptors.



Several molecular mechanisms contributed to the cytotoxic effects of CBD. There were increases in mitochondrial membrane permeability and ROS; both phenomenon are associated with necrosis or apoptosis. Alone or in combination with bortezomib, CBD reduced phosphorylated ERK and phosphorylated Akt. It also reduced Cyclin D1, a protein found in cell nuclei that is required for cell cycle progression in the G_1 phase (Baldin et al.). Finally, CBD reduced the DNA binding activation of p52 and p65, which are classical pathways that activate the nuclear factor NF-κB pathway. NF-kappaB proteins include a family of transcription factors involved in the regulation of immune processes, development, cell growth, and apoptosis (Gilmore). The NF-κB pathway may be associated with the pathogenesis of MM; it is also associated with inflammation.

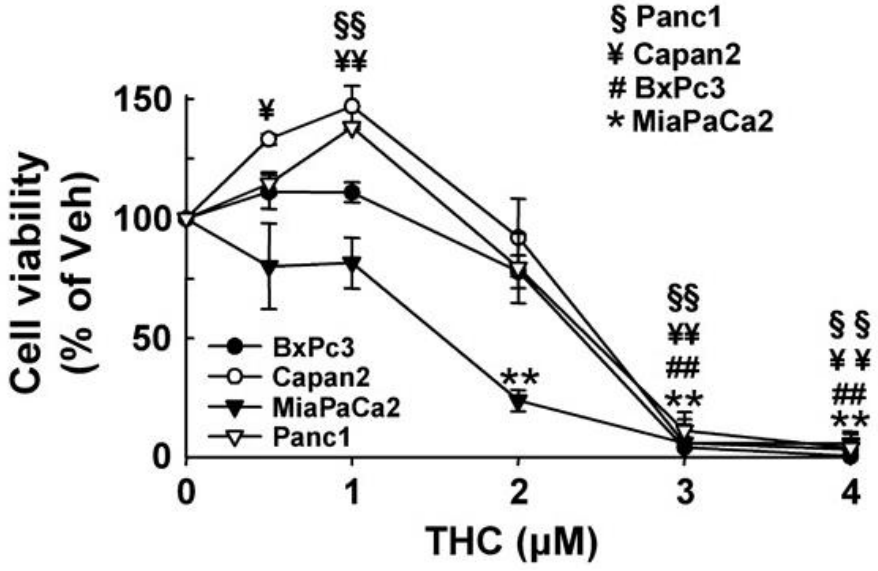
Pancreatic Cancer

Pancreatic cancer is well known to be one of the most aggressive and difficult to treat cancers. A 2006 study by Dr. Manuel Guzmán's team in Spain produced strong *in vitro* and *in vivo* evidence for the effectiveness of THC against pancreatic cancer (Carracedo et al.). First, the researchers demonstrated that in both human and mouse tumor biopsies, CB_1 and CB_2 receptors were expressed at higher levels in the cancerous tissue compared to the surrounding healthy tissue.

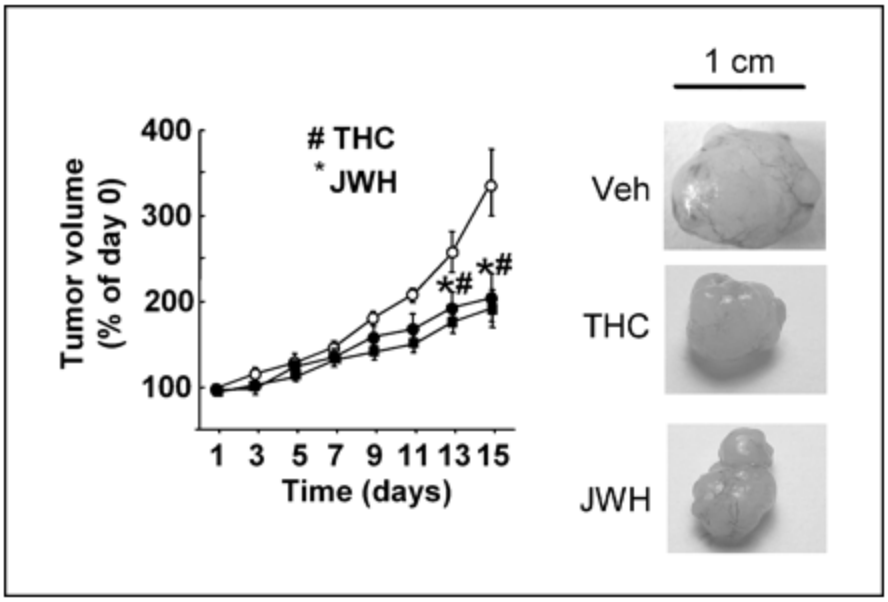
THC induced apoptosis in the human Panc1, Capan2, BxPc3, and MiaPaCa2 cell lines via CB_2 activation. Following receptor activation, there was an increase in ceramide biosynthesis leading to ceramide accumulation and subsequent upregulation of the stress-regulated protein p8. The increase in p8 levels further led to upregulation of the endoplasmic reticulum stress-related proteins activating transcription factor 4 (ATF4) and tribbles homolog 3 (TRB3). Both of these proteins were critical for mediating THC-induced apoptosis.

Ceramide accumulation also activated caspase-3, which is associated with apoptosis. While it was not clear at what point this happened, it is likely the enzyme's activation occurred downstream of TRB3, as TRB3 has been shown to interact with caspase-3 (Shimizu et al.). If this is the case, the pathway to apoptosis would be as follows:

CB_2 activation -> ceramide accumulation -> p8 upregulation -> ATF-4 and TRB3 upregulation -> caspase-3 activation -> apoptosis



THC and a synthetic CB_2 agonist were also shown to be effective in mice. Tumors were generated by subcutaneous injection of MiaPaCa2 cells.


1 cm
THC
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Prostate Cancer

Besides skin cancer, prostate cancer is the most common cancer found in men, with a prevalence rate of almost 15% ("What are"). Moreover, 1 in 38 men will die of prostate cancer, as it is the second leading cause of cancer death in men. Although many types of prostate cancer are slow-growing, it is imperative for patients to take steps to manage or preferably kill the malignancy.

A 1999 study in *FEBS Letters* described the effects of THC on PC3 prostate cancer cells (Ruiz, Miguel, and Díaz-Laviada). THC was shown to dose-dependently reduce cell viability and induce apoptosis in PC3 cells through a CB_1/CB_2 receptor-independent mechanism. Activating both cannabinoid receptors with a synthetic agonist had no effect on cell viability, further reinforcing the receptor-independent nature of THC-induced cell death in PC3 cells. DNA fragmentation also occurred in a dose-dependent manner, consistent with apoptosis.

A previously discussed study regarding the ability of CBD to induce apoptosis in colon cancer cells also showed the cannabinoid could kill LNCaP prostate cancer cells (Sreevalsan et al.). As with the colon cancer cells, CBD induced phosphatase expression, specifically *DUSP1*, *DUSP4*, and *DUSP10*. These phosphatases dephosphorylate (inactivate) kinase molecules like MAPK involved in cell survival. The study did not indicate which kinases were inactivated by the phosphatases, but MAPK was a likely target. Blocking phosphatase induction reduced CBD-induced apoptosis, so there is no doubt that inactivation of some kinases played a role in cell death.

The proapoptotic effect in LNCaP cells was mediated by both CB_1 and CB_2 receptors, but the CB_2 receptors had an apparently greater role (blocking CB_2 inhibited PARP and caspase-3 cleavage; blocking CB_1 only partially inhibited caspase-3 cleavage without affecting PARP). This is in contrast to SW480 colon cancer cells, where CB_1 and CB_2 receptors had apparently equal roles in inducing apoptosis (blocking either receptor inhibited PARP and caspase-3 cleavage). This demonstrates that CBD's interaction with cannabinoid receptors varies between cell lines.

A 2013 study in the *British Journal of Pharmacology* showed how numerous individual cannabinoids and specific extracts inhibited prostate cancer growth (De Petrocellis et al., "Non-THC Cannabinoids"). Specifically, CBD, CBC, CBG, CBDV, THCV, THCVA, THCA, CBDA, CBGA, and CBGV, along with their corresponding whole plant-based botanical drug substances (BDSs), were shown to inhibit androgen receptor-negative DU-145 cells and androgen receptor-positive LNCaP cells. IC_{50} values (the concentration required to reduce viability by 50% as compared to controls) were used to rank the potency of various cannabinoids. In general, CBD and CBC were the strongest cannabinoids, and the extracts were stronger than the isolated cannabinoids, although there were exceptions.

It is important to note that THCA, THCVA, CBDA, and CBGA are the unheated, raw cannabinoids found naturally in the cannabis plant. When heat is applied, the compounds are decarboxylated (removal of a carboxyl [COOH] group) and transformed into neutral cannabinoids (THC, THCV, CBD, CBG, etc.). In practice, the decarboxylated cannabinoids are showing far greater anticancer activity than the raw cannabinoids.

Researchers also compared the effects of the cannabinoids on cancer cells in serum or without serum. In general, the cannabinoids had a much greater effect when used on cells in a serum-free medium, which may be due to components of the serum counteracting the cannabinoids. In any case, the following charts efficiently illustrate the relative strengths of many different cannabinoid preparations.

Note: [A] column is with serum, [B] column is without serum. Lower IC_{50} = Greater potency.

Table 1. Effect of plant cannabinoids on the viability of human prostate carcinoma androgen receptor-negative (DU-145) cells

Pure compound	IC_{50} (μM) on cell viability [A]	IC_{50} (μM) on cell viability [B]	BDS	IC_{50} (μM) on cell viability [A]	IC_{50} (μM) on cell viability [B]
CBD	25.3 ± 8	5.4 ± 1	CBD BDS	9.0 ± 4	7.8 ± 2
CBC	>25 (40.7%)	8.5 ± 3	CBC BDS	9.2 ± 3	7.9 ± 1
CBG	>25 (17.3%)	10.4 ± 1	CBG BDS	10.4 ± 5	6.9 ± 2
CBDV	21.0 ± 4	20.0 ± 5	CBDV BDS	17.1 ± 7	10.3 ± 1
THCV	>25 (38.6%)	20.5 ± 3	THCV BDS	>25 (41.0%)	8.3 ± 1
THCVA	>25 (25.6%)	>25 (36.1%)	THCVA BDS	>25 (30.9%)	12.4 ± 1
THCA	>25 (21.9%)	21.6 ± 2	THCA BDS	18.9 ± 2	9.9 ± 2
CBDA	>25 (11.2%)	10.9 ± 4	CBDA BDS	>25 (27.8%)	15.9 ± 2
CBGA	>25 (7.7%)	11.2 ± 2	CBGA BDS	19.2 ± 2	12.3 ± 3
CBGV	>25 (11.3%)	>25 (23.3%)	CBGV BDS	>25 (21.9%)	10.2 ± 2
CBN	>25 (17.2%)	>25 (21.8%)	–	–	–
THC	>25 (6.6%)	11.7 ± 3	–	–	–

Table 2. Effect of plant cannabinoids on the viability of human prostate carcinoma androgen receptor-positive (LNCaP) cells

Pure compound	IC_{50} (μM) on cell viability [A]	IC_{50} (μM) on cell viability [B]	BDS	IC_{50} (μM) on cell viability [A]	IC_{50} (μM) on cell viability [B]
CBD	25.0 ± 3	5.7 ± 2	CBD BDS	18.1 ± 6	6.6 ± 2
CBC	20.0 ± 5	10.9 ± 3	CBC BDS	>25 (25.6%)	7.9 ± 1
CBG	>25 (34.5%)	11.2 ± 4	CBG BDS	21 ± 8	9.0 ± 1
CBDV	>25 (27.6%)	20.0 ± 3	CBDV BDS	>25 (24.4%)	10.4 ± 1
THCV	>25 (28.5%)	17.5 ± 3	THCV BDS	16.3 ± 5	7.2 ± 1
THCVA	>25 (32.4%)	11.5 ± 5	THCVA BDS	19.4 ± 8	5.6 ± 1
THCA	22.1 ± 2	17.1 ± 1	THCA BDS	15.0 ± 2	4.0 ± 3
CBDA	>25 (30.2%)	16.2 ± 5	CBDA BDS	>25 (34.5%)	9.3 ± 2
CBGA	>25 (7.0%)	11.6 ± 2	CBGA BDS	14.5 ± 2	8.5 ± 2
CBGV	>25 (23.9%)	>25 (41.0%)	CBGV BDS	>25 (40.2%)	9.4 ± 2
CBN	14.5 ± 6	>25 (34.2%)	–	–	–
THC	16.9 ± 3	5.5 ± 3	–	–	–

While many cannabinoids were examined, CBD was the chief cannabinoid under scrutiny. Using receptor antagonists, it was shown that CBD's effects were mediated independently of CB_1, CB_2, $TRPV_1$, $TRPA_1$, and $TRPM_8$ channels. CBD was paired with two conventional treatments for prostate cancer, bicalutamide and docetaxel, to examine potential synergistic effects. CBD enhanced the antiproliferative actions of both drugs in DU-145 and LNCaP cells, although the effective concentrations varied based on the cell line and drug used. The enhancing effect appeared to be mostly additive, but mild synergy may have been at play.

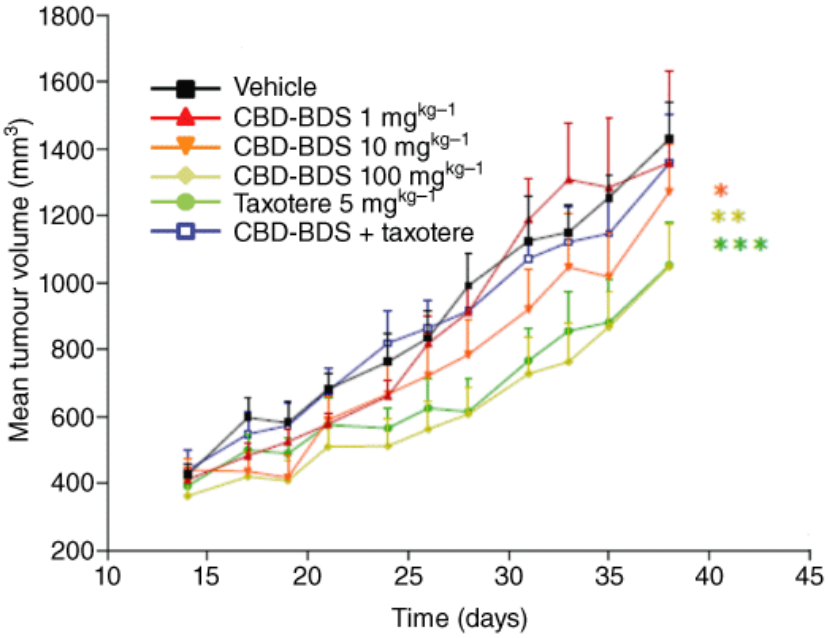
Depending on whether serum was present or not, several cannabinoids had weak or strong pro-apoptotic effects, respectively. In serum-deprived conditions, CBD, CBC, and CBG induced caspase 3/7 activity (indicative of apoptosis) in LNCaP cells. However, only CBD was effective at increasing caspase activity in DU-145 cells, as CBC and CBG had little effect. In serum conditions, THCV, THCVA, and CBGV had a small but significant influence on caspase 3/7 activity in DU-145 cells.

Further analysis confirmed the ability of CBD to induce apoptosis in LNCaP and DU-145 cells, as well as the human prostate cancer cell lines PC3 and 22RV1. CBD stimulated apoptosis by upregulating expression of p53-up-regulated modulator of apoptosis (PUMA), which regulates intrinsic pathways of apoptosis, in all four cell lines. CHOP, another apoptosis-activator, increased as well. CBD also inhibited the G_1-S transition of the cell cycle, likely by strongly boosting expression of the cell cycle inhibitor proteins $p27^{kip}$ and p21.

Furthermore, CBD dose-dependently elevated intracellular calcium levels in an extracellular-calcium-independent manner in the four cell lines. This increase was apparently critical to the subsequent induction of reactive oxygen species in LNCaP cells, but no increase in ROS was observed in the other three cell lines. Both increased calcium and ROS are associated with apoptosis. CBC and CBG also raised intracellular calcium in all cell lines.

High expression levels of G-protein-coupled oestrogen receptor 1 (GPER) were observed in the four cell lines. Blocking this receptor attenuated CBD-induced calcium release and apoptosis, indicating the important role of GPER in mediating the anticancer effects of CBD.

Several *in vivo* experiments were carried out to determine how CBD-BDS worked on its own and in conjunction with chemotherapy. CBD-BDS dose-dependently inhibited xenograft tumors derived from LNCaP cells, but not DU-145 cells. This inhibitory effect was quantitatively similar to that of docetaxel, although in this case the BDS actually impaired the effectiveness of the chemotherapeutic agent. Interestingly, in DU-145 tumors where CBD-BDS alone was ineffective, it significantly potentiated docetaxel. Further experiments with CBD-BDS and bicalutamide showed they worked very well together to inhibit growth and prolong survival, even when either compound alone was ineffective.



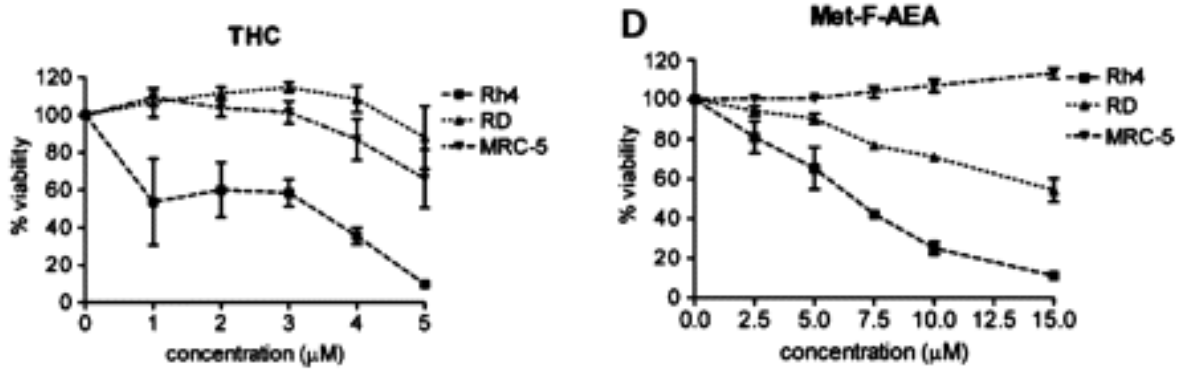
Note: Taxotere is docetaxel

Rhabdomyosarcoma

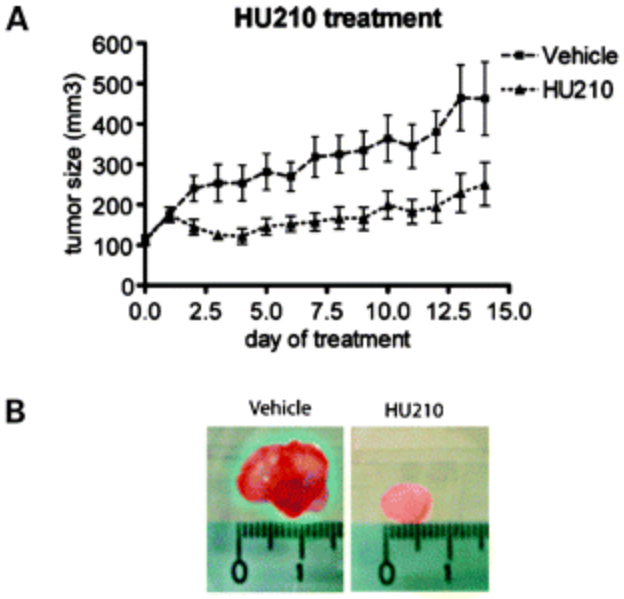
Rhabdomyosarcoma (RMS) is a soft tissue cancer that begins in bone-attached muscles and mostly affects children under 10 ("Soft Tissue"). As with several other cancers, cannabinoid receptors appear to be upregulated in RMS cells. A 2009 study from researchers associated with the University Children's Hospital in Switzerland showed that CB_1 receptor expression was far higher in translocation-positive RMS (tposRMS) cells (Rh4, Rh28, and RMS13 cell lines) than healthy cells as well as translocation-negative RMS (tnegRMS) cells (RD cell line) (Oesch et al.). There are two major subtypes of RMS – embryonal RMS and alveolar RMS. The latter form is less frequent and more aggressive; 80% of patients with this form display chromosomal translocations (translocation-positive) that ultimately increase expression of oncogenic transcription factors. While alveolar RMS can be translocation-negative, it is most often translocation-positive.

THC significantly reduced viability of tposRMS Rh4 cells, but not tnegRMS cells or nontransformed fibroblast MRC-5 cells, apparently because they did not express high levels of CB_1 receptors. Indeed, the viability-reducing effect of THC on Rh4 cells was shown to be mediated by CB_1 receptors.

An anandamide-related compound, Met-F-AEA, also affected RMS cell viability. Met-F-AEA and THC induced cleavage of PARP protein, indicating the observed reduction in viability was due to activation of apoptosis. Finally, both compounds inhibited phosphorylation of Akt and increased p8 levels. While not discussed in the study, given that p8 can stimulate TRB3 activity and TRB3 can inhibit Akt, it is possible that TRB3 also played a role.



The study also used a synthetic cannabinoid similar to THC, HU210, to assess the *in vivo* effect of cannabinoid receptor activation on RMS growth. Using an alveolar RMS xenograft in mice, HU210 was shown to significantly reduce tumor growth, at least partially through increasing apoptosis. It is reasonable to expect that similar results would be seen with THC treatment.

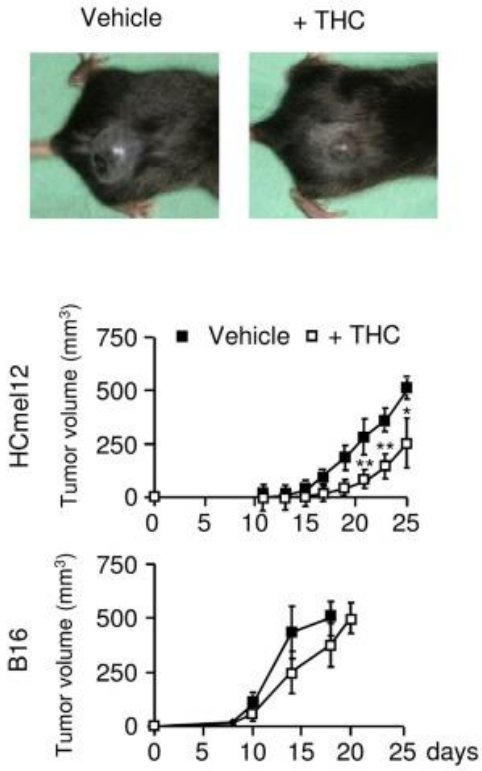

A
HU210 treatment
tumor size (mm3)
600
500
400
300
200
100
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
day of treatment
Vehicle
HU210
B
Vehicle
HU210

Skin Cancer

Skin cancer is the most prevalent form of cancer. Specifically, basal cell carcinoma (BCC) is the most common type in Caucasians, Hispanics, Chinese Asians and Japanese; squamous cell carcinoma (SCC) is the most common skin cancer in African Americans and Asian Indians ("Skin Cancer Facts"). Melanoma is a less frequently diagnosed but more aggressive skin cancer. In general, BCC is the least aggressive and melanoma is the most aggressive, with SCC in the middle.

An April 2015 study from German researchers, published in *Life Sciences*, showed the potential of THC to fight melanoma (Glodde et al.). Interestingly, the *in vitro* experiments showed that THC had no effect on proliferation of mouse melanoma cell lines HCmel12 and B16. However, the *in vivo* experiments were somewhat more promising. In mice injected with HCmel12 cells, THC reduced melanoma tumor volume by 50%; from 500mm^3 to 250mm^3. This reduction was dependent on cannabinoid receptor activation. However, mice with B16-derived melanomas were not affected by THC.

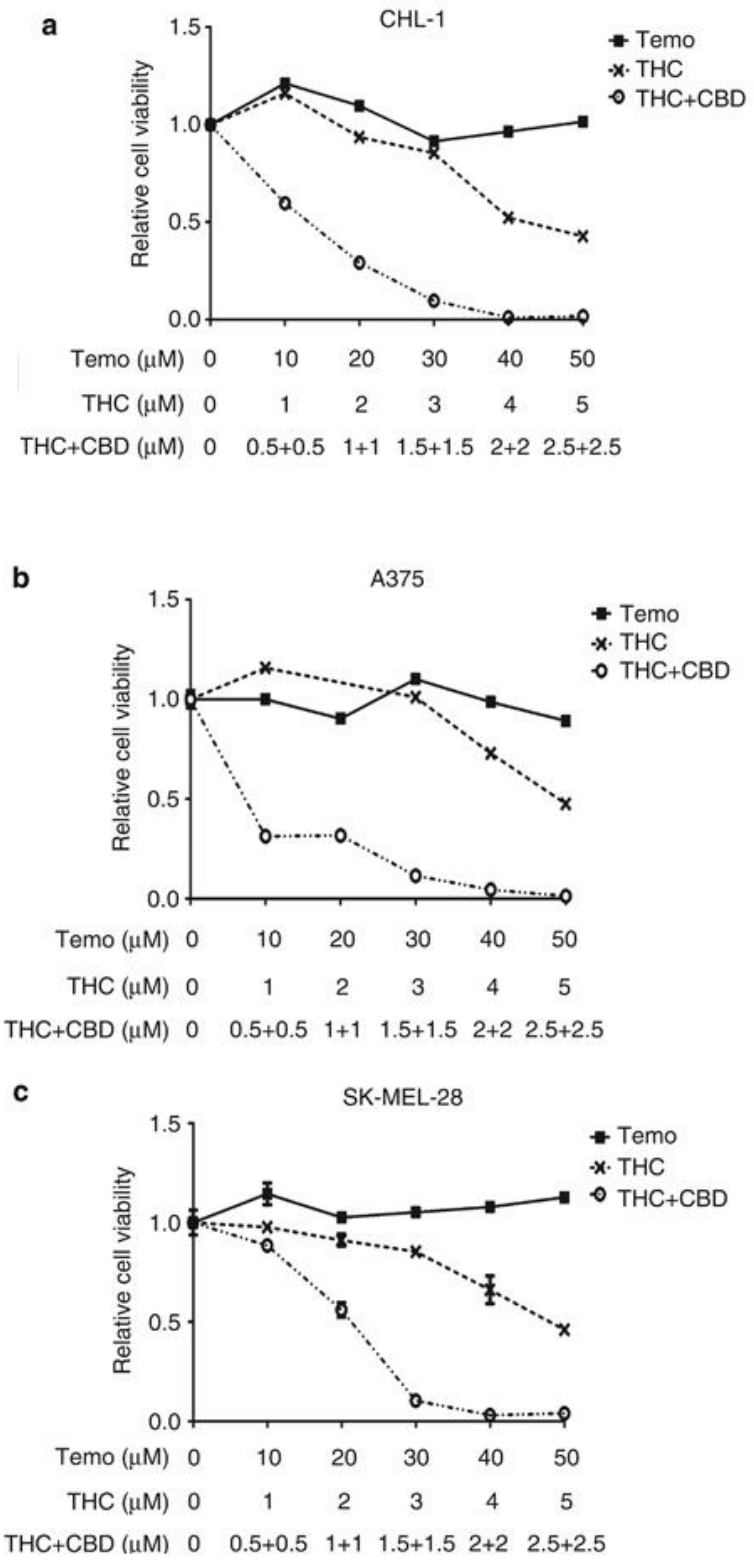
Since THC was not directly effective for inhibiting proliferation *in vitro*, it was hypothesized that more complex mechanisms were responsible for the reduction in mice melanomas. Indeed, THC reduced the infiltration of CD45+ immune cells into melanoma tumors. HCmel12 melanomas are specifically characterized by infiltration of pro-tumorigenic myeloid immune cells, so inhibiting this inflammatory response is a powerful anticancer mechanism. Although not explored in the main part of the study, it is likely that THC decreased production of proinflammatory chemokines, which led to decreased recruitment of immune cells.



Finally, the study showed that the endocannabinoid system was not involved in the pathogenesis of skin cancer by using three different mouse models. Knockout mice without cannabinoid receptors had similar tumor development outcomes as wild-type mice with receptors.

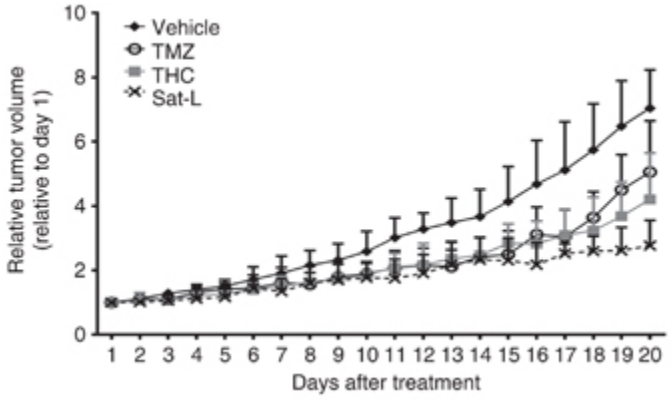
A June 2015 study in *The Journal of Investigative Dermatology* indicated the potential of THC and CBD to treat melanoma (Armstrong et al.). First, THC was shown to activate autophagy and induce apoptosis in BRAF wild-type (CHL-1) and mutated (A375 and SK-MEL-28) melanoma cell lines. Activation of TRB3 and the autophagy-related protein Atg7 were integral to the induction of autophagy; that process was subsequently critical for caspase-3 cleavage and apoptosis. Beclin-1, another protein associated with autophagy and implicated in the anticancer effects of cannabinoids in other cancers, as well as the Beclin-1-interacting protein Ambra1, were not involved in autophagy in this case.

Using very small doses of THC and CBD together resulted in substantial loss of viability in CHL-1, A375, and SK-MEL-28 cells. THC alone was somewhat effective; temozolomide, a standard single-agent treatment for metastatic melanoma, had little effect.

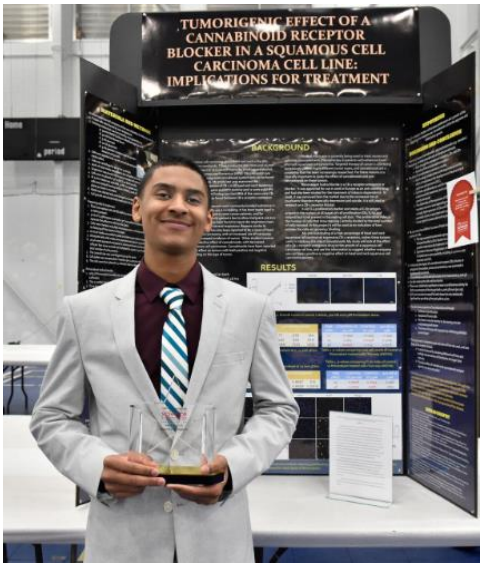


Researchers also assessed the *in vivo* anticancer action of cannabinoids with a mouse CHL-1 xenograft tumor model. THC and the THC+CBD combination reduced tumor cell proliferation

and increased autophagy and apoptosis compared to control or temozolomide conditions. The authors concluded, "Collectively, these data suggest that THC and Sativex-L [THC+CBD] are more effective than temozolomide in terms of apoptosis induction and antitumor response, further validating the therapeutic relevance of cannabinoid treatment for melanoma."



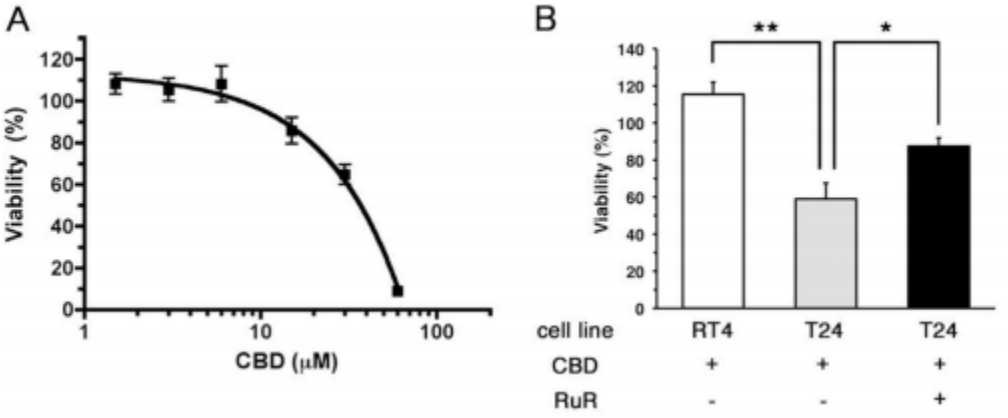
While not a peer-reviewed paper, it is tremendously interesting and notable to mention that a high school student named Daniel Baksh won a local science fair in Lancaster, Pennsylvania for research he did with cannabinoids and cancer cells (Geli). Unfortunately the article nor the picture reveal extensive details about the study, but based on its title, "Tumorigenic Effect of a Cannabinoid Receptor Blocker in a Squamous Cell Carcinoma Cell Line: Implications for Treatment," it appears Daniel tested a cannabinoid receptor antagonist on squamous cancer cells and found it promoted their growth, thus indirectly demonstrating that receptor agonism may have an anticancer effect and/or that impaired cannabinoid receptor activation drives tumor growth.



Urothelial Carcinoma

Urothelial carcinoma (UC) is a cancer that involves parts of the kidney, ureter, and bladder, mostly occurring in the latter ("Urothelial"). A 2010 study in *Urology* from Japanese researchers at Nagoya City University demonstrated the ability of CBD to induce apoptosis in T24 UC cancer cells (Yamada et al.). T24 is a high grade, poorly differentiated UC cell line.

CBD reduced viability and induced apoptosis in T24 cells in a concentration-dependent manner via the activation of $TRPV_2$ receptors. Stimulation of the receptors caused a continuous influx of calcium through $TRPV_2$ channels, which led to apoptosis. RT4 UC cells, which do not express $TRPV_2$ receptors, were not significantly affected by CBD treatment.



Assorted Cancers

A study by Italian researchers in 2006 demonstrated that most of the major cannabinoids exert anticancer effects against many types of cancer, although the study was primarily focused on CBD and breast cancer (Ligresti et al.). The effects of THC, THCA, CBD, CBDA, CBG, CBC, and THC-rich and CBD-rich whole plant extracts (botanical drug substances) on MCF-7 and MDA-MB-231 human breast carcinoma cells, DU-145 human prostate carcinoma cells, CaCo-2 human colorectal carcinoma cells, AGS human gastric adenocarcinoma cells, C6 rat glioma cells, KiMol rat thyroid cells transformed with the v-K-*ras* oncogene, and RBL-2H3 rat basophilic leukemia cells were examined. Results from the impressive array of experiments are summarized in the following chart.

The values of the cannabinoids are measured in micromoles (µM). The measurements reflect IC_{50} values. For example, 14.2 +/- 2.1 µM of THC was required to inhibit MCF-7 cell proliferation by 50% as compared with controls. Lower IC_{50} values indicate greater potency.

	MCF-7	C_6	DU-145	KiMol	CaCo-2	MDA-MB-231	RBL-2H3	AGS
Δ^9-THC	14.2 ± 2.1	23.0 ± 4.2	>25	23.2 ± 1.5	16.5 ± 0.2	24.3 ± 4.2	15.8 ± 3.7	19.3 ± 1.5
THC-A	9.8 ± 0.4	18.0 ± 5.3	>25	21.0 ± 2.7	21.5 ± 1.4	18.2 ± 5.3	10.0 ± 3.4	>25
CBD	8.2 ± 0.3	8.5 ± 0.8	20.2 ± 1.8	6.0 ± 3.0	7.5 ± 0.5	10.6 ± 1.8	6.3 ± 1.5	7.5 ± 1.3
CBD-A	21.7 ± 3.2	18.0 ± 4.2	>25	12.7 ± 3.0	>25	>25	>25	>25
CBG	9.8 ± 3.4	13.0 ± 2.1	21.3 ± 1.7	8.2 ± 0.7	9.0 ± 1.4	16.2 ± 2.1	9.0 ± 0.7	8.2 ± 0.7
CBC	14.2 ± 1.4	13.0 ± 2.6	>25	7.3 ± 3.0	12.0 ± 2.4	20.4 ± 2.6	15.8 ± 4.2	18.3 ± 3.0
THC-rich	21.0 ± 0.5	18.5 ± 3.3	>25	23.0 ± 2.0	16.0 ± 0.5	25.2 ± 3.3	14.6 ± 3.1	22.0 ± 2.0
CBD-rich	6.0 ± 1.0	4.7 ± 0.6	20 ± 4.6	6.2 ± 2.9	12.3 ± 1.2	14.1 ± 1.6	7.0 ± 0.6	10.0 ± 1.9

As demonstrated, isolated CBD and CBD-rich extracts always yielded the most powerful antiproliferative effects. CBG was almost always the second most potent compound, followed by CBC. Interestingly, THCA showed stronger activity than THC in most cell lines. In the case of DU-145 cells specifically, only the highest concentration of cannabinoids tested had an inhibitory effect on proliferation, whereas the lower doses stimulated growth. However, the CBD-rich extract was devoid of pro-proliferative effects even at the lowest doses, potentially indicating that the

cannabinoids work synergistically to prevent any potential pro-cancer effects while maximizing anti-cancer effects. Regardless of that possibility, the lowest doses of the cannabinoids had no stimulatory effect on the other cell lines, and in general appeared to exert dose-dependent anticancer activity on each line.

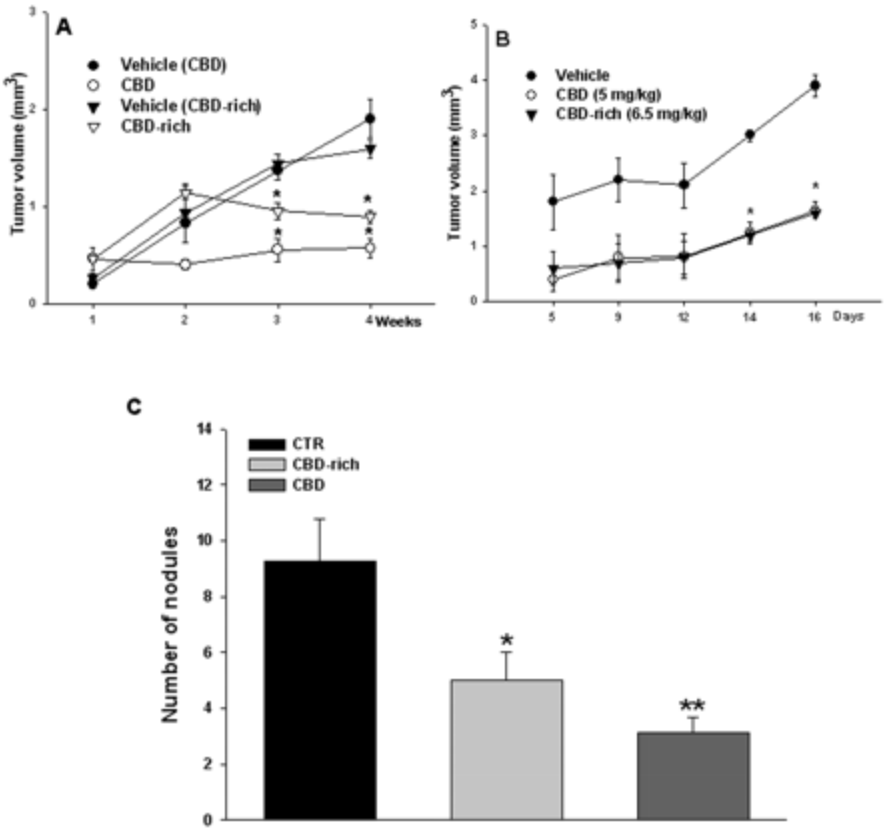
CBD's potency was compared to the standard chemotherapeutic agent cisplatinum to determine relative strengths. The drug was only 2.5-, 8.8-, and 3.9-fold more potent than CBD in MCF-7, MDA-MB-231, and AGS cells. Therefore, it is possible that reasonably higher doses of CBD (or other cannabinoids) could be used to achieve the same effects as standard chemotherapeutic agents, but with none of the physically devastating or fatal side effects. Unlike cisplatinum, CBD was shown to be highly selective against cancer cells. At its IC_{50} concentrations, it did not affect the vitality of healthy cells. However, at the highest concentration (25μM), it began to exhibit a cytotoxic effect.

The mechanisms behind CBD's effects on several cancers were further explored. In MCF-7 cells, CBD blocked the cell cycle at the G_1/S phase transition. In KiMol cells, the antiproliferative effect of CBD was accompanied by proapoptotic action. In C6 and MDA-MB-231 cells, CBD exhibited "a pure proapoptotic effect." Given the latter two cell lines were nonhormone-sensitive, and the former two were **hormone**-sensitive, it is possible that hormones play a role in whether CBD exerts antiproliferative or proapoptotic effects. In MDA-MB-231 cells, CBD caused cleavage of procaspase-3 into caspase-3, a hallmark of apoptosis.

CBD increased intracellular calcium levels in a manner independent of extracellular calcium levels. The cannabinoid also induced ROS formation in a dose-, time-, and calcium-dependent manner. This suggests CBD increased calcium levels, which subsequently caused ROS formation.

The effects of all the cannabinoids on all the cell lines were largely unrelated to CB_1, CB_2, and $TRPV_1$ receptor activation. However, in MDA-MB-231 cells, CBD's effects were partially, but not entirely, mediated by CB_2 and $TRPV_1$ activation. Indeed, the ability of CBD to increase intracellular calcium, and apparently ROS formation, was not mediated by cannabinoid or $TRPV_1$ receptors.

Two xenograft tumor models were used to ascertain the effects of CBD on thyroid (KiMol) and breast (MBA-MD-231) carcinomas. Chart A refers to the KiMol-derived tumors and Chart B refers to the MBA-MD-231-derived tumors. Chart C demonstrates strongly reduced formation of lung metastatic nodules in CBD-treated mice as well.


A
Vehicle (CBD)
CBD
Vehicle (CBD-rich)
CBD-rich
Tumor volume (mm3)
Weeks
B
Vehicle
CBD (5 mg/kg)
CBD-rich (6.5 mg/kg)
Tumor volume (mm3)
Days
C
CTR
CBD-rich
CBD
Number of nodules

Summary

The primary ways cannabinoids fight cancer include inducing apoptosis (programmed cell death), inhibiting angiogenesis (the formation of blood vessels to tumors), reducing proliferation, and impairing metastasis. However, cannabinoids have other unique anticancer effects. One study demonstrated THC and CBD help the immune system digest cancer cells more effectively. Another showed CBD promoted the differentiation of glioma stem-like cells, thus making them easier to treat. CBD also works at the genetic level to inhibit metastasis of breast cancer. It is likely that more research will reveal novel mechanisms of anticancer action.

There are several major pathways by which cannabinoids induce apoptosis. Reducing activation of the MAPK and Akt survival pathways is especially common. Increasing intracellular calcium and generation of reactive oxygen species is seen mostly with CBD but also with THC and anandamide. Cannabinoid effects are not always consistent; for example, CBD activates the MAPK pathway to down-regulate the Id-1 gene or increase TIMP-1 to decrease metastasis and invasion. Another common pathway involves ceramide, which can reduce mitochondrial membrane potential and cause the release of cytochrome c, which then activates caspase-3, one of the chief apoptosis-initiating proteins.

Isolated cannabinoids and whole-plant botanical drug substances (BDSs) tend to exert anticancer activity in the vast majority of cancer cell lines studied. In some cases, exceptionally low doses (usually less than a milligram) of isolated cannabinoids can stimulate cancer cell survival or proliferation. Such pro-cancer effects usually disappear at higher doses or when BDSs are used. In general, using whole-plant formulations maximizes the benefits of cannabinoids while minimizing potential negative attributes. In addition to maximizing anticancer effects, whole-plant cannabinoids are usually better tolerated. For example, CBD can be used to reduce the psychoactivity of THC.

Anandamide exerts effects largely via CB_1 or $TRPV_1$ channels, as well as entirely receptor-independent mechanisms. In one case, CB_2 receptors were implicated. The cannabinoid receptors themselves generally confer anticancer effects when activated, but in some cases, blocking the receptors causes antiproliferative or pro-apoptotic effects. A human study examining the relationship between cannabinoid receptor levels and cancer survival found that increased levels were associated with better disease-free survival.

There seems to be an interplay between phytocannabinoid and endocannabinoid anticancer effects. For example, CBD seems to fight cancer in part by increasing anandamide levels, as theorized by one study and bolstered by the fact that many of its anticancer effects are cannabinoid receptor-mediated, despite CBD not directly activating such receptors. CBD can also increase COX-2, which subsequently increases prostaglandins that induce apoptosis via PPAR-γ activation. One study postulated that COX-2 metabolizes anandamide into prostaglandins to induce apoptosis. Therefore, CBD may increase COX-2 and anandamide, thus enabling more COX-2 to convert more anandamide into the downstream compounds that initiate apoptosis.

THC induces apoptosis in:
U373 MG astrocytoma cells
SF126 glioblastoma cells
C6.9 glioma cells
N18TG2 neuroblastoma cells
RMCCA1 and HuCCA1 cholangiocarcinoma cells
HepG2 and HuH-7 hepatocellular carcinoma cells
CEM acute lymphoblastic leukemia cells
HL60 acute promyelocytic cells
HEL-92 erythroleukemia cells
Jurkat leukemia cells
A549 and SW-1573 non-small cell lung cancer cells
Panc1, Capan2, BxPc3, and MiaPaCa2 pancreatic cancer cells
PC3 prostate cancer cells
Rh4 translocation-positive rhabdomyosarcoma cells
CHL-1, A375, and SK-MEL-28 melanoma cells

THC impairs metastasis, migration or invasion of:
HeLa and C33A cervical cancer cells
RMCCA1 and HuCCA1 cholangiocarcinoma cells
C6.9, SW1088, T98G, U87MG, and U118MG glioma cells
A549 and SW-1573 non-small lung cancer cells

THC inhibits proliferation of:
MCF-7, MDA-MB-231, and N202.1A breast cancer cells
RMCCA1 and HuCCA1 cholangiocarcinoma cells
Caco-2 colon cancer cells
AGS gastric cancer cells
C6 glioma cells
RBL-2H3 leukemia cells
A549 and SW-1573 non-small cell lung cancer cells
DU-145 prostate cancer cells
KiMol thyroid cancer cells

CBD induces apoptosis in:
MCF-7 and ZR-75-1 estrogen receptor-positive breast cancer cells
MDA-MB-231 and SK-BR-3 estrogen receptor-negative cells
SW480 colon cancer cells
C6, U87 and U373 glioma cells

SF126 glioblastoma cells
KSHV-infected HMVECs (Kaposi's Sarcoma) cells
EL-4 lymphoma cells
Jurkat and MOLT-4 leukemia cells
A549 and H460 lung cancer cells
RPMI8226 and U266 multiple myeloma cells (necrosis)
LNCaP, DU-145, PC3, and 22RV1 prostate cancer cells
KiMol thyroid cancer cells
T24 urothelial cancer cells

CBD impairs metastasis, migration or invasion of:
MDA-MB-231 and 4T1 breast cancer cells
HeLa and C33A cervical cancer cells
U87-MG and T98G glioma cells
A549 lung cancer cells

CBD inhibits proliferation of:
MCF-7, MDA-MB-231 and 4T1 breast cancer cells
Caco-2, DLD-1, HCT116, and SW480 colon cancer cells
AGS gastric cancer cells
C6, U87, U251, U373, and SF126 glioma cells
KSHV-infected HMVECs (Kaposi's sarcoma) cells
CEM, HL60, and RBL-2H3 leukemia cells
RMPI8226 and U266 multiple myeloma cells
DU-145 and LNCaP prostate cancer cells
KiMol thyroid cancer cells

III. Human Case Results

The scientific evidence overwhelmingly supports the notion that cannabis extracts could kill cancer in humans. Both endocannabinoids and phytocannabinoids inhibit cancer cells through numerous mechanisms. Furthermore, preclinical results suggesting the efficacy of cannabis extracts for the treatment of other diseases, like epilepsy and schizophrenia, have been proven in large-scale observational studies and double-blind trials to transfer to humans. It is no surprise that for at least a decade, and perhaps far longer, humans have reported cancer remissions after using cannabis extracts.

The following section starts off with discussion of a successful placebo-controlled trial. This trial substantially bolsters the possibility that later cases involve direct anticancer effects of cannabis and not a placebo effect.

Brain Cancer

The UK-based pharmaceutical company GW Pharmaceuticals released details of a Phase II placebo-controlled trial examining cannabis extracts for the treatment of glioblastoma multiforme (GBM) in a February 7, 2017 press release ("GW Pharmaceuticals"). 21 patients with recurrent GBM were included in the trial. They used a proprietary blend of THC and CBD, or a placebo, along with chemotherapy as treatment. The doses were not specified, but based on GW's previous trials and the fact this was an exploratory trial, it is likely the dose was relatively low, probably between 10-25mg per day of total cannabinoids. Patients receiving the cannabinoids had an 83% one-year survival rate compared with 53% for patients receiving placebo. The median survival for the cannabinoid group was 550 days vs. 369 days for the placebo group.

“The findings from this well-designed controlled study suggest that the addition of a combination of THC and CBD to patients on dose-intensive temozolomide produced relevant improvements in survival compared with placebo and this is a good signal of potential efficacy. Moreover, the cannabinoid medicine was generally well tolerated. These promising results are of particular interest as the pharmacology of the THC:CBD product appears to be distinct from existing oncology medications and may offer a unique and possibly synergistic option for future glioma treatment," said Professor Susan Short, PhD, Professor of Clinical Oncology and Neuro-Oncology at Leeds Institute of Cancer and Pathology at St James’s University Hospital and principal investigator of the study. GW's CEO, Justin Gover, also said, "We believe that the signals of efficacy demonstrated in this study further reinforce the potential role of cannabinoids in the field of oncology and provide GW with the prospect of a new and distinct cannabinoid product candidate in the treatment of glioma." The press release went on to describe preclinical results, such as those described in the previous section of this book, which justified this trial.

It is worth noting that, anecdotally, most people have used hundreds of milligrams of cannabinoids for treating cancer. Since GW's trial almost certainly used a far lower dose, and preclinical results have consistently shown a positively-correlated dose-response relationship

between cannabinoids and cancer cell viability, it is not unreasonable to assume that higher doses could achieve even better results than this trial.

Dr. Nicholas Blondin, the medical director of St. Vincent's Brain Tumor Center in Bridgeport, Connecticut, conducted a multi-year study on brain tumor patients using cannabis (Incollingo). His observations are as follows:

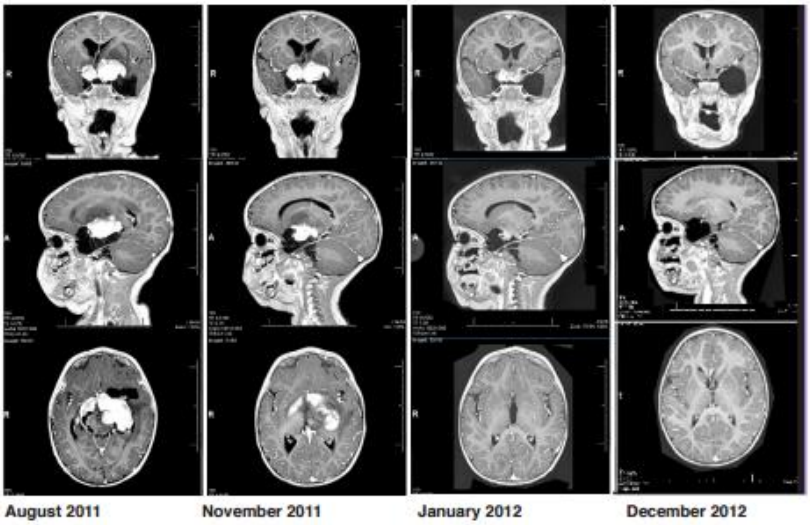
"Tracked were five astrocytoma patients, four of whom used palliatively and one therapeutically; three anaplastic astrocytoma patients, one of whom used palliatively and two therapeutically; and 12 glioblastoma patients, including three low-use patients, two who used palliatively and seven who used therapeutically. Some started earlier in the course of their treatment than others. Blondin authorized the first of his patients to use medical marijuana on March 3, 2014, and that was when he initiated his effort to track outcomes. In all, he approved four patients to use cannabis in 2014, six in 2015, four in 2016 and six so far this year. His data cutoff date for the study presented at SNO was June 12, 2017. All of his patients who are taking cannabis palliatively have reported that it is effective, Blondin said. Among those using cannabis therapeutically, he said, all seven glioblastoma patients were alive at data cutoff; their cannabis use had ranged from two to 30 months."

There was no explanation of the difference between low-use, palliative, and therapeutic doses, but it is likely the therapeutic doses were highest. The fact that all palliative patients said cannabis was effective and all glioblastoma patients were still alive at data cutoff is noteworthy.

A report from doctors in the Division of Pediatric Neurosurgery at BC Children's Hospital in Canada described septum pellucidum/forniceal pilocytic astrocytoma (PA) tumor remissions in two children (Foroughi et al.). Both children received surgery, yet small residuals were left behind in both cases. In the following three years after surgery, one case was dormant while the other showed a slight increase in size. Over the next three-year period, there was a clear regression of both residual tumors. As the authors state, "Neither patient received any conventional adjuvant

treatment. The tumors regressed over the same period of time that cannabis was consumed via inhalation, raising the possibility that the cannabis played a role in the tumor regression."

The Winter/Spring 2013 issue of *O'Shaughnessy's*, an American cannabis journal, described the regression of an optic pathway glioma (Gardner, "Doctors"). Over the course of 16 months, the tumor reduced by 95%; the sole treatment used to achieve this was cannabis oil. The case was reported by Dr. Jeffrey Hergenrather, whose work is further described in the ***Assorted Cancers*** section.

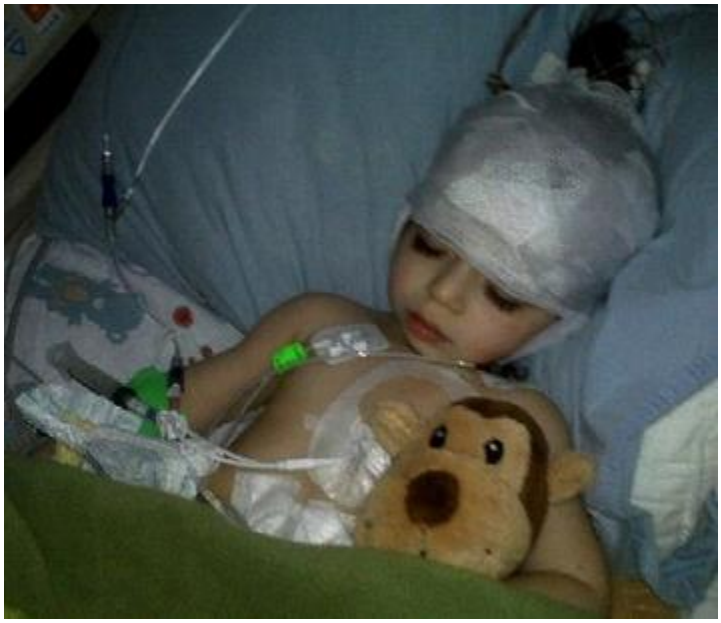


MAGNETIC RESONANCE IMAGING SCANS display coronal (top row), sagittal (middle row) and axial (bottom row) views that document the regression of an optic pathway glioma (white area near center of the brain) by more than 95% over the course of 16 months. Column of three images at left are from initial MRIs taken in August 2011. Most recent scans (column at right) were made in December 2012. Gliomas are known to be sensitive to cannabinoids. Jeffrey Hergenrather, MD, reported that the sole treatment used to achieve these results was cannabis oil applied to the child's pacifier twice daily before nap and bedtime.

Dr. William Courtney is a pioneer of cannabis juicing and raw cannabinoid therapy. In a *Huffington Post Live* video, he described a young child with a brain tumor who received surgery, chemotherapy, and radiation ("Medical Pot"). The treatments failed and the child was sent home on hospice. The parents began administering juice derived from the leaves of cannabis plants, which contain some THCA and CBDA. As of the report, the patient was still alive two years later with no trace of the tumor.

An Israeli physician named Dr. Ephraim Lansky published a case study about a cancer patient who came to him with a golf-ball-sized tumor in his head (Wilson, "Light-Up"). Dr. Lansky treated him with one gram per day of CBD-rich cannabis (most likely oil) ingested orally. Eight months later, the tumor had shrunk by 75% and the patient's seizures had entirely disappeared. "'Cannabis is just another herb, and it belongs within the wider context of herbal medicine,' Lansky told the Jewish Journal. 'Of all the other herbs I use, it's the most useful. I'd even have to put it ahead of garlic.'"

The documentary American Drug War 2 described the journey of child patient Cash Hyde, who arguably launched the pediatric cannabis movement (*American Drug War 2*). On May 3, 2010, Cash was diagnosed with a Stage IV brain tumor. On May 5th, surgery was performed and high-dose chemotherapy was started. The Hydes, Mike and Kalli, were told that even with bone marrow transplants, Cash had an 80% chance of dying. The combination of chemotherapy and other pharmaceuticals resulted in a 2-week ICU stay, where the Hydes were warned of possible organ failure and brain failure. As the documentary graphically depicts, Cash's state was mortally severe, and it is frankly stunning how he was able to survive for so long through so much.



In their search to find some way to help their son, the Hydes discovered stories of cannabis oil healing cancer. The day of this discovery, they managed to acquire oil, and Mike immediately began secretly sneaking it into Cash's feeding tube. Almost instantly, Cash started to drastically improve. Within two weeks, he was able to get off eight medications. He began to eat and laugh again. His quality of life transformed for the better.

Cash was released from the ICU in mid-December 2010. His parents had to teach him how to crawl and walk again, as his motor skills had deteriorated from the cancer ordeal. In January 2011, brain scans revealed Cash was cancer free. After the scans, Mike revealed to the doctors that he had been giving cannabis oil to Cash. The doctors were speechless, and then attributed the healing to prayers rather than cannabis oil. As Mike said, "I believe in prayers and miracles, but I also believe in numbers, and at the end of the day it adds up."

Nonetheless, hospital staff gathered to witness Cash leaving cancer free, believing they had seen a miracle.

Given the possibility that the tumor could recur, the Hydes continued to provide Cash with cannabis oil after his remission. However, in March 2011, a series of federal raids on medicinal cannabis suppliers resulted in Cash's oil supply being cut off. The family ran out of medicine in June.

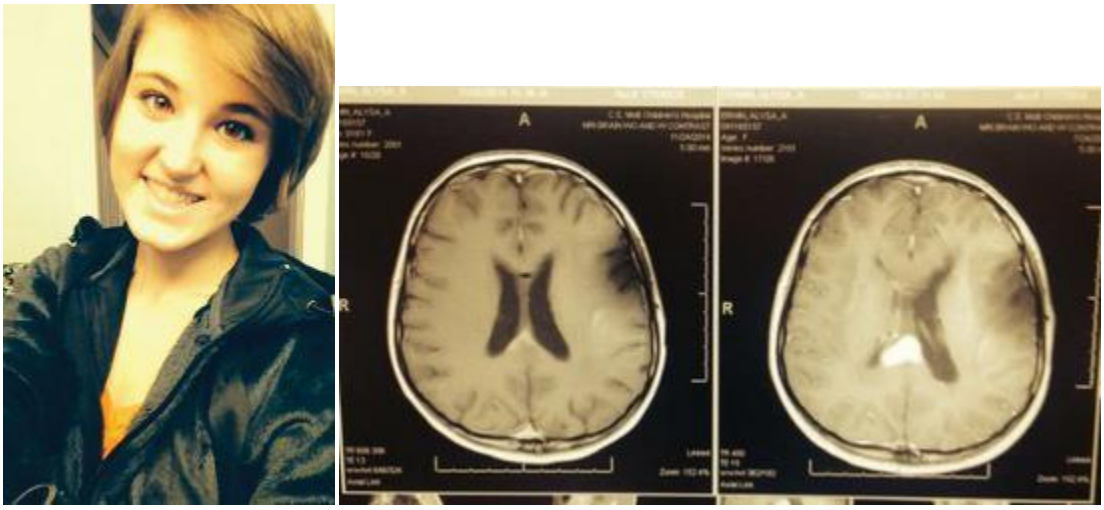
In October 2011, a scan confirmed the Hydes' worst fear - Cash's cancer had returned. They could not reestablish a reliable cannabis oil supplier in Montana, so they went to California in November 2011 to attempt proton therapy. They also hoped to find a supplier in California, and get Cash restarted on cannabis oil as soon as possible. Upon arriving in California, doctors gave a poor prognosis for Cash, and said there was no hope of shrinking the tumor. In December 2011, the Hydes were put in contact with Ringo, a producer who gave them a 90-day supply of cannabis oil for free. With the combination of proton therapy and cannabis oil, Cash went into remission for the second time in January 2012. Cash was the first cancer patient to undergo 30 rounds of proton radiation treatment without using any nausea or pain medications besides cannabis oil.

After running out of oil, the Hydes again were not able to find a sustainable supply. And again, in July 2012, Cash's cancer returned for the third and final time. This fight was ultimately too much for a child so young, and Cash passed away on November 14, 2012 in Mike's arms, a final moment the Hydes are thankful for. Had he died in the hospital while under the influence of strong pharmaceutical drugs, his passing surely would not have been as peaceful. To share Cash's story and information about the healing effects of cannabis oil, the Hydes founded the Cash Hyde Foundation (http://www.cashhydefoundation.com).

In Spring 2011, then 14-year-old Alysa Erwin was diagnosed with Grade III anaplastic astrocytoma (Gabriel, "What if"). Even with chemotherapy treatments, she was only given 18 months to live. Alysa began taking Temodar, which caused terrible side effects. Her family learned about the potential of cannabis oil to eliminate the tumor from the documentaries *What if Cannabis Cured Cancer* and *Run From the Cure*, and Alysa began taking a THC-rich oil in August 2011. After the very first dose of cannabis oil, which Alysa ingested through an infused peanut butter, she experienced a "miraculous transformation." Her mother Carly stated, "About 30 minutes after taking cannabis oil she was out of her room eating and smiling. We knew what we wanted after seeing her, but we wanted to see what she wanted because it was her body. The light was back in her eyes again. She was back to herself. She said she wasn't doing chemo anymore; she was only doing cannabis oil."

After a year of taking high doses of cannabis oil, about three milliliters a day (roughly three grams), the cancer changed into five identifiable tumors, one of which was near Alysa's brainstem. Doctors convinced Alysa to have six weeks of radiation, which her mother said was regrettable because it caused brain swelling. Alysa continued using cannabis oil, and by January 2013 was cancer free.

Astrocytomas of all types tend to recur, which unfortunately proved true for Alysa (Gabriel, "Alysa"). For several reasons, she was not able to continue a steady maintenance dose of cannabis oil; such a practice is often integral to keeping cancers in remission. In late July 2014, the astrocytoma returned in a very aggressive form. Doctors said radiation would only buy her some time, apparently just a few weeks. Alysa combined cannabis oil with the radiation, which allowed her to forego opiate medications as well as gain weight. By April 2015, doctors said she was 75% cancer free (Counts). In June 2015, a Facebook post indicated that doctors said everything looked stable and they did not see any more cancer ("WHAT?!?")



(November 2014 scan)

In a February 11, 2013 video, Amy Jo Clark spoke about how cannabis oil helped her treat a brain tumor ("Amy Jo Clark"). For a significant period of time, she managed the tumor entirely with

conventional treatment. At the time of filming, Amy stated she had received abnormal bloodwork for two years, which reflected the presence of the tumor. After using cannabis oil for at least four months, as well as improving her nutrition, her blood tests were completely normal. When Amy began ingesting oil she discontinued all conventional medications, including opiates, which she had been on for seven years. As of June 2015, Amy is doing well and has become a remarkably strong activist for natural health.

A September 29, 2014 article described Lindsay Carter's battle with a brain tumor (Sawyer). At that point, Lindsay had traveled to the United States three times for cannabis oil treatment. After each visit, the tumor reduced substantially, including by almost half after one seven-week treatment period. However, upon returning to Australia where he could not access cannabis oil, the tumor began growing again. As of June 2015, Lindsay is still fighting, but has not been able to return to the United States for treatment for several months. Hopefully he can complete treatment at home in Australia. As of February 2017, Lindsay is still fighting his brain tumor with cannabis. Unfortunately, his family continues to struggle with procuring medicine due to problems with Australia's medical cannabis system.

An article published on October 10, 2013 detailed the history of child patient Dahlia Barnhart (Jurgensen). Dahlia was born in September 2010, and by May 5, 2013 was diagnosed with a brain tumor. On June 10, she began chemotherapy and other medications, including methotrexate, cisplatin, and morphine, which caused debilitating side effects. Surgery saved her life, but also caused some paralysis on her right side.

Dahlia's mother Moriah learned about Dr. Sean McAllister's research showing that the combination of THC and CBD inhibited glioblastoma tumors. The Barnharts moved from Florida to Colorado in December 2013, and Dahlia began taking about a gram per day of CBD-rich cannabis oil (Cascio). "I saw almost immediate responses cognitively; she developed into a normal 3-year-old from a very critically ill child almost overnight," Barnhart said. According to a May 22, 2015 post on the CannaBabies: Dahlia Strong page, Dahlia is doing well and the tumor is stable or perhaps even just dead mass. The family is preparing to return to Florida ("CannaBabies").

An October 22, 2013 interview with Jeremy Kigar discussed his experience with Grade IV astrocytoma, also known as glioblastoma ("Brain Tumors"). Following his diagnosis, Jeremy was quickly started on 16 medications, including antibiotics, antidepressants, narcotics, and more. After learning about cannabis oil, Jeremy started taking a half gram per day for three weeks. Within five days, significant changes occurred in his overall wellness. He reduced pharmaceutical medications tremendously, including eradication of opiates and antidepressants. Jeremy denied further chemotherapy and used cannabis oil in 90-day cycles, which controlled his cancer. It was only after beginning THC-rich cannabis oil that Jeremy's tumor began to shrink. At the time of filming, the tumor had reduced from Grade IV to Grade II.

A young patient named Jonah Allen was diagnosed in 2013 with an inoperable glioma tumor on the left side of his brain ("Denver Medical"). He began using cannabis oil with substantial levels of THC and CBD. A video posted July 21, 2014 shared that Jonah was continuing to do well with his cannabis extract treatment (Allen). Doctors said Jonah's tumor would only grow and he would need to receive chemotherapy for the rest of his life. Using cannabis extracts as his sole treatment, Jonah's tumor began to shrink. As of May 2015, Jonah is continuing to fight his cancer with cannabis.

A September 9, 2014 video from NBCNews.com featured a young child named Leah Merklin. She was using cannabis oil to treat diffuse intrinsic pontine glioma, one of the most aggressive and fatal brain tumors ("Cannabis Oil"). After diagnosis, she was given 6-12 months to live; doctors said it would likely be closer to 6. The cancer had wrapped around her brainstem, which caused numerous complications including movement and eye problems. Her parents, Eric and Bethany, began administering cannabis oil to her, and at time of filming had worked her up to almost a gram per day. The family quickly saw incredible benefits. Leah began walking, jumping, and going back to school. From January 2014 to July, there was no growth in the cancer. Leah's doctors support her use of cannabis medicine.

A June 5, 2014 article reported the progress of Taylor Rehmeyer, a 15-year-old patient (Toledanes). Diagnosed at 6 years old, the tumor returned three times. Radiation was only partially effective for shrinking the tumor. In August 2013, it began growing again, and Taylor's mother

Karen turned to cannabis oil. She built up her dosage to one gram per day for three months. The psychoactivity of the medicine was especially intense for Taylor and induced hallucinations, but the maintenance dose she currently takes does not seem to create such effects. “She got an MRI (in May) that said no major abnormalities. The doctors at Seattle Children’s Hospital don’t want to admit it was cannabis, but I don’t care. She’s cancer-free,” said Karen.

Kelly Hauf is a 52-year-old woman who used cannabis oil to successfully eliminate a brain tumor (Hauf). She was initially diagnosed on January 18, 2000. Due to slow growth, her surgeon said it would be okay to postpone surgery and monitor the tumor every three months. After a little over three years the tumor grew significantly, and Kelly had surgery on September 4, 2003. At this point the cancer was determined to be Grade II Oligodendroglioma.

Kelly continued to have MRIs every three months, until a November 2013 report showed regrowth of the tumor. Her doctor suggested 4 to 6 months of chemotherapy. Kelly conducted extensive research and decided to try cannabis oil before the chemotherapy. Her neuro-oncologist supported her choice and allowed her to move forward. Kelly began taking the oil in early 2014. Her intention was to work up to a gram per day by April. While she was unable to reach that dosage level, the smaller doses stopped the main tumor’s growth and eliminated a smaller tumor that had been present since Kelly’s first surgery ten years before. This success encouraged Kelly to continue with the oil therapy; over the next few months she attained her desired dosage level.

For the final two weeks before her second MRI in August 2014, Kelly was on two grams per day. The test showed the remaining tumor was only dead scar tissue. In addition to taking cannabis oil, Kelly used supplements, meditation, yoga, organic juicing, and other natural healing techniques to achieve her incredible results. A statement from Kelly described additional benefits she experienced from cannabis oil:

"After establishing residency in San Francisco, I was able to get a medical marijuana card. The card was for cancer treatment but, amazingly, the cannabis oil has helped me with my fibromyalgia pain, joint pain, and chronic headaches. I had this pain for many years and it was getting worse. I literally have no pain now. My blood pressure had been creeping up over the years and was consistently pre-hypertensive, now it's consistently on the low side of normal. I have not taken any other medication except the cannabis oil, supplements, and good clean healthy food over the last 8 months."

A December 24, 2014 article shared the story of Patricia Crone, a scholar who worked as an Islam historian at the Institute for Advanced Study (Arntzenius). The article also announced the screening of a documentary about her battle with cancer. The film, titled *For the Life of Me: Between Science and the Law*, intimately conveyed Patricia's experience. In November 2011, Patricia was diagnosed with lung cancer that had metastasized to her brain. With a poor outlook, she looked to cannabis oil as an alternative therapy. Her academic background impelled her to research the medicine methodically and skeptically.

She read about "Rick Simpson Oil" and claims that cannabis extracts could kill cancer. Seeing that even the National Cancer Institute posted evidence about the anti-cancer activity of cannabinoids, Patricia decided to try it. Remarkably, she acquired cannabis and made the oil herself. Hoping that cannabis oil would shrink her tumors, Patricia delayed whole brain radiation (WBR) for seven months. The growth and proliferation of her tumors decreased, but she still decided to undergo WBR for additional anticancer action. Unfortunately, this had little effect on her tumors, with devastating side effects. Following WBR Patricia also used Avastin, an angiogenesis inhibitor, which apparently was more effective and tolerable than the radiation.

According to her sister, the producer of *For the Life of Me*, Diana C. Frank, as of Thanksgiving 2014 Patricia's tumors were gone. However, her brain was severely damaged by the radiation, and Patricia needed to take an anti-seizure medication to deal with the radiation-induced seizures. On the whole, she was severely weakened. Tragically, Patricia passed away on July 11, 2015.

Having watched Patricia's experience from the beginning, Diana believes the decision to use radiation was a mistake. Indeed, just as the decision to use cannabis oil can be risky due to a lack of research, the decision to use conventional therapies also carries major risks as well. Although cannabis was not as effective as Patricia had hoped, her ultimate desire is that her experience and the film will promote research into the endocannabinoid system.

A page for the film can be found at http://www.forthelifeofmefilm.com.

A February 3, 2015 article briefly described the work of a Filipino oil maker known as Juan Pedro (Jambora). He produces CBD-rich cannabis oil for patients in the Philippines. In the article he stated, "It [cannabis oil] starves the cancer, but not all cancers. I don't want to call it a cure. But this could be an effective treatment… I've seen it stop a brain tumor, in a medication supervised by medical doctors."

Jeff Ditchfield, an experienced cannabis extract producer, author, activist, and lecturer, has treated dozens of cancer patients with cannabis oil. In an interview he shared the following information:

"Your choice of strain depends very much on the cancer you are treating. Many conditions such as lung cancer respond well to high THC oils, however, if you are treating Gliomas or any form

of brain tumour then we have found that a 1:1 THC/CBD strain is the most effective" ("Project Storm").

(Jeff Ditchfield with Dr. Manuel Guzmán)

A February 11, 2016 article from BBC News described Kieran McCrory's experience with cannabis oil for a terminal brain tumor (McGee). He was diagnosed with the tumor in 2014, and after brain surgery and radiation treatment apparently failed to affect the tumor, he began using cannabis oil as the sole treatment in 2015. By February 2016, doctors said the tumor had stopped growing. "I can be optimistic about spending a good length of time on this planet with my wife and child. It is good to see a bit of light. Basically, the tumour has stopped in its tracks. So it's not spread and it's not got any bigger," said Kieran.

A February 22, 2017 article provided a look into one man's journey to fight a recurrent brain tumor (Johnson). Jason Kamara's brain tumor was found to have returned in December 2016, after he had initially beat it five years prior. He was given three weeks to live in January. His daughter, Amy Beaumont, read about cannabis oil online and procured what apparently was a legal CBD oil, likely derived from industrial hemp. "Within a week his speech came back and he could walk again. At his worst, you could have chopped his hands off and he wouldn't have felt a thing but now he is using them again." said Amy. Doctors have been stunned by his progress, with one consultant saying "there was no way he should [have] progressed as much as he has." As of the article's publication, he has exceeded his prognosis by two weeks.

According to a video attached to the article, Jason only takes two drops of the oil on his tongue every morning and every night. In addition to his mobility and speech improvements, Amy described his improvement in energy, appetite, and overall recovery. While this case is still developing, it is notable for the rapid reversal of a massive decline in quality-of-life from a remarkably small dose. Given the progress, at the very least it is likely that Jason will far exceed the three-week prognosis he was originally given.

It was unspecified if Jason received any other conventional anticancer therapies, but the combined factors suggest he was only on the CBD oil.

Unfortunately, Jason passed away on May 6, 2017 from a brain bleed. While his tumor wasn't eliminated, he lived significantly longer than initially predicted (Robson and Robson).

Four-year-old William Frost was diagnosed with an ependymoma brain tumor in 2014 (Waugh). Surgery and chemotherapy were ineffective as treatments, so a private clinic prescribed CBD oil. After a few months, William's tumor had shrunk by two-thirds and he returned to school. This event has stimulated research at Nottingham's Children's Brain Tumour Research Centre, at the

University of Nottingham, into the anticancer effects of CBD. As for May 2017, William is apparently doing well.

A poster from the 2017 International Cannabinoid Research Society (ICRS) described the effects of CBD oil in conjunction with chemotherapy and radiation on two glioblastoma patients (Gardner, "Towards"). A team of doctors from Sirio Libanes Hospital in Brazil documented the response.

"The authors describe two patients with confirmed diagnosis of Glioblastoma Multiforme (WHO-IV), both presenting MGMT methylated and IDH-1 mutated who, after an incomplete surgical resection, were submitted to the Stupp protocol associated with cannabidiol (CBD). Both patients presented very satisfactory clinical and imaging responses in periodic evaluations. Right after the chemoradiation, one of the patients presented a very exacerbated and precocious PSD in the MRI, which was resolved in a short period of time. On the other hand, the other patient presented a marked remission of the altered areas in the MRI (figures 1 and 2 [presented below]). **Such aspects are not commonly observed in patients only treated with conventional modalities.** This observation could highlight the potential effect of CBD increasing PSD response that could impact survival. Further investigation with more patients with critical molecular analyses should be done."

PSD refers to tumor pseudoprogression, which occurs in some glioblastoma patients as an inflammatory response to treatment. Interestingly, PSD is usually a marker of longer survival as it is potentially associated with treatment effectiveness.

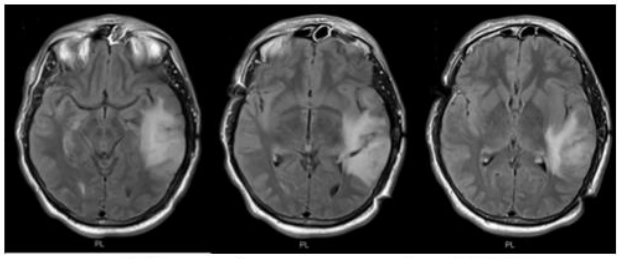


Figure 1: preoperative MRI.

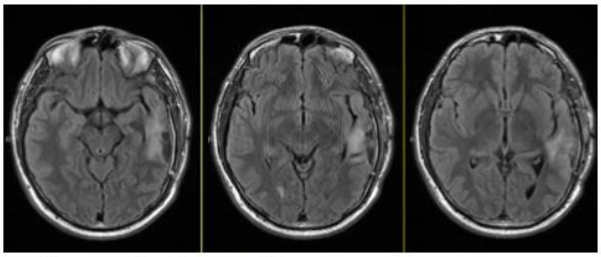


Figure 2: first follow up post-surgery, chemoradiation and CBD.

Lynn Cameron had her story featured across a number of UK newspapers, including *Mirror* (McCourt). In December 2013, the 48-year-old was diagnosed with a brain tumor and given six to 18 months to live. Surgery, chemotherapy, and radiation were all used, but even with these approaches 18 months was the maximum time limit given. Scans showed the conventional treatments were not effective at shrinking the tumor. Lynn then radically changed her diet, cutting out sugar and processed foods and adopting an alkaline diet. She also began using apparently THC-rich cannabis oil under her tongue. After adding on the oil, Lynn said, "Each scan I received after that was showing an improvement. I had been told that chemotherapy and radiotherapy doesn't make much difference, so I knew it must be the cannabis doing it. By the sixth MRI, the cancer had gone." Lynn is now currently fighting to improve access to cannabis in her home country.

While it is normally necessary to ingest cannabis oil to experience anticancer effects, in some cases vaporization may be effective, as shown in a February 2018 story about Phil James, a Wales resident diagnosed with Grade III anaplastic astrocytoma (Hemming). After diagnosis at the end of 2015, he was given two years to live and told nothing could be done. Phil found research showing CBD could have an anticancer effect against glioma brain tumors and began vaporizing a CBD product every night before bed. He also changed to a healthier diet. By the time of the article's publication, he had six brain scans showing only minimal trace of the tumor. "I'm a two-year survivor of brain cancer, I use CBD Indica, and I would rather be illegally alive than legally dead. I do put it down to diet and taking CBD," said Phil.

Breast Cancer

A video posted by the dispensary River Rock in Colorado on September 8, 2013 elaborated on a woman named Karen's experience ("RRTV//Patient Stories"). In April 2011, Karen was diagnosed with Stage III breast cancer in her left breast. She went through eight treatments of chemotherapy, and endured several surgeries. In February 2012, Karen found out the cancer had become metastatic, spreading to her breast bone, hip bone, liver, and lymph nodes, thus making it Stage IV.

Karen learned about cannabis oil treatment from her son and eventually met Tony Verzura, who told them about his Advanced Cannabinoid Therapy program. On May 1st, Karen had her first appointment with River Rock and began CBD-rich treatments. Karen tracked her progress with CA-15 cancer antigen tests. She noted that once she incorporated cannabis extracts with traditional treatments, the test counts dropped significantly.

Around the middle of the A.C.T program, Karen stated her CA-15 score was 25; under 30 is the baseline for a normal person. The blood tests remained below normal for a significant period of time, so she began moving away from traditional treatments. Karen explained to her doctor the sophistication of modern cannabis extract programs, and he expressed support for her treatment. She also asked if it would be necessary to sign something for refusing further conventional treatment, but the oncologist said doing so was not needed due to her progress.

Karen provided an update in an October 16, 2013 video ("RRTV Patient"). She reported the cancer was completely gone as determined by a PET scan. "I killed Stage IV cancer by using River Rock's A.C.T. Now program, and the nutritional support that I gathered for myself."

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A September 26, 2014 article in an Australia newspaper elaborated on Susannah Patch's recovery from metastatic breast cancer (Kirkwood, "Cannabis Oil"). She fought cancer for years before finding relief with cannabis oil.

In July 2011, Susannah was diagnosed with Grade III invasive duct carcinoma in her left breast. The tumor was quickly removed along with two lymph nodes, which revealed metastasized cancer. In August 2011, doctors removed 10 more lymph nodes and Susannah began four weeks of radiotherapy. She was clean for a year until pain in her right hip led to the revelation of a bone

metastasis, along with cancer in her lungs and spine. Two more weeks of radiotherapy in December 2012 were prescribed, but doctors said her condition was terminal.

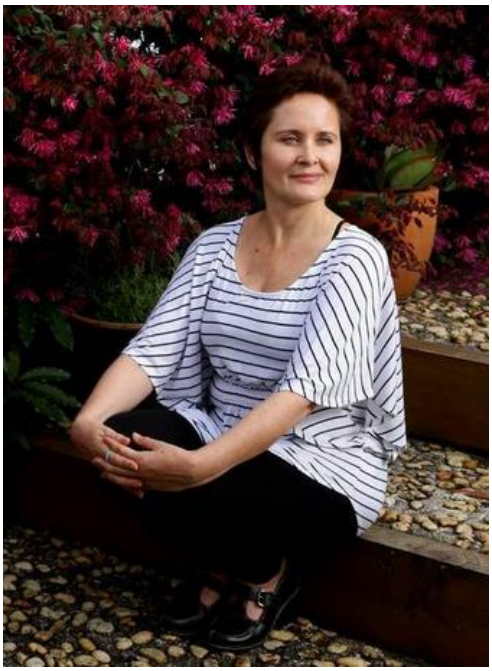
Susannah began taking oral chemotherapy to halt the cancer's progress, but it was ineffective and the disease continued to spread as of June 2013. She started intravenous chemotherapy in August 2013, which doctors said would last for as many months as she lived. It was at this time that she also began ingesting large quantities of cannabis oil.

By October 2013, tests showed a "marked improvement" in lungs and chest space, although she still had metastases in her hip and spine. Susannah stopped chemotherapy in December, placing her full faith in cannabis oil. The article states:

"Her most recent CT scan report, dated July 7 [2014], says her lungs are stable with 'residual scarring at the site of previous lung metastases'. 'These have not progressed and are stable in appearance,' the report says.

'Sclerotic lesions' in her spine, sternum and ribs are stable, 'reasonably extensive bony metastases in the pelvis are stable in appearance' and no 'definite bony metastases' in her femora were detected despite a dedicated CT scan. Ms Patch said she was continuing to take a much smaller daily dose of cannabis oil and was looking forward to her next check-up."

Unfortunately, on March 28, 2016, Susannah passed away (Kirkwood, "Medical"). She had a relapse at some point in 2015 and eventually succumbed to the cancer. It was unclear if or when she ever stopped using cannabis oil. Susannah believed the cannabis treatment helped keep in remission for so long; given she received a terminal diagnosis in December 2012, it is reasonably possible the cannabis influenced her extended survival.



A February 2015 article described the experience of Stefanie LaRue, who battled breast cancer for a significant portion of her life (Renea). After several misdiagnoses, she was diagnosed with Stage IV metastatic breast cancer in 2005. Although she was given at most a year to live, she eliminated the cancer with a combination of diet, supplements, acupuncture, fitness, chemotherapy, and surgery.

Unfortunately, the cancer returned two more times. After the third recurrence in 2013, Stefanie decided not to do chemotherapy and instead only use cannabis oil. “Cannabis oil killed all of the tumors in my body. My monthly lab and quarterly scan results are proof that the cannabis oil treatment worked,” said Stefanie. She now takes a half gram maintenance dose of cannabis oil; as of a scan in December 2014, she was cancer free.

Stefanie appeared in a March 23, 2015 video from BBC News, which explored the topic of cannabis as a direct treatment for cancer ("Can Cannabis Oil").

Sadly, Stephanie passed away on May 31, 2017 at the age of 42 (Hays). While she was ultimately not successful in completely beating her disease, she arguably extended her life via her self-treatment. Stephanie was also a tireless advocate for other young cancer patients. "Be your own voice. Be your own advocate. Jump in, engage, interact, ask for help from others on the same journey. It’s about quality of life. Do the work. Do not live in fear … live in love." – Stephanie LaRue

A professional herbalist and cannabis oil producer named Robin Swan treats patients in California through her business Firebird Touch Therapy. She wrote the foreword for *Taking Control*, a book by Carol Smith which chronicled Carol's endeavor to naturally heal her husband of invasive bladder cancer (Sade). In the book, Robin discussed a woman with breast cancer for whom no traditional therapies worked, including chemotherapy, radiation, diet, and herbs. After being sent home to live out her remaining time, the woman began using cannabis oil as a last resort. In just a few months, she was pronounced cancer free for the first time in twelve years. Robin is pictured below.

A California-based organization called Heavens 2 Betsey posted an article on April 9, 2014 about a woman's experience helping her grandmother fight Stage IV breast cancer, which had

metastasized to her lungs and throat ("Spreading Awareness"). Doctors said chemotherapy could manage the cancer and maybe shrink it, but the disease would eventually kill her.

The patient's granddaughter helped her grandmother get started on a combination of concentrated oils, CBD-rich lozenges, tinctures, edibles, topicals, and vaporized oils. When chemotherapy was completed after a few months, the patient was placed on estrogen blockers and anti-nausea medications while continuing the oil. She soon underwent a new scan which surprised the doctors – the largest tumor around her esophagus had disappeared completely and small nodules remaining in her lungs appeared reduced in size. Doctors declared the patient in remission.

A page on CancerPatientsRights.com featured testimony from Laura DeVille-Sherman (DeVille-Sherman). She turned to cannabis oil after being diagnosed with cancer for the third time. In this case, it was Stage IV breast cancer with metastases to areas of bone and liver. There were so many tumors present the doctors stopped counting.

Laura was told to get her affairs in order due to the severity of the cancer. Instead of following this course, she worked up to a gram per day of cannabis oil. Eventually, a PET scan revealed no cancer. While a couple of shadows remained on a CAT scan, the improvement was lifesaving. The only side effect was the amount "wonderful quality" of sleep Laura experienced, which is generally a part of the healing process. Laura confirmed to the author that a July 2014 scan revealed she is cancer free. As of June 2015, Laura is still doing well.

A November 2012 post on the forum GrassCity.com provided information on a man's experience using cannabis oil as a last resort to treat his wife's terminal metastatic breast cancer ("[Cancer]"). As of May 12, 2013 the woman was doing well, but there have been no further updates.

GD1966 Posted 01 November 2012 - 09:00 PM #1

The Widows Son

Registered Upgraded

911 posts

POPULAR

Some background info: my wife first was diagnosed with Breast Cancer, which metastasized into her brain about two years ago. Two months ago we finally gave up on Chemo and radiation and decided to try and enjoy whatever time we have left. About 6 months according to her Oncologist. I had resigned myself to the fact that my sweetheart was dying. She is the love of my life. August was our 20th wedding anniversary. These last 20 years have been the best of my life because of her. She still takes my breath away!

I mentioned my wife's plight in a thread and Granny Stormcrow suggested we not give up and start using RSO. RICK SIMPSON OIL. she sent us a mountain of Information about it. To make this long story short I made the RSO with one pound of Lemon Skunk from my last grow and immediately started my wife on it.

Within 3 days she was able to eat a meal and keep it down. Then her excruciating headaches completely disappeared! Her color came back too! However I am smart enough to know all of these good things does not equal being cured. Her first MRI showed the tumor growth had stopped.

Today, her oncologist repeated the test and her tumors have actually begun to SHRINK!!!! I don't even know how to say thank you to you Granny. I think you helped save my wife's life!

A January 6, 2016 article in *Santa Maria Sun* mentioned several patients using cannabis oil, including Kate Kytle (Kinkade). Sixteen months prior to publication, she had been diagnosed with Stage IV metastatic triple-negative breast cancer that had spread to her lungs. She was then later diagnosed with HER2-positive breast cancer, another aggressive form of the disease. She used a combination of CBD-rich therapies, including a topical salve applied directly to the breast, a tincture she drank in a tea in the morning, and full-strength CBD oil. Kate did not appear to use any THC-rich preparations. She used no chemotherapy or radiation, but did utilize two antibody therapy drugs. While the timeline is not clear, at some point there was a five week treatment period after which a scan showed the tumors were "basically gone." "It's amazing what happened. It literally stopped my cancer from spreading," said Kate.

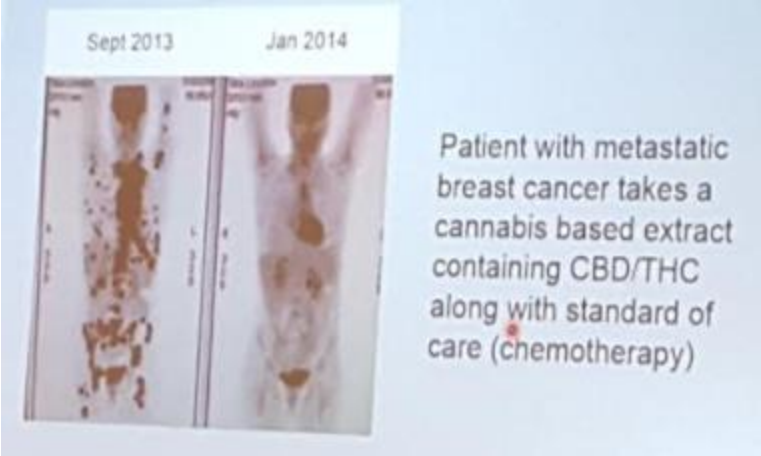
Kate Kytle displays the three forms of cannabis-based medicine that she has successfully been using to fight aggressive breast cancer. Kytle uses cannabis extracts high in cannabidiol (CBD), the highly medicinal and non-psychoactive compound in marijuana, to make a tincture, salve, and a concentrated form. - PHOTO BY DYLAN HONEA-BAUMANN

The legalization of medical cannabis in Florida in 2016 allowed thousands of patients to access treatment. For one woman, Tammy Levent, this change simplified her acquisition of cannabis medicine ("Woman Turns"). She was diagnosed in May 2015 with malignant breast cancer, and after receiving a lumpectomy refused further conventional treatment, traveling outside the state to get what most likely was THC-rich cannabis oil. At some point in 2016, medical tests showed she was cancer free. "'When I looked at Tammy's blood work the tumor markers were all zero – and I couldn't explain it,' said Lisa Genovese, a nurse that is on Levent's medical team." Tammy claims her doctors also said they've "never seen anything like this" in their lives.

Dr. Eduardo Palanca, a physician in Clearwater who oversees Tammy's care, pointed to studies showing that THC has a strong anti-tumor effect. He voiced his support of further research into the anticancer properties of cannabis.

Tammy also wrote a book about her experience, titled "Sink or Swim: A Survival Story." It is available on Amazon at this link: https://www.amazon.com/Sink-Swim-Survival-Tammy-Levent/dp/0692588299.

At the 11th National Clinical Conference on Cannabis Therapeutics held in Berkeley, California from May 18-20th, Dr. Sean McAllister presented about the use of CBD to treat breast cancer. While his presentation was largely focused on his preclinical work, including how CBD can downregulate expression of the pro-cancer Id-1 gene, he also included a human case that was shared with him. The patient took CBD and THC along with conventional therapy to achieve an amazing reduction in metastatic breast cancer. The results were achieved in only four months.



Yvonne DeLaRosa Green, an actress and entrepreneur who has appeared in popular TV programs like *How I Met Your Mother* and *The King of Queens*, was recently awarded the first cannabis business license in Los Angeles county (Burnett). In an October 2017 interview, she revealed her mother was diagnosed with breast cancer in 2007. Yvonne recommended she use cannabis, harboring some hope it would work as a direct treatment. Yvonne was friends with Jack Herer, the iconic cannabis activist who wrote *The Emperor Wears no Clothes* and was an early proponent of using cannabis to treat cancer. He had told Yvonne that some people were cured of cancer with cannabis.

For generations, Yvonne's family embraced totally natural healing, not even using Band-Aids or cough syrup. Yvonne said, "So, I think, when my mom was diagnosed with breast cancer, my mom said to herself, 'Well, what would Grandma do?' That's how she decided to say yes to cannabis. She forewent chemo and radiation, all those drugs—she didn't do any of that. Now, my mom's cancer-free. That's why I do what I do. To a lot of people that sounds like a miracle. And it is. But it's a miracle that can be obtained by anyone as long as they have safe access to this medicine."

Given the family history, it is likely Yvonne's mom used other natural approaches besides just cannabis. Nonetheless, achieving cancer-free status without conventional therapies and cannabis as a central treatment is impressive.

Lin Coxon, a resident of Derbyshire, England, was told by doctors at the Royal Derby Hospital she had a 33mm breast tumor on or around her diagnosis date of June 28, 2017 (Hague, "Grandmother"). The cancer had invaded lymph nodes and muscle as well, so doctors said she would need chemotherapy, radiation treatment, and surgery to remove the lymph nodes. Almost immediately after diagnosis, Lin began researching alternative treatments and came across the story of Karen Roberts, whose case is also described in this book. Lin's chemotherapy was scheduled for August 26th, so in the meantime she got a legal CBD-rich oil and began taking it while waiting. By July 24th she could no longer feel the tumor and arranged a scan for August 21st.

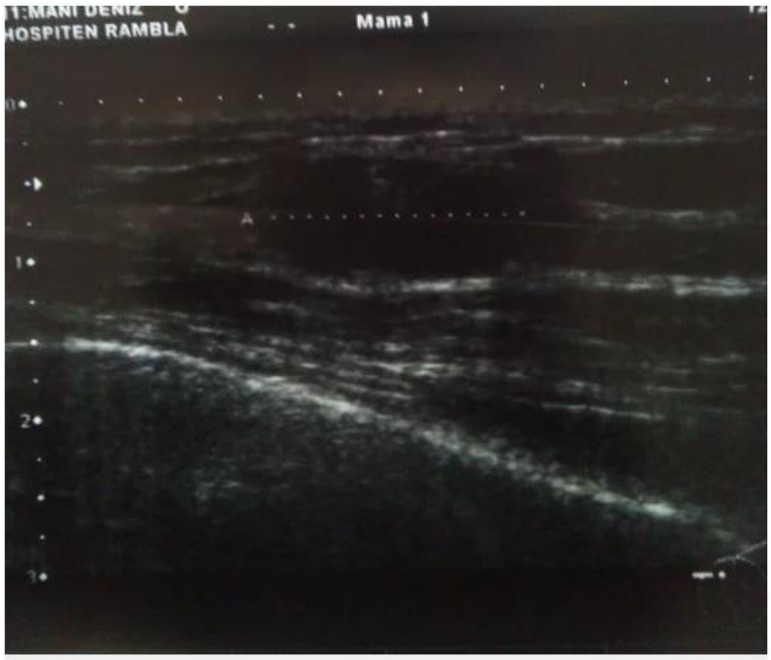
Lin stated, "The doctor at the Nuffield Hospital was staggered when he saw the tumour had shrunk from 33mm to 11mm and my lymph nodes had gone from 25mm to 10mm. He did a mammogram and saw the whole density had changed which was amazing news, so as it was shrinking so dramatically I spoke to my consultant and deferred the chemotherapy. I am still taking the cannabis oil and the tumour is still shrinking and is now down to 7mm with no medical treatment and the lymph nodes are down to 4mm." Lin achieved this using only a few drops a day of the CBD oil. Interestingly, she is also an assistant to a Member of Parliament named Heather Wheeler.

Dr. Wai Liu, a senior researcher with St. George's University who has conducted several studies on the anticancer effects of cannabis, said he was interested when he heard Lin's case and "We have a growing and large collection of testimony from patients using cannabidiol, usually in a cannabis oil type product, who report positive effects on their battle with this dreadful disease."

An updated article on April 16, 2018 revealed that a further scan showed "just small wisps which could be scar tissue," indicating the cancer is completely in remission or nearly so (Thompson, "MP's Assistant").

A February 1, 2018 in *Metro* featured Dee Mani's story of overcoming triple negative breast cancer (Mann). After diagnosis in March 2017, she began using one drop of cannabis oil per night, in a capsule, as the sole therapy. Four months later the cancer had reduced significantly and by August 2017 she was told she was "all clear". She continues to take the cannabis oil to prevent recurrence. Based on the description, it appears the medicine was a THC-rich full-extract cannabis oil.

Dee Mani, 44, found a lump in her breast in March 2017 and after being diagnosed with triple negative breast cancer, she was offered chemotherapy and radiotherapy to save her life. (Picture: Caters)



Dee's scan as her cancer was decreasing. (Picture: Caters)

A June 24, 2018 article on a from a local Oklahoma news station provided an update on Rhonda Gossett, who interestingly enough they had first encountered eight years ago as her son was raising money for her cancer treatments (Stein). She was diagnosed with Stage IV breast cancer in 2010 and was determined to beat it. Despite the conventional treatments, including two brain surgeries for the apparent metastasis to her brain, the cancer returned. She then was administered radiation and drug trials which were not effective for her. At this point, Rhonda was told something to the effect of they didn't know what to do next. She then acquired a CBD-rich oil with relatively high levels of THC, and began feeling better quickly. "Within, what was it, about

three weeks all the scans were coming back positive. The brain started looking better. All the fluid that had built up, everything started dissipating," said her husband Darren (Lett). After two years of keeping this up, she was cancer free. It was unclear whether she continued conventional treatment along with the oil but apparently not.

Colon Cancer

Lindsey Martin, a resident of Cape Town, South Africa, was diagnosed with cancer on September 7, 2011 (Martin, "Lindsey"). A few weeks later, it was determined to be Stage III colon cancer, with metastases to lymph nodes and one spot on her liver. After a tumor in Lindsey's colon was surgically removed, she was scheduled for once-weekly chemotherapy for 30 weeks.

The chemotherapy started on October 14, 2011. It took a great toll on Lindsey; she said it "sucked the life out of me." The only times she felt better were when friends brought around cannabis and she was able to smoke some. The plant enabled her to enjoy food, sleep better, and feel an overall sense of wellness. Lindsey conveyed this to her doctor, who instructed her to take in as much cannabis as she could.

On February 15, 2012, halfway through the chemotherapy sessions, Lindsey went in for a CT scan. In addition to chemotherapy, Lindsey was eating an organic vegetarian diet, berry smoothies, brown rice, green foods, and supplements like Vitamin C, green and hemp powders, spirulina, milk thistle, and sodium bicarbonate. Despite everything, her condition had worsened. She had four lesions on her liver, a 2.8cm stone in her gall bladder, and a cyst on her kidney, all of which had been caused by the chemotherapy. Due to this, Lindsey decided to cease the conventional treatment.

After hearing about the potential of cannabis oil to treat cancer from people on Facebook, Lindsey began using cannabis medicine. She was able to quickly find cannabis oil in her community, and began taking it in small doses. Lindsey consumed 18 grams of the oil in 46 days. She continued eating a healthy diet and ingesting greens-rich supplements.

On March 28, 2012, Lindsey underwent a range of medical tests, then met with four doctors who declared she had no signs of any cancer in her body. Lindsey stated, "Lastly, I have to say that my cancer diagnosis was a true blessing …it facilitated a change within me on every level – emotionally, physically, mentally and spiritually…it formed an unbreakable bond of love and support with my husband. I've become brave and confident in my own power to heal myself…and this is truly the biggest blessing…and I really want to help inspire others to do the same…"

Unfortunately, Lindsey Martin passed away on May 28, 2014 from complications of bowel surgery. She remained cancer-free at the time of her death, and the surgery was unrelated to cancer. The author and many friends were shocked that Lindsey would pass in this manner after fighting so hard to successfully beat colon cancer. Her spirit lives on in the people she helped and inspired.

A December 10, 2016, article reported on an Irish man, referred to as “Stephen” (a pseudonym to protect anonymity), who has used cannabis oil to significantly extend his life (Murray). On December 24, 2014, he was diagnosed with Stage IV terminal colon, liver, and lymph node cancer, with the colon apparently (but not explicitly stated) being the primary source of the cancer. “I was told I only had three months left to live. Here I am now two years later… When you’ve had cancer for so long it can be a very tough thing to deal with. It takes a toll. Cannabis helps me. It picks me up,” said Stephen.

Facing a terminal diagnosis, the father-of-three resorted to cannabis oil. He was initially give free cannabis oil to start, and to be sustainable began growing cannabis and making his own oil. He used the cannabis treatment alongside chemotherapy; given his original prognosis and final statement of the article, it appears the cannabis played a significant role in helping fight the cancer. “I’ve been through more or less all the chemo available to my particular type. The dosages have been reduced over time and, up until a few weeks ago, I was on a mild targeted treatment which works on cutting blood supply to the tumours.”

A June 2017 story in a UK journal featured Marcus Gray's story (Razavi). In February 2016, Marcus was diagnosed with Stage IV colorectal cancer and given just a few months to live. Due to the combination of cannabis oil and chemotherapy, Marcus was doing quite well as of the story's publishing. The metastases in his lungs and apparently the primary cancer diminished significantly. During the height of his treatment, he took a gram per day of apparently THC-rich cannabis oil, and now only takes it periodically. "There is no doubt in my mind that the cannabis oil has had something to do with me living much longer than expected," said Marcus.

A Costa Rica news website detailed the work of Costa Rica Alchemy, which is providing free cannabis oil to patients in Costa Rica (Rico). The oil is apparently a CBD-rich infused olive oil, although some may be THC-rich. One patient, Vladimir Chavez, was diagnosed with terminal colon cancer and at time of publishing was consuming cannabis oil for six months along with chemotherapy. He says his doctors and other patients he knows are surprised at his progress, with markers of his tumor burden having decreased 80%.

Leukemia & Lymphoma

A 2013 article in the journal *Case Reports in Oncology* described the experience of a 14-year-old female patient who had a very aggressive form of acute lymphoblastic leukemia (positive for the Philadelphia chromosome mutation) (Singh and Bali). Prior to undergoing cannabis extract therapy, the patient received 34 months of chemotherapy and radiation. This treatment protocol failed to stop the cancer, and the patient was placed in palliative home care. The family decided to use cannabis oil as a last resort after conducting research indicating potential effectiveness.

The first dose of cannabis oil was given on February 21, 2009. Prior to this, from February 4th to the 20th, the patient's leukemic blast cell count rose from 51,490 to 194,000. Even after beginning the oil, the count continued to rise, peaking at 374,000 on February 25th. However, there was subsequently a sharp decrease in blast count, which correlated with an increase in cannabis dose. By Day 39, the blast count had dropped to 300. The total treatment lasted 78 days, at which point the leukemic blast cells were almost completely gone. Unfortunately, the patient passed away due to a bowel perforation, which apparently was caused by the side effects of the prior intense chemotherapy treatments.

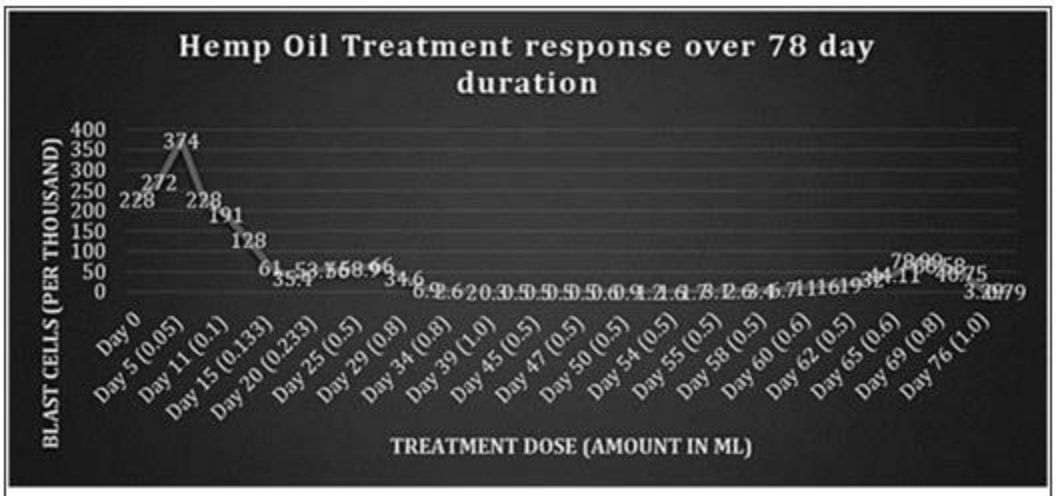


Fig. 6. Response to hemp oil treatment over 78 days.

(Note: Hemp oil means cannabis oil, not hemp seed oil)

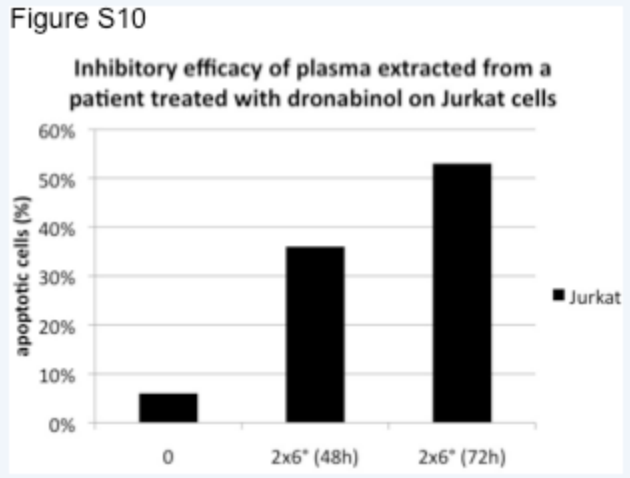
Given the remarkably similar observations between these doctors and individuals treating themselves with cannabis medicine, it is important to convey their final conclusions:

"The results shown here cannot be attributed to the phenomenon of ‘spontaneous remission' because a dose response curve was achieved. Three factors, namely frequency of dosing, amount given (therapeutic dosing) and the potency of the cannabis strains, were critical in determining response and disease control. By viewing figure 6, it can be seen that introducing strains that were less potent, dosing at intervals >8 h and suboptimal therapeutic dosing consistently showed increases in the leukemic blast cell count. It could not be determined which cannabinoid profiles constituted a 'potent' cannabis strain because the resin was not analyzed. Research is needed to determine the profile and ratios of cannabinoids within the strains that exhibit antileukemic properties.

These results cannot be explained by any other therapies, as the child was under palliative care and was solely on cannabinoid treatment when the response was documented by the SickKids Hospital. The toxicology reports ruled out chemotherapeutic agents, and only showed her to be positive for THC (tetrahydrocannabinol) when she had ‘a recent massive decrease of WBC from 350,000 to 0.3' inducing tumor lysis syndrome, as reported by the primary hematologist/oncologist at the SickKids Hospital.

This therapy has to be viewed as polytherapy, as many cannabinoids within the resinous extract have demonstrated targeted, antiproliferative, proapoptotic and antiangiogenic properties. This also needs to be explored further, as there is potential that cannabinoids might show selectivity when attacking cancer cells, thereby reducing the widespread cytotoxic effects of conventional chemotherapeutic agents. It must be noted that where our most advanced chemotherapeutic agents had failed to control the blast counts and had devastating side effects that ultimately resulted in the death of the patient, the cannabinoid therapy had no toxic side effects and only psychosomatic properties, with an increase in the patient's vitality."

It is notable that several years after the above case, in January 2016, German doctors with University Hospital Tübingen offered further supporting evidence (Kampa-Schittenhelm et al.). Their article in *BMC Cancer* stated they had "anecdotal evidence that THC may have contributed to disease control in a patient with acute undifferentiated leukemia." The doctors used an unusual approach to demonstrate this – they extracted blood plasma from an elderly patient treated with dronabinol (synthetic THC) and cultured (Jurkat) leukemia cells in the plasma. The patient received no other anticancer treatment. Doctors found there was an inhibitory effect of the plasma on the cells, and stated, "This observation argues for an antileukemic activity of dronabinol in vivo [in this case, in vivo refers to a human, not animals]. Indeed, one concern about using cannabis to treat cancer is that effective anticancer doses are not possible to obtain. This study offers evidence alleviating that concern. However, it was not entirely clear if a control experiment was conducted (testing dronabinol-free plasma on Jurkat cells).



Also of interest, the doctors tested THC against numerous types of leukemic cell lines. Some lines were more sensitive to THC than others. One such sensitive type of leukemia matched the diagnosis of the previously described leukemia patient in the *Case Reports in Oncology* report. The study concluded, "In this context, a case report of a 14 year old girl with refractory BCR-ABL1 (Ph+) ALL was recently published demonstrating dramatic blast reduction in an individual therapy approach using escalating doses of a cannabis extract. It is remarkable, that the selected case fits into the defined responder cohort of our study."

Mykayla Comstock, a child patient, attracted significant attention related to her battle with cancer. In July 2012, Mykayla was diagnosed with T-cell acute lymphoblastic leukemia (Lupkin). She began receiving chemotherapy at Randall Children's Hospital in Portland, Oregon.

At first, Mykayla was not responding well to the treatments, and doctors said a bone marrow transplant may be necessary. Her family began administering cannabis oil on July 24, 2012 to attempt to kill the cancer and counter the side effects of chemotherapy ("Her Treatment"). After starting oil, Mykayla was instantly able to eat again. She smiled and laughed a lot. Overall, she was much happier.

One week after beginning the oil treatment, Mykayla's physicians reported that the leukemia was gone from her bone marrow and blood; she was in remission and no longer needed a bone marrow transplant. Over the next several years, Mykayla underwent maintenance chemotherapy as required by law. Cannabis oil reduced the side effects and virtually eliminated her need for conventional pain and nausea medications. By May 2015, Mykayla's chemotherapy was completed and she began having her chemo port removed ("Brave Mykayla").

The November 2013 issue of DOPE Magazine shared Silas Tedesco's healing experience (Condon Jr.). Silas was diagnosed with Precursor B acute lymphoblastic leukemia, and began chemotherapy shortly after diagnosis. The conventional treatments were very harsh and caused general sickness, insomnia, and a nearly eight-week period of immobility. Silas' doctor then recommended CBD-rich cannabis oil. As the article concludes,

"After only eight days on cannabis, Silas began to walk, talk, smile and play again. It was a complete turnaround. Silas is now in remission and running around like an average two-year old. His leukemia is in remission and is showing improvements every day."

A May 2013 video detailed Elias Cooper's experience using cannabis oil for the treatment of chronic lymphocytic leukemia (Cooper, "Cannabis HEALS"). Once diagnosed with CLL, Elias desperately wanted to avoid chemotherapy, as it sounded scary to go through. His doctors said as long as his white blood cell count remained under a certain level, they could postpone chemotherapy.

Elias did not take any measures to fight the cancer until his white blood cell count rose high enough to where chemotherapy became an option. He then researched alternative methods and came upon the story of Brave Mykayla, discussed above. Her experience was compelling enough to convince him to try cannabis oil.

After three and a half weeks of taking homemade cannabis oil (produced by his wife Debra) every day, Elias went to the doctor for a blood test. His white blood cell count had dropped by 40,000, which was "life changing news". No other treatments, such as chemotherapy or pharmaceuticals, were used.

Elias provided an update on November 17, 2013 (Cooper, "Cannabis Heals"). Interestingly, the details of his case correlate strongly with the *Case Reports in Oncology* article explored at the beginning of this section. As Elias described, his white blood cell count went up during times he was not using cannabis oil or was using less potent oil, but when he again procured high-quality THC-rich oil, his count fell dramatically. In the journal case, the patient also experienced increases and decreases in cancer cell levels under similar circumstances. At some point in 2014, Elias added

conventional chemotherapy to his treatment. As of June 2015 he appears to be doing very well. The author met him in May 2014, and he is a truly humorous and awesome person.

Logan Ewell, a child patient, was diagnosed with B cell acute lymphoblastic leukemia on April 16, 2009, and quickly began chemotherapy treatments (Volpo). Given that the lymphoblasts were only present in Logan's blood and bone marrow, aggressive therapy was not initially needed. While chemotherapy kept the cancer at bay for two years, in March 2011 tests showed that lymphoblasts had spread to Logan's spinal fluid. Therefore, Logan required an increase in chemotherapy and the addition of radiation. These treatments also apparently kept the cancer under control, until June 2013 when a second relapse occurred.

In October 2013, Logan was admitted to Mott's Children's Hospital to receive a bone marrow transplant, which ultimately proved ineffective. On January 13, 2014, doctors at the University of Michigan stated there were no more options, and advised the family to seek out hospice care for the next three to twelve months.

Immediately after hearing the terminal diagnosis, Kimberly, Logan's mother, began taking steps to procure cannabis oil. She knew it was an option but had not seriously considered it until there was nothing else to try. Logan's first dose of only 0.025 grams resulted in extreme sleepiness but also quickly impacted his lymphoblast count, which dropped eight percent in four days. He maintained a 0.05 grams per day dosage until his next blood tests, which showed rising blast counts. Kimberly then obtained a much more concentrated oil, and after another four day period Logan's blast count began falling again.

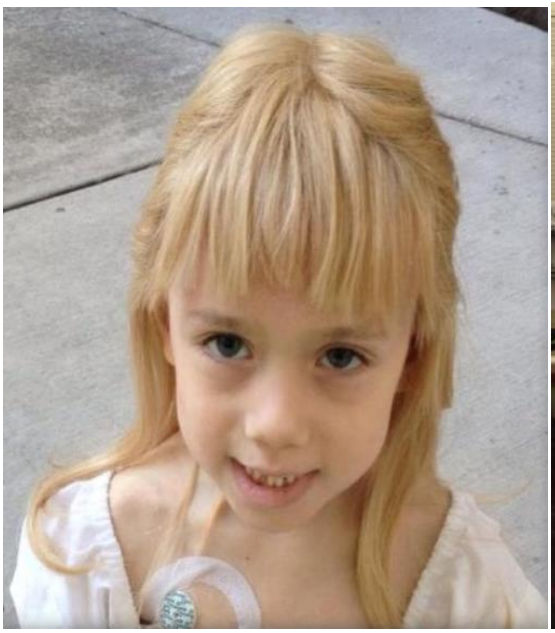
On January 28, 2014, Logan was hospitalized for graft-versus-host disease, an organ transplant-related disorder. His cannabis oil dose was increased to 2 grams per day during his hospital stay, which resulted in further reduction in lymphoblast counts. However, Logan's liver enzymes became abnormally elevated, a potential consequence of using isopropyl alcohol-derived cannabis oil. After switching to 190-proof grain alcohol-derived cannabis oil, Logan's liver enzymes slowly normalized; however, it is unknown whether the solvent was the actual cause. By

April 2014 Logan was pronounced cancer free, and began quickly recovering from the lingering side effects of chemotherapy.

Several months after his primary remission, testicular cancer appeared. Logan continued to use cannabis extract medicine for treatment. It is not apparent whether conventional chemotherapy was added. In any case, as of May 2015, Logan was still doing well.

Lauranne Ackelson is a 6-year old girl who was diagnosed with acute myeloid leukemia three times in her life ("Roar Away"). She endured lengthy hospital stays, two bone marrow transplants, and reached a lifetime max for chemo. Her family decided there had to be something better, and found cannabis oil. Since July 2013, Lauranne has been on one gram of cannabis oil per day, which finally led to her continued remission. She was on chemotherapy when she started the oil but the traditional treatment was apparently discontinued.

Lauranne's story is also mentioned in a news article about children using cannabis in Oregon ("Kids Using"). "Her blood work has been the best we've ever seen since starting retreatment in 2010," Kaleena Brianne, Lauranne's mom, reports. "When we fought this monster the first time, we were inpatient a total of 144 days… but [after cannabis] this time around our total stay was 72 – a drop of 50%. The doctors were impressed with the fact that her bone marrow aspirate also showed no leukemia cells in the marrow."




Landon Riddle's fight against leukemia was chronicled by Dr. Sanjay Gupta of CNN in an August 17, 2013 video (Jammers). Dr. Gupta and Sierra Riddle, Landon's mother, described the severity of his condition. At 2, he was diagnosed with leukemia. Doctors immediately started intense chemotherapy, but said even with that, he only had around an 8% chance of living 24-48 hours.

Dr. Gupta stated, "The chemo made him violently ill. He was in intense pain, he suffered nerve damage in his legs, and he went 25 days without eating." Around the clock, he was on a wide variety of pharmaceuticals and painkillers. Sierra then learned about medicinal cannabis, and found Realm of Caring. As soon as he began cannabis oil, Landon's blood platelet count improved substantially, returning to a healthy level. At the end of the video, Dr. Gupta stated Landon had been off chemotherapy for three weeks, and that Sierra said Landon's cancer was in remission. As of June 2015, Landon has remained in remission by only using cannabis oil. The author met him in April 2015, and given his level of energy it is virtually impossible to tell he ever had cancer.

A September 23, 2014 article in an Australian newspaper talked about the use of cannabis extracts to treat cancer in the Hunter region of New South Wales (Kirkwood, "Claims"). The article was written because so many people reached out to the paper with research and success stories.

"Advocates – including people who have been treated, or helped treat family members with cannabis products for cancer and other illnesses – say their experiences speak for themselves. One Central Coast woman – whose story was typical of those the *Herald* contacted – said her daughter, then 25, was diagnosed with leukaemia in mid-2012 and declared in remission, with clear blood, just months later. 'She did have chemotherapy but the doctors couldn't believe how quickly she recovered,' the woman said yesterday. 'And as for the nausea of chemotherapy, while all the others in the unit were vomiting and sick, she was fine with it all. The doctors didn't really want to know about the cannabis, and just said whatever you're doing, keep doing it because it's working.'"

Joe Crowe described his recovery from cancer in a July 2012 video (Horsley). Joe had a fist-sized tumor in his upper chest, diagnosed as Hodgkin's lymphoma. Over the course of twelve years, he received chemotherapy and bone marrow transplants which failed to eliminate the cancer. In the

fall of 2011, Joe was connected with a caregiver in Michigan and began receiving cannabis oil. Within three months of cannabis oil treatment, Joe felt his tumor begin to shrink. In five months, he was cancer free.

On December 4, 2013, Joe released an update video stating he is still cancer free after a year (O'Toole). He emphasized the importance of continuing to take a maintenance dose of oil to prevent cancer from returning, especially due to the large amount of environmental toxins humans are exposed to daily. Joe now helps other people make and use cannabis oil therapeutically. At the end of the video, he recounted an experience with a Stage IV cancer patient who went into remission by using self-made oil.

Joanne Crowther shared her powerful cancer remission story on the steps of the Vancouver Art Gallery on August 25, 2013 (Crowther). She also spoke with the author extensively about her experience and shared supporting documents.

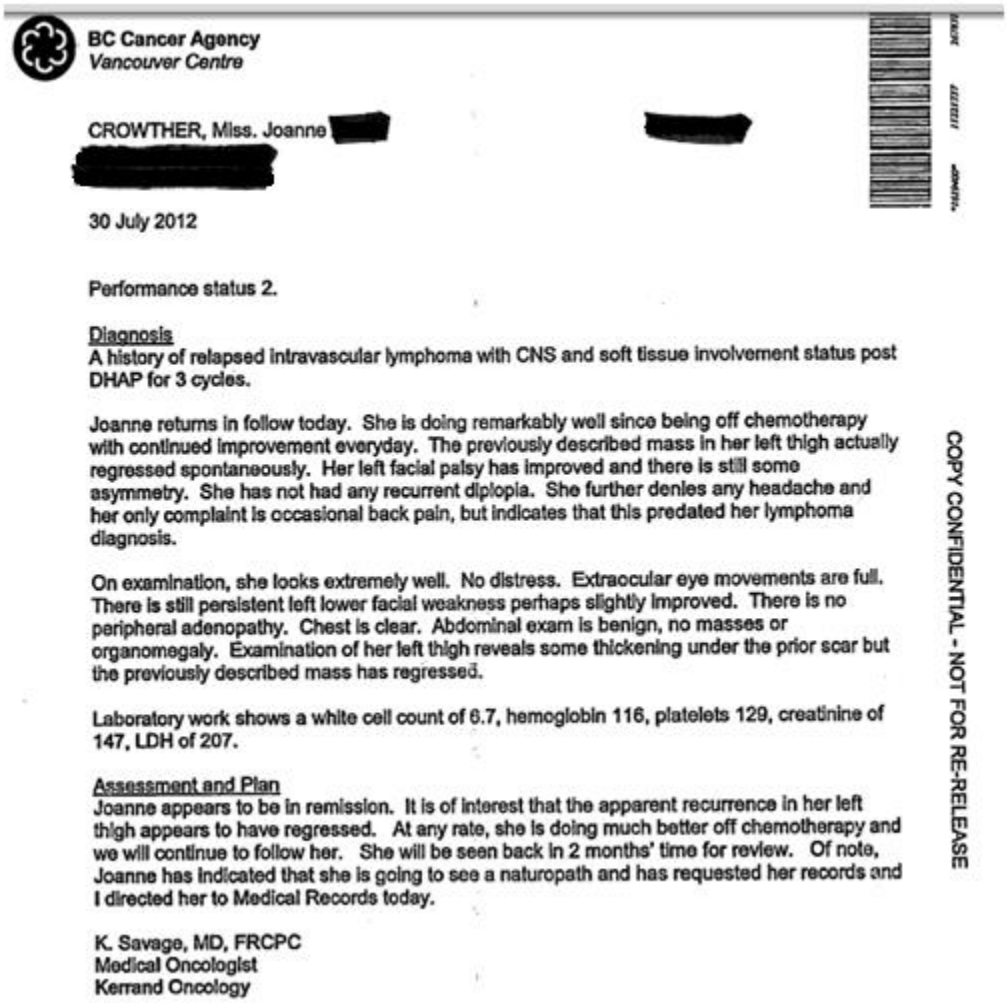
Joanne was diagnosed with large B-cell lymphoma in summer 2009. The lymphoma was eliminated with chemotherapy in February 2010. The treatment caused significant nausea, vomiting, febrile neutropenia (fever resulting from abnormally low white blood cell count), and pneumonia, which required hospitalization. In March 2010, a brain MRI revealed several cancerous lesions. These were resolved by April 2010 with whole brain radiation, as indicated by a post-treatment MRI.

For a year-and-a-half Joanne did very well, even participating in a half-marathon. However, in November 2011 a mass developed in her left thigh. Doctors removed the 3.2 x 2.5cm mass and determined it was consistent with diffuse large B-cell intravascular lymphoma. The removal of this mass did not eliminate the lymphoma.

In early January 2012, Joanne began receiving medications to treat complications of the cancer. Furthermore, another head CT scan revealed a 6mm cancerous lesion in her left superior pons. The test also confirmed resolution of the previous lesions in her right thalamus and basal ganglia. Shortly after the 3.2 x 2.5cm mass excision, Joanne noticed regrowth of some mass in the same area. She received five shots of radiation in January for the new growth.

More scans in February 2012 revealed new adrenal cancerous nodules. Joanne began taking the chemotherapy drugs cisplatin and cytabarine to combat the cancers. She was then hospitalized between April 23, 2012 and May 3, 2012 due to acute renal failure and hepatitis, which had been induced by cisplatin and cytabarine respectively. The complications permanently ended Joanne's chemotherapy regimen, which stopped in late April. Joanne was then diagnosed with relapsed intravascular diffuse large B-cell lymphoma along with leptomeningeal disease.

Without the strength to endure more chemotherapy or radiation, doctors could do nothing more, and Joanne was forced to try an alternative treatment. In early May, she began taking cannabis oil. She started off with small rice-grain sized doses, but after a week felt no effects. She then upped her dosage to a gram of oil per day, and within two weeks noticed positive results. Overall, she felt better and had a greater appetite. On July 30, 2012, Joanne had a follow-up examination. Documentation related to the examination is below. It describes how Joanne was doing much better since being off chemotherapy. It also noted that her left thigh mass "actually regressed spontaneously."



BC Cancer Agency
Vancouver Centre

CROWTHER, Miss. Joanne [redacted]

[redacted]

30 July 2012

Performance status 2.

Diagnosis
A history of relapsed intravascular lymphoma with CNS and soft tissue involvement status post DHAP for 3 cycles.

Joanne returns in follow today. She is doing remarkably well since being off chemotherapy with continued improvement everyday. The previously described mass in her left thigh actually regressed spontaneously. Her left facial palsy has improved and there is still some asymmetry. She has not had any recurrent diplopia. She further denies any headache and her only complaint is occasional back pain, but indicates that this predated her lymphoma diagnosis.

On examination, she looks extremely well. No distress. Extraocular eye movements are full. There is still persistent left lower facial weakness perhaps slightly improved. There is no peripheral adenopathy. Chest is clear. Abdominal exam is benign, no masses or organomegaly. Examination of her left thigh reveals some thickening under the prior scar but the previously described mass has regressed.

Laboratory work shows a white cell count of 6.7, hemoglobin 116, platelets 129, creatinine of 147, LDH of 207.

Assessment and Plan
Joanne appears to be in remission. It is of interest that the apparent recurrence in her left thigh appears to have regressed. At any rate, she is doing much better off chemotherapy and we will continue to follow her. She will be seen back in 2 months' time for review. Of note, Joanne has indicated that she is going to see a naturopath and has requested her records and I directed her to Medical Records today.

K. Savage, MD, FRCPC
Medical Oncologist
Kerrand Oncology

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Another exam from September 24, 2012 stated Joanne was in remission. The report also noted that she had been taking regular hemp oil supplements (referring to cannabis oil, not hemp seed oil).

BC Cancer Agency
Vancouver Centre

OCT 17 2012

CROWTHER, Miss. Joanne [redacted]

[redacted]

24 September 2012

Performance Status 1.

DIAGNOSIS
Relapsed intravascular diffuse large B-cell lymphoma with CNS leptomeningeal disease and soft tissue involvement since November 2011.

Status post DHAP for 3 cycles, last one in April 2012 and it was stopped because of liver and renal toxicity as well as requirement for admission and febrile neutropenia.

History of whole brain irradiation in April 2010 and also again for the left thigh in June 2012.

She is now off chemotherapy and she is on regular follow-ups only with evaluation of her left thigh mass which she is in remission right now.

CLINICAL STATUS
Miss Crowther comes back to the clinic today after being seen in July 2012. She was feeling much better while she has been off chemotherapy and continues to improve. Her last thigh mass, she feels that it has regressed and there are no new masses on her body. Her left facial palsy improved a bit and she says that she can still do some blinking. She has no diplopia and no new weakness or pain. She is not using any pain medications right now. The only thing she is taking is some supplements and naturopath treatment. She is on regular hemp oil supplements.

On examination she looks totally well. She is not distressed. Eye movements are normal. She still has left lower facial weakness. She still can smile but it is still obvious. She has no other lymphadenopathy and her left thigh mass has become very deep and below there is some scar tissue. Chest is clear and abdominal examination is normal. No lower limb edema.

INVESTIGATIONS
Her latest blood work was on September 18, 2012. White blood cell 6.4, hemoglobin 113, and platelets 144. LDH 194, white cells normal and creatinine is stable at 140. Her LFT shows AST of 50, mildly high and gamma GT 190 which is mildly high, but no result for ALT.

ASSESSMENT AND PLAN
Miss Crowther continues to be in remission for the meantime with stable disease. She will continue being off chemotherapy and she will continue to take her naturopath treatment. We

BC Cancer Agency
Vancouver Centre

OCT 17 2012

CROWTHER, Miss. Joanne [redacted]

[redacted]

24 September 2012

will see her again in the outpatient in January 2013 for follow-up and she was instructed to call the office if there are any new symptoms that arose.

Of note, the patient wants to go back to her work again as a secretary and we will prepare the required paperwork she needs.

Walaa Rajkhan, MD, Resident
For:
K. Savage, MD, FRCPC
Medical Oncologist
Kerrand Oncology

c Dr. DENNIS CHIN Dr. MICHAEL VARELAS Dr. JOHN YUN HOME CARE - BURNABY

D 24 Sep 2012
T 12 Oct 2012

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Further documentation of Joanne's final appointments is recorded below. There are a few key things to note. First, there is an error in the line, "She is taking certain organic oils, which rob her of appetite, according to the patient." Upon inquiry of this odd statement, Joanne informed the author this was an error. She had actually said it helped her appetite, but for some reason it was incorrectly recorded. A previous document also misstated that she received radiation in June 2012, which did not happen. These documents include the record of Joanne being told she was looking at a palliative situation after abandoning chemotherapy. Finally, and most importantly, they record her clinical remission, with Dr. John W. S. Yun stating, "She made *miraculous recovery* with stable clinical condition with no further cranial nerve palsy."

Vancouver CoastalHealth
Promoting wellness. Ensuring care.
Richmond Health Services

LOCATION OF PATIENT

FEB 0 1 2013

CONSULTATION

Name of Patient: CROWTHER, JOANNE [redacted]
Medical Record Number: [redacted]
Date of Birth:
Personal Health Number:

[redacted] John W Yun, MD, FRCPC

cc: BC Cancer Agency (Van)
Dennis Chin, MD
Oncology Clinic (RHS)
John W Yun, MD, FRCPC

Date of Consultation: 17/01/2013
Consulting Service: Onco
Consultation Requested By:

This is a 46-year-old lady who first presented with diffuse intravascular B-cell lymphoma involving kidney. She required high-dose chemotherapy with remission. She has been serially followed. Unfortunately she developed left meningeal disease with cranial nerve palsy including left facial nerve palsy. She require intrathecal chemotherapy and was transferred to BC Cancer Agency for ongoing care. She received 2 doses of high-dose methotrexate. Unfortunately her clinical course was complicated with acute renal failure, followed by acute hepatitis. She was found to have hepatitis C reactivation. After 2 cycles of methotrexate, it was felt that she could not tolerate it and the chemotherapy. She was told that we are looking at a palliative situation.

Interestingly she has improved. She has no progression in terms of cranial nerve palsy. She has no headache, visual problems. She has slight improvement in the left facial nerve palsy. She is still losing weight gradually. She attributes this to a change in diet, according to the naturopathic doctor recommendations. She is taking certain organic oils, which rob her of appetite, according to the patient.

She has good recovery from acute renal failure. Creatinine clearance is 38 mg/min, normal being greater than 59. She had liver biopsy last week. Consideration for interferon therapy. CBC is 125, white cells normal, platelet count borderline at 140. The rest of the general exam is normal.

She has no palpable mass head and neck, axilla. Chest sounds normal to IPPA. Abdominal examination shows flat abdomen, no palpable mass. There was a concern for nodule on the right chest and this is normal. No other lymphadenopathy.

Report Not Reviewed by Author Prior to Distribution. Corrected Report will be Redistributed if Necessary.

COPY -- SEND TO: Dennis Chin, MD

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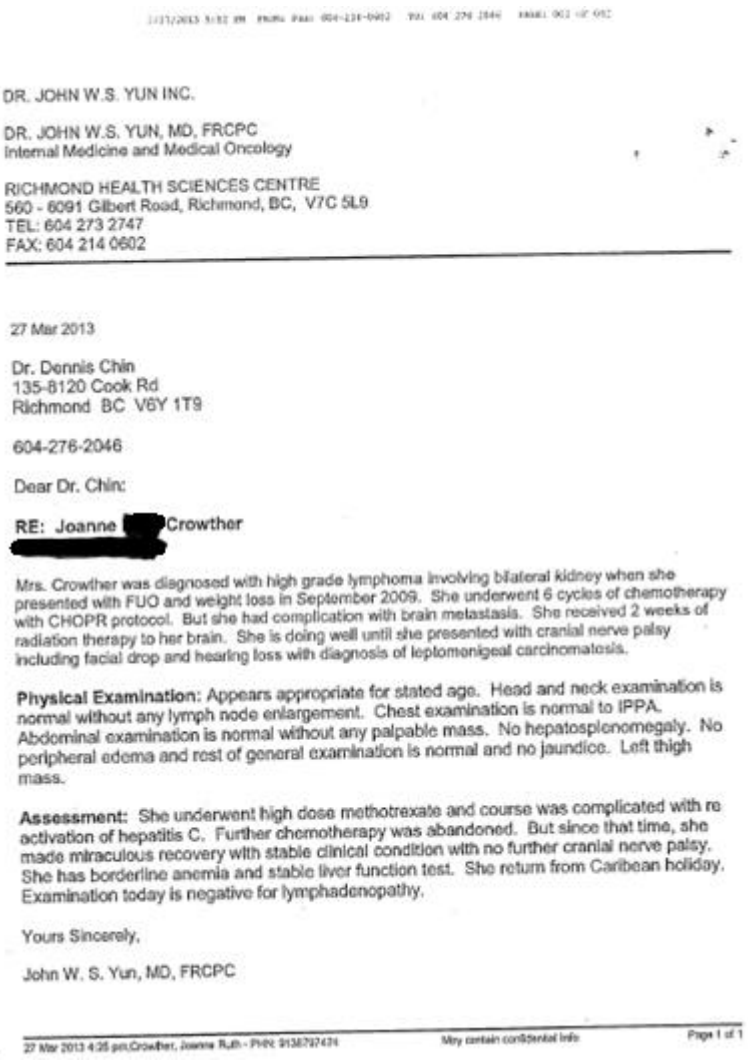
ASSESSMENT
She is in clinical remission. She is relying heavily on naturopathic medication. She is being considered for interferon, but for now in terms of B-cell lymphoma, things have settled. She has declined further chemotherapy. She will be followed serially clinically with some blood work.

Thanks again for having me involved in this patient's care.



DR. JOHN W.S. YUN INC.

DR. JOHN W.S. YUN, MD, FRCPC
Internal Medicine and Medical Oncology

RICHMOND HEALTH SCIENCES CENTRE
560 - 6091 Gilbert Road, Richmond, BC, V7C 5L9
TEL: 604 273 2747
FAX: 604 214 0602

27 Mar 2013

Dr. Dennis Chin
135-8120 Cook Rd
Richmond BC V6Y 1T9

604-276-2046

Dear Dr. Chin:

RE: Joanne [redacted] Crowther

Mrs. Crowther was diagnosed with high grade lymphoma involving bilateral kidney when she presented with FUO and weight loss in September 2009. She underwent 6 cycles of chemotherapy with CHOPR protocol. But she had complication with brain metastasis. She received 2 weeks of radiation therapy to her brain. She is doing well until she presented with cranial nerve palsy including facial drop and hearing loss with diagnosis of leptomenigeal carcinomatosis.

Physical Examination: Appears appropriate for stated age. Head and neck examination is normal without any lymph node enlargement. Chest examination is normal to IPPA. Abdominal examination is normal without any palpable mass. No hepatosplenomegaly. No peripheral edema and rest of general examination is normal and no jaundice. Left thigh mass.

Assessment: She underwent high dose methotrexate and course was complicated with re activation of hepatitis C. Further chemotherapy was abandoned. But since that time, she made miraculous recovery with stable clinical condition with no further cranial nerve palsy. She has borderline anemia and stable liver function test. She return from Caribbean holiday. Examination today is negative for lymphadenopathy.

Yours Sincerely,

John W. S. Yun, MD, FRCPC

27 Mar 2013 4:35 pm,Crowther, Joanne Ruth - PHN: 9138797474 May contain confidential info Page 1 of 1

An April 22, 2015 article in the *Derby Telegraph* detailed the impact cannabis oil had on 55-year-old Karen Roberts aggressive lymph cancer (Crowson, "Derby GP"). She was initially diagnosed as terminal and was too sick to receive a potentially life-saving bone marrow transplant. She began taking cannabis oil and her tumors began to shrink; during this period she used no chemotherapy or radiation. Dr. John Grenville (also pictured below), secretary of the Derbyshire Local Medical Committee, stated he had only seen a handful of other recoveries in his 34 years of experience, and that Karen's experience was "an extremely rare case and she is incredibly lucky." She received the transplant in May 2015 and needs to wait a year for news of its success (Crowson, "Derby Cancer"). The treatment was apparently successful as a December 2017 update article confirmed Karen is in remission (Hague, "Gran").

A particularly unique report of cannabis working against cancer came from Mike Folmer, a Republican state senator from Pennsylvania (Roberts). A December 2016 story revealed Mike broke the law to acquire cannabis in an unspecified legal state and bring it back home. Based on details from the article, he probably ingested CBD-rich cannabis oil, although it is also possible he smoked or vaporized either THC-rich or CBD-rich raw cannabis. In any case, he suggested his regimen may have had some sort of synergistic anticancer effect. “I believe it helped magnify the effect of chemotherapy in a … whirlwind fashion. I mean, my blood work has been immaculate,” Mike said. He is now cancer free.

Jessica Olson's incredible experience overcoming Stage II Nodular Sclerosing Hodgkin's lymphoma was told in a January 19, 2017 article (Hussey). The 21-year-old Australian had beaten the disease twice before with chemotherapy, radiation and surgery, having been first diagnosed at

the age of 15. When the disease returned for a third time, she was told that risky surgery would be required to remove the cancerous lump. Without the procedure, she only had months to live, but with it only had a 10% chance of survival with severely impaired quality-of-life. She was unwilling to take this risk, so doctors said she should go home and write a bucket list.

Jessica refused to accept her terminal diagnosis, and raised money to undergo extensive cannabis treatment. She took high, though unspecified, doses for thirteen consecutive weeks, an intense regimen that caused severe sickness and vomiting. Indeed, high doses of THC-rich cannabis oil, if given too quickly before tolerance has time to build, can be extremely disorienting. The discomfort was ultimately a small price to pay, as after three months she started to regain strength and went to the doctor for a check-up. "We got the results back and it was gone. I was sitting in her (doctor's) office when the CAT scan came up on the computer and she was just in shock, she thought it was a mistake. She rang the CAT scan people who confirmed there was no cancerous activity in my neck." Doctor said she was a "miracle."

10-year-old Hailey Steward was profiled in a July 2017 story from a local NBC affiliate (Goldberg). According to the report, she fought leukemia half her life, going in and out of remission over the course of several years. In May 2017, the cancer became far more aggressive, and after spending a month in Boston for treatment, the family was told nothing more could be done. The cancer was in 60% of her bone marrow, and she was sent home on hospice. At this point, Hailey was only given a couple weeks to live. Her mother began administering cannabis oil to improve Hailey's quality of life, but as weeks turned into more weeks, her doctors could not believe her improvement. One doctor actually asked Hailey's mother if she was giving her any of her old chemo.

After about eight weeks of the cannabis treatment, the cancer had reduced from 60% to 15%. Dr. Dustin Sulak, one of the most respected doctors working with cannabis in the country,

was brought in to help, saying, "Hailey's type of leukemia is one that's been known through previous publications in the literature and certainly in animal studies to respond well to cannabinoids so she had a good shot for not just having an improvement in quality of life but actually having a change in the trajectory of her treatment and her course." While Hailey is not completely cancer free yet, her situation has improved tremendously.

Interestingly, Hailey is a huge fan of Tom Brady and the Patriots, and had the opportunity to meet Tom Brady, pictured below.

Augusta Fleming was diagnosed with Stage III lymphoma in 2014, and as detailed in a June 22, 2018 story began bleomycin chemotherapy (Margolin). The treatment caused terrible side effects including blood clots in lungs. Despite going through the full course, a scan showed no tumor shrinkage. With no other options, Augusta went to Colorado and bought a 90-day supply of cannabis extract, likely around sixty grams. After using high doses for three months, a PET scan came back with "no evidence of disease", and more than a year later her cancer is still "inactive."

The article also included information from Frank Brown, the owner of a Los Angeles dispensary. Frank described his experience treating around 750 cancer patients over the past two

and a half years. He emphasized the importance of using the oil in combination with nutrition and conventional medicine. "This is in addition to a whole combination with nutrition, and with that combination, many go into remission or extend their lives. We've had several patients who were given less than a month to live and then they have a nice quality of life for a year and a half." Nearly 140 of the 750 patients are in remission.

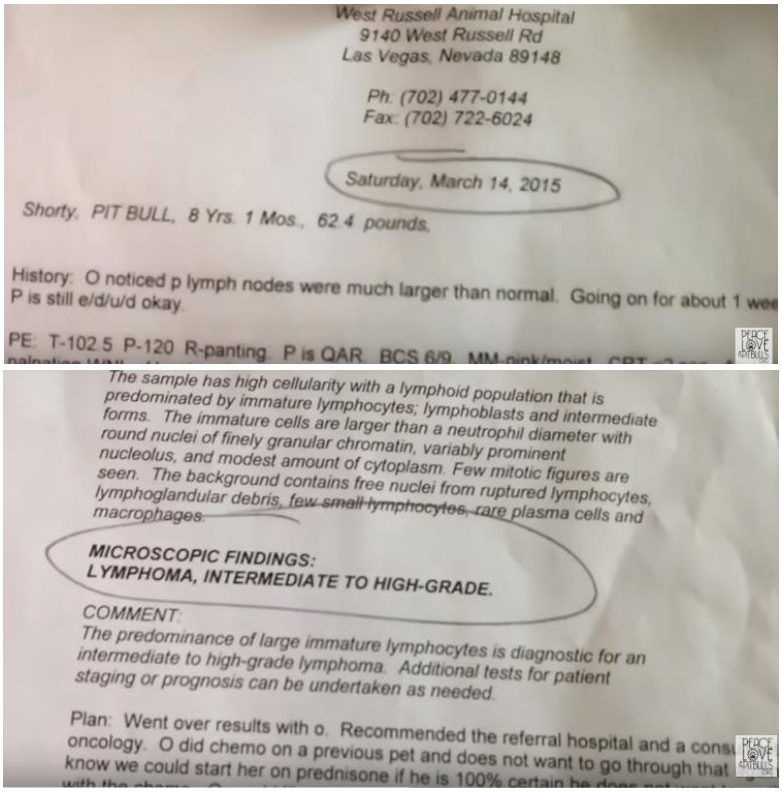
Tiffany Youngs, the wife of Tom Youngs, a professional rugby player in England, credited cannabis oil and nutritional changes for achieving remission from Hodgkin's lymphoma (Hughes). She was diagnosed in 2013 and battled for several years until 2017 when she was told recovery was not possible, as it had apparently progressed to Stage IV. After this news, Tiffany decided she would try cannabis oil as a last hope for achieving remission. She also embraced a strict diet which mainly consisted of fish and green juices, along with intermittent fasting. Tiffany stayed on this diet and used cannabis oil every night for a year, and in February 2018 her cancer had reduced tremendously, with the tumors in her pelvis, ovaries, stomach, and small bowel disappearing. While there is apparently some cancer remaining, Tiffany is no longer in mortal danger and appears to be on the path to complete remission.

Given that all vertebrates have endocannabinoid systems, it is not surprising the benefits of cannabis extend to animals. A November 22, 2013 article featured several people using cannabis to help their pets ("Seen At"). Rowyn Capers discussed how her dog Luna was suffering immensely from late-stage lymphoma and side effects of chemotherapy. Rowyn began giving Luna cannabis oil in capsules; she found as she increased dosage, her dog's symptoms improved. Vomiting and diarrhea stopped, and Luna's general condition got better. Rowyn said the results were remarkable. "When you see them enjoying life and feeling better and not being sick you know you've hit something," she said.

Tino, the owner of a pitbull named Shorty, shared a video on January 20, 2016 detailing the results of using cannabis oil to treat lymphoma, which according to medical documentation was intermediate to high grade ("Cannabis Oil Works"). She was diagnosed March 14, 2015 and given about eight weeks to live. She began cannabis oil in April along with a changed diet (specifically the Demian Dressler Dog Cancer Survival diet) but was administered no chemotherapy. Both THC and CBD were used in treatment (specifically medical cannabis-derived CBD, not hemp-derived CBD as revealed in the update). While Tino did not update the status of the cancer at this point, Shorty was still alive and had a great quality of life well beyond the prognosis.

An update video posted on March 14, 2018 showed that Shorty was still alive and well ("3 Yrs Later"). The veterinarian said they had never seen a dog with that form of cancer live beyond a year even with conventional treatment, which Shorty had not received besides a small amount of prednisone as an anti-inflammatory shortly after diagnosis. Around early 2018 blood work was done to ascertain the status of the lymphoma - the lymphocytes test came at 17% (normal is 12-30%), white blood cell count was 6.9 (5-15 is normal), and liver was great. The vet said the blood work was not indicative of cancer. She is 13 years old now.

Tino runs a Facebook group called "My dog beat cancer with Cannabis (canine cancer)" on Facebook, which features powerful testimonials from many other dog owners (https://www.facebook.com/groups/myDogbeatcancer). The group has over 4,300 members at this time.


West Russell Animal Hospital
9140 West Russell Rd
Las Vegas, Nevada 89148

Ph: (702) 477-0144
Fax: (702) 722-6024

Saturday, March 14, 2015

Shorty. PIT BULL, 8 Yrs. 1 Mos., 62.4 pounds.

History: O noticed p lymph nodes were much larger than normal. Going on for about 1 wee
P is still e/d/u/d okay.

PE: T-102.5 P-120 R-panting P is QAR BCS 6/9

The sample has high cellularity with a lymphoid population that is predominated by immature lymphocytes; lymphoblasts and intermediate forms. The immature cells are larger than a neutrophil diameter with round nuclei of finely granular chromatin, variably prominent nucleolus, and modest amount of cytoplasm. Few mitotic figures are seen. The background contains free nuclei from ruptured lymphocytes, lymphoglandular debris, few small lymphocytes, rare plasma cells and macrophages.

MICROSCOPIC FINDINGS:
LYMPHOMA, INTERMEDIATE TO HIGH-GRADE.

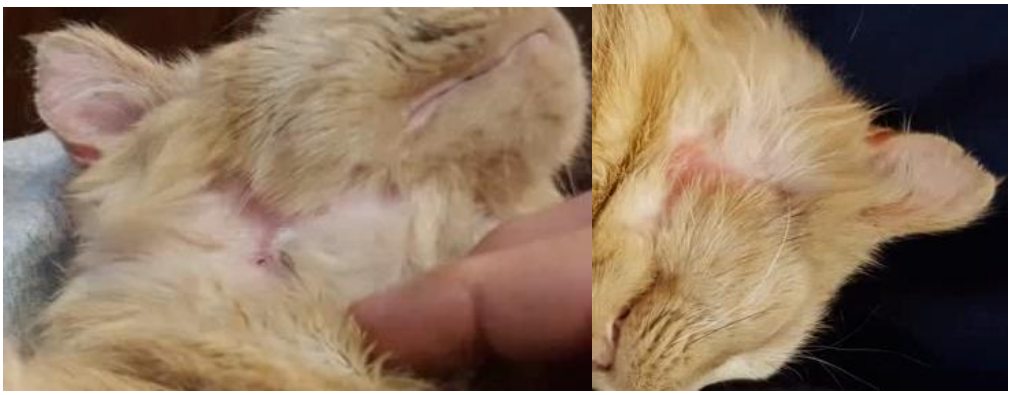
COMMENT:
The predominance of large immature lymphocytes is diagnostic for an intermediate to high-grade lymphoma. Additional tests for patient staging or prognosis can be undertaken as needed.

Plan: Went over results with o. Recommended the referral hospital and a consu
oncology. O did chemo on a previous pet and does not want to go through that
know we could start her on prednisone if he is 100% certain he does not

At the website CannabisOilCat.com, the owner detailed the experience of an old feral male cat she adopted and domesticated, naming him Chad [Note: Website is down now but available through Archive.org]. When a large growth appeared on his face, Chad was taken to the vet and given the diagnosis of late stage leukemia, with nothing able to be done. The owner brought him home and began administering cannabis oil combined with coconut oil on the tumor and after a few days began administering orally as well. The tumor started to shrink after about a week and in four weeks the initial tumor fell off. Continuing treatment, more cancer was drawn out.

One major issue was Chad kept trying to scratch at the tumor area. As a unique solution, the owner put kief (the crystal trichomes of the cannabis plant) on the area, which caused a hard scab to form which was resistant to the scratches. The entire process of healing took about four months, and at time of publication it was 17 months since the veterinarian had suggested euthanasia.

A video posted on December 28, 2016 featured a slideshow of the process ("Removing an Inoperable"). While the whole video is worth watching, some pictures are featured below.



Liver Cancer

Michael Cutler's life was significantly extended with cannabis oil. In 2009, Michael was diagnosed with liver cancer, which was eliminated with a liver transplant ("Mike Cutler's"). In late 2012, the disease returned, and Michael was sent home to die with "a big bag of morphine." For at least a couple months, he was bedridden and substantially disoriented from the morphine. In a moment of clarity, Michael decided he did not want to die and began looking for alternatives.

He found a video about Rick Simpson on YouTube, who described how to kill cancer with cannabis oil. Michael took Rick's advice and produced his own oil. Within three days of consuming the oil, Michael stopped using morphine. His doctor was more interested in why he did not suffer opiate withdrawals than in his use of cannabis oil. Michael continued to feel better as he sustained his intake of oil.

There was a scare when Michael apparently began coughing up blood. He went to the doctor, who was uncertain about the material's nature but stated it was not blood. Michael's wife purchased him a microscope and software package so he could personally analyze the mass. After taking a picture and using the software's assistance, he determined it was dead cancer cells. Michael then returned to the Royal Free Hospital in London in May 2014, where a biopsy found he no longer had cancer. His total treatment time was between three and four months.

Michael spoke about his healing experience at the launch of United Patients Alliance, a United Kingdom-based organization dedicated to legalizing medicinal cannabis, on July 17, 2014 ("Michael Cutler").

Tragically, Michael passed away on December 3, 2014 ("Timeline Photos"). United Patients Alliance announced he had developed lung cancer and was unable to procure more cannabis oil. As has generally been observed, especially with aggressive cancers, it is imperative to stay on a maintenance dose of cannabis oil, as residual cancer cells often lay dormant waiting to reproliferate. Ensuring safe access to cannabis extracts will help prevent tragedies like this.

Michael referred the author to the case of Steve Danks, who healed himself of terminal liver cancer with cannabis extract therapy. Steve contracted hepatitis C in his 20s from a blood transfusion, which eventually led to cirrhosis of the liver and cancer (Liosatos). He traveled to India and began juicing cannabis, which is an efficient method of ingesting large quantities of nonpsychoactive THCA and CBDA.

Within 17 days, he felt and looked much better. After three months he returned home, having improved considerably during his trip. Steve then began taking cannabis oil and apparently stopped juicing. This protocol lasted for a summer. Steve's last medical test over 15 months ago (from the time of the interview) showed no liver cancer, no nodules in the liver, and no scar tissue. Steve insisted his doctor put cannabis use in his medical notes.

Ed Moore was diagnosed with Stage IV liver cancer in March 2012 after going to the ER for pain (Lovere; Moore). The doctor said not much could be done, as his tumor was 7 inches long. Furthermore, the cancer had spread to his lymph nodes. He was given two weeks to two months to live, put on hospice, and prescribed morphine for pain. Ed hated the drug, as it made him vomit and adversely affected his mind.

Interestingly, two of Ed's friends from different parts of California who did not even know each other happened to bring him cannabis oil on the same day. They told him he needed to get started on it. Ed was treated by his wife Beate, who began by switching his opiate medication with cannabis oil every other day. She had learned online that "a gram per day" was around the dosage level needed to kill cancer, but at first the goal was just to get Ed off the pain pills. Within three weeks, he was able to completely manage his pain with the sole use of cannabis oil. Ed did not have any problems with psychoactivity; that which he did experience diminished very quickly as he built a tolerance. He took a half gram dose four times a day in capsules.

About half a year into treatment, Ed came down with what he and Beate thought was the flu. This led him to get a scan to check on the cancer, which revealed the primary tumor had shrank from 11.5cm to 5cm. The cancer in his lymph nodes had also regressed. Ed then began feeling better and gaining weight. Beate theorized the flu-like reaction may have been a healing crisis and potential result of the cancer dying off.

As of April 2015, Ed was still fighting the remains of his liver tumor, but for three years has had a wonderful quality of life with no pain. He has only employed natural treatment methods with no conventional modalities. In addition to cannabis oil, Ed used over 20 nutritional supplements and primarily consumed an organic vegetarian diet. He also juiced fresh cannabis buds and leaves. Ed and Beate believe that nutrition is integral to the success of cannabis extract therapy. Finally, Ed emphasized the importance of working closely with a doctor, even if chemotherapy and radiation are not being pursued. Medical guidance is crucial for understanding whether one is responding to cannabis oil or not.

A story from February 14, 2017 on an Australian news website described the experience of Craig Goodwin (Saunokonoko). Craig, a father-of-four and a deacon at church, has been arrested three times and even spent time in prison just for supplying others with cannabis oil. He was driven to help others after beating cancer with the medicine. Diagnosed with terminal liver cancer in 2012, he found out about cannabis oil by searching for alternative treatments online. Craig decided to "saturate" his body with cannabinoids by ingesting cannabis oil (likely THC-rich) morning, noon, and night, and by juicing raw cannabis every day. By 2013 he was cancer free and has been in remission until 2017.

The article also mentioned three terminal cancer patients Craig had been helping. "When he was sent to prison for 10 months, Goodwin was in the midst of supplying medicinal cannabis to three terminal cancer patients, including two children with brain tumours. Tragically, those two children are now dead, while the other man is alive and in remission, Goodwin claimed."

Craig Goodwin and Jenny Hallam. Ms Hallam is a compassionate supplier of medicinal cannabis and was raided by police in January 2017.

Lung Cancer

A January 2012 video featured three patients who used cannabis oil to overcome various diseases ("Medical Marijuana"). The third patient, Jeff, found out he had five tumors on his left lung, diagnosed as mesothelioma in July 2011. He learned about cannabis oil from Mike Stone, the first patient in the video. After Mike showed Jeff how to make his own cannabis oil, he began treating himself by putting two drops on his tongue every morning with an eyedropper.

On December 21, 2011, Jeff was told all his tumors were gone and he was cancer free. "Best Christmas present I ever had," remarked Jeff. He also stopped taking his blood pressure medication, as his pressure had normalized. In addition, the oil controlled Jeff's diabetes; his sugar levels never rose above 110. He discontinued his allergy and cholesterol medicines as well. Jeff still had some breathing problems as a result of emphysema, but overall felt his life had drastically improved.

Michelle Aldrich, a cannabis activist who was instrumental to passing the medical cannabis law in California, used cannabis oil in her fight against lung cancer (Aldrich). Her cancer experience began on November 15, 2011, when Michelle missed a lunch appointment because she felt too sick. On November 22nd, Michelle went to the doctor and was evaluated by a physician's assistant named Sally Holland. Michelle received a chest x-ray and was given antibiotics for bronchitis, although the following day she was informed she had pneumonia. Michelle returned on November 30th, when she was told she had a growth on her right lung.

Over the next couple months, Michelle went to several appointments to determine a solid diagnosis. A CT scan on December 23rd revealed a 23 x 28mm lung tumor. A growth on her left kidney was also observed. On January 12, 2012, Michelle was notified by Dr. Gary Feldman, her primary care physician, that the cancer was poorly differentiated non-small cell adenocarcinoma. Michelle immediately started reaching out to friends for support. One of the first people she spoke with was Dr. Donald Abrams, a long-time friend. Dr. Abrams appeared in the documentary *American Drug War 2*, mentioned above in the story about Cash Hyde, to talk about medicinal

cannabis. Dr. Andrew Weil, another friend of Michelle, offered help and support. These people, along with other oncologists, were Michelle's "dream team".

In mid-January, Michelle spoke with Jeannie Herer, widow of the late Jack Herer, one of the most well-known cannabis activists in history. Towards the end of his life, Jack became a major supporter of Rick Simpson, a pioneer of using cannabis oil to treat cancer. Jeannie told Michelle to begin using "Rick Simpson oil" to help fight the cancer. Michelle acquired oil from Valerie Corral, founder of the Wo/Men's Alliance for Medical Marijuana. Valerie calls her medicine "Milagro oil" (Spanish for miracle). Michelle received her first batch of milagro oil on January 21, 2012. Three days later, a PET scan showed Michelle's tumor had grown to 30 x 31mm. This measurement could have been either a "better picture" or the tumor had really grown. After a January 25th endobronchioscopic
ultrasound fine-needle aspiration biopsy, the final diagnosis was determined to be "Stage 3A poorly differentiated non-small cell metastatic adenocarcinoma of the right lung with bulky lymph node involvement." At least three of her lymph nodes were cancerous as well.

On February 1st Michelle had her final test, a colonoscopy. Three polyps were removed and an inflammatory condition called diverticulitis was identified. Michelle then underwent combination treatment of chemotherapy and milagro oil. She initially diluted the cannabis oil in hempseed oil. Eventually, Michelle worked up to taking pure, undiluted oil. She had four chemotherapy sessions, the last of which was April 5, 2012. She finished her cannabis oil treatment on May 16th.

Michelle experienced complications from chemotherapy during treatment, including nausea and food tasting strange. Even drinking water burned her mouth. It was not until the beginning of July that she could eat properly again. Thankfully, an April 17th CT scan showed her tumor had reduced by 50%. Her lymph nodes were significantly smaller as well. The scan also revealed absence of diverticulitis. As Michelle stated, "Chemo does not touch diverticulitis… it had to be the oil that healed it."

On May 10th, Michelle received a PET scan, which reported "virtually complete resolution of the tumor". On May 18th, Michelle's surgeon, Dr. Peter Anastassiou, removed six lymph nodes and the 2.5cm remains of the tumor. These remains turned out to be dead cancer tissue. Michelle endured complications from the surgery and had to remain in the hospital, but was finally discharged on May 31st. Dr. Anastassiou said he had "never seen lung cancer totally eradicated by chemo, much less in four months." Michelle believes cannabis oil made the difference.

Michelle recovered from her ordeal throughout June and July, steadily regaining her energy and appetite. Michelle finished the article with the following statement:
"I truly believe that if it wasn't for Valerie and the oil I would not be alive today. Every day I read about people dying of cancer and I know I was able to heal my body of cancer. Why is this health-giving plant not available to everyone? People should not have to go through the suffering that cancer brings. We need to get this information out to the world. Cannabis is a healing plant and can even heal cancer if we let it."

A January 2014 story on a Croatian news station detailed the story of a 38 year old man, referred to as Mark for confidentiality reasons, fighting non-small cell lung cancer (Boson). He was given four to six months to live; twelve if fortunate.

Mark initially used chemotherapy and radiation, which left him in a state he said "you can not even call human." His face was destroyed, his upper lip swollen, tissue was falling off his fingers, and his skin was overly soft. The pain was especially devastating. Three times a day, Mark thought of killing himself. Despite the barrage of conventional treatments, a medical test revealed the cancer had doubled.

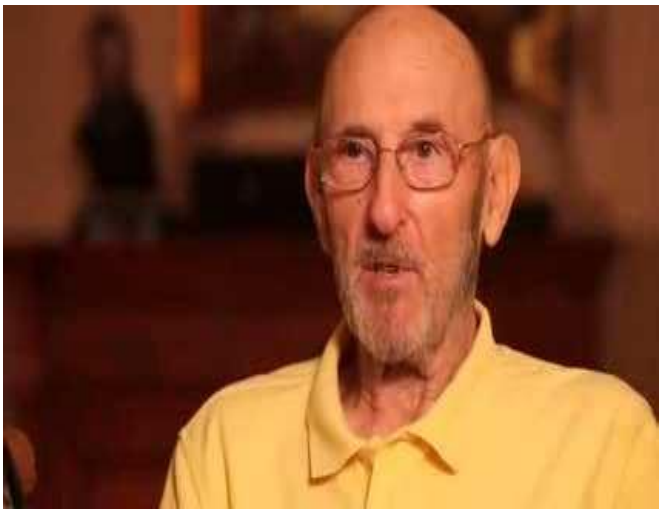
After the news, Mark stopped the treatments and began using cannabis oil. He immediately started feeling better, including pain relief. A month into treatment, Mark began spitting out sizable amounts of dark matter, which was confirmed to be cancerous. After three months, the cancer was no longer visible on X-rays.

Stan Rutner eliminated lung cancer with metastasis to his brain with cannabis oil therapy (Hernandez). Initially, Stan received chemotherapy and radiation treatments for the cancer. These

treatments started in March 2011. Brain radiation ended on June 25, 2011. On July 13, Stan entered the hospital for radiation pneumonitis (inflammation of the lungs due to radiation therapy). On the last of three hospital visits during this period, Stan was kept for a week and put on oxygen 24/7. Ultimately, the traditional treatments were ineffective.

Stan entered hospice on August 12 and was given less than six months to live. With no other traditional options, the Rutner family looked into alternatives and found cannabis extracts to be a potential solution. In early November 2011, Stan started taking small doses of cannabis oil-infused coconut oil in the morning. In less than two weeks, he was able to give up the extra oxygen. Stan soon started gaining weight, sleeping better, and getting stronger.

About six months into treatment, Stan started using higher doses of THC-rich oil from Aunt Zelda's, a medical cannabis organization in California. Stan continued this protocol until January 27, 2013, when an MRI revealed the brain cancer was gone. The lung cancer was gone as well. From hospice to cancer-free health, Stan's experience is truly remarkable. The author met Stan in California at the United Patients Group conference on November 1, 2014. As of June 2015, Stan is still cancer free and doing well.

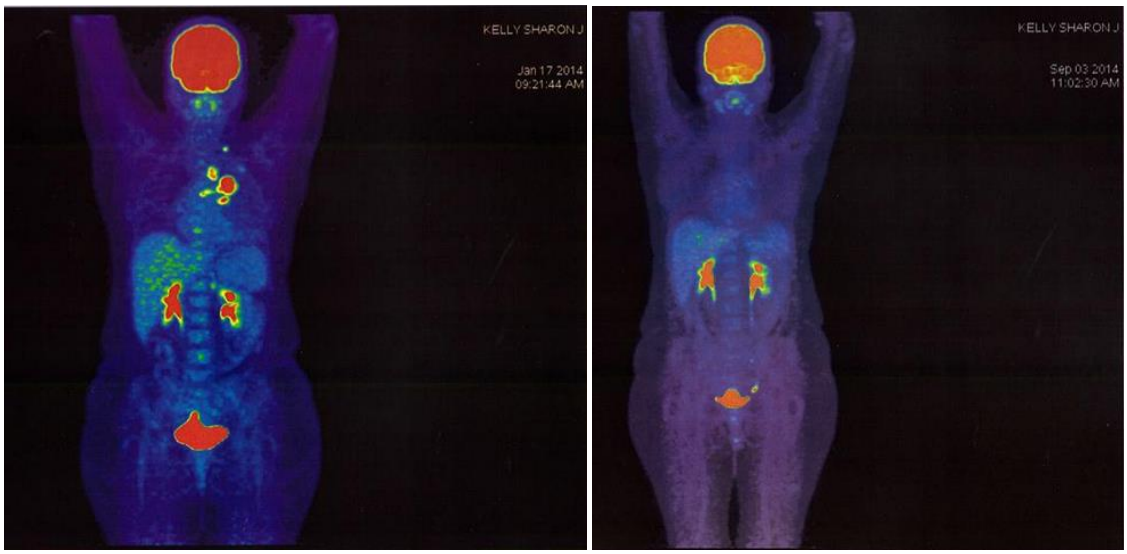


Stan Rutner is the father-in-law of John Malanca, who started United Patients Group after Stan's successful experience. UPG has helped hundreds of people learn about and find cannabis medicine. In a June 17, 2015 interview with CannaEffect, John shared a success from a doctor in Florida who contacted him because his wife had brain cancer ("John Malanca"). He did not know what to do and needed support. John provided advice on how to legally procure cannabis in California, and the physician soon found a reliable source of medicine. In seven months, the doctor's wife received clear scans. It was not stated if the woman underwent conventional treatment.

Sharon Kelly is an Australian woman who overcame terminal lung cancer with cannabis oil (Kelly). She was diagnosed with Stage IV non-small cell lung cancer on January 17, 2014. She had a 5cm tumor in her left lung. At least three lymph nodes were infected and there was a small cancer spot on her left collar bone along with cancer in her lung lining. Sharon's doctors described

her situation as terminal, but said chemotherapy could prolong her life by 6 to 9 months. Sharon had two intravenous chemotherapy treatments shortly after her diagnosis in January, a 5 hour session and a 1 hour session. Doctors then determined her cancer had a EGFR-positive mutation, which qualified Sharon for a chemotherapeutic drug called Tarceva. They said this drug could prolong her life, but there was no hope for a cure at this stage.

Sharon learned about cannabis oil as a method of potentially saving her life rather than just extending it. After doing extensive research, she determined the treatment was right for her. She began cannabis oil in February 2014. At first, she only orally ingested the oil, but then also began using it rectally as a means of getting more cannabinoids into her system. In addition, she juiced raw cannabis leaf early on. By September 3, 2014, another PET scan indicated Sharon was cancer free. The scans are below.



Several months later, Sharon's cancer returned in a less aggressive form. Again, she successfully managed it with a combination of cannabis oil and chemotherapy. However, at some point around mid-2016 cancer developed in her liver. Sharon attempted to fight it with cannabis oil suppositories, but complications prevented her from maintaining stable therapy. Furthermore, in general, suppositories have poor bioavailability and she may not have been able to reach an effective dose. It is also possible this particular manifestation of the cancer was resistant to cannabinoids. Sadly, Sharon passed away on September 11, 2016. Her life was doubtless extended by cannabis therapy and her efforts to help others were honorable.

A July 2014 article in a North Carolina newspaper featured statements from James McLemore, who discussed the benefits of medicinal cannabis for Stage III inoperable lung cancer (Moss). He consumed cannabis through eating and juicing. The cannabis juice likely consisted of raw buds and leaves, but it is unclear whether he was eating raw cannabis or cannabis oil. Therefore, McLemore was almost certainly ingesting large quantities of THCA and/or CBDA, and potentially ingesting large quantities of THC and/or CBD.

"My doctor said he had never seen anyone take the amount of chemo and radiation I took and gain 20 pounds. It's not about getting high. I never felt better in my life than when I was eating and juicing it. I was able to come off of oxygen for four straight months while juicing the plant. I'm in remission. I have another year and a half before I'm considered cancer-free but I've been in remission for 3½ years," said James.

Asbestos.com, one of the leading resources for individuals and families affected by mesothelioma, published a November 14, 2014 story about a man named Andy Ashcraft whose life was tremendously improved with cannabis extract treatment (Povtak, "Mesothelioma Survivor").

Mesothelioma is one of the most aggressive cancers; 60% of patients die within a year of diagnosis. Andy was diagnosed with Stage IV pleural mesothelioma, which had metastasized outside his lungs, in February 2010. At the apparent end of his battle an experimental chemotherapeutic drug had stopped working, so doctors told Andy's wife Ruth it was time for palliative care or a hospice facility. He had already survived past expectations, and around this time had three gallons of fluid drained from his lungs and abdomen at once. Despite the doctor’s prognosis, Ruth refused to give up and acquired cannabis oil through California’s medical program.

The cannabis oil worked remarkably well and pulled Andy from the brink of death. "The man is healthy today, and there is no other explanation for that. Beyond a shadow of doubt, this cannabis oil has worked wonders for him. I’d recommend it for anyone with cancer. I’m not saying it will work every time on everyone, but it’s working for us," Ruth told Asbestos.com.

After using oil Andy was able to cease chemotherapy, along with his cholesterol, diabetes, and blood-pressure medicines. His last scan in October 2014 showed no tumor growth, and he had another scan scheduled for December. Stopping the growth of mesothelioma at this point was quite a feat in itself. Most importantly, Andy’s quality of life dramatically improved. "I feel great right

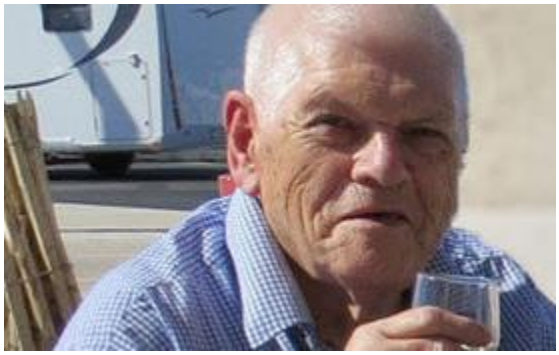
now. I don’t know why, or exactly how, this [cannabis oil] works. My wife knows the details, but I’m healthy, moving and grooving again, living my life," Andy said.

An update on April 4, 2016 confirmed that Andy was still doing well. It was confirmed he had stopped conventional treatment in July 2014 (Povtak, "Mesothelioma Survivor's"). Andy exercises every day and is able to spend a lot of time visiting friends and family. The article also revealed that Andy has primarily used high-CBD cannabis oil, and sometimes uses edibles containing THC-dominant cannabis.

A January 22, 2016 article from a CBS affiliate described the experience of 50-year-old Darren Miller, who was diagnosed with "incurable, inoperable" lung and pericardial heart sac cancer (Blume). With chemotherapy, he was told by doctors he would live about a year. He looked for alternatives as a hope for complete remission, and found evidence that cannabis oil may work for him.

With the support of his wife, Darren moved to California and began using cannabis oil, eventually even learning how to make it himself. He continued with chemotherapy as well. The combination achieved exactly what Darren was hoping for. "And then today, which is seven months later, they tell me I am completely cancer-free – not remission. I’ve cured my cancer. Now, am I giving credit to the cannabis oil? Absolutely. Am I giving credit to chemo? I would have to say yes, too. I did both," said Darren. He backed up his claims with medical records.

A June 11, 2018 article on *Express.co.uk* shared Gary Hill's story (Atherton, "Lung"). He was diagnosed with lung cancer in autumn 2016 and his oncologist gave him 6-12 months to live without treatment. Given that Gary was 83 years old, he declined the treatment to maintain his quality of life. A friend said he should try CBD oil, so he began using a legal version purchased from a health store. He apparently only took the oil for a month, starting with 2-3 drops three times a day and moving up to 9 drops twice a day. Gary administered the oil sublingually although didn't like the taste. Before using CBD, his cancer measured between 30-40mm, which was apparently the primary tumor. In November 2017, Gary had a CT scan which revealed near total resolution of the left lower lung mass and showed most of his lymph nodes were normal size. Gary's physician was amazed the cancer had shrunk. At time of publishing Gary was in remission.



Multiple Myeloma

There is unfortunately quite little anecdotal evidence for cannabis and multiple myeloma, but some promising stories exist. First, at the 2017 Patients Out of Time conference, the author spoke with a man who had been battling multiple myeloma for many years. He was using cannabis oil while participating in a clinical trial for a new agent against the cancer. Everyone else in the trial passed away, indicating an apparent lack of effectiveness, while the man was doing quite well. His cancer markers had reduced substantially although not completely gone away. Nonetheless, the fact he was the only survivor is impressive.

In May 2017, the author corresponded with a woman named Ilona Werner (Werner). She described her husband's experience fighting multiple myeloma with cannabis oil and chemotherapy. Based on the details, it is reasonably likely cannabis played a role in the anticancer effects. Below is Ilona's testimony:

"My husband Dietmar has Multiple myeloma (blood and bone cancer). After several visits to our physician our Dr. finally made a blood test to check for cancer cells. This was October 2016 and they found out his bones are full lesions, stage 4 multiple myeloma, one surgery on his leg, he got a metal rod to avoid breaking the bones (2 lesions where very close and his leg where almost broken). He had kidney problems because of hypercalcemia. High protein level, lost of weight and pain all over his body.

After 3 month of chemo we met Molly and Bill and used the marijuana oil they made after Rick Simpsons recipe. 68% [THC] clean oil. My husband took daily one gel caps filled with one gram [of] oil. Our oncologist was open minded and know about our own treatment but he never believed in it and he already set up a plan for SCT and a bone marrow check up. The first bone marrow check up was a catastrophe and the hematologist was shocked of his soft bones and the bone marrow flow easily out. After the Marijuana oil treatment and the second bone marrow they all were surprised that he was in remission. No cancer cells were detected. My husband stopped all chemo treatments and he did not went to the sct because this goes with a higher chemo and it kills not only the bad blood cells they kill all good ones too and the sct should be done to bring my husband in remission. But surprisingly he was in remission thanks to the oil and his diabetes disappeared after 8 years. He is still in pain and his bones are fragile, we are eating organic food and avoid everything unhealthy. Dietmar takes every evening marijuana oil for maintenance. Once per month his blood work is done and its all fine."

Ovarian Cancer

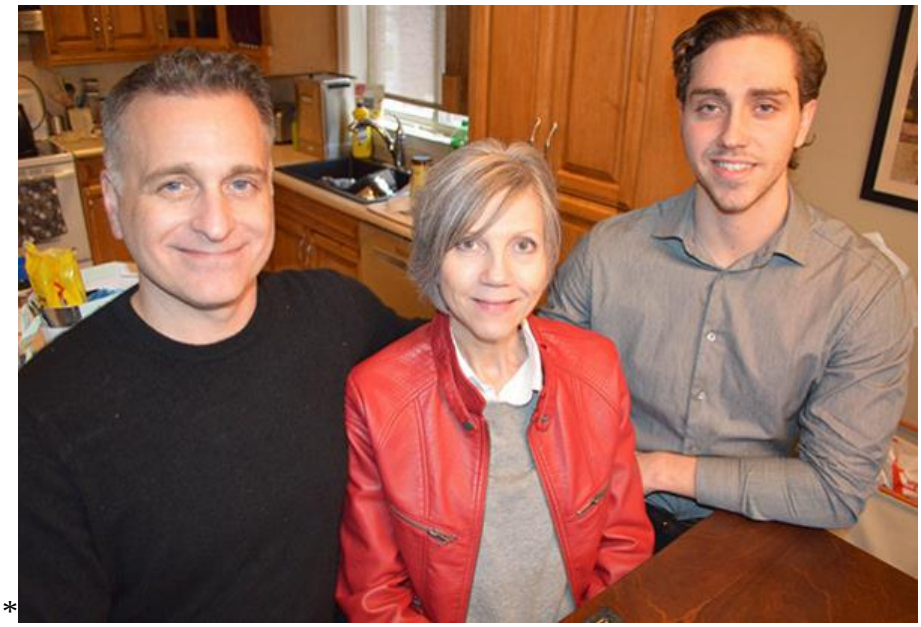
In July 2016, 52-year-old Joy Smith was diagnosed with inoperable ovarian cancer (Atherton, "Cannabis"). Even with chemotherapy the cancer was apparently not curable, so Joy combined with conventional treatment with apparently a CBD-rich oil. With this combination Joy's cancer was eliminated. "Doctors were amazed at how the cannabis oil fought off the cancer," Joy claimed. The timeline of her treatment was not clear but was apparently at least six months.

Cheryl Pearson's experience with terminal Stage IV ovarian cancer was detailed in a March 29, 2016 article in a Canadian newspaper (Parnell). The cancer initially manifested in 2009, but was not diagnosed until 2013. Two large tumors were found, and doctors planned chemotherapy as a means to extend Cheryl's life. Even with that, she had only about six months to live. Her husband Chris began researching alternatives, and discovered cannabis oil. He did not entirely believe it could eliminate her cancer, but would at least be able to help her with the pain and allow her children to remember her in a better light. Interestingly, it was the head pharmacist for the Canadian Cancer Society who ultimately convinced Cheryl to try the oil.

"'My wife is dead set against cannabis, doing something that she grew up to believe is criminal,' said Chris, noting that the meeting with the pharmacist started to change her mind. 'When I asked if it would work, he said there are no clinical trials but he advised us that three of the world's largest pharmaceutical companies had applied for patents for synthetic forms of this specifically for the treatment of cancer, so there is obviously something to the concept.'"

After a few chemotherapy treatments, it became apparent that Cheryl was allergic to the chemotherapy and could no longer take it. Doctors told the family to prepare for her death. Cheryl kept taking cannabis oil as her only treatment; after five weeks, a CT scan showed the tumors had reduced by 25%. The cancer kept decreasing to the point where Cheryl was eligible for surgery. When doctors removed the tumors, they were already "completely dead." By March 2014, Cheryl was officially proclaimed to be in remission.

"I guess I never would have believed it—the results I saw from this plant. Initially I only thought you could smoke it and I was not going that route. I didn't have the knowledge. I was just thinking it was a puff of smoke and if I have cancer I'm not going to add to it," said Cheryl.

* 

Pancreatic Cancer

Andy Hospodor, a member of the Society of Cannabis Clinicians, presented at the Pancreatic Cancer: Innovations in Research and Treatment Conference in May 2014 in New Orleans ("We Are"). His presentation abstract is below:

"In over 20 states, cancer patients have access to cannabinoids (aka medical marijuana) and use them to treat symptoms of chemotherapy, such as nausea and lack of appetite. However, new evidence, both scientific and empirical, suggests that higher doses of cannabinoids may be an effective adjuvant alongside traditional chemotherapy agents, such as Gemcitibine. While nausea is controlled with daily dosages of 10 to 40mg, pancreatic cancer cells are known to over express the endo-cannabinoid receptor CB1 one hundred fold. Cannabinoids target different receptors than traditional chemotherapy agents and have low combinatorial toxicity, and as such present a class of new treatments.

In an n=1 study of a patient with stage IV pancreatic adeno-carcinoma, we augmented the standard Gemcitibine chemotherapy with balanced initial doses 50mg THC and 50mg CBD and increased over a four week period to achieve a 12.5 mg/kg dosage. Curiously, after ten days the patient stopped presenting signs of cannabinoid use, such as red eyes, slurred speech and clumsiness. However, the patients CA-19-9 marker increased from 8,800 at diagnosis to 26,000.

Over the next four weeks, dosage of CBD was held constant and THC was increased to 1050mg daily for a dosage of 20 mg/kg. At week 6, the CA-19-9 marker began decreasing and cannabinoids were leveled off, although a higher dosage was planned for weeks 8-12. At week 15, CA-19-9 markers dropped to pre-diagnosis levels and a CAT scanned revealed shrinkage of the tumor. We anticipate continued tumor shrinkage and reduction of CA-19-9 marker levels to normal levels by week 20. Although many pancreatic cancer patients have access to cannabinoids, issues such as potency, purity and bio-availablity will impact future adjuvant cannabinoid therapies. We have addressed the issues with existing technology and hope to conduct large scale trials to examine the efficacy of Gemcitibine + cannabinoids in the treatment of pancreatic cancer."

In August 2013, Wallace "Buddy" Rose was told he had a tumor on his pancreas, as indicated by a CT scan ("Amazing"). The cancer was Stage I. Therefore, Wallace's doctor said surgery could save him, but he needed to see an oncologist for a referral to a surgeon. At the meeting with the oncologist, Wallace was told surgically removing the tumor would save his life. However, Wallace did not have insurance and could not afford the surgery. It took six weeks for him to raise the money, after which surgery was scheduled for November 4, 2013.

During surgery, doctors observed the pancreatic tumor had grown through Wallace's pancreatic wall and attached to his stomach and spleen. There were numerous tumors in his liver and a spot in his kidney. The surgery was stopped at this point, and Wallace was formally diagnosed with Stage IV pancreatic cancer. Doctors said nothing more could be done. On December 18, it was confirmed the cancer had metastasized throughout his body; Wallace was told he could expect to start declining in three weeks and may starve to death in a month. He was

explicitly told he could not be cured, but that chemotherapy may prevent the cancer from spreading further and extend his life by six to eight months. The following panel shows Wallace's CA 19-9 scores increasing over the months following his diagnosis.

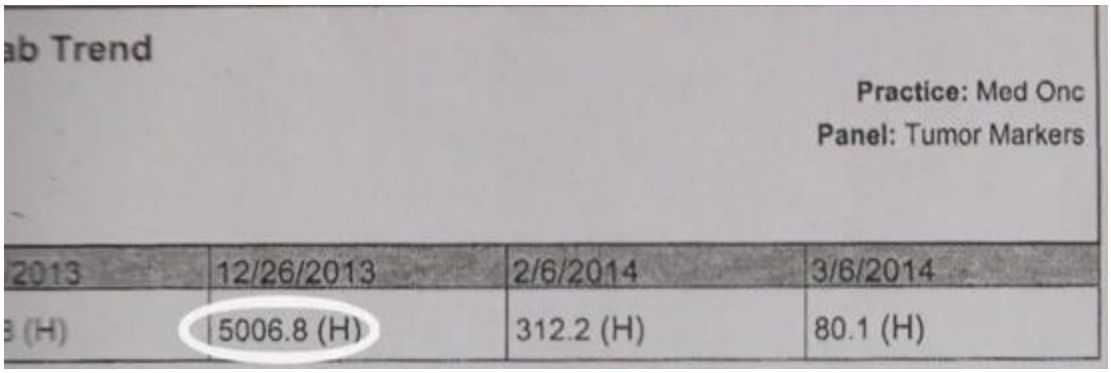
Patient: ROSE, WALLACE
Patient Id: 549292
DOB: 07/28/1951
Diagnosis: Pancreatic Cancer

Lab	9/19/2013	11/21/2013	12/18
CA 19-9	287 (H)	1406.7 (H)	4587.

On December 26, 2013, Wallace began the chemotherapeutic drugs Gemcitabine and Abraxane. On that day, his CA 19-9 score was determined to be 5006.8. Shortly before this, Wallace had a "saying goodbye" party. During the event, one of his relatives slipped some cannabis oil in his wife Cathy's Christmas stocking.

Wallace was initially very skeptical of cannabis oil, believing it to be propaganda for the pro-cannabis legalization movement. With such a bad prognosis he realized he had nothing to lose, so he began taking two to three grams of cannabis oil each day (a notably high dose). He did not know what to expect and wanted advice from a doctor. Thankfully, he found Dr. Kathleen Smith, who helped him obtain his medical cannabis license.

Wallace ingested cannabis oil over the last few days of December and every day in January. He did not believe in the medicine until a scan in February indicated a dramatically reduced cancer cell count.



ab Trend

Practice: Med Onc
Panel: Tumor Markers

2013	12/26/2013	2/6/2014	3/6/2014
(H)	5006.8 (H)	312.2 (H)	80.1 (H)

The combination of cannabis and chemotherapy nearly eliminated Wallace's cancer. The tumors in his liver, spleen, stomach wall, and kidney were gone. The only thing remaining was a small portion of the original pancreatic tumor. On March 30, 2014, his CA 19-9 was at 42; normal is 35. Wallace stated his intention to continue using cannabis oil and began working again. On May 28, 2014, CT scans showed no cancer and a normal cancer cell count.

The author spoke with Wallace several months after he became cancer free. Among other things, he said he had given away the cannabis oil he was using for maintenance doses to someone in a more urgent situation. Apparently due to this noble decision, the cancer returned. Tragically, Wallace was unable to reinitiate his former treatment protocol. His son reported to the author that Wallace passed away in February 2015. It is hopeful that his experience will encourage clinical trials as well as the use of cannabis extracts by other pancreatic cancer patients.

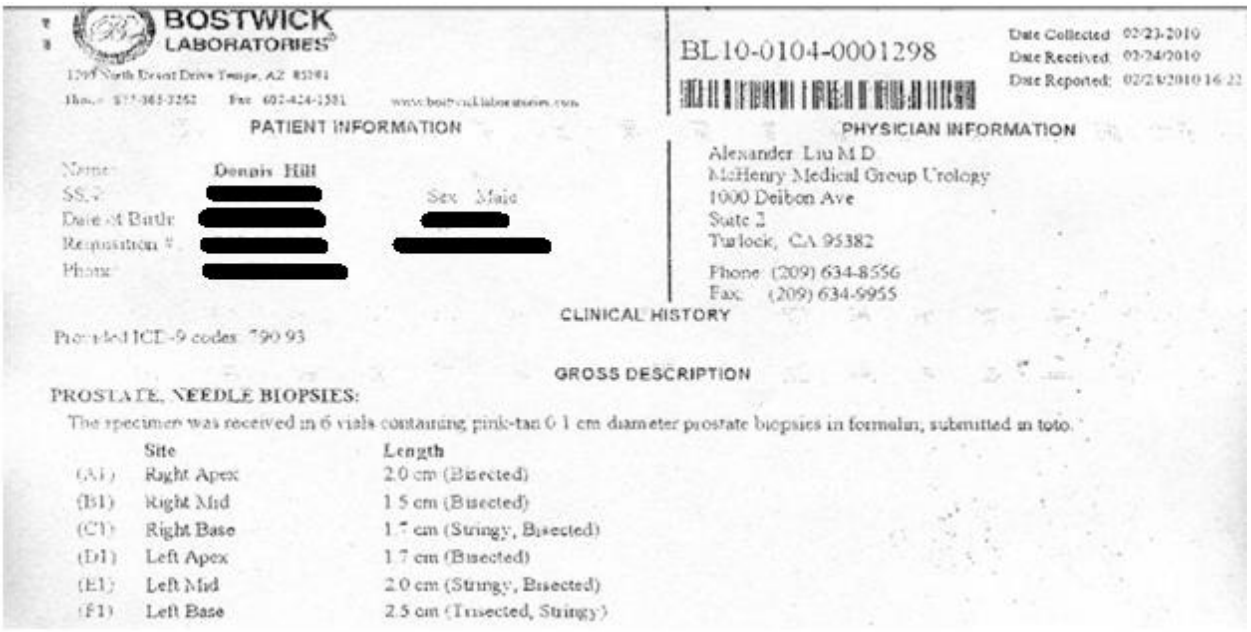
A March 2018 article in *Independent* detailed the experience of its author, Ethan Stewart, and his journey into using medical cannabis for treating metastatic pancreatic cancer, which started growing significantly in March 2016 (Stewart). Having been a writer about and grower of medical cannabis, Ethan had heard about the potential anticancer properties of cannabis. He decided to go all-in on high-dose therapy and consume 60 grams over 60-90 days. It was unclear whether he used conventional therapy concurrently. Against the advice of others he started Day 1 at a full gram instead of working up. This caused significant side effects including fainting in the shower and sleeping for 15 hours. By Day 12 the "stoned" feeling was gone and by Day 19 Ethan journaled, "Without doubt, this is the best and healthiest I have felt in years."

When going in for liver surgery, it was found that the largest of six tumors, previously 16-18mm in size, had shrank to less than 6mm. A growth marker was also low and not indicative of a patient with metastatic pancreatic cancer. '"This is better than anything we could have hoped for,' said my surgeon in disbelief on a phone call that I'll never forget." After getting the call, Ethan started a second 60-gram protocol of oil. After that was complete by September 2016 he went into Stanford for more tests, which found "zero signs" of disease. At this point Ethan began weaning off the oil.

Ethan returned to Stanford in Spring 2017 for more tests, which showed multiple tumors on his liver. Doctors recommended immediate hormone treatments, which Ethan decided to postpone for three months so he could restart high-dose cannabis oil therapy. He returned in September for another round of tests, prepared to start hormone therapy if necessary. It turned out to be unnecessary, as the medical tests showed he was stable (it was not specified if this meant remission or just no growth). Ethan continues to take the cannabis extracts.

Prostate Cancer

Dennis Hill is a friend of the author and an established meditation teacher. He has written several books on meditation and yoga. For ten years, he also worked in the field of preclinical cancer research. In February 2010, six biopsies revealed highly invasive and aggressive prostate cancer.



BOSTWICK LABORATORIES

BL10-0104-0001298

Date Collected: 02/23/2010
Date Received: 02/24/2010
Date Reported: 02/26/2010 16:22

PATIENT INFORMATION

Name: Dennis Hill
SS #: [redacted]
Date of Birth: [redacted]
Sex: Male
Requisition #: [redacted]
Phone: [redacted]

PHYSICIAN INFORMATION

Alexander Liu M.D.
McHenry Medical Group Urology
1000 Delbon Ave
Suite 2
Turlock, CA 95382
Phone: (209) 634-8556
Fax: (209) 634-9955

CLINICAL HISTORY

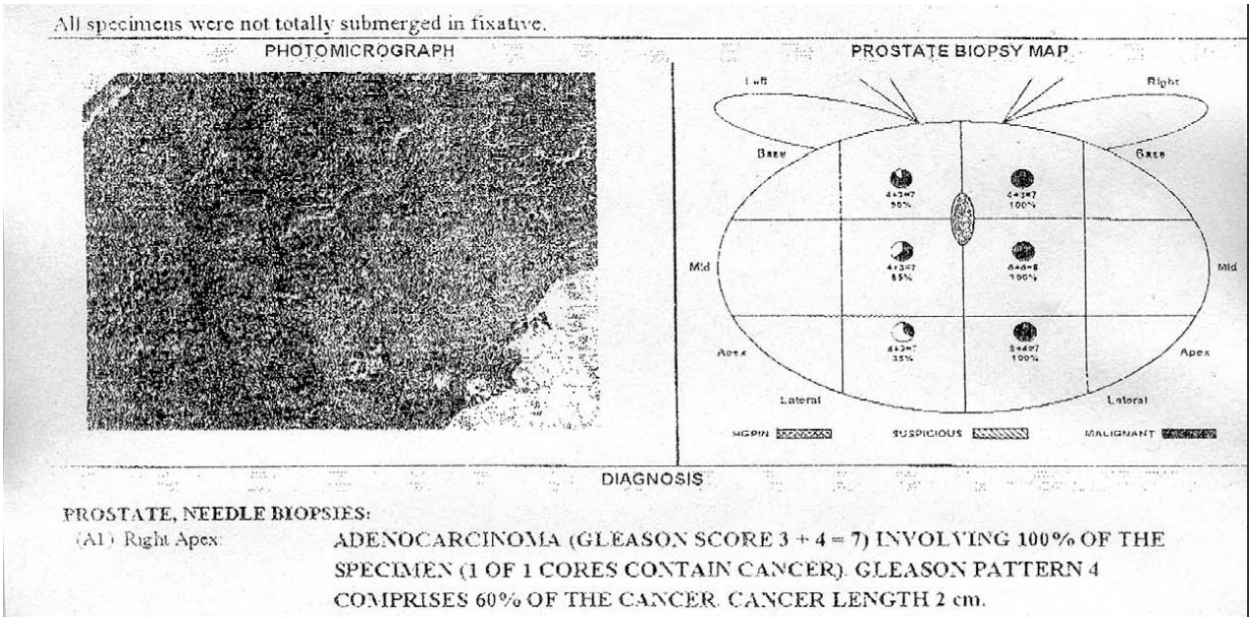
Prostate ICD-9 codes: 790.93

GROSS DESCRIPTION

PROSTATE, NEEDLE BIOPSIES:

The specimen was received in 6 vials containing pink-tan 0.1 cm diameter prostate biopsies in formalin, submitted in toto.

	Site	Length
(A1)	Right Apex	2.0 cm (Bisected)
(B1)	Right Mid	1.5 cm (Bisected)
(C1)	Right Base	1.7 cm (Stringy, Bisected)
(D1)	Left Apex	1.7 cm (Bisected)
(E1)	Left Mid	2.0 cm (Stringy, Bisected)
(F1)	Left Base	2.5 cm (Trisected, Stringy)



All specimens were not totally submerged in fixative.

PHOTOMICROGRAPH

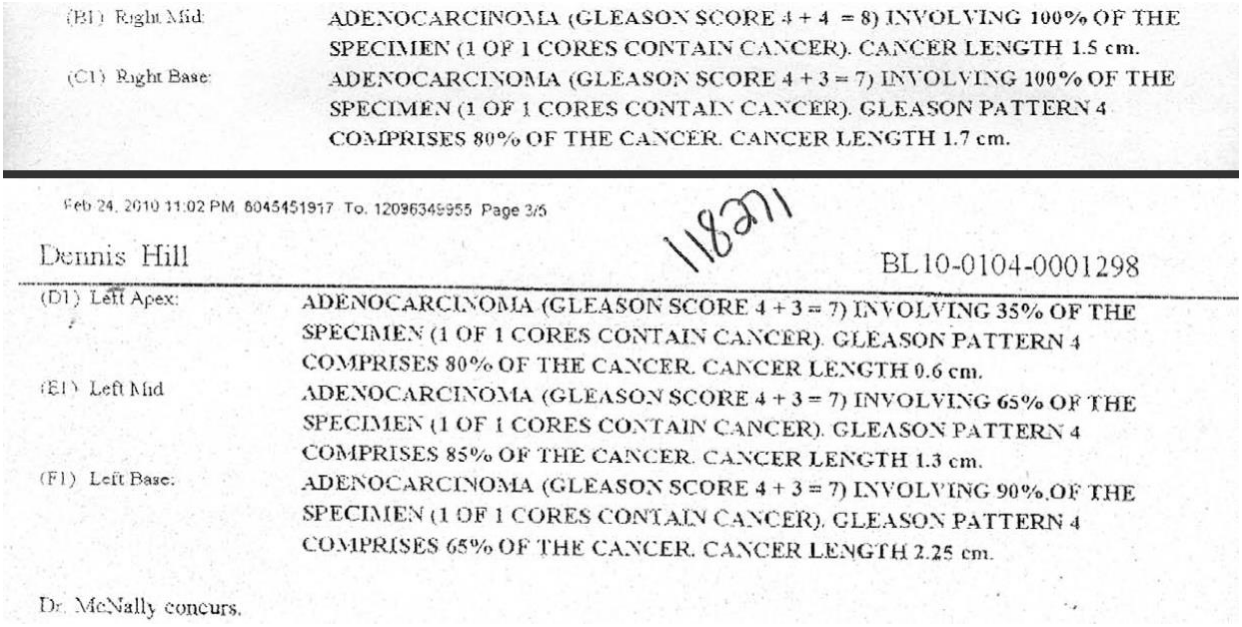
PROSTATE BIOPSY MAP

Left
Right
Base
Base
Mid
Mid
Apex
Apex
Lateral
Lateral
HGPIN
SUSPICIOUS
MALIGNANT

DIAGNOSIS

PROSTATE, NEEDLE BIOPSIES:

(A1) Right Apex: ADENOCARCINOMA (GLEASON SCORE 3 + 4 = 7) INVOLVING 100% OF THE SPECIMEN (1 OF 1 CORES CONTAIN CANCER). GLEASON PATTERN 4 COMPRISES 60% OF THE CANCER. CANCER LENGTH 2 cm.



(B1) Right Mid: ADENOCARCINOMA (GLEASON SCORE 4 + 4 = 8) INVOLVING 100% OF THE SPECIMEN (1 OF 1 CORES CONTAIN CANCER). CANCER LENGTH 1.5 cm.

(C1) Right Base: ADENOCARCINOMA (GLEASON SCORE 4 + 3 = 7) INVOLVING 100% OF THE SPECIMEN (1 OF 1 CORES CONTAIN CANCER). GLEASON PATTERN 4 COMPRISES 80% OF THE CANCER. CANCER LENGTH 1.7 cm.

Feb 24. 2010 11:02 PM 8045451917 To. 12096349955 Page 3/5

11827

Dennis Hill BL10-0104-0001298

(D1) Left Apex: ADENOCARCINOMA (GLEASON SCORE 4 + 3 = 7) INVOLVING 35% OF THE SPECIMEN (1 OF 1 CORES CONTAIN CANCER). GLEASON PATTERN 4 COMPRISES 80% OF THE CANCER. CANCER LENGTH 0.6 cm.

(E1) Left Mid ADENOCARCINOMA (GLEASON SCORE 4 + 3 = 7) INVOLVING 65% OF THE SPECIMEN (1 OF 1 CORES CONTAIN CANCER). GLEASON PATTERN 4 COMPRISES 85% OF THE CANCER. CANCER LENGTH 1.3 cm.

(F1) Left Base: ADENOCARCINOMA (GLEASON SCORE 4 + 3 = 7) INVOLVING 90% OF THE SPECIMEN (1 OF 1 CORES CONTAIN CANCER). GLEASON PATTERN 4 COMPRISES 65% OF THE CANCER. CANCER LENGTH 2.25 cm.

Dr. McNally concurs.

Dennis was stunned to hear this diagnosis after having lived such a healthy life, but given the prevalence of prostate cancer in his family, he always knew he was at risk. His prior experience in cancer research made Dennis averse to the traditional routes of chemotherapy, radiation, or surgery, as he was aware of the potentially devastating side effects. He began to research alternative methods of cancer treatment and learned about cannabis oil. After thoughtful consideration, he decided this was the path for him. Dennis' treatment journal, starting on July 8, 2010, is recorded online (Hill, "Treatment").

Prior to the first entry, Dennis had been consuming cannabis-infused butter, as he had not acquired full-strength cannabis oil yet. After procuring oil his condition steadily improved. A prostate biopsy was taken on January 25, 2011 to determine if the cancer was going into remission, and on February 8, 2011, Dennis learned he was cancer free (Hill, "Cured"). The only pharmaceutical-type treatment Dennis received was three injections of Lupron, an androgen antagonist which can potentially slow the rate of cancer growth. However, it does not attack cancer cells directly.

FINAL for HILL, DENNIS (S2011-001000)

ODL

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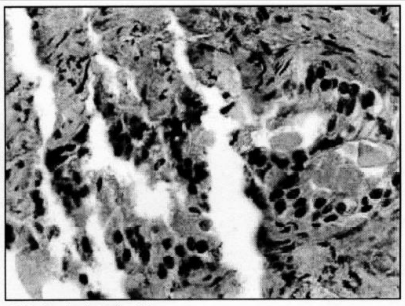
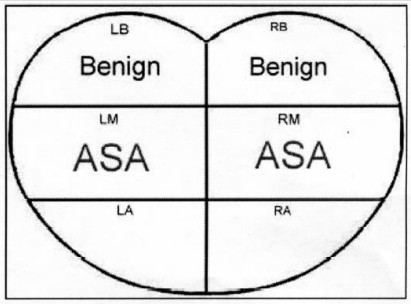
Patient Name: HILL, DENNIS
Case Number: [redacted]
Date of Birth: [redacted]
Age: [redacted]
Collection Date: 01 25 2011
Received Date: 01 26 2011



RM: Atypical small acini



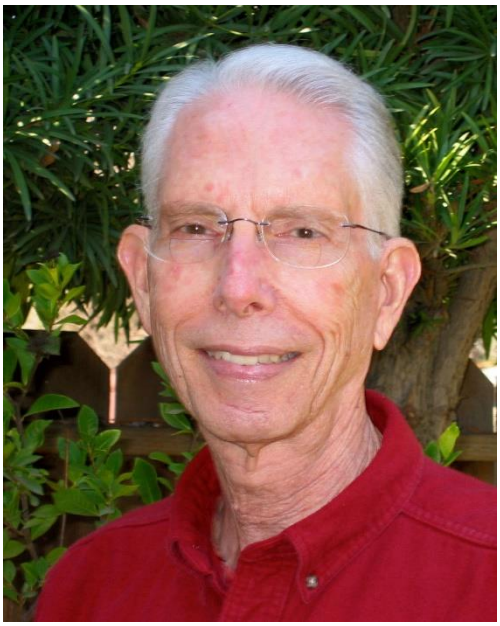
Diagnosis summary

PROSTATE DIAGNOSIS

Site	Diagnosis	Site	Diagnosis
LM:	ATYPICAL SMALL ACINI WITH MARKED DRYING ARTIFACT (SEE COMMENT).	RM:	ATYPICAL SMALL ACINI WITH MARKED DRYING ARTIFACT (SEE COMMENT).
LB:	BENIGN PROSTATIC TISSUE.	RB:	BENIGN PROSTATIC TISSUE.

JB/GS/pp

Dennis appeared on a program called "Spiral Up with Ava Marie" to tell his story ("Spiral Up").



As of October 2017, Dennis is still cancer free and working to share his knowledge. On September 14, 2017, he taught a class on cannabis and cancer at a shop called Turlock Vitamins & More, which sells CBD oil and has been in existence since 1947 (Martin, "Curing"). The owner, Lee Duchscherer, stated "He's [Dennis] been cancer free for quite a while now, and I hear a lot of this from customers that we sell CBD oil to. We have a lot of people that come in who have gotten rid of all kinds of different cancer."

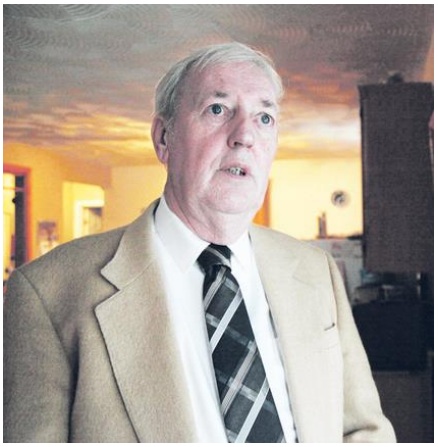
Taras Wybaczynsky, the founder of a cannabis extract company called Rimidya, revealed his battle with prostate cancer in a blog interview (Volpe). "My motivation came from my own personal disease. I was diagnosed 17-years -ago with metastatic prostate cancer. This product has allowed me to be the longest-lived metastatic prostate cancer patient at the medical facility I am involved with," said Taras. He also recounted experiences from others who used his brand of cannabis medicine. "The results of both topical and ingestion of our product have been astonishing with psoriasis, pain, neuromuscular and neuroskeletal pain, and so much more."

A September 18, 2013 article from *The Telegram* reported Paul Morrissey's experience with Stage IV prostate cancer (Sweet, "Man Convinced"). He had put off medical treatments for about a year while trying to source cannabis oil. During this time, the cancer began spreading to his back and lymph nodes. At some point early in his battle, he used a pill medication for about a month and an injection prescribed by his oncologist, but refused conventional chemotherapy or radiation (Sweet, "Man Says"). Paul discontinued the pills and injections after acquiring cannabis oil and experiencing its profound benefits. He said his prostate-specific antigen (PSA) levels (a marker of prostate cancer) plummeted after six weeks of cannabis oil ingestion.

Dr. Randy Hart, Paul's physician, confirmed that his PSA levels had dropped substantially, from 29.5 to 3.3. Some regression in his lymph nodes and abdomen was also observed. Dr. Hart said there was a "major improvement in his situation," and Paul had a "really good response." He also cautioned that there was no way to be certain cannabis oil was responsible for his recovery, as the conventional medication may have contributed to his lower PSA levels.

However, Paul credits the cannabis oil with the majority of his recovery. "It makes me feel 20 years younger, that's what the marijuana oil does," said Paul. He also remarked on how he was able to shovel snow for three hours during a recent blizzard. "There was pretty ferocious wind and snow. I came out of it looking like a walking popsicle. However after all that work and so forth I was in excellent condition. Even without cancer, I wouldn't suspect I'd last that long or do that well."

Adding to the likelihood that cannabis oil worked for Paul is a January 14, 2015 article, which shared Paul's continued wellness (Sweet, "Marijuana Oil"). He is still only using cannabis oil and has become a major advocate for clinical trials.



A story published July 4, 2017 in a Canadian paper shared the successes of many older patients using medical cannabis (Carson). One man, 67-year-old Fred Harris, had suspected prostate cancer due to a substantially elevated PSA level. One side of his prostate was also lumpy. After researching life after prostate cancer surgery, Fred postponed a biopsy and decided to try medical cannabis before pursuing the traditional route. He made his own apparently CBD-rich tincture and took it for six months. He then went to a urologist, who revealed Fred's PSA had returned to normal and his prostate was smooth. Given all the factors, Fred believes cannabis medicine eliminated his prostate cancer.

A story on Leafly.com published October 25, 2017 profiled the Canadian comedian Alan Park (Jordan). After becoming a regular cast member on the hit CBC sketch comedy show *Royal Canadian Air Farce*, Alan became well known throughout Canada. His comedy career was

imperiled when he was diagnosed with terminal Stage IV prostate cancer. The cancer was in most of his skeleton and his PSA number was over 700, an incredibly high level. Alan stated that taking increasing doses of Rick Simpson Oil (full-extract cannabis oil) helped put his cancer into remission. He used no conventional therapy other than a single round of radiation. A November 2017 article stated his last quarterly check-up revealed healthy markers on his cancer test and he is indeed cancer-free (Siebert).

Rhabdomyosarcoma

Chico Ryder was diagnosed with Stage III/Group III parameningeal embryonal rhabdomyosarcoma, an especially aggressive soft tissue cancer, in December 2012 (Kander, "13-Year-Old"). He immediately began chemotherapy after diagnosis. From February to March 2013, Chico also completed a 28-session protocol of radiation, which consisted of one session per day five days a week. The intense combination of these treatments caused horrendous side effects, including near-daily vomiting and painful nerve damage. Chico eventually needed to stay in the hospital every time he received chemotherapy.

Chico's parents, Paul and Angela Ryder, knew they needed to do something to mitigate the damage from conventional treatments and boost their cancer-fighting power. After Angela learned about cannabis oil and extensively researched the treatment option, the family decided it was the right thing to do.

Chico first tried Marinol, a synthetic form of THC, which moderately improved his symptoms. However, the drug's benefits diminished over time. He then began receiving cannabis oil from Aunt Zelda's in July 2013. The impact from this better form of cannabis extract therapy was remarkable. While the oil did not fully reverse the side effects of the large doses of chemotherapy and radiation, Chico experienced significant benefits. His vomiting reduced by half and his neuropathy stopped progressing. By August 2013 he was able to get off intravenous nutrition and begin using a G-tube, which is better for liver function.

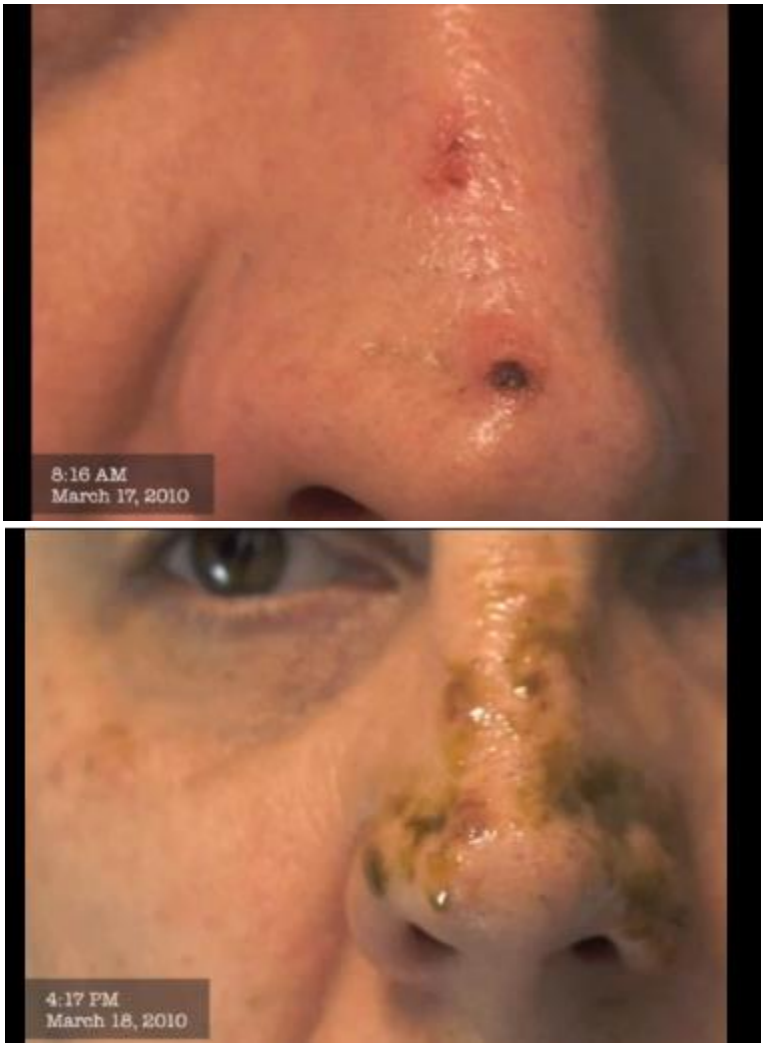
To fight the pain, Chico was prescribed substantial amounts of opiates, including methadone. Cannabis oil enabled Chico to wean off opiates while controlling pain. Furthermore, Chico's white blood cell counts recovered faster than expected after chemotherapy sessions, and he did not need to delay chemotherapy at all once he began using cannabis oil.

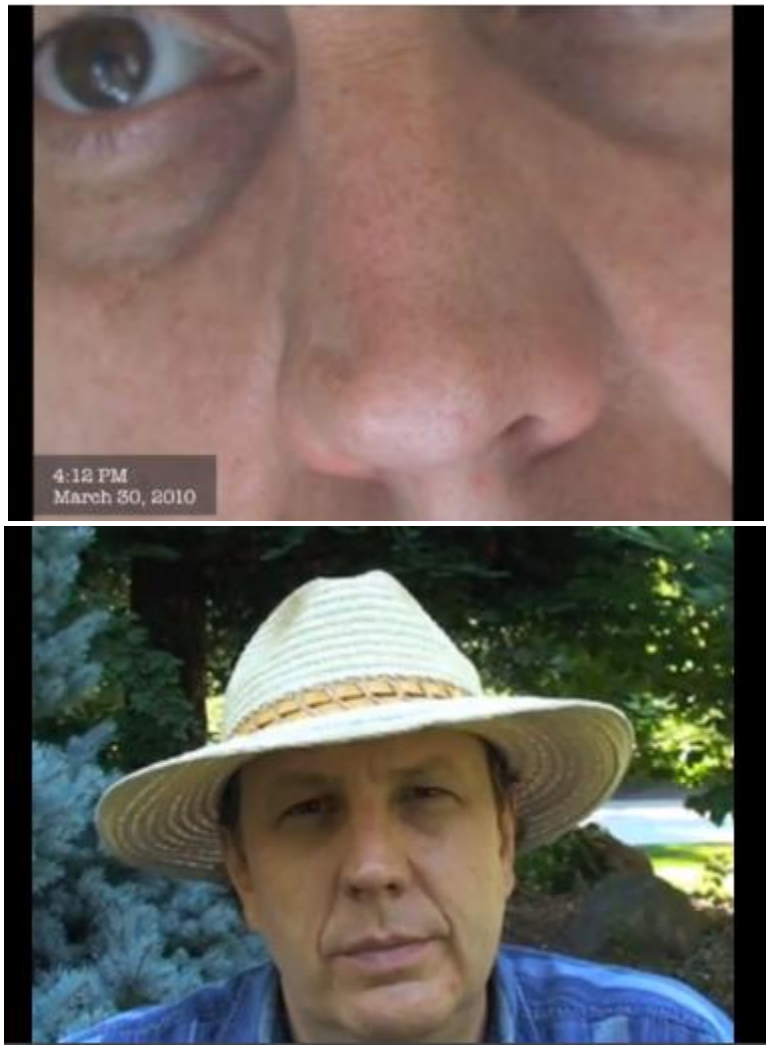
Chico utilized a range of integrative therapies alongside conventional treatment, including cannabis oil, mistletoe, acupuncture, medicinal mushrooms, IP6 and many other supplements. By November 2013, Chico was declared in remission. He substantially reduced his cannabis dose to 85mg of THC and 100mg of CBD per day for maintenance. Chico has since recovered from much of the damage he endured, but he still has a fair way to go before he is completely healed.

A story from a local ABC affiliate alluded to the impact of cannabis oil on rhabdomyosarcoma (Bowman). Seven-year-old Nattaly Brown was diagnosed with the disease in 2014 and went through intense rounds of chemotherapy and radiation. She eventually started using cannabis, trialing several forms including tinctures, vaporizers, edibles, and topical preparations. This allowed her to gain weight, sleep better, eliminate anxiety medication, and improve mood. The most recent scan, as of the article's publishing in May 2017, showed no cancer. At some point, Nattaly had stopped chemotherapy early and was only using cannabis.

Skin Cancer

David Triplett treated skin cancer on his nose with cannabis oil and documented his results in a short film titled *Cured: A Cannabis Story*, released on July 6, 2010 ("Cured").





Maggie Peron discussed her 65-year old father's use of cannabis oil in a December 23, 2009 video (Avery). He had squamous cell carcinoma on his hands and had to live with constant scabs, pus, sores, and pain. She convinced her dad to try topically-applied cannabis oil one night; the very next day he reported substantially reduced pain. After a month, the scabs and sores almost completely disappeared. There was hardly any scarring, and the pus had gone away completely. "That’s the main thing, there’s no pain," said Maggie.

Michael McShane turned to cannabis oil after trying to find a more effective way to treat his recurring skin cancer (Gholson). In the late 1980s he was diagnosed with HIV, which subsequently led to many bouts with cancer. For years, Michael fought these cancers with surgery, chemotherapy, and radiation. In June 2011, the cancer on his face returned in a spot where it was previously removed with surgery. Although initially skeptical, Michael gave cannabis oil a chance. "I got Simpson oil and started putting it on and after ten days, ten days I saw it. The cancer started to break up before my eyes. It looked like a big white callous, and it started to fragment and break up. I was crying. It was unbelievable."

In an August 2011 Detroit CBS News article, Michael's dermatologist Dr. Ali Moiin said the cancer cells had decreased up to 60 percent after two months, and the results warranted scientific study into cannabis extracts for skin cancer (McNeill, "Skin Cancer Patient Says Oil"). An article a month later confirmed all visible signs of cancer were gone, and Dr. Moiin was no longer recommending surgery (McNeill, "Skin Cancer Patient Says Medical").

Michael has since had some recurrences of skin cancer, but has continued to manage them with cannabis oil.

Brian Stewart is a Canadian Motorsports Hall of Fame inductee who successfully treated his cancer with cannabis oil ("Rethink Cannabis"). After noticing a progressively growing tumor in his ear, Brian went to his doctor, who said he would have to remove Brian's entire ear to get the tumor. Brian accepted this and made an appointment to see a specialist.

In the meantime, a friend told Brian about cannabis oil and gave him some. Despite having never smoked a cannabis cigarette in his life, Brian decided to trial it. Within a week of topically applying the oil, bits of the tumor were falling off in the shower. Treatment was interrupted when Brian took a trip to Dallas, but upon returning he finished the treatment. From start to finish, not including his time in Texas, it took three and a half weeks for the tumor to disappear.

Brian didn't stop with his own healing; he helped at least two other skin cancer patients. A friend's wife had skin cancer in her ear, and topically applying around three grams of oil over three and a half weeks (about the same amount of time as Brian) eliminated the cancer. Another friend's wife developed melanoma on her leg. Most of it was eliminated with surgery, but some cancer apparently remained between the stitching. Brian gave the woman cannabis oil, which eradicated the remnants. After seeing his video, it is clear why Brian is often referred to as one of the greatest personalities in Canadian racing history.

A June 9, 2013 video shared how a man named Jack used a comprehensive cannabis treatment program to control skin cancer ("RRTV // Jack"). For 40 years, Jack had to regularly see doctors due to the aggressiveness of the cancer. For the most recent decade of this history, he needed to undergo surgery to remove continuously reappearing skin cancer lesions.

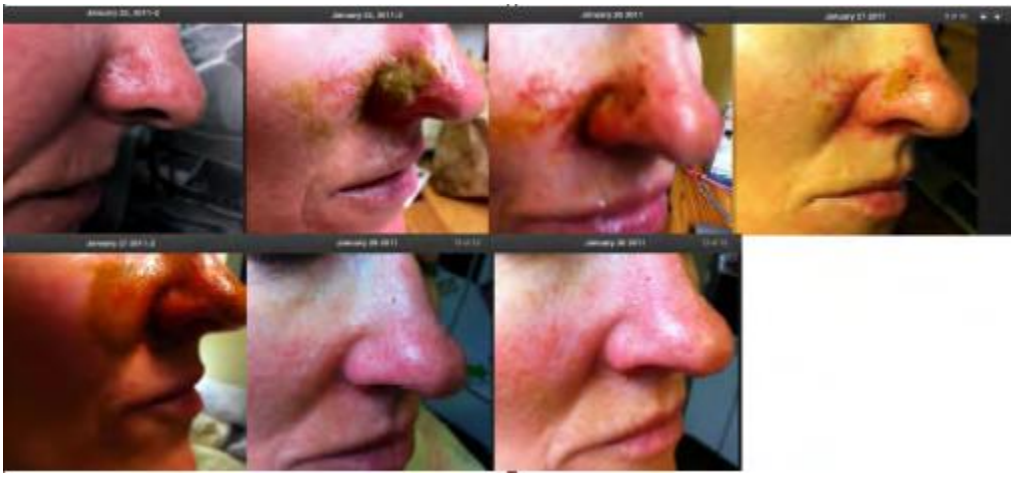
After a year of being part of River Rock, he talked with Tony Verzura, a proprietor of the dispensary, about a plan to combat his skin cancer. They created a complete program that included teas, tinctures, capsules, oils, and raw juices. Within a month, Jack's skin had improved dramatically. After another two weeks, he went into his three-month regularly scheduled

appointment, where normally he would have lesions excised or froze off. At this appointment, for the first time in at least ten years, the doctor found nothing to remove.

Jack also used small amounts of topically-applied cannabis oil for single spots of skin cancer that appeared. He said that by putting oil onto a bandage and then onto a spot, it disappeared in days.

Harborside Health Center, the largest dispensary in the world, supplies cannabis extracts for a wide variety of uses. The owner, Stephen DeAngelo, is an accomplished activist and businessman in the United States. He appeared in *Run From the Cure 2*, the sequel to Rick Simpson's original documentary about cannabis extracts treating cancer ("Run From"). In a segment from the documentary's trailer, Stephen said, "We have skin cancer patients who are coming to Harborside every week. They take the oil, they put the oil on their lesions, the lesions stop growing immediately."

Cannabis Science, a Colorado-based corporation, posted documentation of basal cell carcinoma being eliminated with the topical use of cannabis oil in 2011 ("Cannabis Science"). Dr. Robert Melamede, the former CEO of the company, has shared additional documentation of skin cancer remissions at medical cannabis conferences.



Dear Adriene,

Re:
D.O.B: [redacted]

I saw [redacted] again last week and undertook some biopsies.

As you know we have been keeping an eye on her right cheek for a couple of years. She treated the biopsy proven BCC with a tar extract which seemed to get rid of the BCC from a clinical point of view. A persistent red spot in the middle of the area was biopsied last week, the result of which showed benign fibrous papule only. There was certainly no evidence of BCC. I reassured [redacted] of this result over the phone today.

Over the last couple of months [redacted] has noticed a scaly area on the right alar. To exclude BCC we also took a shave biopsy of this last week. The pathology result was simply solar keratosis.

At this stage I have not arranged to see [redacted] again routinely but I would be happy to see her at anytime if necessary.

[redacted] knows to report any suspicious changes that occur. Thank you again for referring her.

Yours sincerely,

[redacted]

[redacted]

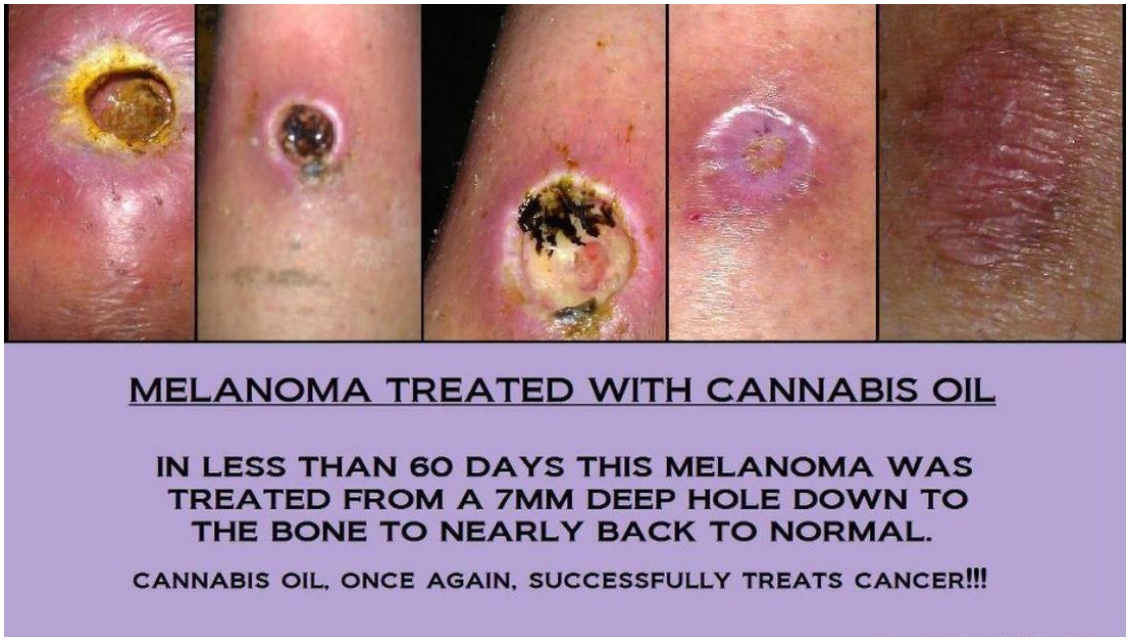
[redacted]

Robert Platshorn is the founder of The Silver Tour, an organization dedicated to educating senior citizens on the benefits of cannabis for age-related diseases. He spent almost 30 years in prison for importing cannabis into the United States. A couple years after being released, Robert began having many skin cancers appear on his body (Platshorn). He had one carcinoma surgically removed, but the resulting wound would not heal and the cancer began returning. Robert acquired cannabis oil and began topically treating the cancer. After three days, the wound began growing fresh skin rather than scar tissue, and the cancer died. Over the next few months, Robert continued to successfully treat new skin cancers with cannabis oil.

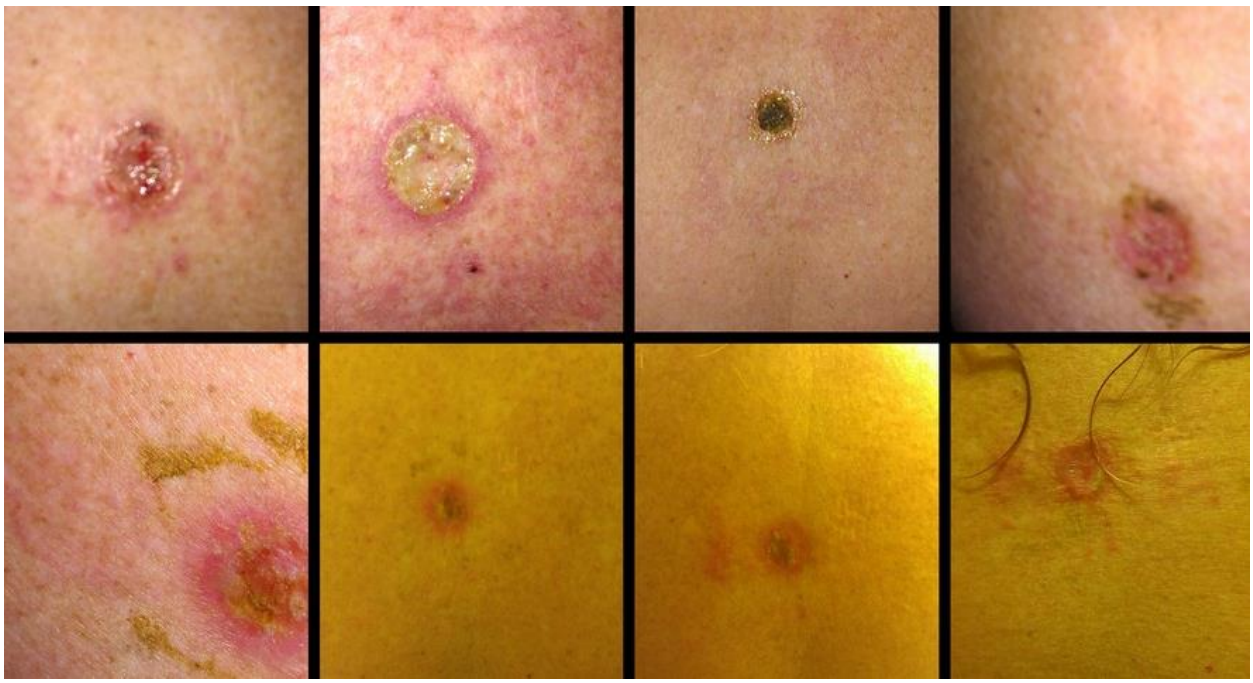
Robert also lamented that his parole officer, a man named Tony, was unable to use cannabis for the debilitating disease he became afflicted with. Tony was aware of Robert's use of cannabis for skin cancer and had no objections. He was currently undergoing chemotherapy, and talked with Robert about his desire to use cannabis. However, he never did out of fear of losing his job and pension. He eventually passed away, leaving behind a wife and two daughters.

After Tony's passing, Robert was given a new parole officer who was not as sympathetic to his situation. He was ordered to stop using cannabis oil. This caused great hardship to Robert, as he was no longer able to self-treat the cancer and had to undergo at least some surgery. As of June 2015, Robert was still vibrantly sharing his message and attending conferences. He shows no signs of slowing down.

A graphic featured on CureYourOwnCancer.org showed a melanoma remission from a woman named Tricia Dennis ("Cannabis Oil Testimonials"). Jon Marsh, the founder of Cannabis Oil Success Stories, a popular Facebook group, originally created this graphic.

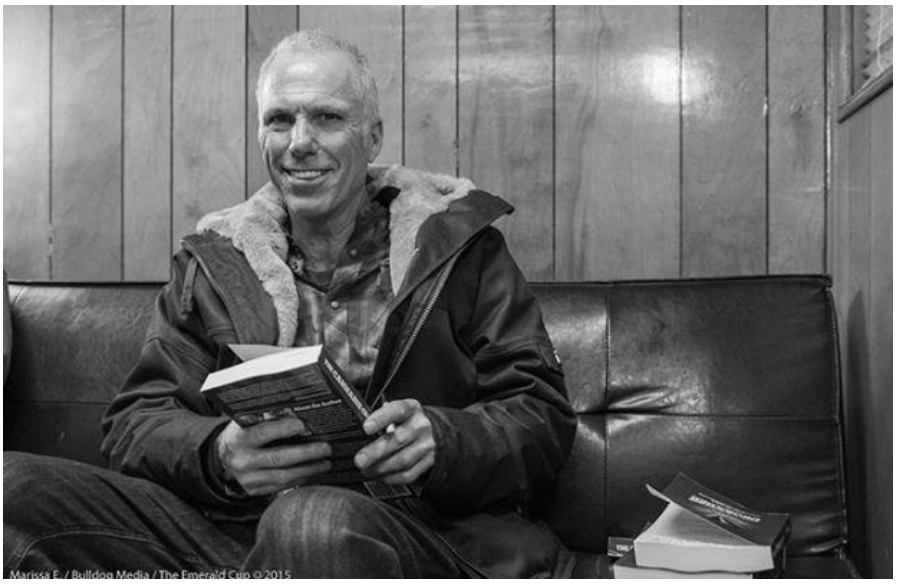


Another image from the same website demonstrated an anonymous success with basal cell carcinoma. The cancer was treated with cannabis oil over a three week period ("5078532_orig.jpg").



Tim Blake is the founder of the Emerald Cup, one of the most respected competitions for judging organic, outdoor-grown cannabis. In a November 29, 2016 interview, he revealed his use of cannabis for treating skin cancer (Coulson). “Cannabis has saved me from dying of cancer – I’ve

had 12 skin cancers that have metastasized into my bone – one ate an inch of my bone. I use it as a lotion on my face to kill the skin cancers," said Blake.



A case report in the January 2017 issue of the *Journal of Pain and Symptom Management* provided strong evidence of the topical anticancer effectiveness of cannabis (Maida). It described a 44-year-old man using vaporized and topical cannabis for pain associated with a recurrent squamous cell carcinoma. Vaporization of 0.5g to 1.0g of dried cannabis (7.25% THC/8.21% CBD) allowed him to discontinue some pain medications and tremendously reduce others. He switched to topical use of a cannabis-infused sunflower oil (5.24% THC/8.02% CBD) after vaporization became impractical. As the chart below shows, the tumor size was increasing rapidly until it reversed course once topical treatment commenced.

Table 1
Clinical Data

Date	Tumor Size (cm^2)	Average Daily Pain Score (0–10)	Analgesics	MC Therapy	PPSv2 (%)
November 12, 2015	8.75	9	Hydromorphone 30 mg/day Pregabalin 150 mg/day Decadron 4 mg/day	Vaporized	90
December 10, 2015	12.33	3	Hydromorphone 8 mg/day	Vaporized	90
January 21, 2016	26.44	3	Hydromorphone 8 mg/day	Vaporized	80
March 17, 2016	44.16	4	Hydromorphone 10 mg/day	Topical Oil	70
April 21, 2016	41.90	4	Hydromorphone 20 mg/day	Topical Oil	60

MC = medical cannabis; PPSv2 = Palliative Performance Scale, version 2.

Dr. Vincent Maida, the doctor who wrote the case report, stated, "Before the use of topical MC oil, the patient's wound was growing rapidly. Yet, after a few weeks, a modest regression of his malignant wound was observed while the patient used topical MC. This secondary outcome suggests that topical MC may promote antineoplastic activity as per the findings of Casanova et

al. [referring to a study showing cannabinoid receptor activation reduces skin tumor growth]." Unfortunately, the patient still passed away from apparent metastasis of the cancer. This is not surprising; the oil used here was substantially weaker than oils used by other skin cancer patients - 13% vs. 50-80% in more concentrated extracts. Furthermore, the patient ingested very little cannabinoids internally. This action would have been needed to fight metastasis. Nonetheless, the charted growth of his tumor strongly argues for an antitumor effect of cannabis.

A May 2017 article in an Australian paper described Wayne's journey in overcoming terminal cancer with cannabis oil (Osborne). His last name was withheld for legal reasons (his picture is also obscured for apparently the same reason). Wayne was diagnosed with skin cancer; despite radiation, it spread to his lymph nodes, lungs, and liver. With chemotherapy he had twelve months to live, and without it, just six. With this grim diagnosis, he stopped the conventional treatment and tried cannabis oil. Within twelve weeks, the lung and liver metastases were gone, along with cancer in one of his lymph nodes. There has yet to be detail of whether that final lymph node is clear, but most of the cancer disappeared.

A May 2017 article in a Colorado Springs journal included a couple mentions of cannabis fighting skin cancer (Woods). The focus was on Laurie Gaddis, who moved to Colorado from Arizona after being diagnosed with a rare form of skin cancer. For almost ten years, she has apparently keep the cancer under control with cannabis oil as her main treatment, as she has not undergone chemotherapy or radiation at any point. Laurie uses the oil, likely THC-rich, topically and internally as treatment. Although she has been relatively successful, she has not achieved sustained total remission, as the article mentions she still struggles.

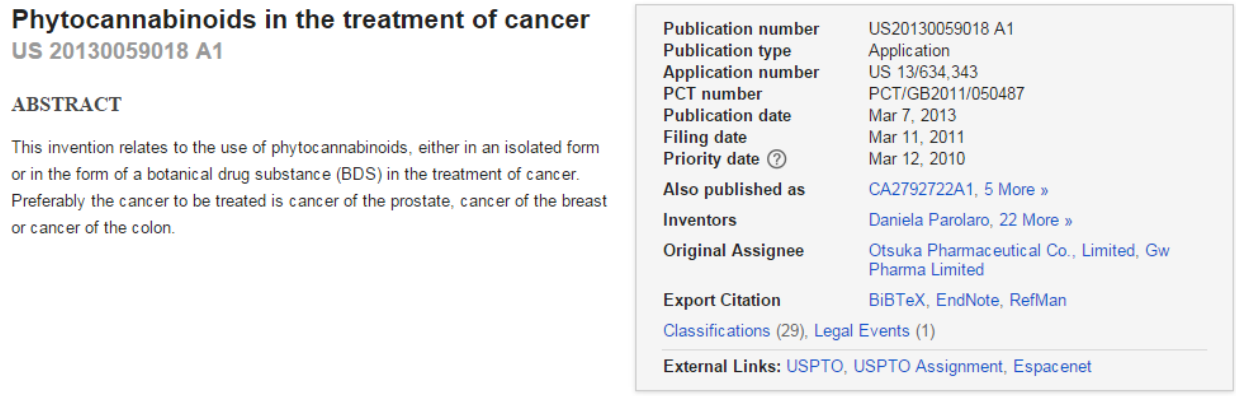
The article also included a statement from Dr. Stuart Titus, the CEO of Medical Marijuana Inc., a producer of industrial hemp-derived CBD oil. While this type of cannabis oil is seemingly inferior to medical cannabis-derived THC or CBD oil, it may retain some anticancer effects. Sadie Higuera's case, discussed later, is especially hopeful (although in that case, THC-rich oil was used in addition to the hemp CBD). Furthermore, the author can recall two cases where hemp CBD reportedly fought cancer in humans. First, at the 2013 Drug Policy Alliance Reform conference, the author saw before-and-after pictures of skin cancer reducing in response to hemp CBD oil. The

author also met a patient at the 2014 Americans for Safe Access conference who said she had gone into remission from terminal liver cancer with hemp CBD oil. Given these observations, the statement from Dr. Titus that he has anecdotal stories about hemp CBD's success for skin cancer should be taken more seriously. Nonetheless, all patients should do their best to seek out medical cannabis derived oils. As an absolute last resort, a clean hemp CBD oil is better than nothing. Care should be taken to ensure absence of pesticides, molds, and heavy metals in any hemp CBD oil.

An Oklahoma affiliate of ABC News published a story on November 7, 2017 about Ray Jennings, who grew up as an honest farmer believing cannabis was bad since it was illegal (Haddican). In February 2014, he was diagnosed with Stage IV squamous cell carcinoma, with a tumor on the base of his tongue the size of a golf ball. He started chemotherapy and radiation, but halfway through the therapy was doing very poorly. On his third trip to the hospital when he was on a stretcher, his family begged him to try medical cannabis, so he moved to Colorado to stay with his son and began putting CBD oil, apparently high-potency extract, onto the tumor. His vomiting and weight loss decreased dramatically, and by August 2014 was cancer free. Ray believes cannabis saved his life.

Assorted Cancers

There are many reports of doctors or caregivers observing success against a wide range of cancers through the use of cannabis oil. In addition to a patent mentioned earlier in this book, another patent published March 7, 2013 related to the use of phytocannabinoids like THC and CBD for the treatment of cancer, particularly prostate, breast, or colon cancer ("Patent US20130059018").



Phytocannabinoids in the treatment of cancer
US 20130059018 A1

ABSTRACT

This invention relates to the use of phytocannabinoids, either in an isolated form or in the form of a botanical drug substance (BDS) in the treatment of cancer. Preferably the cancer to be treated is cancer of the prostate, cancer of the breast or cancer of the colon.

Publication number	US20130059018 A1
Publication type	Application
Application number	US 13/634,343
PCT number	PCT/GB2011/050487
Publication date	Mar 7, 2013
Filing date	Mar 11, 2011
Priority date	Mar 12, 2010
Also published as	CA2792722A1, 5 More »
Inventors	Daniela Parolaro, 22 More »
Original Assignee	Otsuka Pharmaceutical Co., Limited, Gw Pharma Limited
Export Citation	BiBTeX, EndNote, RefMan

Classifications (29), Legal Events (1)

External Links: USPTO, USPTO Assignment, Espacenet

Dr. Jeffrey Hergenrather is a former emergency room physician, President of the California Cannabis Research Medical Group, and one of the first licensed doctors to treat patients with cannabis. Dr. Hergenrather has presented at numerous CME-accredited medical conferences, and a presentation he delivered on June 15, 2014 succinctly captured his observations (Futcher). He shared how cannabis was positively affecting many conditions, including inflammatory bowel disease, Alzheimer's, and many forms of cancer. Results seen with IBD and Alzheimer's were dramatic and many patients refused to return to their original medicines after using cannabis.

In terms of treating cancer, Dr. Hergenrather said he has seen good results by topically applying cannabis oil on carcinomas. The article summarizes:

"Not all tumors are sensitive to cannabinoids. Hergenrather said common lung cancer, and some thyroid and breast carcinomas do not appear to respond well to cannabis treatment.
Cancers that have responded, he said, are: neuroblastomas; certain types of breast cancer; hepatic, renal, pancreatic cancer; colorectal, cervical and prostate cancers; Hodgkins, Non-Hodgkins, and Mantle cell lymphomas; some leukemias; skin cancers, and sarcomas."

An oncology nurse with 17 years of experience named Valerie Warwick remarked on her cannabis extract observations in a December 17, 2014 interview (Wark). She has seen many cancers completely healed or significantly improved with cannabis treatment, including lymphoma, leukemia, breast cancer, colon cancer, and more.

A biotechnology research organization known as Emerald Bio is one of many working to develop cannabinoid-based drugs to fight cancer. The CEO, Johan Pontin, casually alluded to the fact that cannabis extracts were already being used to treat cancer in humans in a January 28, 2014 *Boston Globe* article (Stockman). A segment from the article states:

"Pontin, who applied for a license through an offshoot company, says it’s not just a chance to ease the pain of a couple of hundred cancer patients. It’s a chance to develop new drugs that might actually cure cancer itself.

That’s right. He says that caregivers in Rhode Island who’ve been working with marijuana for years have beaten back cancer with highly concentrated oils derived from cannabis.

'There was an 80-year-old patient with esophagus cancer,' he said. 'Today, she is 91 years old and totally cancer-free. Even the insurance company couldn’t believe it.'"

The Wo/Men's Alliance for Medical Marijuana (WAMM) is a health cooperative in Santa Cruz, California, founded by Valerie and Mike Corral. They specialize in treating seriously and terminally ill patients, including cancer patients. Michelle Aldrich, whose case was shared in the ***Lung Cancer*** section, used WAMM's medicine and Valerie's general support in her fight against lung cancer. According to United States Federal Judge Jeremy Fogel, "WAMM is the gold standard of the medical marijuana movement" (Krassner).

Valerie has presented her work at several conferences. At the Eighth National Clinical Conference on Cannabis Therapeutics she shared information about six late-stage patient cases, including data on THC:CBD ratios, dosage levels, and cancer markers decreasing (Kander, "RECAP").

In a May 11, 2015 article in a local Santa Cruz paper, Corral alluded to the amazing results she is seeing (Clark). "We treat many cancer patients with our cannabis extract Milagro Oils, and the results are staggering. Every day people call to tell us that instead of their condition worsening, there’s no evidence of disease."

Dr. Allan Frankel revealed his cancer-related observations in a March 9, 2014 interview (Mercola). Dr. Frankel has treated patients with cannabis for the past seven years. He has seen "tumors virtually disappear in some patients using no other therapy except taking 40 to 60 milligrams of

cannabinoids a day." He has seen tumors shrink and metastatic areas disappear. Interestingly, in some cases he has observed tumors vanish, reemerge in other areas, then shrink or vanish again.

Corrie Yelland is a cancer survivor and prominent activist who eliminated terminal anal canal cancer with cannabis oil (Yelland). She also used the oil to overcome a long-term, treatment-resistant chronic pain condition stemming from heart surgery she received in 2007.

In July 2011, Corrie was diagnosed with anal canal cancer. Shortly before, she had also been diagnosed with two spots of skin cancer on her collar bone. She underwent two surgeries to remove the anal canal cancer, but was told radiation would be necessary to treat the deepest parts of the cancer. After learning of radiation's potentially devastating side effects, including 2nd and 3rd degree vaginal and rectal burns, Corrie decided she did not want to pursue the conventional treatment. Without it, she was given two to six months to live. She learned about the anticancer potential of cannabis oil from a friend, and after doing substantial research decided she would move forward with cannabis therapy.

Corrie started with small doses of orally-ingested cannabis oil, slowly working her way up to higher doses. She also applied the oil topically to her skin cancers. There were visible changes within 48 hours, and in just over a week the spots were completely gone. Two weeks into her regimen, the pain in Corrie's sternum, as well as her nerve pain, had become almost nonexistent. This pain had been with her 24/7; she never imagined she would be pain free again. This allowed her to sleep through the night and stop taking sleeping pills.

In addition to taking cannabis oil orally, Corrie used cannabis suppositories in the form of gelatin capsules filled with cannabis and olive oils. Her experience with skin cancer led her to believe that getting the medicine as close to the cancer as possible would maximize effectiveness. By May 2012, the doctor who discovered Corrie's cancer could no longer detect it. Corrie went to

a specialist on September 20, 2012 for more extensive testing, where it was confirmed that she was completely cancer free.

A report from a local ABC News station reported on Brett Strauss' experience with neck cancer ("Medical Marijuana Cancer"). Brett was first diagnosed with cancer in 2007. After beating it with conventional treatments, the cancer returned as five malignant tumors in January 2010. He decided to try topically applying cannabis extract balm on his neck, and in March 2010 doctors identified only one tumor as malignant. After his experience, Brett wanted to research the effects of cannabis oil for other cancer patients. However, there does not seem to be any further information available about his intended research.

A December 7, 2014 story from an NBC affiliate reported on Cecilia von Harz ("Toddler Using"). She was diagnosed with a rare kidney cancer called Wilms' tumor in 2013. Surgeries, radiation, and chemotherapy were all attempted, but damage to Cecilia's liver prevented further treatment. At this point, parents Jim and Jaclyn sought out alternative treatments, which consisted of cannabis oil and an organic sugar-free diet. The effects were powerful. "She was sick, she was in pain," Jaclyn said. "But she's so much better now. She's happy, she's energetic." The parents also said the treatments have shown great promise in shrinking Cecilia's tumors.

David Adkins was diagnosed with a spinal tumor stretching from the second thoracic vertebrae to the ninth ("Introducing"). After seven weeks of cannabis extract therapy, the tumor disappeared. David stated:

"It does work. It's not just that it makes me feel better, it's taken care of the problem, the tumor's gone. We never did a biopsy to know whether the tumor was cancerous or non-cancerous, but either way it didn't matter because it was growing in a spot that was going to paralyze me or kill me, and they can't find it now. So… there's no doubt that it works. Not only do I feel better, I see the results on the MRIs."

Steve Kubby is an accomplished businessman and activist who assisted in the drafting of California Proposition 215 ("Steve Kubby"). In 1968, Steve was diagnosed with malignant pheochromocytoma, a rare, fatal form of adrenal cancer. Despite an extremely high mortality rate, Steve was able to control the disease for decades by smoking large amounts of cannabis. His original doctor stated, "In some amazing fashion, this medication has not only controlled the symptoms of the pheochromocytoma, but in my view, has arrested its growth."

Steve talked about putting the disease into apparent remission in a November 2015 article (Kubby). In February 2012, he began using a cryogenic extract from fresh cannabis plants. This enabled him to take in large amounts of raw cannabinoids. He got the idea from Dr. Raphael Mechoulam, who had said drying cannabis results in the loss of important cannabinoids. After making the extract, Steve began taking a quarter teaspoon every day.

On May 16, 2012, he experienced severe vomiting that lasted four days. Although he initially blamed food poisoning, the fact his cancer symptoms ceased after the event led him to believe tumor cell death was the real cause.

Steve concluded the article by saying, "Of course I realized that extraordinary claims require extraordinary proof, so I decided to wait a year and see if my symptoms returned. They did not and I began to experience excellent health. It’s now been 3.5 years since this event and my health continues to improve. Recently, I took a lab test and was stunned to find out that my catecholamines in my blood have dropped from 10 times normal to normal. To the best of my knowledge, this is the first time in medical history that someone with adrenal cancer (malignant pheochromocytoma) has ever recovered from this terrible disease." Catecholamine levels are the chief measurement by which pheochromoctyoma is diagnosed ("Pheochromocytoma").

A story from October 2015 about a Pennsylvanian man, anonymized for his legal protection, described his success against terminal cancer with a combination of cannabis and chemotherapy (Nichols, "Cancer"). The man was diagnosed with a rare bile duct cancer and given a two-percent chance of survival. Even with chemotherapy, it had metastasized to his liver and lungs. He began ingesting THC-rich cannabis oil his wife made for him; after almost three months of the oil and continuing chemotherapy, the cancer in his lungs was gone, and the tumors in his liver shrank, disappeared, or remained the same.

"I was shocked. I dropped to the ground. I could not believe it," said the man. "I thought it would be a miracle drug for him and it has been," said his mother. The oncology nurses were also surprised at the man's progress, but due to legal reasons he could not inform them of his secret medicine. Furthermore, the man kept his hair and gained weight despite chemotherapy.

An update from ABC27 published February 16, 2016, revealed that the above patient decided to identify himself in an effort to instigate faster change (Nichols, "Update"). Randal Ray Robertson, 56, had been given 9-11 months to live after the bile duct cancer had spread to his liver and lungs. Interestingly, Randal actually invited ABC27 to his CAT scan, and the doctor allowed the family to record the results. The doctor stated, "The CAT scan looks great. There are no nodules in the lungs. Now, there are just a couple subcentimeter lesions on the liver. The rest of the liver looks great." Randal's lungs were also still clear and the remaining small tumors in his liver had decreased even more. "There was no denying at that point that this was not normal and this was not just the chemotherapy," Randal said. His wife Molly stated, "We could have gone to jail when we were actually using it. I mean, we were in jeopardy, but we had such amazing results that we had to step out."

Unfortunately, Randal did eventually succumb to the cancer, passing away on August 5, 2016 (Kiner). The nature of his continued cannabis or chemotherapy treatment between February and August is unclear.

Todd Mitchem is an accomplished cannabis entrepreneur with several successful ventures in the industry. In a December 2015 interview, he described what led him to leaving the traditional corporate world in 2012 (Mitchem). At some point in her life, his mother was diagnosed with breast cancer, which she beat with radiation and chemotherapy. Around 2008, she was diagnosed with cancer again. This time, it was adenocarcinoma of the chest wall and pleura. Tumors had spread throughout her body, and doctors said she had four to six months to live.

A nurse suggested to Todd's mother that she use cannabis to ease her pain as she dies. For six months, she ate a cannabis-infused muffin before bed, which significantly helped with sleep. Surprisingly, the cancer was eventually completely eradicated, and as of December 2015 Todd's mother is still alive. "That diagnosis was almost seven years ago and my mother is STILL ALIVE today. Her cancer is completely eradicated. I believe she is still alive and has beaten terminal cancer because of her choice to consume cannabis," said Todd.

A January 2016 news article described the experience of David Hibbitt (Chow). The father-of-one was diagnosed with Stage III bowel cancer in July 2012, which was initially eliminated with a combination of chemotherapy, radiation, and surgery. However, the cancer eventually returned and was deemed terminal by David's doctors. He started taking cannabis oil in May 2014 alongside chemotherapy, but stopped that treatment around the end of August 2014 because it was making him feel bad. However, he had radiation therapy and an operation at the end of October 2014 as well. In January 2015 he was pronounced cancer free. The combination of cannabis oil and traditional treatments appeared to prove effective in eliminating a terminally diagnosed cancer.

The article on David also mentioned Gary Cartlidge, a 59-year-old cancer patient. He stated, "I was diagnosed with terminal cancer in October 2014 and the doctors only gave me between three and six months to live. I started using cannabis oil about 12 months ago, and I am still here. What David is doing is tremendous because there are people out there who need help, but don't know where to go for advice on alternative treatments."

An October 31, 2016 article detailed the effectiveness of CBD for extending the life of an 11-year-old German shepherd named Pixel (Cauguiran and McCrea). The owner, John Blair, used the treatment after the vet suspected she had cancer and said nothing more could be done. Pixel was in terrible pain and could not eat. The week before the euthanizing was scheduled, John began giving Pixel a CBD product called Treatibles. The dosage was not mentioned in the article, but based on the 1 and 2.5mg CBD per treat options, it is probable the daily dose of CBD was between 3 and 20mg per day. This approach was effective in quickly restoring Pixel's health. In just two days, there was a dramatic change, including significant improvements in energy. Most importantly, the CBD remedy appears to be the chief reason Pixel is still here. "Yeah, there's no evidence to back it up except the fact that here she is … she's not dead. And she would have been."

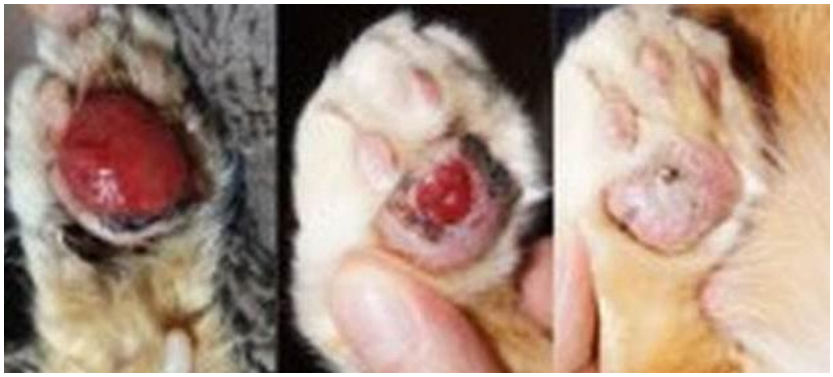
A January 2018 article in Metro Times shared a first-person account from Larry Gabriel about treating his dog Kai for a cancerous lump (Gabriel, "How"). Interestingly enough, Larry

also wrote about Alysa Erwin's experience with cannabis and cancer. Around 2015, a lump appeared in Kai's side. After the vet dismissed the seriousness of it, the lump began growing fast and other lumps appeared on his body. His mobility and energy decreased dramatically. Larry then took Kai to another vet who confirmed he had cancer and gave him 2-3 months to live. After remembering meeting a man who said he healed his dog's cancer with cannabis extract ("Rick Simpson Oil"), Larry procured THC-rich cannabis extract and began administering a rice grain size of oil twice per day. The first few weeks Kai was still tired, but then started to improve. A big breakthrough came when he jumped up onto the porch, whereas previously he could not even walk up the steps at all. Smaller tumors disappeared while the big one stopped growing.

Due to availability, Larry moved Kai to a 1:1 THC:CBD oil and then a 1:2 THC:CBD oil. The higher CBD oil seemed to result in less lethargy. As of the article's end, Kai still had some bumps which had stopped growing but they were not completely gone. Nonetheless, the original prognosis was well exceeded and Kai's quality of life is exceptional. "Kai is not suffering. No crying and moaning. He's alert enough to participate in our day most of the time. He still has a hearty appetite and his bowels are moving. He's an old dog; a good dog. And he's still alive 18 months after I was told he would die. That's good enough for me."

An April 2018 article on *Daily Mail* included photographic evidence of how cannabis oil helped a cat named Ginge overcome a large tumor on his paw (Thompson, "A Cat"). Ginge began getting sick in late 2017 and was taken to the vet on January 10, 2018, where the vet gave a poor prognosis for survival. Steroids and antibiotics did nothing to improve his condition. After reading about a cancer patient who used cannabis to overcome cancer, Ginge's owner Jacek Matusiak began giving him CBD oil in his food, starting around January 15th. Within a couple days of putting just five drops in the food, Ginge's tumor shrunk significantly and he began gaining weight. In addition to shrinking the tumor, Jacek says the oil has helped Ginge regain overall vitality and strength. "He completely perked up and started being more responsive. Most of all, his voice came back. Ginge

now walks around the garden, climbs the stairs, washes himself and overall has regained his vitality and strength. Now he can walk around the garden and he is back to his usual self again. He's put on weight too, as he was underweight and skeletal before," said Jacek.



A RollingStone.com article about an upcoming cannabis documentary made two brief allusions to the anticancer effects of cannabis (Doucette). Once the full documentary is published, this will be updated with more details. The filmmaker, Lindsey Ward, "shoots hoops with an ex-professional basketball player, diagnosed with terminal cancer and given three months to live over five years ago who's convinced the only reason he's still alive is because of cannabis. There's the mother of a child with a brain tumor who was told not to expect her baby to live past one – now, the child has been tumor free for four years."

A profile of Lazy Bee Gardens, a Tier-III legal outdoor cannabis farm in Winthrop, Washington, included a testimonial from the organization's founder Matthew Bernhard (Kersten). He initially started growing cannabis and processing it into oil to help his father with an unspecified Stage IV cancer. "He didn't do chemo or any of the pills they wanted to keep him on. Now, here we are, seven years later—he goes in for a checkup once a year, and they tell him, 'You're fine.' That's what ignited my passion," said Matthew.

Bob Blake is the owner of 5th LMNT, a dispensary in Oregon. In August 2015 he testified before the Georgia Commission on Medical Cannabis ("Georgia"). Bob came highly recommended from an esteemed physician in the state, which is why he had the privilege of speaking to this group of Georgia legislators. He spent most of his 30 years in the healthcare industry providing anesthesia services. Bob was accompanied by the chemist he works with, Ken White, as well as a patient, Ashley Lovely, who survived cancer.

Bob learned about cannabis oil for the treatment of cancer in February 2013 from a nurse friend. He described his work with six late-stage cancer patients, most of whom had been given weeks or months to live. Those six achieved remission using high-doses of THC-rich cannabis oil, although significant amounts of CBD were present as well. "At first I thought it was a miracle, I thought it was crazy. But not six for six," said Bob. The cancers he treated were lung cancer, pancreatic cancer, neuroendocrine cancer, breast cancer, and brain cancer (two patients shared one of those forms of cancer). He noted that his patients took in very high doses and slept around 12 hours per day while they were healing.

After Bob and Ken spoke, Ashley described her experience with medical cannabis. She was diagnosed with Stage IIIB Hodgkin’s lymphoma at the age of 13 in 2004. She had an inoperable tumor in her neck and chest. She was initially prescribed Marinol, the synthetic form of THC, which worked very well for her. She achieved remission with the conventional treatment, but the cancer returned in April 2015. Having been through chemotherapy before, the possibility of doing it again terrified her. She researched medical cannabis oil and eventually began using a medical cannabis oil with THC and CBD. She started on low doses of the oil and worked up to 1.5 grams per day. After 10 weeks, she returned to her oncologist, and the lesion on her lymph was gone. She is now on a low maintenance dose. She said medical cannabis oil worked better for her than any other medication she ever took in her life. "Medical cannabis does work to cure cancer or at least put that cancer into remission."

An October 2016 article from a London-based publisher deeply explored the use of cannabis oil by cancer patients in the United Kingdom (Quirk). It mentioned a woman diagnosed with peritoneal cancer who was told by doctors to "sort her affairs out", appearing to imply a terminal diagnosis. She used cannabis oil along with chemotherapy, reducing the cancer to a point where surgery was possible. She refused the second half of chemotherapy treatment, apparently continuing on cannabis oil, and at the time of the article's publishing had been cancer free for one year.

An article from January 13, 2017 written by a California physician named Bonnie Goldstein (MD) reported on a bone cancer patient who achieved remission with a combination of cannabis oil and chemotherapy (Goldstein). She stated,

"I am currently taking care of a teenager who was diagnosed two years ago with osteosarcoma with lung metastasis. He was treated quite aggressively with chemotherapy and multiple surgeries. When his parents brought him to see me, he had lost a large amount of weight, was in terrible pain and was on palliative chemotherapy of gemcitabine. The oncologist reported to me that there was no further treatment available. The patient was started on a regimen of high dose THC and CBD oil sublingually, starting low doses and ultimately increasing to 1,000 mg cannabinoids/day divided in three doses with a 1:1 CBD:THC ratio with instructions to continue chemo. He immediately gained weight and stopped using opiates for pain. After three months of cannabis treatment, repeat bone and PET scans revealed no evidence of disease. The patient continued on cannabis treatment but due to development of anxiety, the CBD:THC ratio was adjusted to 3:1. After another three months of oil treatment, repeat radiological evaluation revealed no evidence of disease. It is now over 18 months since starting cannabis treatment and one year off chemotherapy. The cancer has not returned despite its aggressive metastatic nature. The patient is still on cannabis

and is living his life normally. What is notable in this case is that research in mice with grafted pancreatic cancer cells showed that the gemcitabine's ability to kill cancer cells was enhanced by the addition of cannabinoids. I believe that the synergy between the chemo and cannabinoids is the reason why this teenager is in remission and that continued use of cannabis has kept the cancer from returning." [Note: This was originally published in a booklet called Mary's Cannabis Primer, by the company Mary's Medicinals. The author also contributed an article in that booklet along with Dr. Goldstein.]

The potential for cannabis to treat tumors derived from rare disorders is promising. Sadie Higuera was born with Schinzel-Giedion syndrome, a severe genetic disorder that prevents most patients from making it to their second birthday (Brainard). Seizures and tumors are hallmarks of the condition. No medications were effective, and according to her parents just made things worse. After doctors suggested a suicide pill as a final option, Sadie's father started researching other options and turned to a combination of hemp CBD oil and a source of THC ("Photo Release"). At some point, the treatment produced radical results – as of a May 2017 article, Sadie had reached her fourth birthday tumor-free and with dramatically reduced seizures. She is more alert, responds to music, and participates in class.

A local story from New Haven, Connecticut news station included a brief statement from Zachary Nere, the President of Zach Attacks Cancer, an organization dedicated to helping patients use cannabis and nutrition to fight cancer (McDonnell). "I had originally 19 tumors, and that got down to where I am only down to four. Each day is my life is working with patients willing to work on this lifestyle change and treat cannabis as the medicine that it is," said Zach.

Zach's website at ZackAttacksCancer.org revealed more about his story. In January 2014 he was diagnosed with a mid-stage cancer which had spread to his lymph nodes (Nere). Using only cannabis and other natural modalities, he has achieved significant reduction in his cancer.

An August 2017 story in a local California ABC affiliate briefly mentioned the reported anticancer effects of two women (Rivera). While little detail was provided about the two women or the oils they used, their experiences are still important.

"Margie Bruno of Lodi says she started drinking cannabis oil to rid herself of Stage 3 Cancer. 'Went to the dispensary out in Stockton and in four months I was cured,' said Bruno. That was three years ago and now her sister, Doris, who's suffering from terminal cancer says the oil has shrunk her tumors, giving her hope. 'When she put me on cannabis. It changed. The whole thing,' said [Doris]."

Margie Bruno

Doris Cruz

An August 2017 story in *Teen Vogue* recruited Emma Chasen, director of education at a dispensary, Farma, in Portland, Oregon, to dispel cannabis myths (Corcione). Emma studied

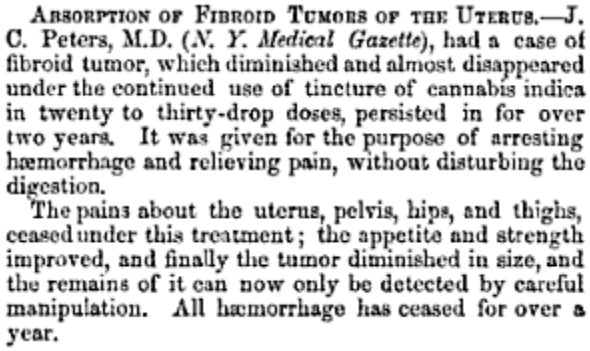
medicinal plants at Brown University prior to moving to Oregon. She shared information debunking the notion that cannabis causes cancer while alluding to the success she's seen. "THC codes for cell death and this is why we see tumor reduction when people who have cancer do use cannabis therapy. CBD [or cannabidiol], the second-most prominent compound found in cannabis, also helps with anti-proliferative properties."

("Emma_Chasen")

Jack Krosinski, the director of a Canadian company called Krosinski Enterprises Ltd., is currently looking to start a medical cannabis facility after his family's personal experiences with cannabis for cancer (Wilson, "Krosinski"). In summer 2014, Jack's father was diagnosed with esophageal cancer. He combined cannabis oil therapy with chemotherapy, radiation, and apparently surgery. The cannabis virtually eliminated the side effects of the conventional treatments.

Six months later, the cancer apparently metastasized to the liver (while that could have been a new primary cancer, given the rarity of primary liver cancer it was probably a metastasis). Jack's father initially declined to use cannabis this type around; by late 2016, his health had gotten worse and nothing was working. Cannabis oil was added back to his treatment, and by April 2017 his cancer had shrunk 50% and many cancerous spots had disappeared. "This solidified our belief that this substance is indeed medicine for many ailments, and should be made widely available as an extra choice in the treatments of various diseases," said [Jack] Krosinski.

The March 1868-February 1869 issue of *The Medical Record* documented several cases of physicians using cannabis extracts in their practices, among hundreds of other general reports from across the United States (Shrady). One such case on Page 371 described the use of cannabis tincture to treat a fibroid tumor.



ABSORPTION OF FIBROID TUMORS OF THE UTERUS.—J. C. Peters, M.D. (*N. Y. Medical Gazette*), had a case of fibroid tumor, which diminished and almost disappeared under the continued use of tincture of cannabis indica in twenty to thirty-drop doses, persisted in for over two years. It was given for the purpose of arresting hæmorrhage and relieving pain, without disturbing the digestion.

The pains about the uterus, pelvis, hips, and thighs, ceased under this treatment; the appetite and strength improved, and finally the tumor diminished in size, and the remains of it can now only be detected by careful manipulation. All hæmorrhage has ceased for over a year.

An even older potential allusion to the antitumor properties of cannabis occurred in a 1640 text called *Theatrum Botanicum, The Theater of Plants*, as shared by Ethan Russo in a 2007 article published in *Chemistry & Biodiversity* (Russo [full text at http://letfreedomgrow.org/cmu/Russo2007.pdf]). After noting that phytocannabinoids have shown cytotoxic properties in many cancer cell lines, Russo shares the following quote from the book: "The same decoction of the rootes, easeth the paines of the goute, the hard tumours, or knots of the joynts, the paines and shrinking of the sinewes, and other the like paines of the hippes: it is good to be used, for any place that hath beene burnt by fire, if the fresh juyce be mixed with a little oyle or butter." It's possible the statement only concerns the pain associated with tumors, but nonetheless the mention is noteworthy and possibly extends beyond pain. Also interestingly, concerns cannabis roots, which do not contain cannabinoids but contain other compounds like terpenoids with anticancer properties.

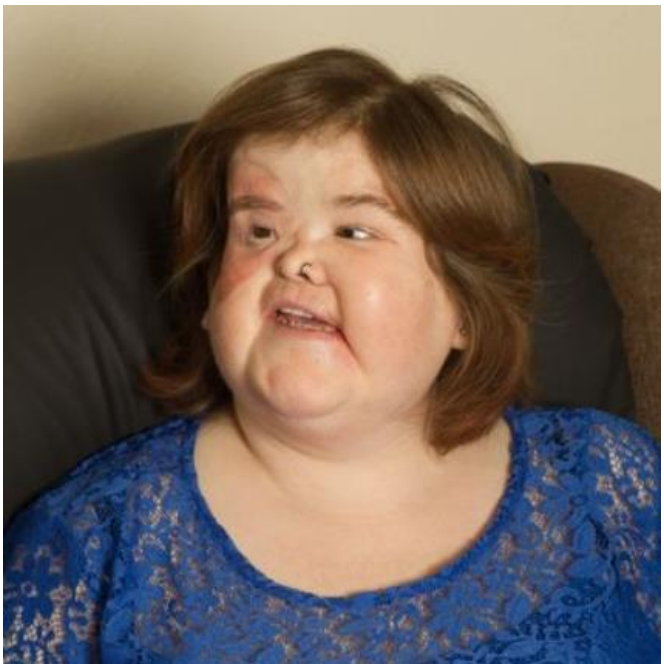
A November 2017 article written by Johnny Green described his stepfather's experience with bone cancer (Green). He beat prostate cancer once but upon his second diagnosis was only given a year to live. Johnny convinced him to add cannabis oil to his conventional treatment this time around, and the doctor supported this decision given the terminal prognosis. The combination treatment resulted in almost complete elimination of the cancer, to a level where Johnny's stepfather is considered cancer free. The doctor was surprised by this and specifically referred to the remission as a "miracle". Johnny was also adamant about mentioning the importance of combining cannabis with the conventional therapy and not advising people to use cannabis alone.

On February 3, 2018, an article was posted on *Daily Mercury* about Shona Leigh's battle with Stage II cervical cancer (Bradley). She was diagnosed in October 2013 and found a caregiver online who supplied cannabis oil. Shona monitored the progress of her cancer every six weeks, and in September 2014 received clean test results. Four months after stopping cannabis oil, large lumps appeared in her left breast, so she found another supplier who gave her a cannabis-coconut oil blend. Within two weeks of using that, the lumps were gone.

Gemma Elsworth, a Wales resident, has dealt with cancer her entire life (Smith). At just 10 months old she was diagnosed with rhabdomyosarcoma, which resulted in needing surgical removal of her right eye and facial reconstruction after the disease spread. Gemma has dealt with the cancer and the aftereffects her entire life. Around early 2015, evidence of brain tumors

emerged when she developed epilepsy. It was unclear whether this was metastasized rhabdomyosarcoma or an alternative primary tumor [this lack of certainty is why this case is in the **Assorted Cancers** section]. In any case, scans showed three large tumors in her brain and several smaller tumors on her brainstem. She was given weeks or possibly a couple months to live. Her mother procured CBD oil and began putting three to four drops under her tongue alongside meals, which resulted in symptomatic improvement within days.

Due to the expense of the CBD oil, Gemma could not continue it regularly. She resorted to street cannabis, which her mother ground up and put in her meals. After the combination of CBD oil, raw cannabis, and chemotherapy, a scan revealed the three brain tumors have shrunk and the brainstem tumors are gone. Doctors have revised their prognosis to 1-2 years.



In late 2017, the United States Food and Drug Administration began collecting comments from the public on their experiences with CBD (Hunter). The author examined every comment which mentioned "cancer" and found many contributors claiming to have fought cancer directly with CBD oil or cannabis oil in general. These are shown below.

Comment from Robert Clayton

The is a Comment on the **Food and Drug Administration** (FDA) Notice: **International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; Ocfentanil, Carfentanil, Pregabalin, Tramadol, Cannabidiol, Ketamine, and Eleven Other Substances; Request for Comments**

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Comment

I am 67 years old. I used CBD oil on two painful squamous cell cancers on my arms. In each case I used one drop in the morning and one drop at night for three days, I also used two drops sublingual daily for each of those days. In both cases the cells went away in three days. They shrank away and they have not returned. There is no pain and no evidence of scarring or anything at the sites. The bottle cost $65. There are hundreds of drops in a bottle which makes the cost of the treatment about $4.00 apiece.

I could not otherwise afford cancer care. I am grateful I can stop these problems when they are small before they develop into major problems.

I have also used CBD to heal lesions in my mouth that would not heal in a month.

The doctor said my thyroid is pre-cancerous and wanted to remove it. I refused. I take CBD. Swelling in my throat has gone away. I no longer get sleep apnea. Sore throats went away.

My father died of ALS at 62. My cousin died of ALS at 54. I am grateful that CBD helps ALS.

Comment from Patricia Anderson

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Comment

I use CBD oil in conjunction with my chemo for stage 4 colorectal cancer. The CBD has been very important to my blood tests that show the presence of tumor markers. Those tumor markers have consistently gone down after I began taking the CBD oils. I believe the impact of theses results cannot be overstated. Since no THC is in these extracts it's ridiculous to include CBD oils in the same category as opiods. These oils are saving my life.

Comment from Cheryl Alley

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Comment

I have been a cancer patient since January 2016. Later that year I was diagnosed with metastatic cancer in my hip. I was put on multiple cancer drugs in March of 2017 that made me very ill and therefore I only took one dose. I had been taking CBD since April 2016 and when I was rechecked for the mets in April of 2017 they were gone. I use CBD daily as an anti-inflammatory. They also control the hot flashes and night sweats from the one cancer med I can take for hormone suppression. I truly believe that without CBD my mets would still be here and the reaction from the drug I can take would be unbearable. Please legalize this drug for all.

Comment from E Meredith Long

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Comment

I use CBD oil as a topical for skin cancers and as an internal for treating enlarged prostate and prostate pain and as a potential prophylactic for prostate cancers and cancers of the GI tract. It is a phenomenal substance for overall health in my opinion, and I cannot imagine being without it. I have been using it for 2+ years now. My wife also takes it daily as a potential prophylactic for breast and skin cancer. I once had to wait 3 weeks for an exam of a suspicious skin lesion which turned out to be melanoma (this happened just as I started to take CBD oil.) On the lesion I placed CBD oil twice dialy while waiting for my derrnatologist to return from vacation. In the interim the melanoma began to break and fade. Though I took no chance with using just CBD alone and had the melanoma excised I was astonished by the effect the CBD had on the lesion, and my doctor was very interested in this development.
I have periodically been without my CBD for one reason or another and have noticed no withdrawal effect whatsoever

Comment from Heather Gookin

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Comment

I am a 42 year old teacher from Mesa, AZ. Several years ago, my uncle was diagnosed with pancreatic cancer. He was not eligible for the Whipple Procedure due to the advanced stage of his cancer. It had already spread to several major organs/arteries/glands. He was given 4-6 weeks to live and began chemo in attempt to give him a little more time. After 3 months, we approached the holidays knowing he was living on borrowed time, and his quality of life was, in all honesty, awful. He had lost 50lbs, had chronic diarrhea, and was so lethargic (from the high doses of pain medication) that he could barely function. We all recognized something needed to change and felt that there was nothing left to lose - so my grandfather, the most Christian, conservative, honorable man I know, sought out cannabis oil in an attempt to help his youngest son. My uncle's experience was nothing short of a miracle. He gained back the 50lbs he lost, he dropped the use of pain medication to what my pharmacist husband described as "broken pinky dosing". He regained an appetite, his chronic GI issues stopped. He felt so well that he shared the driving responsibilities with my grandfather as they traveled from Florida to New Hampshire to open up the family bussiness. My uncle then helped open twelve cottages, swept 4 acres of leaves, painted docs, drove boats, and enjoyed life. We are certain he was able to continue chemo because of the cannabis oil - there were NO other changes that took place except for the addition of the oil. In the end, my uncle passed away over 14 months after his initial diagnosis. His suffering was limited to the two weeks prior to his passing. I recognize this is anecdotal evidence but I urge you to explore the possibilities that cannabis oil can provide.

Comment from Geoffry Thomas

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Comment

I was terminal with stage 4 squamous cell cancer last year. I had 3 months to live . I started taking CBS oil. I had a tumor the size of a softball. In 3 months it shrank to an egg yolk size using Charlotte's web. The bad side effects were it cured my rheumatoid arthritis , reversed the onset of diabetes , and alleviated my back pain due to a herniated disc and a ruptured disc. I now have more energy and movement. I've been helping others with its benefits. Our existence and health has declined ever since 1937 removal, classifying, and making illegal hemp and marijuana. Cancer has run rampant. Allergies, autoimmune diseases, obesity, blood pressure, and 100's more malledies and diseases.

Comment from Brandy Miceli

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Comment

I am fully in support of rescheduling cannabidiol (CBD). This medicine heals diseases and disorders like epilepsy, cancer and anxiety. A friend of mine had stage four breast cancer with tumors all over her breasts. Without chemotherapy or radiation, her tumors diminished using a high-dosage CBD regimen.

CBD is legal in my state of California. Personally, I have anxiety. Since recently beginning a CBD regimen, I've noticed much more clarity in my thoughts and conversations. I have a better ability to remain calms in times of high stress, and that's something that I had a very hard time doing without CBD.

I hope to see CBD off Schedule I, so that we can fully unlock this medicine's potential. If it has already cured so many ailments, we owe it to the substance to study what other things it can help with.

Comment from Polly Goltche

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Comment

When my beloved pet, an American Staffy, at the age of only 4, was diagnosed with advanced lymphoma, her life was near an end. I had heard about the use of CBD oil, and we immediately traveled to California, and began treating her. At that time, she had not been eating and had gone in a matter of weeks from 85 to 40 pounds. With the addition of the CBD oil, her appetite came back, and on a repeated xray, her tumor had shrunk to half its former size. While we lost her months later, I am certain that the CBD oil was the reason for her rallying, for the shrinkage of the tumor, for the stimulation of her appetite, and for the fact that we had her with us with a dramatically increased quality of life for an additional 4 months. We had to try to dose her properly- amount and frequency- as there was no regulated prescriptive medicinal information available to us. It was a crapshoot, and we were working in the dark. I AM CERTAIN THAT CBD HAS IMMENSE VALUE IN THE FIGHT AGAINST CANCER, AND IT MUST BE EVALUATED BY THE FDA, ACCEPTED, AND REGULATED FOR PHARMACEUTICAL USE. Our story is not a unique one. I have heard this time and again, and there is no reason that CBD should not be available to people as a tool in the fight against cancer.

Comment from CHRISTANIA MARIENTHAL

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Comment

My husband was diagnosed with prostate cancer in May 2015. His results were high in his biopsy:
5 out of 12 cells were positive for cancer. The cell results were: 33, 58, 53, 65, 86,

He consulted with three physicians, including Sloan Kettering who said we could watch his cancer as it is slow growing and as long as he had a biopsy every year he should be o.k.

I read every article, news letter, cancer blog available, and found that diet and the use of homeopathic chemical free cannabinoid had helped several people, had even shrunk tumors. We were skeptical at first but determined to try everything we could to try and become cancer free and avoid the enormity of prostate removal or radiation. We visited our local health food store and they were very knowledgible about using CBD oil along with turkey tail mushroom and Cucamin to keep up the immune system. We also began juicing organic carrots and he has consumed about 6-8 oz daily since then.

He began taking CBD Oil Gold plus in June 2015. His second PSA was listed as 9.5. His primary physician and prostate surgeon advised him that he was going to have to start treatment. The surgeon performed the second biopsy on July 21, 2017: The cell results out of 12 biopsied: 3, 8, 30 and 35.

The surgeon sent the cells out for further analysis as he could not believe they had come down so dramatically and advised that there was no need for treatment.

Comment from Michael Barrow

The is a Comment on the **Food and Drug Administration** (FDA) Notice: **International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; Ocfentanil, Carfentanil, Pregabalin, Tramadol, Cannabidiol, Ketamine, and Eleven Other Substances; Request for Comments**

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Comment

I was diagnosed with mantle cell lymphoma in February 2012. This is a type of non-Hodgkins Lymphoma that is particularly resistant to treatment using conventional chemotherapy. My prognosis, even with conventional treatment, is not good (4-1/2 years average life expectancy). I have avoided chemotherapy as a treatment option and have participated successfully in a trial involving high-CBD cannabis hash oil, and I continue to self-administer medical cannabis treatments. The before-after CT scans around my trial showed that the CBD treatment had reduced the size of a majority of my swollen lymph nodes, and I continue to be in the best health of my life. My oncologist has been practicing since the late 1980's and he's only had one other patient in his whole career who lasted as long as 3-1/2 years with mantle cell lymphoma without having to undergo chemotherapy. I have now been going for 5-1/2 years and counting without needing conventional treatment, and my expectation is that cannabis will help me completely heal this cancer without any conventional treatments.

Comment from Michael Davis

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Comment

I am a retired doctor and a patient of medical marijuana for the last 3 1/2 years using a combination of THC and CBD for prostate cancer. My experience is as a case study for myself and not scientific research. The results are that my PSA numbers are significant down for the last 2 years from 6.6 to 3.8. I have been on 4 rounds of whole plant cannabis extract oil with 57% THC and 38% CBD for 90 days per round. every 6 months.

Comment from Denise Roelke

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Comment

I was diagnosed with stage 4 ovarian cancer in 2016. A friend told me I should look into CBD oil, as a doctor had told him its benefits for cancer patients. I started taking it immediately and by the time of my surgery and first chemo treatment, my tumors had shrunk to almost nothing, and surgery went well..better than expected. I believe the oil was a key to my success . It also helped with chemo effects including appetite, sleep, etc. I take it as maintenance now. The CBC oil that works on cancer has to have at least a small amount of THC to activate or work on the cancer. I take oil with 5 percent THC, and I do not feel any buzz at all. This needs to be legal and available to all who need it. It helps a list of diseases.

Comment from Kaiulani Facciani

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Comment

In October, 2012 I was diagnosed with HER2+ metastatic breast cancer. I had lost full use of both legs and one arm due to tumors crumbling my vertebrae and splitting my hip.Tumors also populated my lungs, liver and lymph and I was given 2 weeks to 2 months to live. I employed intensive western and naturopathic medical protocols, and got through that. A year later, 9 tumors/metastases were discovered in my brain. Worse, they were leptomeningeal, making them highly deadly very quickly and I was once again given weeks to live. At that point, the only things western medicine had to offer me to "buy time" was whole brain radiation, which I refused and Tykerb, a chemo that does cross the blood-brain barrier was was too toxic for me to tolerate. With nothing to lose, I quadrupled my daily dosage of CBD-only oil. 3 weeks later, 4 of the 9 tumors were gone without a trace. Doctors were shocked, never having seen it before. See, CBD crosses the blood-brain barrier and kills cancer. I would be happy to provide references to the published research upon request. Because I now had only 5 tumors and they were close together, I was eligible for SRS, or targeted radiation, which I did to remove the remaining 5. I now take a low-dosage blend of THC and CBD every night before bed because I don't like to be "high" and further research has shown me that it is more effective at killing cancer if there is SOME THC. I have been NEAD (no evidence of active disease) throughout my entire body, including my brain since May, 2014.... a "miracle" and medical impossibility. I believe I may have the world record for survival of MBC leptomeningeal carcinomatosis. AND I'm NEAD! I fully credit BOTH western and naturopathic medicine for my miraculous survival and recovery, including CBD. This healing substance MUST be freed from the Schedule I classification restrictions so that is freely accessible to all the people who need it as well as making the necessary research possible to discover it's healing properties for a variety of chronic disease conditions. Any one is free to contact me.

The author met Kaiulani at the 2016 Annie Appleseed conference where he heard her story firsthand.

Direct links to the above comments are respectively listed below:

Robert - https://www.regulations.gov/document?D=FDA-2017-N-4515-0975
Patricia - https://www.regulations.gov/document?D=FDA-2017-N-4515-3831
Cheryl - https://www.regulations.gov/document?D=FDA-2017-N-4515-0749
Meredith - https://www.regulations.gov/document?D=FDA-2017-N-4515-3489
Heather - https://www.regulations.gov/document?D=FDA-2017-N-4515-2965
Geoffry - https://www.regulations.gov/document?D=FDA-2017-N-4515-2378
Brandy - https://www.regulations.gov/document?D=FDA-2017-N-4515-0614
Polly - https://www.regulations.gov/document?D=FDA-2017-N-4515-4684
Christania - https://www.regulations.gov/document?D=FDA-2017-N-4515-5032
Michael B - https://www.regulations.gov/document?D=FDA-2017-N-4515-0461
Michael D - https://www.regulations.gov/document?D=FDA-2017-N-4515-4845
Denise - https://www.regulations.gov/document?D=FDA-2017-N-4515-0587
Kaiulani - https://www.regulations.gov/document?D=FDA-2017-N-4515-0735

I would like to share my own observations with cannabis and cancer. I have worked for Aunt Zelda's since July 15, 2015 (this update was published October 2017). Aunt Zelda's specializes in creating individualized dosage protocols for seriously ill patients, many of whom have cancer. Since joining, I have spoken with hundreds of cancer patients and tracked the progress of many. The results have been incredible. I recently met with a prostate cancer patient whose doctors said his progress was literally the best they had ever seen at their clinic. An older woman with lymphoma not only reduced her tumor size with cannabis oil but improved her bone density, a feat which she said was "against all odds." Another patient with an aggressive lymphoma put it into remission in a matter of weeks with a combination of chemotherapy and cannabis oil. Another patient has managed liver cancer with cannabis oil and has avoided chemotherapy. While I did not personally speak with them, I recently heard that two patients, one with glioblastoma and one with Stage IV breast cancer, achieved complete remission. Some patients with late-stage cancers have unfortunately passed away, which is to be expected given this treatment is not 100% effective, but the successes have clearly outweighed the failures.

Conclusion

The evidence demonstrating the ability of cannabis extracts to fight cancer in humans is truly overwhelming. As shared in this book, there are studies indicating how both phytocannabinoids and endocannabinoids can directly kill or inhibit most major forms of cancer. They induce apoptosis, inhibit angiogenesis, mitigate proliferation, and stop metastasis of cancer cells, among other unique modes of anticancer activity. While most studies utilized cell and animal models, a few indicated anticancer effects in humans, such as one of Dr. Guzmán's studies showing THC reduced VEGF, a pro-angiogenic molecule, in cell cultures and humans. The scientific evidence alone strongly suggests cannabinoids could work in people.

Many now-accepted medical benefits of cannabis were first reported in preclinical studies. These studies have shown the potential of cannabinoids to treat chronic pain, spasticity, nausea, anxiety, Crohn's disease, and even intractable forms of epilepsy. Large-scale observational or double-blind, placebo-controlled trials have proven that cannabinoids can treat these conditions. Therefore, it has been definitively proven that the benefits observed in preclinical studies extend to humans in many cases. Cancer is no exception.

Indeed, there are now many well-documented testimonials of human beings eliminating or controlling cancers with cannabis extracts. These experiences are being reported directly by patients as well as doctors, dispensaries, corporations, and caregivers. Moreover, such experiences have been consistently reported for almost a decade. If cannabis were not fighting cancer, it is highly doubtful that successful experiences would have kept being reported over such a long time period. As shown in the previous section, there is even evidence from the 1860s pointing to antitumor activity of cannabinoids. And as of the 3rd update of this book, there is now a placebo-controlled trial proving THC and CBD work with chemotherapy to significantly extend the lives of glioblastoma patients.

I personally have three close family friends who used cannabis extracts to successfully treat their cancers. One of them, Dennis Hill, is described in this book. I have attended numerous CME-accredited medical cannabis conferences where I met many people, doctors and patients alike, who were reporting direct anticancer results. Several individuals I met were sent home on hospice yet are now cancer free because of cannabis oil.

In the past almost ten years, I have spoken with hundreds of patients and caregivers who have used cannabis and seen success against cancer and other diseases. The cases included in this book are only a fraction of the testimonials that exist. There is absolutely no doubt – *cannabis extracts can fight cancer in humans.*

Despite the amazing potential, there are many limits of cannabis extract medicine. First, there are some people who seem to be resistant; their cancers do not decrease when treated with cannabis. This could be due to genetic variations or environmental factors. For example, while everyone has CB_1 and CB_2 receptors, individuals possess naturally varying levels of these receptors, as well as somewhat different types. It is now being reported that there are "splice

variants" of cannabinoid receptors which may impact their signaling. There are certainly other factors which impact the effectiveness of cannabis.

Furthermore, cannabinoids largely fight cancer via the endocannabinoid system. If the system is damaged by poor nutrition, then cannabinoids will probably not work as well. For example, a proper Omega-6 fatty acid to Omega-3 fatty acid balance is integral to the endocannabinoid system's health, yet many people are deficient in Omega-3. Maintaining the right essential fatty acid balance, avoiding excess sugar and processed foods, and eating lots of vegetables contribute significantly to optimal healing.

It is also clear that maintenance doses of cannabis oil are required for long-term health. Many individuals who have stopped taking cannabis oil after becoming cancer-free see their cancers return, while those who continue to ingest small amounts tend to stay healthy. Thankfully, by using CBD-rich oils and/or very small amounts of THC-rich oil, psychoactivity can be entirely avoided, so people can continue using cannabis with no impairment. In fact, virtually everyone should be taking at least small doses of CBD-rich oil to help prevent cancer and provide cardioprotective/neuroprotective benefits.

Cannabis medicine can stand side-by-side with conventional medicine. Some people do not respond to cannabis oil alone, and see incredible progress by adding conventional therapy. Since it is impossible to know if someone will be resistant to cannabinoids or not, there is absolutely no question that the most prudent approach is to use conventional treatment as well. Furthermore, chemotherapeutic agents are generally much more potent against cancer cells than cannabinoids on a milligram-for-milligram basis. Since cannabinoids are shown to work synergistically with chemotherapy/radiation and greatly diminish side effects, they can tremendously improve standard treatments. Cannabinoids may also allow much lower doses of chemotherapy and radiation.

Even if no conventional anticancer therapy is utilized, a doctor's oversight is critical. Patients should **always** work with their doctor throughout treatment. This is the only way to track progress and prevent potential medical issues.

While there is still much to learn, what has been discovered so far is enough to justify the immediate use of cannabis for cancer treatment. Patients who desire to use this therapy **must** be free to do so, now.

As of the Fourth Edition, a **Common Objections** section is included to overcome the reasonable objections people have that cannabis can actually treat cancer. Some of this includes repeated material from above.

Objection: Preclinical evidence with cells and animals rarely translates to humans.
Response: That is correct. What makes cannabinoids different is the fact our own self-made endogenous cannabinoids have been shown to kill cancer cells through similar mechanisms as plant cannabinoids like THC. For example, our main endocannabinoid, anandamide, has been shown to kill cancer cells by activating CB1 receptors on the surface of those cells, just like THC. Two preclinical studies also had a clinical component in which humans injected with THC

experienced the same anticancer effects as the cells and mice. There is also a placebo-controlled study on glioblastoma which found a significant difference in survival (6 months) between those on THC/CBD and chemotherapy versus those on placebo and chemotherapy. This can only logically be explained by the synergy between THC/CBD and the chemotherapy, as was posited by the principal investigator herself. Furthermore, other preclinical evidence has translated extraordinarily well for humans. There are several preclinical studies showing CBD has an antiepileptic effect, but those studies are tremendously weak, showing that CBD can only stop seizures caused by the injection of certain chemicals. Such seizures are far less complex than those produced by genetic conditions like Dravet syndromes. Yet CBD has been shown in several double-blind studies to stop seizures, sometimes with 100% efficacy where all pharmaceuticals failed, in Dravet syndrome and Lennox-Gastaut syndrome, another epileptic condition. If the preclinical evidence translated so well to humans in that complex case, it makes it more likely the preclinical cancer evidence would too.

Objection: Anecdotal evidence is worthless.
Response: The nature of the anecdotal evidence in this case is extraordinary. Cases have been reported by thousands of people across the world, across many years, from many sources. Doctors, caregivers, corporations, dispensaries, and patients themselves have reported these effects in detail. The chances that every single one of them is lying or grossly misunderstanding the nature of the situation (as in they think cannabis healed them but it was really something else) is absurd. It is tremendously improbable that all of this is coincidence, especially with hard scientific evidence that simply can't be made up. Come on, endocannabinoids and phytocannabinoids killing cancer through similar mechanisms? An advocate could not possibly dream of stronger basic scientific support.

Objection: What about the side effects of high-dose cannabinoid therapy?
Response: This is a legitimate concern. The use of high doses of THC has been linked to some issues, particularly psychological ones. However, from years of anecdotal evidence of people using high doses of THC, there do not seem to be overwhelming adverse effects. Furthermore, most patients do not need to stay on high doses of THC for an extended period of time. Yet further, many can significantly reduce their required THC by using CBD as well. Studies show that high doses up to 700mg of CBD per day are safe, and some studies suggest that using CBD alongside THC can counteract negative effects. Nonetheless, more long-term research is needed. Considering that many far more dangerous pharmaceutical drugs are regularly approved without such long term research, there is no reason to hold back on allowing this historically safe medicine.

Objection: What about studies showing cannabinoids promotes cancer cell growth?
Response: There are some studies showing cannabinoids, mainly THC, can promote the growth of some cancers, such as the Ligresti study. However, these studies are overwhelmingly dwarfed

by those showing anticancer effects. Large epidemiological studies of cannabis users show no increased risks of cancer, besides potentially testicular cancer, and potentially a protective effect, so in the population THC is clearly not causing cancer at a grand scale (Huang). In the studies where THC is shown to be pro-cancer, an exceptionally low dose is used, and at higher doses the pro-cancer effect usually turns anti-cancer. Those using cannabinoids for cancer treatment use far higher doses than recreational users, so if the recreational users are not experiencing increased cancer rates, it is highly doubtful higher doses would feed cancer. And indeed, the vast anecdotal evidence supports it does not.

Objection: How can cannabis be claimed as a general treatment for cancer when there are hundreds of types of cancer?
Response: Preclinical studies have showed that phytocannabinoids have anticancer effects against all the major types of cancer – brain, breast, colon, liver, lung, pancreatic, prostate, skin, and more. Other rare cancers like Kaposi's sarcoma, rhabdomyosarcoma, and cholangiocarcinoma have also been shown to respond. There are surely some subtypes of these cancers which are resistant, and this will be revealed with further research. For example, diffuse intrinsic pontine glioma (DIPG) is a form of brain cancer which appears resistant to cannabinoids. This seems to be due to the tumor's location in the brainstem, which has virtually no cannabinoid receptors. Other tumors with low cannabinoid receptor expression may be harder to treat. Nonetheless, even with DIPG, life extension has been reported in a couple cases. The fact some cancers are resistant to cannabinoid therapy is certainly no excuse to prohibit it altogether, especially since it seems far more cancers are responsive.

Furthermore, although cancers are caused and fueled by a wide variety of factors, at its heart cancer is abnormal cells rapidly dividing and failing to die. The endocannabinoid system may have a role in controlling this fundamental process, which would apply to all cancers. While this is theoretical and far more research is needed, the existing preclinical and human evidence suggests this is not as far-fetched an idea as it seems.

Objection: What about the failures? Are all these successes cherry-picked to obscure a huge number of failures? After all, just the successes get reported on.
Response: It is not necessarily true that only successes get reported on. Given this book is now in its fourth edition, many patients have since been reported to have passed away. More importantly, there are dozens of caregivers who have worked with dozens to hundreds of cancer patients who have seen anticancer effects apply to most of their patients. It is unlikely there would be so many reported successes if the success rate was tremendously low. Also, given the fact that every single human possesses endocannabinoids which are known to kill cancer cells, it is not unreasonable that cannabis extracts would work for many people with many cancers. Nonetheless, pure failures with no level of success are not reported in this book, so the fact these are cherry-picked is certainly the strongest objection. However, the author attests that there

seems to be no large repository of pure failures hiding out there, and he has seen very few throughout the last nearly ten years.

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