

# How Cannabis Kills Cancer

## Cancer-specific Cytotoxicity of Cannabinoids

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First let's look at what keeps cancer cells alive, then we will come back and examine how the cannabinoids CBD (cannabidiol) and THC (tetrahydrocannabinol) unravels cancer's aliveness.

In every cell there is a family of interconvertible sphingolipids that specifically manage the life and death of that cell. This profile of factors is called the "Sphingolipid Rheostat." If ceramide (a signaling metabolite of sphingosine-1-phosphate) is high, then cell death (apoptosis) is imminent. If ceramide is low, the cell will be strong in its vitality.

Very simply, when THC connects to the CB1 or CB2 cannabinoid receptor site on the cancer cell, it causes an increase in ceramide synthesis which drives cell death. A normal healthy cell does not produce ceramide in the presence of THC, thus is not affected by the cannabinoid.

The cancer cell dies, not because of cytotoxic chemicals, but because of a tiny little shift in the mitochondria. Within most cells there is a cell nucleus, numerous mitochondria (hundreds to thousands), and various other organelles in the cytoplasm. The purpose of the mitochondria is to produce energy (ATP) for cell use. As ceramide starts to accumulate, turning up the Sphingolipid Rheostat, it increases the mitochondrial membrane pore permeability to cytochrome c, a critical protein in energy synthesis. Cytochrome c is pushed out of the mitochondria, killing the source of energy for the cell.

Ceramide also causes genotoxic stress in the cancer cell nucleus generating a protein called p53, whose job it is to disrupt calcium metabolism in the mitochondria. If this weren't enough, ceramide disrupts the cellular lysosome, the cell's digestive system that provides nutrients for all cell functions. Ceramide, and other sphingolipids, actively inhibit pro-survival pathways in the cell leaving no possibility at all of cancer cell survival. The key to this process is the accumulation of ceramide in the system. This means taking therapeutic amounts of cannabinoid extract, steadily, over a period of time, keeping metabolic pressure on this cancer cell death pathway.

How did this pathway come to be? Why is it that the body can take a simple plant enzyme and use it for healing in many different physiological systems? This endocannabinoid system exists in all animal life, just waiting for its matched exocannabinoid activator. This is interesting. Our own endocannabinoid system covers all cells and nerves; it is the messenger of information flowing between our immune system and the central nervous system (CNS). It is responsible for neuroprotection, and micro-manages the immune system. This is the primary control system that maintains homeostasis; our well being.

Just out of curiosity, how does the work get done at the cellular level, and where does the body make the endocannabinoids? Here we see that endocannabinoids have their origin in nerve cells right at the synapse. When the body is compromised through illness or injury it calls insistently to the endocannabinoid system and directs the immune system to bring healing. If these homeostatic systems are weakened, it should be no surprise that exocannabinoids perform the same function. It helps the body in the most natural way possible.

To see how this works we visualize the cannabinoid as a three dimensional molecule, where one part of the molecule is configured to fit the nerve or immune cell receptor site just like a key in a lock. There are at least two types of cannabinoid receptor sites, CB1 (CNS) and CB2 (immune). In general CB1 activates the CNS messaging system, and CB2 activates the immune system, but it's much more complex than this. Both THC and anandamide activate both receptor sites. Other cannabinoids activate one or the other receptor sites. Among the strains of Cannabis, *C. sativa* tends toward the CB1 receptor, and *C. indica* tends toward CB2. So sativa is more neuroactive, and indica is more immunoactive. Another factor here is that sativa is dominated by THC cannabinoids, and indica is predominately CBD (cannabidiol).

It is known that THC and CBD are biomimetic to anandamide, that is, the body can use both interchangeably. Thus, when stress, injury, or illness demand more from endogenous anandamide than can be produced by the body, its mimetic exocannabinoids are activated. If the stress is transitory, then the treatment can be transitory. If the demand is sustained, such as in cancer, then treatment needs to provide sustained pressure of the modulating agent on the homeostatic systems.

Typically CBD gravitates to the densely packed CB2 receptors in the spleen, home to the body's immune system. From there, immune cells seek out and destroy cancer cells. Interestingly, it has been shown that THC and CBD cannabinoids have the ability to kill cancer cells directly without going through immune intermediaries. THC and CBD hijack the lipoxygenase pathway to directly inhibit tumor growth. As a side note, it has been discovered that CBD inhibits anandamide reuptake. Here we see that cannabidiol helps the body preserve its own natural endocannabinoid by inhibiting the enzyme that breaks down anandamide.

This brief survey touches lightly on a few essential concepts. Mostly I would like to leave you with an appreciation that nature has designed the perfect medicine that fits exactly with our own immune system of receptors and signaling metabolites to provide rapid and complete immune response for systemic integrity and metabolic homeostasis.

## **The Human Endocannabinoid System Meets the Inflammatory Cytokine Cascade**

The Endocannabinoid System (ECS) started revealing itself to researchers in the 1940s and by the late '60s the basic structure and functionality had been laid out. Today we know the ECS is a comprehensive system of biochemical modulators that maintain homeostasis in all body systems including the central and peripheral nervous systems, all organ systems, somatic tissues, and all metabolic biochemical systems, including the immune system.

This homeostatic matrix is not a recent evolutionary twist just for humans; we find the Endocannabinoid System in every chordate creature for the last 500 million years. It is a fully mature biochemical technology that has maintained health and metabolic balance for most of the history of life itself.

The two major interactive systems within the ECS are (1) the cannabinoid receptors that we find on all cell surfaces and neurological junctions and (2) the endocannabinoids that fit the receptors to trigger various metabolic processes. Looking at a cannabinoid receptor distribution map we see that CB1 receptors, that are most sensitive to anandamide, are found in the brain, spinal nerves, and peripheral nerves. CB2 receptors preferred by 2-arachidonoylglycerol (2-AG) are found largely in the immune system, primarily the spleen. A mix of CB1 and CB2 receptors are found throughout the rest of the body including the skeletal system. And yes, 2-AG or CBD will grow new trabecular bone. It is also useful to note that both anandamide and 2-AG can activate either CB1 or CB2 receptors.

The nature of the endocannabinoids are functionally much like neurotransmitters, but structurally are eicosanoids in the family of signaling sphingolipids. These signaling cannabinoids keep track of metabolic systems all over the body. This information is shared with the nervous system and the immune system so that any imbalance is attended to. If the body is in chronic disease or emotional stress, the immune system can fall behind and lose control of compromised systems. It is here that phytocannabinoids can pitch in to support the stressed body in a return to health. The cannabis plant provides analogues of the body's primary signaling cannabinoids. Tetrahydrocannabinol (THC) is mimetic to anandamide, and cannabidiol (CBD) is mimetic to 2-AG, and has the same affinity to CB1 and CB2 receptors; providing the body with additional support for the immune and endocannabinoid systems.

Phytocannabinoids supercharge the body's own Endocannabinoid System by amping up the response to demand from the immune signaling system in two modes of intervention: one, of course, is in bonding with the cannabinoid receptors; the other is in regulation of innumerable physiological processes, such as cannabinoid's powerful neuroprotective and anti-inflammatory actions, quite apart from the receptor system. It is interesting to note here that the phytocannabinoids and related endocannabinoids are functionally similar, but structurally different. As noted above, anandamide and 2-AG are eicosanoids while THC and CBD are tricyclic terpenes. Let us look more closely at the two primary therapeutic cannabinoids, THC and CBD. The National Institutes of Health tell us that THC is the best known because of its signature psychotropic effect. This government report shows THC to be effective as an anti-cancer treatment, an appetite stimulant, analgesic, antiemetic, anxiolytic, and sedative.<sup>2</sup>

CBD (cannabidiol) is a metabolic sibling of THC, in that they are alike in many ways but are also different in important properties. First we see that CBD has no psychotropic effects and there are few CB2 receptors in the brain and peripheral nerves. There appears to be a broader therapeutic profile associated with CBD, which is listed here:

- anxiolytic
- anticancer
- antipsychotic
- antidiabetic
- antiepileptic
- antispasmodic
- neuroprotective intestinal
- anti-prokinetic
- vasorelaxant
- analgesic
- antispasmodic
- bone-stimulant
- anti-ischemic
- anti-inflammatory
- antiproliferative
- immunosuppressive
- antiemetic
- antibacterial

One of the most important health benefits of cannabinoids is their anti-inflammatory property. In this, they are strong modulators of the inflammatory cytokine cascade. Numerous disease

states arise out of chronic inflammation; such as, depression, dementias including Alzheimer's, cancer, arthritis and other autoimmune disorders, viral infection, HIV, brain injury, etc.

Inflammatory cytokines can be activated by oxidative stress and disease states. Cannabinoids, being immunomodulators interrupt the cytokine inflammatory cascade so that local inflammation does not result in tissue pathology. Thus we are spared morbid or terminal illnesses.<sup>4</sup>

If our own endocannabinoid system can maintain metabolic homeostasis and even cure serious disease, why are we plagued by illness? We know that the body produces only small amounts of anandamide and 2-AG; enough to maintain the body but not enough to overcome chronic stress, illness, injury, or malnutrition. Cannabis is the only plant we know of that produces phytocannabinoids that mimic our own endocannabinoids. One of the great benefits of this mimetic medicine is that cannabinoids are essentially natural to our biology and do no harm to our tissues and systems.

It is well known that most diseases of aging are inflammatory in origin, thus making cannabis the best anti-aging supplement we could take to avoid arthritis, dementia, hypertension, diabetes, osteoporosis, and cancer. This is our key to good health and long life.

Since it is such an important attribute, as well as being independent of the cannabinoid receptor system, let's look a little deeper into the ability of cannabinoids to inhibit the inflammatory cytokine cascade. Inflammation is good for us, a little here, a little there; it brings T-cells and macrophages to infection sites. This is good. However, chronic inflammation can cause serious illness and death. How do phytocannabinoids rescue us from dreaded infirmities? When the call comes in to the immune system to send troops, the first thing to happen is that the immune system signals glial cells to produce cytokines. Once this cat is out of the bag, the process can go one of two ways.

A) Killer cells clean up the infection and all is well.

B) Cytokines can stimulate more cytokine production and cause many more cytokine receptors to awaken. Unchecked, this becomes a cytokine storm showing symptoms of swelling, redness, fatigue, and nausea; even death.

Phytocannabinoids have the ability to suppress this inflammatory cytokine cascade by inhibiting glial cell production of the cytokines interferon or interleukin. Here we see the seeds of chronic inflammation dissolved by the modulation process of cannabinoids bringing homeostasis to systems out of balance. This is a good example of how cannabinoids normalize biological processes all throughout the body and allows us to keep that glow of well-being through a long and happy lifetime.

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