



# ENHANCING YOUR ENDOCANNABINOID SYSTEM

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## I. Introduction

Health is the most important asset you have. Without health, everything else in life becomes meaningless. Some people can live well with minor health problems, while others are confined to their homes or beds because of debilitating disease. Regardless of severity, everyone seeks a life without any medical issues. When in a perfectly healthy state, you are free to live life to the fullest.

Of course, health is more than just the absence of disease. There are many people who are not formally diagnosed with a condition, but still exhibit signs of imperfect health. General anxiety, lethargy, lack of energy, mental fog, and a disconnected mindset plague many otherwise healthy people. Alleviating these impediments is critical to optimal living and society's progress, but modern medicine has little to offer. Even for major diseases, traditional pharmaceutical options can usually only help manage symptoms and delay disease progression. In too many cases, synthetic pharmaceuticals are completely ineffective and impair health by causing terrible side effects. While pharmaceuticals certainly help millions of people, better options are direly needed for so many others. Furthermore, individuals having adequate success using conventional therapies could benefit more from healing methods that lack side effects.

The endocannabinoid system (ECS) may be the ideal pharmacological target for restoring overall health. This chemical messaging system is responsible for maintaining homeostasis, or stable balance, in all vertebrates. When an organism is in homeostasis, there is an absence of disease. Essentially by definition, if an organism is not in perfect homeostasis, there will be some level of disease. How disease manifests is dependent on a variety of genetic and environmental factors, but most conditions involve some dysfunction of the ECS.

Given the above fact, it makes sense that enhancing the ECS, as well as using medicines that work within it, could potentially treat a wide variety of diseases. If homeostasis can be restored, then theoretically diseases should go into remission. While the nature of ECS dysfunction or deficiency varies between diseases, and thus may require different approaches, the predominant goal of restoring normal function is always the same.

At its heart, the ECS is all about communication. When cells communicate efficiently, everything works as it should. The body will be disease-free, and the mind will be clear and focused. Every human should work to optimize their health as a means of preventing disease and living well. By targeting the ECS, there is a clear map to achieving great health.

The ECS can be enhanced through a variety of non-cannabis and cannabis-based techniques. Cannabis is especially powerful because its plant cannabinoids (phytocannabinoids) are structurally similar to the endogenous cannabinoids (endocannabinoids) used by the ECS. Phytocannabinoids mimic the actions of endocannabinoids, such as activating specific cannabinoid receptors. Instead of the body needing to devote limited resources and energy to producing more endocannabinoids, phytocannabinoids can take over the same roles and more efficiently correct imbalances. There are also situations where it is simply impossible for the

body to make enough endocannabinoids to overcome a disease state. While extracts from cannabis are undoubtedly very valuable, it is critical to use other enhancement measures to facilitate the body's optimal use of phytocannabinoids.

The following section discusses the basics of the ECS, its role as a protective network, and the research showing how it is connected to virtually any disease imaginable. It is not completely necessary to understand all these scientific details, and many people may prefer to skip to the ECS enhancement section. However, it is always good to know more about how something works, and seeing the incredible research behind the ECS provides confidence that enhancing it is really worthwhile.

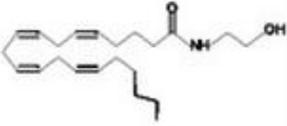
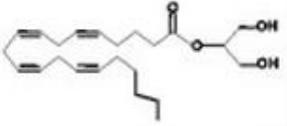
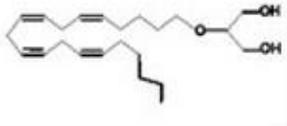
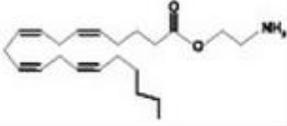
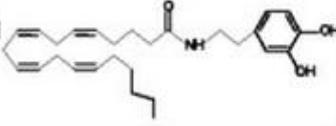
## II. The Endocannabinoid System's Components

The endocannabinoid system is a chemical messaging system in vertebrates that consists of endocannabinoids, cannabinoid receptors, and enzymes that synthesize and degrade endocannabinoids. These endogenous compounds produced within the body have similar chemical structures to the external phytocannabinoids in the cannabis plant. The purpose of the ECS is ultimately to maintain homeostasis in organisms, which consists of regulating stable energy and hormone levels, neurotransmitter concentrations, temperature, and more.

The two primary endocannabinoids include N-arachidonoyl ethanolamine and 2-arachidonoyl glycerol (2-AG) (McPartland, "The Endocannabinoid"). The former is better known as anandamide. They are synthesized from essential fatty acids, including Omega-6 and Omega-3 fatty acids like arachidonic acid and eicosapentaenoic acid (EPA) respectively. Anandamide specifically is derived from N-arachidonoyl phosphatidylethanolamine via multiple pathways (Pacher, Bátkai, and Kunos). Therefore, if one pathway is blocked, others means of production still exist. The compound is degraded by fatty acid amide hydrolase (FAAH). 2-AG is generated from diacylglycerol by a biosynthetic enzyme known as diacylglycerol lipase alpha (Pacher, Bátkai, and Kunos). It is degraded by monoacylglycerol lipase (MAGL).

There are three other known endocannabinoids and one additional compound that may be an endocannabinoid. These include 2-arachidonoyl glycerol ether (2-AGE), O-arachidonoyl ethanolamine (also known as virodhamine), and N-arachidonoyl dopamine (Pacher, Bátkai, and Kunos). Lysophosphatidylinositol may be the sixth endocannabinoid based on its interaction with a novel cannabinoid receptor (Piñeiro and Falasca). Other endocannabinoid-like compounds and analogs exist, like oleoylethanolamide and palmitoylethanolamide, but currently they are not officially classified as endocannabinoids.

### C. Endogenous cannabinoids (eicosanoids)

<b>Anandamide (AEA)</b>		CB <sub>1</sub> >> CB <sub>2</sub> agonist TRPV <sub>1</sub> agonist	Mechoulam et al., 1995 Khanolkar et al., 1996 Schowalter et al., 1996 Felder et al., 1995 Zygmunt et al., 1999
<b>2-Arachidonoyl glycerol (2-AG)</b>		CB <sub>1</sub> = CB <sub>2</sub> agonist	Mechoulam et al., 1995 Ben-Shabat et al., 1998
<b>2-Arachidonoyl glycerol ether</b>		CB <sub>1</sub> >> CB <sub>2</sub> agonist	Hanus et al., 2001
<b>O-Arachidonoyl ethanolamine (virodhamine)</b>		CB <sub>1</sub> >> CB <sub>2</sub> agonist	Porter et al., 2002
<b>N-Arachidonoyl dopamine</b>		CB <sub>1</sub> >> CB <sub>2</sub> agonist TRPV <sub>1</sub> agonist	Bisogno et al., 2000 Huang et al., 2002

(Pacher, Batkai, and

Kunos)

Cannabinoid receptors are the next integral components of the ECS. These receptors are known as G protein-coupled receptors (GPCRs), because attached to them are G (guanine nucleotide binding) proteins. Compounds which activate receptors are known as agonist ligands.

Compounds which block receptors are known as antagonist ligands. When receptors are stimulated by agonists, the G protein detaches from the receptor and attaches to something else. This induces a biological response by initiating a signaling cascade (McPartland, “The Endocannabinoid”). These cascades, or biochemical pathways, involve a series of second messengers which amplify the signal produced by the ligand, and eventually affect molecules producing the cellular response.

GPCRs have different subtypes, such as G<sub>0</sub>, G<sub>i</sub>, and G<sub>s</sub>. These subtypes indicate what the G protein will subsequently couple to after receptor activation, such as ion channels or enzymes (McPartland, “The Endocannabinoid”). The cannabinoid receptors couple primarily to the G<sub>i</sub> and G<sub>0</sub> subtypes, practically meaning they inhibit adenylate cyclase (a key regulatory enzyme throughout nearly all cells) and activate ion channels respectively (Pacher, Batkai, and Kunos). However, there are other subtypes affected by cannabinoid receptors, and different ligands can preferentially activate different G protein subtypes (McPartland, “The Endocannabinoid”).

The primary cannabinoid receptors are CB<sub>1</sub> and CB<sub>2</sub>. CB<sub>1</sub> is the most abundant receptor in the mammalian brain, but is also found throughout the body in much lower concentrations (Pacher, Bátkai, and Kunos). Its activation is responsible for the psychoactive effect of tetrahydrocannabinol (THC), one of the main compounds in cannabis. Distribution of CB<sub>1</sub> is not uniform; the highest concentrations are in the basal ganglia, hippocampus, cerebral cortex, cerebellum, and amygdaloid nucleus. There are virtually no cannabinoid receptors in the brainstem, which controls breathing. This layout explains why THC (cannabis-derived or synthetic) and other CB<sub>1</sub> agonists affect memory, emotion, cognition, motor function, and pain (McPartland, “The Endocannabinoid”). Also, the lack of receptors in the brainstem accounts for why overdosing on cannabis cannot cause death. However, there are numerous opioid receptors in the brainstem, which is why opiate drugs have the potential to stop respiration.

CB<sub>2</sub> receptors are distributed primarily throughout the immune and hematopoietic systems, meaning the receptors are found on white blood cells and tissues in the spleen, lymph nodes, bone marrow, and tonsils (Pacher, Bátkai, and Kunos). In lesser quantities, they are found in the brain, pancreas, and liver. Activation of CB<sub>2</sub> receptors can be immensely therapeutic, but unlike CB<sub>1</sub>, its stimulation does not cause psychoactivity. One of the chief effects of CB<sub>2</sub> activation is a reduction in inflammation (Toguri et al.).

Although CB<sub>1</sub> and CB<sub>2</sub> are the most distinguished receptors in the ECS, endocannabinoids bind with other receptors as well. The transient receptor potential vanilloid type 1 (TRPV<sub>1</sub>), which provides sensations of extreme heat and pain as well as regulates body temperature, interacts with anandamide. In fact, activation of TRPV<sub>1</sub> regulates anandamide synthesis (Tóth, Blumberg, and Boczán). Cannabinoids also activate TRPV<sub>2</sub>. The image on the previous page shows which receptors are activated by specific cannabinoids. As shown, most endocannabinoids activate CB<sub>1</sub> with the greatest efficacy and CB<sub>2</sub> with low efficacy (indicated by the >> symbol). 2-AG stands out as equally activating both CB<sub>1</sub> and CB<sub>2</sub> (indicated by the ~ symbol). Anandamide and N-arachidonoyl dopamine are also distinguished by their affinity for TRPV<sub>1</sub>.

Compounds with a high tendency to bind to a specific receptor are said to have a high affinity for that receptor. Endocannabinoids or phytocannabinoids with low affinities for certain receptors can still activate them, but can usually only do so when significant quantities are present or in other special situations.

Peroxisome proliferator-activated receptors are nuclear receptors found within cells. Anandamide and oleoylethanolamide (OEA), the monounsaturated analog of anandamide, mediate neuroprotection and lipid breakdown by activating PPAR-alpha (O’Sullivan). 2-AG and anandamide activate PPAR-gamma to confer anti-inflammatory effects. This receptor’s activation can also cause vasorelaxation in isolated arteries. More research is needed to identify the effects of endocannabinoids on other subtypes of PPAR.

There are a number of receptors whose endogenous ligands we do not know. These “orphan receptors” are designated with GPR and a number. Several such receptors may be novel cannabinoid receptors, including GPR55, GPR119, and GPR18. Of these, GPR55 has received

the most attention, although little is known about its function. It may be involved in pain signaling and vasculature actions. Anandamide is the chief endocannabinoid agonist of GPR55; interestingly enough, the plant cannabinoid cannabidiol (CBD) is an antagonist (Brown). Evidence suggests that GPR119 works in the pancreas to regulate energy balance. It is activated by OEA, and anandamide has measurable affinity for it as well (Overton, Fyfe, and Reynet). Palmitoylethanolamide (PEA), another compound with endocannabinoid-like effects, is weakly active at GPR119 (Brown).

N-arachidonoyl glycine (NAGly), an analog of anandamide, activates GPR18 (Burstein). The receptor also responds to a synthetic form of CBD known as abnormal cannabidiol (McHugh et al.). One of GPR18's primary functions is directing microglial migration in the central nervous system. Microglia are immune cells in the brain which help protect neurons.

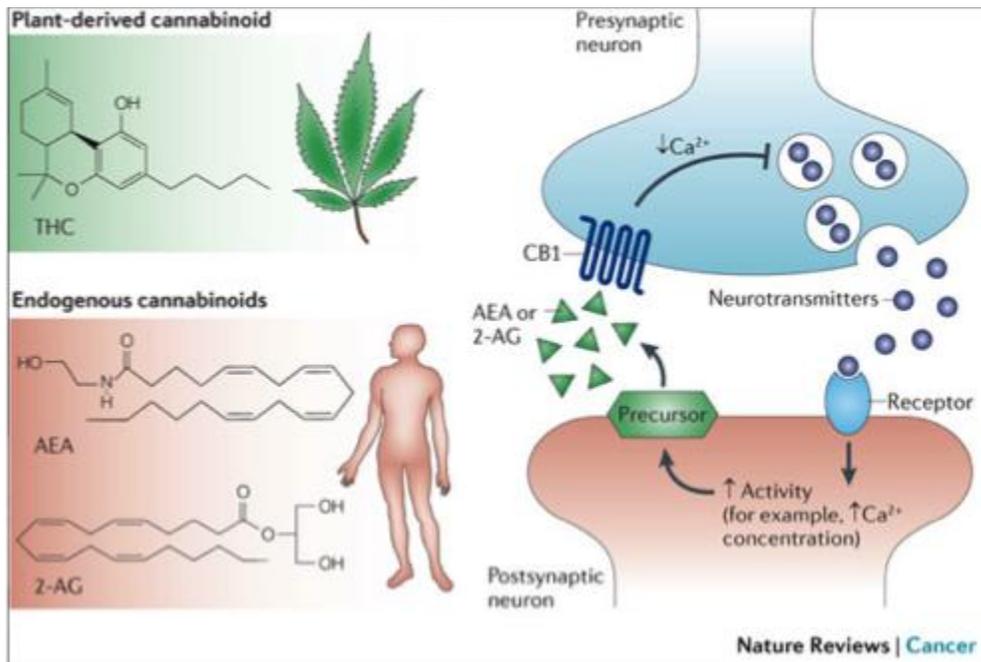
OEA, PEA, and NAGly are currently not considered to be true endocannabinoids, but they are endocannabinoid-related compounds (Caraceni et al.; Burstein). They also work to improve general ECS function. PEA, several of its analogs, and OEA act as “entourage” compounds to reduce uptake and metabolism of anandamide, thereby increasing its concentration (Jonsson et al.). Several plant cannabinoids also act through similar mechanisms to increase anandamide. The status of endocannabinoid-like compounds may change as ECS science further develops.

One of the key methods by which endocannabinoids maintain homeostasis is through retrograde feedback. When neurons communicate, neurotransmitters are sent from the presynaptic neuron to the postsynaptic neuron. Endocannabinoids travel in the reverse direction, from the postsynapse to the presynapse, where they bind with presynaptic CB<sub>1</sub> receptors to reduce neurotransmitter release (Hermanson and Marnett). This reduction is achieved via inhibition of N-type voltage-dependent calcium (Ca<sup>2+</sup>) channels. Another mechanism of presynaptic regulation involves activation of G protein-coupled inwardly rectifying potassium (GIRK) channels (Guo and Ikeda).

Uniquely, endocannabinoids are synthesized “on demand” from phospholipids in the postsynaptic membrane. They are utilized when neurotransmission needs to be slowed down. In essence, if a postsynaptic cell recognizes that a presynaptic cell is firing too rapidly, endocannabinoids will be released upstream to instruct the sending cell to suppress or cease transmission. Such recognition is usually triggered by increased intracellular calcium levels in the postsynaptic cell. By completing the circuit of cellular communication, the ECS facilitates whole-organism unity. Anandamide, 2-AG, and 2-AGE all exhibit similar levels of regulatory efficacy; each displays approximately 50% maximal signal inhibition (Guo and Ikeda). Although these endocannabinoids share efficacy, their potencies are different. 2-AGE is the strongest, followed by 2-AG and anandamide. Therefore, it takes much less 2-AGE to achieve 50% inhibition than anandamide.

Interestingly, whereas 2-AG and 2-AGE rely on the CB<sub>1</sub> receptor to inhibit calcium channels and neurotransmitter release, anandamide can inhibit such channels through a CB<sub>1</sub>-

independent mechanism (Guo and Ikeda). It may be that when one endocannabinoid cannot induce inhibition via a certain mechanism, another utilizes a different pathway as an alternative.



(Velasco, Sánchez and Guzmán)

Research surrounding the ECS is constantly expanding and changing. New receptors and endocannabinoids will likely be discovered as the field advances. Although there is much more to learn about how the ECS modulates health, it has already been linked in some way to virtually every disease.

### III. The Endocannabinoid System and Disease Pathology

There is hardly a disease which the endocannabinoid system does not touch. While its dysfunction or deficiency may not be the main cause of every disease, the ECS plays a major or minor role in nearly everything.

An excellent article titled “The Endocannabinoid System as an Emerging Target of Pharmacotherapy”, published in *Pharmacological Reviews*, is one of the best summaries of the ECS’s relationships with various diseases (Pacher, Bátkai, and Kunos). The following is an analysis of those relationships, which exemplifies the ECS’s importance and the utility of enhancing it. Unless otherwise noted, all information is derived from the aforementioned *Pharmacological Reviews* paper. However, many of the details have been simplified due to the remarkable specificity, complexity, and extensiveness of the article.

#### *Obesity and Diabetes*

One of the most recognized functions of the ECS relates to appetite. Most people know smoking cannabis often increases the desire to consume food. This phenomenon is driven by THC activating CB<sub>1</sub> receptors. Anandamide and 2-AG also increase appetite through the same receptor, and thus play a significant role in hunger-induced food intake. Endocannabinoids are involved in both initiation and consummation of eating, interacting with a variety of orexigenic (appetite stimulant) and anorexigenic (appetite suppressant) hormones and neurotransmitters. These processes help maintain energy homeostasis.

CB<sub>1</sub> receptors do more than just encourage appetite; they also affect peripheral energy metabolism. They are expressed on fat cells, where their activation regulates hormone and enzyme production and activity. The receptors help the body store energy as fat. In general, endocannabinoids “regulate energy homeostasis by interacting with central and peripheral targets, including adipose [fat] tissue, muscle, liver, and endocrine pancreas” (Bermúdez-Silva et al.)

Given these properties, it is no surprise the ECS affects obesity. While there are many cases where endocannabinoid deficiency contributes to disease pathology, excessive activity of the ECS is linked to weight gain. The CB<sub>1</sub> receptor is particularly important. Endocannabinoids and CB<sub>1</sub> receptors are upregulated in the liver and fat tissues in various forms of obesity. Drug antagonists of the CB<sub>1</sub> receptor can significantly reduce caloric intake and weight in obese animals and humans. Mice genetically engineered to lack the CB<sub>1</sub> receptor (CB<sub>1</sub> knockout mice) resist diet-induced weight gain, even when consuming a high-fat diet.

From an evolutionary viewpoint, the function of CB<sub>1</sub> receptors to conserve energy is integral to survival. Animals, including humans, constantly endured famine during evolution. The ability to store energy efficiently, as mediated by the ECS, was necessary. At no point during evolution did organisms have free, almost unlimited access to high-fat and high-sugar

foods (Neuschwander-Tetri). In this new environment the ECS's protective mechanisms backfire, storing too much energy and causing obesity.

Given the ECS's involvement in so many different areas throughout the body, it makes sense that increased endocannabinoid activity could cause problems in some instances. However, directly blocking this activity with drug antagonists has proven problematic, as CB<sub>1</sub> receptors control a lot more than weight. Other techniques must be used to correct this imbalance, including dietary and lifestyle changes.

Curiously, cannabis consumption has been found to negatively correlate with obesity. This phenomenon succinctly demonstrates the complexity of cannabinoid medicine and the ECS. After all, cannabis activates CB<sub>1</sub> receptors, so theoretically it should increase weight gain via appetite stimulation and peripheral energy regulation mechanisms. However, that does not seem to be the general case. The concurrent activation of CB<sub>2</sub> receptors and receptor-independent effects by THC and other cannabinoids may help explain the negative correlation.

A 2011 study using two sets of high-quality survey data found that obesity rates are about a third lower in people smoking cannabis at least three times a week than people who do not use cannabis at all (Strat and Foll). This correlation was maintained even after other factors were accounted for, like cigarette smoking, age, and gender.

A later 2013 study determined that current cannabis users had 16% lower fasting insulin levels and a 17% lower homeostasis model assessment of insulin resistance (HOMA-IR) score (Penner, Buettner, and Mittleman). Furthermore, the cannabis users had higher levels of high-density lipoprotein, the good kind of cholesterol, as well as a smaller waist circumference. People who had used cannabis more recently had better measures.

Significant anecdotal evidence of overweight or obese individuals achieving healthier weights with cannabis extracts has accrued over the past several years. Therefore, while cannabis consumption has not been outright proven to control weight or improve insulin measures, it clearly does not lead to widespread weight gain and may offer therapeutic options.

The above evidence suggests that the ECS is involved in glucose regulation and potentially diabetes. Indeed, there are many studies which implicate the ECS in these functions. CB<sub>1</sub> activation has been found to impair plasma glucose clearance, while CB<sub>2</sub> activation facilitates glucose clearance (Di Marzo). Cannabinoid receptors are found in alpha and beta cells of the pancreas, where they regulate glucagon (increases plasma glucose) and insulin (decreases plasma glucose) release respectively. Unbalanced endocannabinoid concentrations can increase intra-abdominal fat, thus contributing to atherosclerosis and type 2 diabetes (Di Marzo). Anandamide and 2-AG are upregulated in non-obese patients with type 2 diabetes.

A 2008 study using CBD further bolstered the ECS's connection to diabetes (Weiss et al.). Mice in a latent diabetes stage or with initial symptoms of diabetes were administered CBD or no treatment. Only 32% of the CBD-treated group was diagnosed with diabetes, whereas the figure was 100% for the untreated group (Weiss et al.). While it is clear endocannabinoids at least partially modulate obesity and diabetes, more research is much needed.

## *Pain Disorders*

Pain is a symptom of many diseases and a condition in itself. Severe pain is one of the worst things someone can live with, and there are few medical options available for those with long-term, chronic pain. The ECS is deeply involved in pain signaling, and its manipulation with phytocannabinoids has been proven in clinical trials to benefit multiple forms of pain.

Anandamide, THC, and CBD can effectively reduce acute pain stemming from mechanical, chemical, or thermal stimuli. They also work against neuropathic and inflammatory chronic pain conditions. Acetaminophen, the most commonly used painkiller, confers its analgesic effects indirectly through CB<sub>1</sub> activation (Mallet et al.). Endocannabinoids work synergistically with non-steroidal anti-inflammatory drugs to enhance their efficacy.

CB<sub>1</sub> receptors are distributed throughout areas of the central and peripheral nervous systems associated with pain. Anandamide confers its analgesic effects predominantly through CB<sub>1</sub> receptors, and levels of the compound increase in relevant brain areas after pain experiences. CB<sub>2</sub> receptors are also involved, most notably with inflammatory pain. The TRPV<sub>1</sub> receptor may mediate some of the analgesic effects of anandamide, but more research is needed (Starowicz et al.).

Inflammation is a major contributor to several forms of pain, as well as the development of chronic diseases. This complex immune response to injury can induce tissue swelling, which presses against nerves to cause pain. Chemicals released during the inflammatory process increase pain as well.

Cannabinoid receptors, especially CB<sub>2</sub>, are an integral part of immune function. CB<sub>2</sub> receptors are expressed on immune cells; the magnitude of their expression is affected by stimuli that activate the immune system. The response to toxins also increases endocannabinoid levels, which regulate immune function through receptor-dependent and independent mechanisms. Specifically, cannabinoids modulate inflammatory cell signaling proteins (cytokines) like tumor necrosis factor-alpha and interleukin-6, as well as many other signaling molecules. They also affect the migration, proliferation, and apoptosis of inflammatory immune cells. This evidence demonstrates how the ECS is deeply embedded in immune function, and how influencing it could profoundly benefit disorders stemming from excessive inflammation.

It is likely the ECS interacts with the endogenous opioid system, as activation of cannabinoid receptors may release endogenous opioids. Since the ECS communicates with many other bodily systems, and is so intertwined in pain signaling, its interaction with endorphins is logical.

## *Rheumatoid Arthritis*

Rheumatoid arthritis (RA) is a relatively prevalent pain condition that arises from chronic autoimmune inflammation. The inflammation progressively destroys joints, leading to

continuously impaired function and increased pain. By targeting inflammation and suppressing overactive immune activity, the ECS could dramatically alleviate RA.

In many animal studies, various plant and endogenous cannabinoids have been shown to benefit RA through anti-inflammatory, analgesic, and immunosuppressive mechanisms. Analgesia is largely mediated through CB<sub>1</sub> receptors whereas immune-related effects are mediated through CB<sub>2</sub> receptors. CBD reduces inflammatory markers like tumor necrosis factor-alpha and stops progression of collagen-induced arthritis in mice. Anandamide and THC are effective against arthritis-related pain. This evidence suggests RA progression may be connected to an endocannabinoid deficiency, and that using CB<sub>1</sub>/CB<sub>2</sub> agonists could provide significant benefit.

A double-blind, placebo-controlled trial found that a mix of THC and CBD produced significant analgesic effects and reduced disease activity in patients with RA (Blake et al.). More research is needed in many areas surrounding RA, including studies with larger patient populations and preclinical exploration of further ECS involvement. However, the existing evidence and proven effectiveness of cannabinoids confirms an important role of the ECS in RA pathology and treatment.

### *Neurodegenerative Disorders and Neuroprotection of the ECS*

A critically important job of the ECS is to protect the body from all kinds of harm, including damage originating from internal or external sources. With physical injuries, the ECS contributes to healing and neuroprotection. Having a strong ECS could even improve survivability from head trauma, as discussed later in this section.

Studies have implicated the ECS in conferring neuroprotection in a wide variety of cases, including acute injuries and chronic neurodegenerative diseases. From traumatic brain injuries to multiple sclerosis to Alzheimer's, the ECS is involved in nearly everything.

There are a few common mechanisms by which cannabinoids mitigate neurotoxicity. Retrograde feedback is an especially integral tool. In many cases, neurotoxicity stems from overstimulation of neural receptors by the excitatory neurotransmitter glutamate. Too much glutamate causes neurons to die. Endocannabinoids travel upstream from the postsynaptic to the presynaptic neuron, where they bind with CB<sub>1</sub> receptors and instruct the sending cell to stop firing. This mechanism reduces destructive excitatory transmission (excitotoxicity) and protects cells.

The ECS offers additional protection by extensively influencing neuronal and non-neuronal signaling. Endocannabinoids modulate the release of inflammatory mediators from many cell types (astrocytes, microglia, macrophages, lymphocytes, neutrophils, and neurons) via CB<sub>1</sub>, CB<sub>2</sub>, and other receptors. Since excessive inflammation often leads to neurodegeneration, these mechanisms can be quite powerful.

The ECS activates multiple cytoprotective signaling pathways and regulates calcium homeostasis by affecting calcium, potassium, and sodium channels, as well as non-cannabinoid

receptors. In certain situations, the ECS may protect cells by reducing metabolic rate and oxygen demand through a CB<sub>1</sub>-dependent mechanism. Lack of oxygen causes cell death, so if endocannabinoids can reduce the need for oxygen, this would enable cells to survive longer. Another strong contributor to neurotoxicity is oxidative stress, which results from an imbalance of free radicals. Cannabinoids act as antioxidants and disable these radicals. Oxidative stress can also result from excitotoxicity, in addition to causing it. Therefore, cannabinoids can reduce oxidative stress by stopping it at its source (preventing excitotoxicity) *and* disabling radicals directly.

Many of the processes triggered by traumatic brain injury (TBI), such as excitotoxicity, inflammation, and cell death, could effectively be reversed with cannabinoid therapies. Endocannabinoids like 2-AG increase in direct response to injury, as an apparent attempt by the body to protect cells. Anandamide and 2-AG protect neurons in the cerebral cortex from glucose and oxygen deprivation.

The above information suggests that enhancing the ECS or using phytocannabinoids could therapeutically benefit head injuries. Indeed, an October 2014 study solidly demonstrated the reality of cannabinoid neuroprotection. Researchers analyzed 446 patients treated for TBI, and compared results from those testing positive for THC to those testing negative. After adjusting for factors like injury severity, THC-positive patients were found to have an 80% lower probability of dying than THC-negative patients (Nguyen et al.). These are incredible results, but more research is needed to determine the effective doses of THC along with the potential utility of other cannabinoids like CBD.

### *Multiple Sclerosis*

Multiple sclerosis (MS) is an autoimmune disease caused largely by the inflammation-mediated loss of neural myelin sheaths, which amplify communications between neurons. Like most neurodegenerative disorders, MS gets worse with time as more neurons lose their sheaths and die.

CB<sub>1</sub> and CB<sub>2</sub> receptors influence spasticity and tremors, two common symptoms of MS. Mice with experimental autoimmune encephalomyelitis (EAE, a lab-model of MS) given cannabinoid receptor antagonists experienced worsening of these symptoms. Naturally higher levels of anandamide, 2-AG, and PEA are found in areas with nerve damage; like brain injury, this is an apparent survival mechanism to protect cells.

Further evidence of ECS involvement comes from mice bred without CB<sub>1</sub> receptors. CB<sub>1</sub> knockout mice have revealed much about the receptor's function. First, the mice cannot tolerate inflammatory or neurotoxic damage well, and have naturally higher levels of pro-apoptotic compounds in their cells. CB<sub>1</sub> knockout mice with EAE experienced greater cell death and more myelin sheath and axonal protein loss than regular mice. These results suggest the CB<sub>1</sub> receptor has a general neuroprotective function.

In humans, those with an active form of MS have a higher concentration of anandamide than those with a silent form (Eljaschewitsch et al.). The ECS is activated during nervous system inflammation and protects neurons from damage through the complex modulation of enzymes. Double-blind, placebo-controlled trials have determined that THC and CBD therapeutically improve many aspects of MS, including pain, spasticity, bladder problems, and mobility issues (Rog et al.; Wade et al.). Therefore, it has been conclusively proven that ECS manipulation can benefit MS.

### *Parkinson's Disease*

Parkinson's Disease (PD) is a neurodegenerative disorder characterized by impairments in motor function and coordination. It is caused by a loss of dopamine-producing (dopaminergic) neurons, although exactly what leads to their death is unknown. Many of the factors involved in MS, such as excitotoxicity, oxidative stress, and inflammation, are also present in PD, which suggests it too can benefit from ECS therapy.

PD causes problems with movement because most of the dying neurons are found in the basal ganglia, which helps control motor function. CB<sub>1</sub> receptors and endocannabinoids are highly abundant in these regions, and become dysregulated in experimental models and human forms of movement disorders. A feature of these disorders is that CB<sub>1</sub> receptors often increase in the basal ganglia, which may be a mechanism of normalizing motor function in a dopamine-deficient state. This theory is supported by the fact that CB<sub>1</sub> agonists confer numerous benefits. These include decreasing tremors, reducing motor impairment, and preventing dopaminergic cell death. However, overactivity of CB<sub>1</sub> signaling may be associated with some symptoms of PD, like bradykinesia (slow movement). Depending on the individual manifestations of PD, different ECS-based treatments will likely be warranted.

### *Amyotrophic Lateral Sclerosis*

One of the fastest progressing neurodegenerative diseases is amyotrophic lateral sclerosis (ALS). It results from rapid degeneration of motor neurons in the brain and spinal cord, which ultimately paralyzes most patients and leads to death within 3 to 5 years. Cannabinoids can benefit ALS by reducing excitotoxic and oxidative damage, but unlike MS and PD, the neuroprotective effects are apparently mediated by non-CB<sub>1</sub> receptor mechanisms.

The utility of cannabinoids for ALS is efficiently summarized in a 2010 study. The authors state, "Ideally, a multidrug regimen, including glutamate antagonists, antioxidants, a centrally acting anti-inflammatory agent, microglial cell modulators (including tumor necrosis factor alpha [TNF-alpha] inhibitors), an antiapoptotic agent, 1 or more neurotrophic growth factors, and a mitochondrial function-enhancing agent would be required to comprehensively address the known pathophysiology of ALS. Remarkably, cannabis appears to have activity in all of those areas" (Carter et al.).

## *Alzheimer's Disease*

A large percentage of people develop some form of dementia as they get older. The most common form is Alzheimer's Disease (AD). It begins with the accumulation of beta-amyloid plaque and hyperphosphorylated tau protein, which leads to neuroinflammation and cell death. While there are currently no conventional options to safely and effectively treat AD, the ECS offers a promising route for dealing with this traumatic condition.

As with other forms of neurodegeneration, the CB<sub>1</sub> receptor is closely linked to mitigating the underlying biological processes of AD. Anandamide, working through CB<sub>1</sub>, inhibits neurotoxicity via numerous mechanisms. It activates cytoprotective pathways and dose-dependently inhibits release of nitric oxide, a molecule which may be responsible for the neurotoxic effects of beta-amyloid plaque. Interestingly, CB<sub>1</sub> receptors decrease while CB<sub>2</sub> receptors increase in the brains of AD patients. Endocannabinoids may be released from neurons and glial cells in response to beta amyloid deposition, where they activate neuroprotective pathways via CB<sub>1</sub> and modulate inflammation via CB<sub>2</sub>.

The synergistic potential of co-activating CB<sub>1</sub> and CB<sub>2</sub> receptors was explored in a small study with six patients suffering from late-stage dementia. The patients were given small doses of synthetic THC, which activates CB<sub>1</sub> and CB<sub>2</sub>, at doses of 2.5mg daily for two weeks (Walther et al.). Despite the low doses and short timespan, the treatment was very effective at improving symptoms, including aberrant motor behaviors, nighttime behaviors, agitation, and general neuropsychiatric measures.

Another observation in AD is that the anandamide-metabolizing enzyme FAAH becomes overexpressed. Too much FAAH decreases anandamide levels and thus limits its neuroprotective capabilities. CBD, which inhibits the degradation of anandamide, could potentially be even more effective than THC for AD. A 2014 study administering CBD to AD-mice elicited strong results (Cheng et al.). Dr. Tim Karl, one of the study's authors, stated, "It basically brings the performance of the animals back to the level of healthy animals. You could say it cured them, but we will have to go back and look at their brains to be sure" (Corderoy). CBD also directly reduces amyloid precursor protein (APP). As the name suggests, this molecule is the precursor to beta amyloid protein, so inhibiting it could effectively reduce plaque.

## *Epilepsy*

Epilepsy is a term that encompasses a wide range of disorders characterized by seizures. The seizures derive from uncontrolled electrical activity in the brain, but what causes the underlying problem is unknown. Since one of the ECS's prime functions is to inhibit excitatory transmissions, its role in epilepsy is not surprising.

Strong evidence implicates the CB<sub>1</sub> receptor in abolishing and likely preventing seizures. Presynaptic CB<sub>1</sub> receptors are upregulated in epileptic rats, and the levels of anandamide and 2-

AG increase during seizure activity, suggesting a protective role of the ECS. Anandamide dose-dependently decreases electroshock-induced seizures in rats via CB<sub>1</sub>; blocking the receptor increases seizure frequency. Activation of CB<sub>1</sub> receptors may protect against excitotoxicity by inhibition of calcium channels, stimulation of potassium channels, and activation of enzymes.

The use of CBD to treat epilepsy has proven effective, as indicated by observational studies and mass anecdotal evidence (“GW Pharmaceuticals”). In practice, cannabis extracts rich in CBD are effective for controlling many types of epilepsy, although not all patients respond to the therapy. Since CBD enhances anandamide signaling and thus indirectly activates CB<sub>1</sub> receptors, relatively high efficacy is to be expected. Other plant cannabinoids, including CBDV and even THC, have shown promise as anticonvulsant agents.

### *Mental Disorders*

A healthy mental state is maintained by balanced electrical and neurotransmitter activity in the brain. When this activity becomes dysfunctional, a wide range of mental disorders can arise. The ECS offers hope as a therapeutic option. Several mechanisms that benefit neurodegenerative disorders, like retrograde feedback, may also have relevance in healing mental conditions.

### *Schizophrenia*

As the second most common mental disorder and one of the most psychologically debilitating, schizophrenia severely impairs quality of life for millions throughout the world. The condition features positive and negative symptoms, in which abnormal behaviors are present and normal behaviors are absent, respectively. Positive symptoms include delusions and hallucinations, while negative symptoms consist of apathy, inability to experience pleasure, and loss of motivation. The manifestation of these symptoms varies significantly in different individual patients.

The involvement of the ECS in schizophrenia is more layered due to the numerous underlying biological processes that cause symptoms. A deficiency in glutamate or dopamine transmission may underlie negative symptoms, whereas overactive dopamine transmission may drive positive symptoms. Interestingly, an overactive ECS could lead to both excessive dopamine and deficient glutamate signaling. The psychoactive cannabinoid THC has been shown, in some cases, to cause psychotic symptoms in healthy individuals and precipitate psychosis in susceptible individuals. There is also increased CB<sub>1</sub> receptor density in certain parts of the brain in schizophrenic patients, as well as higher levels of anandamide in the blood.

The above evidence suggests blocking the CB<sub>1</sub> receptor or inhibiting anandamide could treat schizophrenia. Yet curiously, the opposite effect has proven beneficial; again, it may be that upregulation of CB<sub>1</sub> and anandamide is an attempted protective mechanism. A 2012 double-blind, randomized clinical trial compared CBD to the traditional antipsychotic amisulpride. It found CBD was generally as effective as amisulpride, and even suggested the cannabinoid was

more effective in alleviating negative symptoms (Leweke et al.). It also had very few side effects. Patients taking CBD experienced increases in serum anandamide levels, which the authors suggested may contribute to antipsychotic effects.

In this case, the seemingly contradictory observations clearly indicate the need for more research. However, it is also clear the ECS is involved in schizophrenia, and modulating it can produce clinically-significant benefits.

### *Anxiety*

The role of cannabinoids in anxiety is the perfect example of the bidirectional effects of the ECS. When there is too much or too little of something, the ECS exerts its characteristic homeostasis-restoring effects to increase or decrease a factor. The ECS and especially plant cannabinoids are also biphasic - low doses induce one response, whereas high doses cause an opposite response. CB<sub>1</sub>/CB<sub>2</sub> agonists have been shown, in small quantities, to confer anxiolytic (antianxiety) effects. The same agonists can cause anxiety in higher doses. The reason for this is currently unknown, but may relate to the distribution of receptors in the brain and their varying sensitivities to cannabinoid receptor agonists.

The high concentration of CB<sub>1</sub> receptors in brain regions associated with anxiety regulation suggests the ECS's involvement in controlling anxiety. For example, the blockade of CB<sub>1</sub> increases anxiety. In this case, it is interesting that both blocking and overstimulating the CB<sub>1</sub> receptor has the same effect, further demonstrating the remarkable complexity of the ECS.

### *Depression*

The initial causes of depression can be varied, but underlying neurological processes factor into virtually all forms of the condition. Neurogenesis, the formation of new brain cells, decreases under depressive and high-stress conditions. It is possible that impaired neurogenesis also contributes to depression. The ECS and phytocannabinoids alike promote neurogenesis, and evidence suggests CB<sub>1</sub> receptors are required for survival of neurons in the hippocampus. The ECS has been implicated in having an anti-depressant function, and augmentation of the system has anti-depressant events (Patel and Hillard).

The role of CB<sub>1</sub> in depression is significantly supported by the effects of traditional antidepressants. Specifically, chronic tricyclic antidepressant treatment increases CB<sub>1</sub> density in the hippocampus and hypothalamus, which may mediate the treatment's therapeutic effects. Increasing anandamide, which enhances activation of CB<sub>1</sub> receptors, produces antidepressant-like effects. The anti-inflammatory properties of the ECS may also be involved in controlling depression. However, like anxiety, long-term overstimulation of CB<sub>1</sub> receptors could potentially induce depression.

## *Cardiovascular Disorders*

The ECS is extensively involved in cardiovascular regulation. It has direct effects on vasculature and myocardium (heart muscle) function. CB<sub>1</sub> receptors mediate many cardiovascular processes, including vasodilation. CB<sub>2</sub> and TRPV<sub>1</sub> receptors may also be involved in some of these functions, but CB<sub>1</sub> is apparently dominant. Depending on the specific condition, the relevance of different receptors varies.

### *Hypertension*

High blood pressure is a problem that is most dangerous because of what it can lead to. Hypertension damages the arteries, heart, brain, kidneys, eyes, and more (“High Blood”). Anandamide and THC lower blood pressure by activating CB<sub>1</sub> receptors. These hypotensive effects are greater in hypertensive individuals than those with normal blood pressure, suggesting cannabinoids exert stronger effects when a metric is too far from homeostasis. In mice and rats with regular blood pressure, both CB<sub>1</sub> agonism and antagonism cause little change. However, in hypertensive rats, CB<sub>1</sub> antagonism further increases blood pressure. This suggests CB<sub>1</sub> receptors only get significantly involved when blood pressure becomes dysregulated.

The ECS may play a key role in limiting high blood pressure levels through CB<sub>1</sub> receptors. They become upregulated in hypertensive rats, which enhances the cardiovascular effects of anandamide. The ECS seems to increase activity when necessary, upregulating itself to reduce blood pressure and prevent hypertension.

### *Atherosclerosis*

Like hypertension, atherosclerosis causes numerous other cardiovascular problems, including increased risk of heart attack or stroke. It is characterized by accumulation of immune cells, cholesterol, and fat in arteries, which leads to plaques that inhibit blood flow. Inflammation and oxidative-nitrosative stress are major components of atherosclerosis. Given the anti-inflammatory and antioxidant functions of cannabinoids, they may be ideal compounds for treating hardened arteries.

CB<sub>2</sub> receptors are expressed on immune cells in human atherosclerotic plaque. THC exerts several anti-inflammatory effects via CB<sub>2</sub> activation, including the inhibition of white blood cell movement. In mice, THC significantly slows progression of atherosclerosis. The CB<sub>1</sub> receptor does not seem to be largely involved, despite the fact that other aspects of cardiovascular regulation are primarily controlled through CB<sub>1</sub>. Therefore, 2-AG is likely the ECS component most responsible for controlling atherosclerosis, as it is the only endocannabinoid with a strong affinity for the CB<sub>2</sub> receptor. Other endocannabinoids and phytocannabinoids may benefit atherosclerosis through additional mechanisms, such as receptor-independent antioxidant effects.

## *Ischemia*

When there is restricted blood flow to the heart, brain, or other parts of the body, cells cannot absorb the nutrients required for survival. Heart attacks and strokes occur in extreme acute cases of ischemia and can be fatal. Atherosclerosis and hypertension are high risk factors for this condition.

The role of the ECS in ischemia is illuminated by the effects of CBD, which enhances anandamide signaling and activates numerous types of receptors. A 2010 study administered CBD to mice before induction of coronary ischemia or before reperfusion (the restoration of blood flow after it has been cut off) (Walsh et al.). Like ischemia, reperfusion can damage cells. CBD caused a dose-dependent reduction in tissue death when given prior to ischemia and reperfusion. It also attenuated the number of irregular heartbeats.

Another 2010 study examining CBD's effects on a diabetes-related heart problem revealed more about the compound's protective benefits (Rajesh et al.). CBD reduces many types of inflammatory and fibrosis biochemical markers as well as oxidative and nitrative stress. At least partially through these mechanisms, it can normalize general myocardial dysfunction. CBD also protects human heart cells from the increased free radical damage induced by high glucose exposure (Rajesh et al.). While more research is needed on the ECS and ischemia, the effectiveness of plant cannabinoids demonstrates it must have some role.

## *Eye Disorders and Glaucoma*

One of the earliest modern uses of medicinal cannabis was for eye disorders. Glaucoma is the most well known of these disorders, and involves abnormally high intraocular pressure (IOP) that eventually leads to blindness. Significant evidence implicates the ECS in the regulation of IOP. CB<sub>1</sub> receptors and endocannabinoids are found in many parts of the eye, including the retina, where their activation lowers IOP. CB<sub>2</sub> receptors are much sparser and activating them has little to no effect, indicating their lack of relevance in managing glaucoma.

The importance of endocannabinoids for IOP regulation was suggested in a 2005 study that compared endocannabinoid content in normal and glaucomatous eyes (J. Chen et al.). The glaucoma patients' eyes had significantly decreased levels of 2-AG and PEA, as well as somewhat lower levels of anandamide. The endocannabinoids were found to have decreased in a specific tissue associated with IOP regulation, the ciliary body. Several mechanisms contribute to the pressure-reducing ability of cannabinoids, including vasodilation and retrograde feedback. By acting through presynaptic CB<sub>1</sub> receptors, cannabinoids inhibit norepinephrine release and production of aqueous humors. Other pathways may also help lower IOP.

The ECS is likely involved in other eye disorders besides glaucoma. Cannabinoids protect against retinal neurotoxicity and have powerful anti-inflammatory effects, making them potential candidates for the treatment of many inflammatory and degenerative eye disorders.

Phytocannabinoids like THC and CBD have been shown to reduce intraocular pressure and preserve the blood-retinal barrier in diabetes, respectively.

### *Inflammatory Bowel Disease*

Inflammatory bowel disease refers to ulcerative colitis and Crohn's disease, which are inflammatory conditions of the intestines. Severe abdominal pain, malnutrition, and other problems often result from inflammation. The ECS is involved in many functions of the gastrointestinal system, including gastric acid secretion and gastrointestinal motility (the movement of food through the gastrointestinal system via muscle contractions). Pain and malabsorption of nutrients can be caused by increased motility, which itself is a symptom of inflammation.

CB<sub>1</sub> receptors are widely distributed across the enteric (gastrointestinal) nervous system, along with the endocannabinoids anandamide and 2-AG. CB<sub>2</sub> receptors are also present, including on macrophage white blood cells (which lack CB<sub>1</sub> receptors). CB<sub>1</sub> and CB<sub>2</sub> receptor activation inhibits gastrointestinal motility, although depending on the situation one or both of the receptors may mediate the effects. A clinical trial with a CB<sub>1</sub> antagonist found increased rates of diarrhea, suggesting CB<sub>1</sub> receptor blockade hastens motility. Furthermore, mice with intestinal inflammation had an increased quantity of intestinal CB<sub>1</sub> receptors, which accounted for the enhanced efficacy of cannabinoids in regulating motility. Mice genetically programmed to lack CB<sub>1</sub> receptors experience greater inflammation than wild-type mice with CB<sub>1</sub> receptors. Numerous studies have shown anandamide protects against colitis. As with other conditions, cannabinoid receptors and endocannabinoids may become upregulated as a protective mechanism.

The effectiveness of phytocannabinoid therapy for Crohn's disease was examined in a 2013 double-blind, placebo-controlled study (Naftali et al.). 5 of 11 subjects in the cannabis group achieved complete remission compared to only 1 in the placebo group. Almost all of the cannabis subjects, 10, experienced significant therapeutic benefits, compared to 4 in the placebo group. The cannabis group also reported better appetite and sleep, with no strong side effects. The scientific and clinical evidence has undeniably demonstrated the utility of ECS manipulation for inflammatory bowel disease, yet more trials are needed in larger populations.

### *Liver Disease*

Liver disease encompasses more than a hundred specific conditions. The most well known sources of damage to the liver include hepatitis C and excessive alcohol consumption. Some autoimmune diseases also attack the liver. Cirrhosis is a common result of prolonged damage. It is characterized by the formation of fibrous scar tissue, which inhibits the ability of the liver to

add and remove substances from blood. Furthermore, scar tissue can cause other complications like localized hypertension.

CB<sub>1</sub> receptors are distributed throughout various specialized cells of the liver. CB<sub>2</sub> receptors appear in cirrhotic but not normal liver tissue, indicating they may help prevent the production of more scar tissue. Indeed, mice without CB<sub>2</sub> receptors have worse liver fibrosis than regular mice, and CB<sub>2</sub> stimulation inhibits the activated liver stellate cells which generate scar tissue.

Endocannabinoids are present in the liver at concentrations similar to those in the brain. Like CB<sub>2</sub> agonists, anandamide confers antifibrogenic effects by inhibiting or killing stellate cells, although the effects are mediated by mechanisms not related to CB<sub>1</sub>/CB<sub>2</sub> or TRPV<sub>1</sub>. In fact, CB<sub>1</sub> receptor activation may increase fibrogenesis, as indicated by the ability of CB<sub>1</sub> antagonists to slow progression of liver fibrosis. Therefore, ECS-related treatments that avoid direct activation of CB<sub>1</sub> are probably best suited for liver disease.

### *Cancer*

There are over 100 different types of cancer, but they all share the properties of uncontrolled abnormal cell proliferation and potential of abnormal cells to spread to other tissues (“What is Cancer”). In a multicellular organism, individual cells are born with the internal machinery to undergo programmed cell death, also known as apoptosis. When they become damaged or aged, cells will kill themselves for the benefit of the organism. Cancerous cells lose the ability to self-induce apoptosis, continuing to reproduce when they should otherwise die. Strong evidence suggests the ECS protects against cancer, and the progression of malignant cancers may be a failure of the ECS to adequately execute its protective function.

The role of the ECS in cancer is apparent by the anti-cancer effects of endocannabinoids. Anandamide induces apoptosis in neuroblastoma and lymphoma cells via the TRPV<sub>1</sub> receptor (Maccarrone et al.). Palmitoylethanolamide (PEA) and oleoylethanolamide (OEA) also work with anandamide to inhibit neuroblastoma cell proliferation through CB<sub>1</sub>/CB<sub>2</sub>- and TRPV<sub>1</sub>-independent mechanisms (Hamtiaux et al.). An analogue of anandamide was found to inhibit adhesion and migration of breast cancer cells via a CB<sub>1</sub> receptor-dependent mechanism in a 2006 study, which also stated the ECS regulates cancer cell proliferation in human breast cancer (Grimaldi et al.). Another study found the development of precancerous lesions in mice was associated with an increase in 2-AG, and that increased endocannabinoid levels reduced the development of those lesions (Izzo et al.).

Cannabinoid receptors become upregulated in certain types of breast and prostate cancers, and likely other cancers as well (Caffarel et al.; Carracedo et al.). This upregulation, combined with the pro-apoptotic and anti-proliferative capabilities of endocannabinoids, suggests that the ECS intimately protects against cancer. If normal cells are programmed to develop more cannabinoid receptors when they become cancerous, they would become more susceptible to the anti-cancer effects of endocannabinoids.

The importance of cannabinoid receptors for cancer survival was demonstrated in a 2006 study. Researchers examined the expression levels of CB<sub>1</sub> and CB<sub>2</sub> receptors in liver cancer patients, and determined through statistical analysis that patients with high expression levels had significantly better disease-free survival than patients with low expression levels (Xu et al.). This makes sense, as individuals with more cannabinoid receptors have more opportunities for their endocannabinoids to kill cancer cells.

A multitude of phytocannabinoids and endocannabinoids, including THC, CBD, anandamide, and 2-AG, can induce apoptosis in the following types of cancer cells: Glioma, astrocytoma, neuroblastoma, breast, prostate, colon, thyroid, pancreatic, leukemia, lymphoma, pheochromocytoma, and more. Conversely, some studies have found that cannabinoids can encourage proliferation of cancer cells. However, this pro-proliferative effect usually only occurs when very small concentrations of cannabinoids are used, and only in certain cases. The vast majority of the evidence indicates phytocannabinoids and endocannabinoids have predominantly anti-cancer activity.

Human evidence indicates phytocannabinoids can protect against cancer. A 2009 study found that moderate cannabis consumers with 10 to 20 years of use had significantly reduced rates of head and neck squamous cell carcinomas (Liang et al.). Cannabis smokers also do not have higher rates of lung or upper airway cancer, despite the presence of carcinogens in cannabis smoke (Tashkin). Most importantly, a 2013 study directly linked cannabis extract intake to abolishment of leukemic cancer cells in a human patient (Singh and Bali).

The ECS has a clear role in cancer regulation, and phytocannabinoids have a definite place in future cancer care. More research is desperately needed to find which cancers respond best to different types of cannabis extracts in different patient populations.

#### **IV. Enhancing Your Endocannabinoid System**

As the previous section demonstrates, the endocannabinoid system is involved in practically every major disease. In most cases, a deficiency of endocannabinoid activity contributes to disease, but excess activity can also be pathological. The aim of enhancing your ECS does not necessarily entail upregulating cannabinoid receptors and endocannabinoids throughout your whole body, although it may. Healthy practices that support your ECS will help it regulate itself, including increasing or decreasing receptors and endocannabinoids where necessary. Ultimately, ECS empowerment can help anyone return to true homeostasis.

The practices discussed below are non-cannabis methods of ECS enhancement. The use of phytocannabinoids as a tool for enhancement is examined after these methods. Cannabis extracts are certainly one of the most powerful ways to support your ECS. However, direct ingestion of cannabis, especially long-term consumption of extracts with high levels of psychoactive THC, seems to be one of the few ways that ECS function could be dysregulated through overstimulation. As described earlier, THC and particularly excessive CB<sub>1</sub> activation contribute to pathology in certain cases. It is very difficult and perhaps even naturally impossible to overstimulate your ECS through non-phytocannabinoid techniques. Despite the potential for harm, the actual and comparative risk of THC consumption is extremely low, and long-term ingestion of extracts with a balanced phytocannabinoid profile is probably good for most people. Strengthening the ECS through other means would likely reduce the amount of phytocannabinoid supplementation necessary for many patients.

##### ***Nutrition***

Nutrition is arguably the most important factor in the health of the ECS. The foods you eat can be the ECS's greatest source of fuel or its biggest challenge. Avoiding harmful foods substantially aids the ECS by reducing the amount of protective work it must perform. For example, foods that cause inflammation will increasingly deplete endocannabinoids, as they work to reduce inflammation. A regular diet that incorporates anti-inflammatory meals and excludes pro-inflammatory foods has been proven to benefit many of the most fatal conditions.

An article on WebMD featured several experts discussing the advantages of the anti-inflammatory diet and what comprises it (Doheny). Diets with a strong anti-inflammatory focus, like the Mediterranean diet, are associated with reduced cardiovascular disease risk (Martinez-Gonzalez and Bes-Rastrollo). A review of several studies also indicated protective effects against cancer and Alzheimer's (Verberne et al.; Sofi et al.). It is very likely that a contributing source of these protective effects is ECS enhancement.

Any diet can be modified depending on an individual's preferences. All anti-inflammatory plans include lots of fruits, vegetables, and Omega-3 rich foods like walnuts, flaxseed, fish, and eggs. Whole grains, nuts, and seeds are also prominent, as is extra-virgin olive oil. Many meals are well-spiced with anti-inflammatory herbs or blends like ginger and curry. Refined and

processed foods are avoided, including most vegetable oils and white bread. Red meat and whole dairy products are minimized as well. These cuts help reduce saturated fat, trans fat, and blood sugar levels. A HuffingtonPost article listed the top pro-inflammatory foods as:

- Trans fats
- Sugar
- White bread
- Cheeseburgers
- Alcohol
- Omega-6 Fatty Acids
- Milk (especially whole and 2%)
- Monosodium glutamate
- Gluten

(Klein)

The effects of wheat on inflammation and digestion are controversial. People with celiac disease cannot tolerate gluten (the protein in wheat) at all, but there is also a subsection of the population that is moderately gluten intolerant. Anyone trying to actively fight inflammation should at least temporarily remove wheat to see what happens. There are many high quality, nutritious gluten-free grains like brown rice, amaranth, quinoa, buckwheat, and millet. Some forms of wheat are reportedly less inflammatory, such as sprouted varieties like Ezekial bread or ancient breeds like spelt.

While the negative health impact of whole wheat is seriously debated, the harm of refined grains is generally agreed upon. White grains, including gluten-free options such as white rice, are stripped of beneficial nutrients. Furthermore, the body processes them like sugar, so refined grains can cause spikes in blood sugar and inflammation. A 2010 study found that refined grain consumption was associated with higher inflammatory markers, whereas whole grain consumption did not have this relationship (Masters et al.).

An article on Prevention.com listed some of the best anti-inflammatory foods:

- Raisins
- Salmon
- Basil
- Ginger
- Sweet potatoes
- Cherries
- Kale
- Walnuts

- Tea  
(Chia)

A 2004 study determined that diet significantly affects inflammatory markers in the body (Lopez-Garcia et al.). One group of women consumed a traditional Western diet with high intakes of red and processed meat, desserts, fries, and refined grains. The other group on a “prudent” diet primarily consumed fruits, vegetables, whole grains, fish, poultry, and legumes. The Western diet was positively correlated with numerous inflammatory markers while the prudent diet was inversely correlated with them.

Organic foods can contribute to a healthy ECS. A variety of pesticides may inhibit FAAH, the enzyme that degrades anandamide. Although inhibiting FAAH is a positive effect of many compounds, pesticides seemingly exert too strong of an inhibitory influence (Quistad, Sparks, and Casida; Carr, Borazjani, and Ross.). A comprehensive 2014 study determined that organic foods are generally more nutritious than conventionally grown crops, containing up to 69% higher levels of antioxidants as well as lower levels of the toxic metal cadmium (Barański et al.). In general, the evidence and even common intuition support the value of eating organic foods.

Extra-virgin olive oil, mentioned earlier as a component of the anti-inflammatory diet, interacts with the ECS. One study showed olive oil and its phenolic extracts upregulated CB<sub>1</sub> receptors in human colon cancer cells, and this effect may be a novel therapeutic mechanism for treating or preventing colon cancer (Di Francesco et al.).

Evidence strongly suggests that chronic alcohol consumption is not good for the ECS. A 1998 study determined that chronic ethanol exposure downregulated CB<sub>1</sub> receptors in mice (Basavarajappa, Cooper, and Hungund). A later study found ethanol downregulated CB<sub>1</sub> receptors and impaired receptor signaling, but increased anandamide levels (Vinod et al.). Long-term exposure to alcohol is associated with neurological damage, which the ECS must work to slow down. Therefore, avoiding excessive alcohol consumption is the safest way to ensure optimal endocannabinoid signaling.

### *Essential Fatty Acids*

The foundation of the ECS is essential fatty acids (EFAs). Both Omega-6 and Omega-3 EFAs are required for the production of endocannabinoids and cannabinoid receptors. It is necessary to consume both types of EFAs because the body cannot synthesize them.

In addition to requiring adequate amounts of Omega-6 and Omega-3, maintaining the proper balance, or ratio, is critical. EFAs are metabolized through the same pathways, so eating too much Omega-6 or Omega-3 will inhibit proper metabolism of the other fat. While overconsuming Omega-3 can be problematic, the vast majority of people suffer from an excess of Omega-6. This is because Omega-6 is so readily available, primarily in vegetable oils derived

from canola, corn, cottonseed, peanut, safflower, and sunflower seeds. These oils are found in a wide variety of packaged and processed foods. Unfortunately, sources of Omega-3 are relatively lacking in society, which further impairs EFA balance. Most people get some quality Omega-3 through eggs and fish, but it is often not enough to compensate for the high Omega-6 intake.

Omega-3 fatty acids are generally anti-inflammatory, whereas Omega-6 fatty acids are proinflammatory (Covington). The early human diet had a dietary ratio of 1:1 Omega-6 to Omega-3, whereas the modern diet's ratio is 10:1 or higher. Omega-3 consumption has been proven to protect against cardiovascular damage, and large doses reduce high triglyceride levels and improve rheumatoid arthritis symptoms. An anti-inflammatory diet alone alleviates rheumatoid arthritis, but adding Omega-3-rich fish oil significantly enhances those benefits (Adam et al.). Omega-3 supplementation can also, to a lesser extent, help people who eat a proinflammatory Western Diet.

Omega-6 to Omega-3 ratios exert protective effects at ratios as high as 5:1, but between 2:1 and 3:1 is more powerful (Simopoulos). When dealing with a serious disease, aiming for between 1:1 and 2:1 seems ideal. Ratios of 10:1 or higher promote the development of cardiovascular diseases, cancers, autoimmune disorders, and inflammatory diseases.

Given that Omega-3 acids and endocannabinoids share similar benefits, it is very possible that enhanced endocannabinoid production or function is the healing mechanism behind increased EFA consumption. While endocannabinoids are also produced from Omega-6, an imbalance of it promotes inflammation. Most people need to work on getting more Omega-3 into their diets rather than Omega-6, but if large quantities of the former are being taken, the latter's consumption will need to increase as well.

The importance of Omega-3 to the ECS was conveyed in a 2011 study titled "Nutritional Omega-3 Deficiency Abolishes Endocannabinoid-Mediated Neuronal Functions" (Lafourcade et al.). Using mice, the study found that a deficiency in Omega-3 caused presynaptic CB<sub>1</sub> receptors to uncouple from their effector G proteins, essentially disabling them. This dietary-induced impairment of CB<sub>1</sub> function adversely affected emotional behavior. Increased Omega-3 consumption has been linked to upregulation of CB<sub>1</sub> and CB<sub>2</sub> receptors, as well as increased levels of endocannabinoid synthesis enzymes (Hutchins-Wiese et al.). However, it is important to maintain a balanced ratio of Omega-6 and Omega-3, or the latter's supplementation may not be as therapeutically effective. Other negative dietary habits could also impair proper metabolism of fatty acids.

Foods like flax, hemp, and chia seeds, along with walnuts, are excellent vegetarian sources of Omega-3. The form of Omega-3 in these products is alpha-linolenic acid, which must be converted into the longer-chain Omega-3 compounds known as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Due to the relatively low efficiency of this conversion, it is important to directly consume EPA and DHA as well. These acids are almost only found in animal sources like fish, eggs, and meat. Fish oil is an easy way for anyone to adequately supplement their Omega-3 intake, as long as it is properly manufactured and distilled to eliminate heavy metals. There are also vegetarian algae-based products which provide DHA.

Supplementation with algal DHA is likely as effective as fish-based DHA, as it can reduce serum triglycerides and improve cholesterol (Bernstein et al.). However, more research is needed on this particular supplement.

### *Probiotics*

The body contains an enormous quantity of microorganisms that comprise the human microbiome. Under normal conditions, these bacteria assist the body and contribute to general health. There are an estimated 10 times more microbes than human cells in our bodies (Zimmer). The gastrointestinal system hosts many of these positive bacteria, where they directly support the immune system. In fact, 70% of the immune system resides in gut-associated lymphoid tissue (Vighi et al.). Humans can take probiotics, or good bacteria, to improve their digestive and immune health. Studies have shown probiotic ingestion could potentially treat diarrhea-related conditions, inflammatory bowel disease, and autism (Culligan, Hill, and Sleator; Hsiao et al.). Probiotics reduce inflammation, and some strains can even fight cancer, such as the *Acetobacter indonesiensis* and *Acetobacter syzygii* bacteria found in Iranian yogurt (Haghshenas et al.).

The anti-inflammatory and immune-supporting properties of probiotics suggest the bacteria would enhance the ECS. There are also direct studies linking probiotic consumption to improved cannabinoid signaling. Interestingly, depending on the situation, probiotics can either upregulate or downregulate cannabinoid receptors to optimally benefit their host. This characteristic exemplifies the homeostatic-regulatory nature of probiotics, and bolsters their connection to the ECS.

Human intestinal cells incubated with the common probiotic *Lactobacillus acidophilus* have increased CB<sub>2</sub> receptor expression (Rousseaux et al.). Incredibly, probiotic administration confers analgesic effects in the colon by acting through a CB<sub>2</sub>-dependent mechanism.

Probiotic treatment was shown to upregulate CB<sub>1</sub> receptors in a species of fish (Palermo et al.). However, in obese mice with elevated levels of CB<sub>1</sub> receptors in the colon, probiotic administration (which increases intestinal probiotic count by acting as food) decreased CB<sub>1</sub> density and anandamide production (Muccioli et al.). This change was accompanied by a reduction in fat mass. The ECS interacts with intestinal bacteria to control gut permeability and the creation of new fat cells. As demonstrated, probiotics seem to have an innate intelligence that enables them to correct ECS imbalances.

Probiotics can be acquired from many sources, and should be consumed through various methods for optimal gut colonization. Supplements are an excellent way to quickly get a lot of good bacteria in you. Quality supplements should be designed to survive digestion and contain at least 10 billion colony forming units. More effective supplements have higher CFU counts and a greater variety of bacteria strains. In addition to taking a probiotic supplement, you should consume fermented foods and beverages. Yogurt, sauerkraut, tempeh, kimchi, and some forms of coleslaw deliver viable bacteria. Kombucha, kefir milk, and speciality probiotic drinks work as well.

You can also protect your microbiome by avoiding harmful foods. The anti-inflammatory diet described earlier naturally enhances your gut microorganisms. Some aspects of the Western diet, such as a high intake of animal-derived saturated fat, are linked to the expansion of pathological bacteria (Devkota et al.).

An amazing resource that answers the top questions about probiotics can be found here: <http://whole9life.com/2012/04/probiotics-101>.

### *Herbs and Foods with Endocannabinoid System Activity*

There are many herbs and foods that affect the ECS. An excellent, comprehensive article titled “Care and Feeding of the Endocannabinoid System: A Systematic Review of Potential Clinical Interventions that Upregulate the Endocannabinoid System” summarizes these effects (McPartland, Guy, and Di Marzo). This article was also very useful as a guide and source of ideas for other enhancement techniques.

- Copal incense from the *Protium* plant species has a terpene with high affinity for CB<sub>1</sub> and CB<sub>2</sub>
- Thujone, a constituent of wormwood (used in absinthe), has weak binding affinity for CB<sub>1</sub>
- The Vitamin E derivative alpha-tocopheryl phosphate modulates synaptic transmission in rodent hippocampi, possibly through an indirect CB<sub>1</sub>-mediated mechanism
- The flavonoids biochanin A (from red clover), genistein (from soybean), and kaempferol (from true tea, *Camelia sinensis*), inhibit FAAH and thus indirectly increase anandamide. EGCG, the compound most responsible for tea's health benefits, has a low binding affinity for CB<sub>1</sub>
- Curcumin from the popular Indian herb turmeric elevates endocannabinoid levels and brain nerve growth factor in certain brain regions, likely through a CB<sub>1</sub>-dependent mechanism. However, like Vitamin E, curcumin has not been definitively shown to bind with CB<sub>1</sub>, indicating an indirect effect on the receptor
- Cocoa powder may contain small amounts of anandamide
- Semiplenamamide A, an anandamide-like fatty acid from the blue-green algae *Lyngbya semiplena* has a low binding affinity for CB<sub>1</sub> and inhibits anandamide breakdown. Another blue-green algae, *Lyngbya majuscula*, produces a fatty acid called grenadamide with low affinity for CB<sub>1</sub> receptors. Other forms of algae like *Chlorophyta*, *Laminaria angustata*, and *Mycale micraanthoxea* contain many endocannabinoid-like compounds
- The *Echinacea* genus, especially the species *purpurea*, has constituents that activate CB<sub>2</sub> receptors with relatively high affinity. The compounds also inhibit anandamide uptake and thus increase its levels. Interestingly, some constituents are weak CB<sub>1</sub> antagonists

- Common black pepper contains the terpenoid beta-caryophyllene, which has a strong binding affinity for the CB<sub>2</sub> receptor. Beta-caryophyllene has been proven to exert anti-inflammatory and analgesic activity via CB<sub>2</sub>
- The medicinal herb *Ruta graveolens* contains rutamarin, which has some affinity for CB<sub>2</sub>
- An unidentified compound in the superfruit noni has weak affinity for CB<sub>2</sub>
- Fish are useful for enhancing the ECS because of their long-chain Omega-3 fatty acids. Some types of shellfish contain anandamide and/or 2-AG, including the mussel *Mytilus galloprovincialis*, the clam *Tapes dicussatus*, the oyster *Crassostrea sp.*, the sea urchin *Paracentrotus lividus*, and the sea squirt *Ciona intestinalis*

Consuming a variety of these foods can naturally enhance ECS activity. Depending on one's health goals, focusing on foods high in CB<sub>1</sub> or CB<sub>2</sub> agonists may optimize results. For example, combining black pepper and *Echinacea purpurea* could potentially be a very effective cannabis-free method of stimulating CB<sub>2</sub> and reducing inflammation.

### ***Stress and Depression***

The mind is intimately connected to the body. It has been proven that mindset, attitude, and thoughts have potent effects on many physiological functions. Therefore, a critical part of being healthy is keeping stress levels low and thinking positively. The ECS plays a major role in the stress response. It maintains hypothalamic-pituitary-adrenal (HPA) axis homeostasis through multiple mechanisms, including glucocorticoid regulation (Riebe and Wotjak). Endocannabinoid signaling both activates and terminates the HPA axis response to acute and chronic stress (Hill et al.). During stress, endocannabinoids are recruited by stress hormones to modulate various cognitive functions. They are also involved in physiological and behavioral habituation processes related to chronic stress. If long-term stress depletes the ECS through overrecruitment of endocannabinoids, that would explain its propensity to aggravate various diseases.

As described in the previous *Essential Fatty Acids* section, high Omega-6 to Omega-3 ratios increase the risk for inflammatory diseases. They may also enhance the risk of depression. Depressive symptoms exacerbate the inflammation caused by high ratios; as depression increases, inflammatory markers rise as well (Kiecolt-Glaser et al.). Epidemiological and other studies suggest that Omega-3 deficiency may directly cause some types of depression (Kiecolt-Glaser). On average, depressed patients have lower plasma levels of Omega-3 than non-depressed patients, and Omega-3 supplementation can produce therapeutic benefits. The ability of Omega-3 to reduce inflammation, potentially through its fueling of the ECS, may effectively treat depression.

Omega-3 supplementation is one of the most powerful methods for reducing depression and generally enhancing endocannabinoid activity. However, using other techniques to alleviate stress and depression can further lighten the workload of your ECS. Some practices that mitigate

stress, like meditation and exercise, are covered more extensively in later sections. Below are a few science-backed stress-relief techniques that work:

- Aromatherapy is an effective stress management method for students (Seo)
- Certain kinds of music may trigger stress-reducing effects, but the variation between individuals is high (Cervellin and Lippi). It is important for people to find the music that is most relaxing for them
- Laughter reduces stress in postpartum women (Shin, Ryu, and Song). These clinical results support the general notion that laughter is therapeutically beneficial
- A double-blind, placebo-controlled study demonstrated six weeks of black tea consumption reduces the stress hormone cortisol and leads to greater relaxation (Stephoe et al.)
- Touch massage significantly decreases heart rate, cortisol, and insulin levels, indicating a reduced stress response (Lindgren et al.)
- Midday naps after sleep restriction reduce stress levels and alleviate other problems caused by a lack of sleep (Faraut et al.)
- Art therapy may be an effective add-on treatment to tone down the stress component of many conditions (Mimica and Kalinić; Chapman et al.; Avrahami)
- Relaxing activities like walking and reading reduce mental and emotional stress (Jin)

An article on Prevention.com listed some of the top stress-fighting foods:

- Asparagus
- Avocados
- Berries
- Cashews
- Chamomile tea and green tea
- Dark chocolate
- Garlic
- Grass-fed beef
- Oatmeal
- Oranges
- Oysters
- Walnuts

(Glassman)

## *Yoga and Meditation*

The practices of yoga and meditation have been used for thousands of years. Meditation is a central tenet of several Eastern religions, as it is believed to be essential for attaining enlightenment. Throughout history, meditation has been reported to have significant health benefits. It is only now that science is catching up.

Breathing is a major component of meditation, and deep breathing alone can reduce cortisol levels (Cea, Gonzalez-Pinto, and Cabo). Chronically high cortisol levels keep blood sugar levels high by releasing more glucose and inhibiting insulin production (Aronson). Over time, cortisol suppresses the immune system, and probably the ECS as well given its integral connection to immune function.

Meditation-like practices known as mindfulness-based stress reduction and mindfulness-based cognitive therapy, along with Zen meditation itself, have broad-spectrum antidepressant and antianxiety effects (Marchand). They also contribute to general psychological health and improved stress management. Incredibly, mindfulness meditation can positively change gene expression to reduce inflammation, potentially combating chronic inflammatory disorders (Kaliman et al.). Over time, meditation directly modifies physical brain structures. For example, it can reduce the size of the amygdala, which is associated with fear, and increase cortical thickness in brain regions associated with attention and sensory processing (Taren, Creswell, and Gianaros; Lazar et al.). Meditation may even offset age-related cortical thinning. These physical cognitive modifications augment stress resilience and may reduce symptoms of other disorders.

Yoga breathing, known as pranayama, synergistically enhances the effects of meditation (Brown and Gerbarg). Clinical evidence supports therapeutic effectiveness of yoga breathing for depression, anxiety, and post-traumatic stress disorder. The yoga practice itself is a combination of meditation and exercise, employing a variety of stretches that range from relaxing to incredibly challenging. Yogic exercises have been shown to reduce life stress and blood glucose levels (Kim). By combining yoga with traditional meditation, truly immense benefits can be realized.

The scope of meditative and yogic practice is very extensive. Over 200 free guides are located at <http://www.yogaoutlet.com/guides>. One such guide, <http://www.yogaoutlet.com/guides/how-to-practice-mindfulness-meditation>, efficiently describes how to do mindfulness meditation. Below is a summary of this guide:

1. Sit in a comfortable position with your head, neck, and spine in a straight line. There are many suitable positions for meditation.
2. Close your eyes and focus on your breathing. Regulate it at first, inhaling through your nose for five seconds, and then exhaling through your nose for five seconds.
3. Breathe naturally. Continue focusing on your breath. When your mind naturally wanders, gently return to your focus.

4. Do this for between 10 and 30 minutes. It really is that simple, and maintaining concentration gets easier over time.

Given the proven ability of meditation to modify the nervous system, it probably also directly influences the ECS. While no formal research has made this connection, the established therapeutic benefits strongly suggests some interaction between meditation and the ECS.

### *Acupuncture and Massage*

Various types of mind-body medicine have been used since antiquity to treat specific conditions and improve overall health. Although benefits have been reported throughout this period, the mechanisms underlying them remained elusive. The ECS may just be the primary therapeutic system affected by acupuncture and massage techniques.

Acupuncture is the practice of using needles to stimulate healing in the body. A specific form called electro-acupuncture (EA) has been proven to influence the ECS. EA is like regular acupuncture, except electrodes are attached to the needles after insertion to provide sustained stimulation (Dharmananda). Using electrodes simplifies treatment for the practitioner, improves control, and provides the ability to increase strength for serious conditions.

EA reduces thermal and mechanically-related pain through a CB<sub>2</sub> receptor-mediated mechanism (L. Chen et al.). The therapy is associated with an increase in anandamide in the applied area. It also upregulates CB<sub>2</sub> receptors in inflamed skin tissue, specifically in keratinocytes (the primary cell type in the epidermis) and inflammatory immune-related cells (Zhang et al.).

While the analgesic effects of EA have been attributed to CB<sub>2</sub> receptors, there is evidence the therapy also works through CB<sub>1</sub> receptors to confer neuroprotection. A 2011 study showed EA pretreatment activates CB<sub>1</sub> and protects against ischemic damage via an anti-apoptotic mechanism (Wang et al.).

Although there are no current studies directly linking regular, non-electro acupuncture to enhancement of the ECS, it is quite possible a relationship exists. A 2012 case report described a woman with chronic neuropathic pain from multiple sclerosis who used acupuncture and the endocannabinoid-like molecule palmitoylethanolamide (PEA) to improve her condition (Kopsky and Hesselink). Acupuncture alone was partly and temporarily effective in reducing pain, but adding PEA significantly enhanced pain relief and lessened the amount of required acupuncture sessions. Both acupuncture and PEA influenced activated glial cells.

Osteopathic manipulative treatment (OMT) is a hands-on practice used by osteopathic physicians to diagnose, treat, and prevent illness or injury (“Osteopathic”). A double-blind, controlled trial found OMT increased anandamide levels by 168%, decreased oleoylethanolamide levels by 27%, and did not change 2-AG levels (McPartland et al.). The authors suggested that the ECS mediates the therapeutic effects of OMT.

Given the similarities between other forms of massage and OMT, they could also convey benefits mediated through the ECS. Massage therapy reduces stress levels in cancer patients, and these effects can extend to anyone (Keir; Taylor et al.). Swedish massage therapy lowers blood pressure, heart rate, and inflammatory markers in hypertensive women (Supa'at et al.); chair massage alleviates anxiety in individuals withdrawing from drugs (Black et al.); shiatsu massage reduces pain in burn patients (Ardabili et al.). Theoretically, it makes sense that at least part of this effectiveness stems from enhanced endocannabinoid activity.

### *Exercise*

Organisms have been constantly moving since the inception of life. Therefore, it is intuitively reasonable that movement supports overall wellness. Since the ECS is closely connected to general wellness, the influence of exercise on the system is expected. A 2003 study reported that exercise activates the ECS (Sparling et al.). Running or cycling for 50 minutes was associated with increased endocannabinoid levels, which could contribute to exercise-induced analgesia and “runner’s high”. A later 2012 study showed 60 minutes of intense cycling increased anandamide, but not 2-AG, levels (Heyman et al.).

Exercise has been linked to improvements in the brain that lead to better cognition and antidepressant effects. A key protein thought to explain these exercise-induced cognitive improvements is brain-derived neurotrophic factor (BDNF). This compound increases significantly after strenuous exercise (Reynolds). The aforementioned 2012 study posited that anandamide is a middleman in the exercise-BDNF relationship; exercise increase anandamide, which increases BDNF to exert pro-cognitive effects (Heyman et al.).

Several types of physical activities help upregulate endocannabinoid signaling. Both high and low-altitude hiking cause increased anandamide production (Feuerecker et al.). The best exercises for ECS enhancement are medium or high-intensity voluntary activities (McPartland, Guy, and Di Marzo). Ideally, you should exercise at this level for at least 30 minutes 5 days per week. Very high or very low intensity exercises do not significantly impact anandamide levels.

The increase in anandamide could explain many proven benefits of exercise. These benefits include reduced stress, anxiety, and depression, along with improved mood (“Exercise and Stress”). Furthermore, moderate intensity exercises reduce risk for cardiovascular diseases and cancer (Woodward). Not surprisingly, such exercises also burn intra-abdominal fat. Reducing such fat is important and effective for protecting against heart disease, cancer, and diabetes (McTiernan et al.).

The National Cancer Institute states that exercise can:

- Help control weight
- Maintain healthy bones, muscles, and joints
- Reduce the risk of high blood pressure and diabetes
- Promote psychological well-being

- Reduce the risk of death from heart disease
  - Reduce the risk of certain cancers
  - Reduce the risk of premature death
- (“Physical Activity”)

### *Cannabis*

The cannabis plant produces phytocannabinoids which are very similar in structure to the endocannabinoids made by our bodies. Assessing the consistent effects of cannabis on health or the ECS is difficult because of the plant’s complexity. All strains of cannabis contain THC, CBD, and hundreds of other cannabinoids, terpenoids, flavonoids, and other constituents. Many of these compounds interact directly or indirectly with the ECS. For example, THC activates CB<sub>1</sub> and CB<sub>2</sub> receptors, and CBD increases anandamide levels. The utility of cannabis to enhance the ECS may include direct substitution of endocannabinoid agonist functions and other, less direct supportive roles.

Some isolated cannabinoids have been studied for their effects on the ECS. Short-term use of THC is linked to upregulation of CB<sub>1</sub> receptors in certain brain regions like the cerebellum and hippocampus (Romero et al.; Zhuang et al.). There is also a bidirectional potentiation relationship between THC and endocannabinoids, with THC being able to enhance analgesic effects of endocannabinoids and vice versa (Suplita et al.). However, chronic THC consumption is associated with decreased CB<sub>1</sub> density and impaired cannabinoid signaling (Romero et al.; Breivogel et al.; Suplita et al.). The rate and magnitude of CB<sub>1</sub> downregulation varies by brain region and in some places is unchanged. Levels of endocannabinoids like anandamide and 2-AG are relatively unaffected by long-term ingestion of THC, although anandamide increases can occur in the limbic forebrain (Di Marzo et al.). Indeed, THC administration stimulates the biosynthesis of anandamide by mobilizing its precursor compound arachidonic acid (Burstein and Hunter). Although chronic high-THC cannabis consumption causes CB<sub>1</sub> downregulation, levels of the receptor can be reversed to normal levels with just a few weeks of cannabis abstinence (Hirvonen et al.).

The effects of chronic high-CBD cannabis consumption are unknown, but likely carry far less risk than high-THC cannabis. CBD is non-psychoactive and does not cause impairments (short-term memory problems, decrease in motor skills, etc.) attributed to THC, although exceptionally large doses (hundreds to thousands of milligrams) can increase some impairment metrics associated with low-dose THC (Hayakawa et al.). High-dose CBD combined with low-dose THC upregulates CB<sub>1</sub> expression in the hippocampus and hypothalamus. One study reported that THC impaired learning without affecting neurogenesis (the creation of new brain cells), while CBD did not impair learning and increased neurogenesis through a CB<sub>1</sub>-dependent mechanism (Wolf et al.). A 2013 study showed CBD conferred anxiolytic effects in chronically stressed mice through enhanced neurogenesis (Campos et al.). Some of these benefits may stem

from CBD's ability to increase anandamide levels by inhibiting the compound's uptake and breakdown (Bisogno et al.; De Petrocellis et al.). Enhanced anandamide signaling is thought to account for CBD's therapeutic effectiveness against schizophrenia, so it may explain other healing effects as well (Leweke et al.).

Other cannabinoids increase anandamide via uptake inhibition, including cannabigerol (CBG) and cannabichromene (CBC), which are actually more potent in this respect than CBD (De Petrocellis et al.). A variety of other neutral (decarboxylated, heated) and acid (raw, unheated) cannabinoids, including cannabigeravarin (CBGV), tetrahydrocannabidivarin (THCV), tetrahydrocannabinolic acid (THCA), and cannabidiolic acid (CBDA), exert a range of complex effects on the ECS. The complexity is increased given that humans normally consume whole-plant extracts with all the most common cannabinoids present in varying quantities. Thankfully, such extracts have been proven to enhance the ECS and are usually more potent than isolated cannabinoids, including when it comes to inhibiting anandamide uptake (De Petrocellis et al.). Interestingly, cannabis extracts, but not isolated cannabinoids, can inhibit monoacylglyceride lipase (MAGL), the enzyme that degrades 2-AG. In this way, whole-plant extracts can effectively increase both anandamide and 2-AG concentrations.

Evidence suggests that long-term, continuous consumption of high-THC cannabis is safe but not optimal for the ECS's functioning. However, regular intake of therapeutic cannabis extracts with moderate amounts of THC and significant amounts of other non-psychoactive cannabinoids can probably benefit most people. What works best for each individual varies widely, although there are useful starting guidelines. For general health, cannabis extracts with very high levels of CBD are ideal for maintenance and well-being. When it comes to treating diseases, the ratio of THC to CBD is critical, but precision is less important for maintaining overall health.

There is virtually no research on adequate maintenance doses and THC:CBD ratios for healthy people, but 10 to 50 milligrams daily of whole-plant high-CBD extract (which contains other cannabinoid and therapeutic constituents as well) is probably a good level to aim for. Some evidence shows that even very low levels of THC, including just a few milligrams, confers protective benefits (Fishbein-Kaminietsky, Gafni, and Sarne; Waldman et al.). It is likely that CBD also provides these benefits at low doses, but more research is needed.

The best cannabis extracts are derived from organically-grown material and processed with organic food-grade ethanol. They are tested with laboratory equipment to confirm cannabinoid content and safety metrics, including absence of pesticide and solvent residues. Tinctures and oils are the most effective and efficient extracts. Alcohol-based tinctures have been used for thousands of years, and many such tinctures featuring non-cannabis herbs are popular in health stores. For people who want more potency and absolutely no alcohol, full-strength oils are better. Both cannabis oil and cannabis tincture should ideally be consumed alongside coconut oil, olive oil, hemp seed oil, or other healthy oils to increase absorption and bioavailability. Consuming extracts under the tongue, rather than normally eating them or swallowing capsules, also improves absorption. Detailed information on the rates of absorption between different

intake methods and cannabinoids is found at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2689518> (Huestis).

Project CBD, a non-profit educational service, has provided a useful guide on how to properly dose. You can find this resource here: <http://www.projectcbd.org/medicine-2/dosage>. For convenience, the key steps are shown below:

1. Decide how you want to take cannabis. Dosed cannabis medicine infused with CBD-rich oil extracts is available in sublingual sprays, capsules, edibles, topicals, tinctures and other products.
2. Find your ratio. Cannabis products have varying amounts of CBD and THC. A high CBD strain or product (with little THC) is not necessarily superior to a strain or product with a more balanced CBD:THC ratio. Find the proper combination for you.
3. Begin with a low dose—especially if you have little or no experience with cannabis.
4. Take a few small doses over the course of the day rather than one big dose.
5. Use the same dose and ratio for several days. Observe the effects and consider if you need to adjust the ratio or amount.
6. Don't overdo it. Often with cannabinoid therapeutics, "less is more." Cannabinoid compounds have biphasic properties. This means that higher doses of CBD may not be as effective as low or moderate doses. Also, too much THC—while not lethal—can increase anxiety and mood disorders.
7. Consider the condition you're treating. For anxiety, depression, spasms, and pediatric seizure disorders, you may do better with a moderate dose of a CBD-dominant remedy—look for a CBD:THC ratio of more than 14:1. For cancer or pain, you may need more THC, for instance, a 1:1 ratio.

An excellent post from United Patients Group, a premier organization assisting cannabis patients and caregivers, has provided detailed examples of cannabis dosing here: <http://www.unitedpatientsgroup.com/blog/2013/11/26/what-is-a-cannabis-dose-by-aunt-zeldas-oils/>.

## V. Conclusion

The science of the endocannabinoid system is constantly evolving. We are always learning more about how it maintains general health and influences disease. While there is still so much more knowledge to discover, we know enough to justify the use of cannabis extract medicine and ECS enhancement techniques. In time, humanity will learn new ways to empower the ECS and treat many diseases in a far more natural way.

### *Top 10 Ways to Enhance Your Endocannabinoid System*

1. Consume more Omega-3 fatty acids and less Omega-6 fatty acids. Therefore, increase consumption of fish, eggs, hemp seeds, flax seeds, chia seeds, walnuts, and certain forms of algae. Reduce consumption of cheap vegetable oils, and stick to using olive oil, coconut oil, hemp seed oil, avocado oil, or walnut oil.
2. Eat primarily a plant-based diet with as much organic content as possible. Avoid inflammatory foods like refined grains, sugar, whole-fat dairy, processed meat, and hydrogenated vegetable oils. Avoid artificial ingredients.
3. Do at least 15 minutes of meditation every day.
4. Do at least 15 minutes of exercise every day.
5. Make time to reduce your stress levels by reading, listening to music, or walking.
6. Take a high-quality probiotic supplement and eat probiotic foods like yogurt, sauerkraut, kimchi, and fermented vegetables.
7. Do not excessively consume alcohol and antibiotics.
8. Get some form of acupuncture, massage, or osteopathic manipulation at least a couple times a year. In general, the more the better.
9. Do not consume excessive amounts of very high-THC cannabis, especially through the smoking route.

10. Consume moderate amounts of high-CBD cannabis extracts in the forms of tinctures or oils. Ideal dosage is highly individualized, but between 10 and 50 milligrams a day should benefit most people.

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