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The discovery that different plants beyond cannabis contain multiple compounds that can modulate the endocannabinoid system means that we can no longer define plant cannabinoids as merely a product of cannabis ~Juerg Gertsch
As research into medical cannabis continues to capture the attention of many in the scientific and medical communities (as well as many in the general public), we are also learning more about the health benefits brought on by the best combination of non-cannabis botanical compounds, foods, and lifestyle activities (e.g., acupuncture, exercise, and aromatherapy) that interact with the endocannabinoid system (ECS). The ECS is a lipid-signaling network that regulates most metabolic, immune, neurodegenerative and inflammatory diseases. You can think of it as the global system in our body that naturally produces ligands (binding molecules) that activate the receptors that regulates inflammatory cytokines, lipid, sugar and neurotransmitter release. And, because the ECS is responsible for neural plasticity, neuroprotection, immunity and inflammation, apoptosis, pain, appetite, and metabolism (McPartland, 2008), supporting this system is important for halting chronic disease expression.

Although we have Cannabis sativa to thank for much of the emerging information about and interest in the ECS, we are now discovering that plants and compounds other than cannabis can directly and indirectly affect the ECS.

In Beyond Cannabis, I will explore the synergistic use and potential health benefits of plant compounds, including polyphenols, terpenes, and dietary cannabinoids, other than the cannabis plant. I propose that combining terpenes, polyphenols, and dietary cannabinoids (not from Cannabis sativa) provides a “super additive” anti-inflammatory effect that we can apply to combat autoimmune, metabolic, neurodegenerative, and other inflammatory diseases.

The fact that we can intentionally manipulate our ECS by choosing how we interact with it is as fascinating as it is promising. Indeed, understanding the profound anti-inflammatory effects offered by gently stimulating the ECS with diet, herbal medicine, and other lifestyle choices can bring tremendous relief to those struggling with chronic inflammation and immune dysfunction. And the more we understand the synergistic use of these compounds (in plants and through their essential oils, polyphenols, and dietary cannabinoids), the more we can personalize combinations to shore up our defenses and improve our health.
As we live longer, regulating sugar, fat, and inflammatory gene expression has become a top priority for healthy aging and for controlling and even halting chronic disease. Given that many experience an over-expression of inflammatory genes, as seen in metabolic syndrome and autoimmune and neurodegenerative diseases, we need to apply the most advanced anti-inflammatory strategies to effectively offset inflammation and immune reactions. This includes using polyphenols, terpenes, and dietary cannabinoids that specifically target key anti-inflammatory gene transcription factors NFKB (Nuclear Factor KB) and PPAR’s (Peroxisome Proliferator-Activated Receptors) associated with improved insulin signaling, immune modulation, carbohydrate and fat metabolism.

Otherwise, we are left with using ulcer-inducing NSAIDs, steroids, cholinesterase inhibitors, biologics, thiazolidinediones, anti-depressants and anti-anxiety agents for the rest of our lives.

**REGULATING INFLAMMATORY GENE EXPRESSION**

Epigenetic studies show that we have the power to affect our genetic expression by changing the environmental signals that trigger the over-expressions of inflammatory genes. According to the latest science, environmental signals (including food, botanicals, and air quality) have the power to inform the promoter region genes that translate genotype into phenotype. Knowing how to manipulate these environmental inputs can therefore result in some powerful health benefits.

Nutrigenomics is an emerging science that studies the role of phytonutrients as a treatment for inflammation. By personalizing combinations of the most potent dietary cannabinoids, polyphenols and terpenes that act on CB2, NFKB and PPAR’s we can experience the benefits of nutrigenomics.

Research on cannabidiol (CBD) has helped elucidate the mechanisms through which cannabis impacts our physiology. The surprise about cannabidiol (CBD) is that this non-psychoactive component of cannabis exerts its effects not on cannabinoid receptors, but on the precise metabolic and inflammatory regulation points or gene transcription factors that we will explore, namely PPARs and NFKB.

It is through these same exact pathways that many common foods and medicinal herbs exhibit similar anti-inflammatory effects to CBD, largely due to the chemical constituents that act on NFKB and PPARs (PPARα and PPARγ) namely, terpenes, phytocannabinoids and polyphenols.

The potent anti-inflammatory and therapeutic effects that come with specific combinations of these compounds have been demonstrated for centuries via the enduring success of traditional herbal medicine. All medicinal herbs have marked therapeutic effects on their own and synergistic effects when combined in remedies. In effect, plant foods and botanicals containing these potent compounds exert their impact through PPAR interaction, NFKB inhibition as well as improved histone and DNA
methylation. This results in a less inflammation, and the greatest possible health.

**NFKB and PPARs**
Most health conscious people are familiar with polyphenols, flavonoids, antioxidants, vitamins, minerals, and omega-3 fatty acids to maintain health and prevent disease. What’s becoming increasingly clear is how these compounds exert beneficial effects not only via PPAR activation but also through interactions with the NFKB system.

NFKB (nuclear factor KB) and PPAR (Peroxisome Proliferator-Activated Receptors) pathways are important therapeutic targets for inflammation and metabolic dysfunction (i.e., glucose and lipid dysregulation).

NFKB is a protein that acts like a switch to turn inflammation either “on” or “off” when cells sense “danger” in the form of infections, emotional, and/or metabolic stress. If this protein group is over-active, it will continually produce the inflammation response where none is needed. Knowing how to counteract inflammatory gene expression once the NFKB switch has been turned “on,” can help decrease inflammation while you treat and heal any chronic disease.

Obviously, getting rid of infections and other stressors is the first step in preventing NFKB from turning inflammation “on” in the first place. Yet, since inflammation is the common denominator in all chronic diseases, it makes sense to use natural agents that inhibit the over-expression of NFKB. That over-expression may result in feeling inflamed, lethargic, and lacking in mental clarity, to name a few examples.

**Polyphenols, terpenes and dietary cannabinoids that inhibit NFKB**
We now know that safe and effective NFKB inhibitors are are available from foods, herbal medicine and essential oils. The following NFKB inhibitors are promising candidates for both the prevention and treatment of chronic inflammation. Keep in mind going forward that many of these also act on the PPAR receptors and some, like Beta-Caryophyllene also acts directly on the CB2 receptor.

<table>
<thead>
<tr>
<th>Common Natural NFKB Inhibitors</th>
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<tbody>
<tr>
<td>• Allicin in garlic</td>
<td>• Sulphoraphane (found in cruciferous vegetables like broccoli)</td>
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<tr>
<td>• Curcumin in turmeric</td>
<td>• Vitamins A, C, E</td>
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<tr>
<td>• ECGC and theanine in green tea</td>
<td>• Berberine in barberry, scutellaria baicalensis, and goldenseal</td>
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<tr>
<td>• Gingko biloba</td>
<td>• N-acetylcysteine (NAC)</td>
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<tr>
<td>• Melatonin</td>
<td>• S-adenosyl-methionine (SAMe)</td>
</tr>
<tr>
<td>• Quercetin</td>
<td>• Lipoic acid</td>
</tr>
<tr>
<td>• Resveratrol</td>
<td>• Zinc</td>
</tr>
<tr>
<td>• Silymarin in milk thistle</td>
<td>• EPA/DHA</td>
</tr>
<tr>
<td>• Carnosol in rosemary</td>
<td>• Ginger</td>
</tr>
</tbody>
</table>
- Beta-Caryophyllene in copaiba
- Myrcene in lavender and frankincense essential oil
- Limonene in lemon, orange and grapefruit essential oils
- Alpha-pinene in pine, sage and eucalyptus essential oils

**PPARs**

When it was discovered that THC and other cannabinoids were not the only plant compounds that can affect the ECS, the story about other modulatory partners began to include PPAR agonists (Davis, MP, 2014).

Peroxisome Proliferator-Activated Receptors (PPARs) are nuclear transcription factors (like NFKB) that regulate antioxidant and anti-inflammatory pathways. There are 3 main PPARs studied to date, each one possessing distinct tissue distribution and function in the regulation of energy metabolism.

In general, PPARα promotes fatty acid (FA) catabolism, PPARγ enhances insulin sensitivity and lipid storage while PPARδ (also referred to as PPAR-β) changes the body’s fuel preference from glucose to lipids and suppresses macrophage-derived inflammation. Recently it was discovered that all three PPARs PPARα, PPARγ and PPARδ are found on macrophages and when activated, decrease TNF alpha and IL6 (associated with inflammation) (Wang., 2014). These findings suggest the anti-inflammatory and immune modulating benefits of PPAR activation in many chronic diseases.

**PPAR activation**

It is now known that PPAR activation is linked to the suppression of pro-inflammatory genes via an interference with the NFKB signaling pathway. Once PPARs are activated by hormones, terpenes, fatty acids, and/or polyphenols they bind to nuclear DNA to promote or prevent transcription of specific genes involved in energy homeostasis, lipid uptake and metabolism, insulin sensitivity, and other metabolic functions. Since each of these mechanisms overlaps with observed effects in the ECS like alterations in energy, lipid and glucose metabolism, hunger and satiety, inflammation and pain, we must consider PPAR modulation as a means to regulating the ECS.

The ability of certain plants and compounds to modulate PPAR's has promising therapeutic implications, particularly with respect to autoimmunity, neurodegenerative and metabolic disorders. Our ability to access natural PPAR modulating ligands through foods and herbs (see below) offers us a much safer alternative in comparison to the currently available synthetic drugs for these diseases.

**PPARγ**

PPARγ expression is mostly found in adipose tissue, colonic epithelia, macrophages, and endothelium, as well as the kidney, liver, and small intestine. PPARγ most significantly increases insulin sensitivity that in turn decreases blood glucose.
While Big Pharma has been selling drugs for type II Diabetes that act on this receptor for years, you may be interested to know that there are a number of herbs (such as Gymnema sylvestrae) and foods that possess natural PPARγ ligands. Personalized combinations of these compounds may be effective in improving insulin sensitivity.

Some potent constituents in common foods that act on PPARγ include the catechins in green tea, tocotrienols in palm oil, 2-Hydroxy chalcone in cinnamon, Psi-baptigenin and hesperidin in red clover, resveratrol in grapes and wine, astaxanthin in microalgae and crustaceans, carnosic acid in sage and rosemary, rosmarinic acid in marjoram, EPA/DHA in fish oil, flavonoids in licorice, conjugated linoleic acid in meat, carvocrol in thyme oil, quercetin in dill, bay leaves, and oregano, 6-shogaol in ginger roots and the triterpenes in ginseng.

PPARγ agonists have also been shown to be regulators of brain inflammation and oxidative stress (Bernardo., 2006., Collino., 2006). The majority of studies have shown that PPARγ agonists inhibit the expression of inflammatory mediators such as inducible nitric oxide synthase, by antagonizing activation of transcription factors such as NFKB. Since PPARγ is also suspected to be a neuroprotective agent (Yu., 2008), it would make sense to include natural ligands that activate PPARγ in cases of epilepsy, neuroinflammation, and Alzheimers.

**PPARα**

PPAR-α expression is relatively high in hepatocytes, enterocytes, vascular and immune cell types such as monocytes/macrophages, endothelial cells, smooth muscle cells, lymphocytes, non-neuronal cells like microglia and astroglia and mainly regulates genes involved in the metabolism of lipids and lipoproteins (Fruchart, 2009).

Studies about PPARα also show that like PPARδ/PPAR-β, and PPARγ, this transcription factor is expressed in macrophages, and that PPARα agonists inhibit animal models of autoimmune conditions such as MS (Racke et al., 2006). Since microalgae (e.g. astaxanthin), olive oil, EPA and DHA are known PPARα ligands (binding molecules), it makes sense to consider these in a personalized program for autoimmune disease.

The fatty acid family N-acylethanolamides (including oleamides in chocolate, N-palmitoylethanolamide [PEA]) also bind directly to PPARα. Remember that PPARα is the transcription factor which regulates fatty acid lipolysis. By suppressing the FAAH enzyme oleamides may not only help increase anandamide levels, but also keep PPARα activated which may result in enhanced PPARα transmission. PPARα activation in an of itself is considered anti-inflammatory (Costa., 2012).

**PPARδ/PPAR-β**

PPARδ/PPAR-β is an important regulator of lipid metabolism and energy balance in adipose tissue, skeletal muscle, and the heart and is highly expressed in the colon, small intestine, liver and keratinocytes, as well as in heart, spleen, skeletal muscle, lung, brain
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and thymus (Wright, et al., 2000). PPARδ/PPAR-β, known to suppress macrophage derived inflammation, has also been shown to inhibit Th1 and Th17 responses (Kanakasabai, et al., 2010).

It is interesting to note that PPARδ/PPAR-β is mostly found in keratinocytes which constitutes about 90% of the cells found in the epidermis. Keratinocytes form tight junctions with the nerves of the skin and modulate the immune system by producing anti-inflammatory mediators such as IL-10 and TGF-β. I believe that this is not only one of the mechanisms through which many herbal medicines can influence the ECS topically but also one of the ways in which bodywork may influence the ECS i.e. through mechanical stimulation via the keratinocytes.

Herbal Medicine and PPARs
Many natural remedies and herbal extracts have been studied for their effect on suppressing NFκB, the key regulator of inflammation, as well as on peroxisome proliferator-activated receptors PPARs.

Many herbs in Traditional Chinese Medicine (TCM) have been shown to not only inhibit TNF-α-induced NFκB activation, but also to act as agonists toward the peroxisome proliferator-activated receptors (PPAR) PPARα and PPARγ. In one study, 43% of Chinese Herbal Medicines showed NFκB inhibitory and 50% PPARα and PPARγ activating effects (Rozema et al., 2012). Traditional herbs excel in the treatment of chronic conditions by working not only on PPAR’s and NFκB, but also on improved DNA methylation. The takeaway is that you may want to consider using specific botanicals from the Chinese Herbal Medicine pharmacy for your chronic inflammatory, autoimmune or neurodegenerative condition.

Reviewing the literature on this subject makes it clear that the herbal compounds that contain terpenes, polyphenols, and/or phytocannabinoids all exert their anti-inflammatory effects at the precise intervention point by interacting with gene transcription factors (PPARs and NFκB). In effect, these herbal compounds can regulate glucose and lipid metabolism while also keeping the inflammation switch turned “off.” Since many of the proven effects of these constituents are associated with their ability to control PPAR receptors, it makes sense to incorporate these into an anti-inflammatory diet.

THE ENDOCANNABINOID SYSTEM (ECS) DEFINED

“Metaphorically the endocannabinoid system represents a microcosm of psychoneuroimmunology or mind-body medicine.” John McPartland

The endocannabinoid system (ECS) was originally thought to be comprised of cannabinoid receptors (CB1 and CB2), two lipid-signaling molecules known as the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) and the enzymes MAGL and FAAH,
(that break down AEA and 2AG). More current thinking, however, deems the ECS to include the orphan receptor GPR55 and arachidonic acid-derived ligands, which target other receptors such TRPV1 and PPARγ (De Petrocellis and Di Marzo, 2010) along with other ligands (e.g. polyphenols and terpenes) used to regulate endocannabinoid levels and activity at the receptors.

The main function of the endocannabinoid system is thought to be in neuromodulation i.e. controlling motor functions, cognition, emotional responses, homeostasis and motivation. However, in the periphery, the ECS is considered an important modulator of the ANS, the immune system, and microcirculation (Nagarkatti. 2009). Given the broad reach of the ECS, knowing how to increase the tone of this system may prove to be your most powerful tool for halting many chronic diseases.

ENDOCANNABINOIDS
Cannabinoids are the entire class of compounds that influence the cannabinoid receptors both in the central nervous system and the immune system. Ligands (binding molecules) for these receptors include both endocannabinoids that our body naturally produces and dietary cannabinoids aka phytocannabinoids (e.g., Beta-Caryophyllene, in copaiba, cloves, basil, rosemary, oregano, lavender, cinnamon, and black pepper).

Endocannabinoids are the fatty acid substances produced in the body that activate cannabinoid receptors. *N*-arachidonylethanolamide (anandamide, AEA) and 2-arachidonoylglycerol (2-AG) are considered endocannabinoid ligands that are released from phospholipid precursors embedded in cell membranes.

Anandamide and 2-AG are the two most studied endocannabinoids that bind to and activate our cannabinoid receptors (CB1 and CB2). However, the latest thinking about the entire ECS has expanded with the discovery of secondary receptors (PPAR’s) that are now considered part of the endocannabinoid system. We are learning more about non-CB1 non-CB2 endocannabinoid receptors (PPARs), endocannabinoid-related molecules with little activity at CB1 and CB2 level, and new enzymes for the biosynthesis and degradation of these molecules (Di Marzo, 2009). As you shall soon discover, some of the precursors can be easily sourced through diet to increase endocannabinoid tone.

**Anandamide**
In 1992, Raphael Mechoulam of Hebrew University was the first to identify anandamide, the endogenous fatty acid ligand (arachidonoyl ethanolamine- AEA) that binds to the CB1 receptor. Anandamide, i.e. our endogenous cannabinoid, activates the same receptor (CB1) as THC *Delta*-9-tetrahydrocannabinol (Δ⁹-THC, THC) in cannabis sativa.

Anandamide, which is found in nearly all tissues of animals, is about as potent as THC at the CB1 receptor. (Grotenhermen, et al., 2005).
Anandamide mainly plays a role in the regulation of feeding behavior, memory and the neural generation of motivation and pleasure. Another important finding is that anandamide not only acts as a ligand for both cannabinoid receptors (CB1 and CB2) and vanilloid receptors (TRPV) that attenuate pain sensation (DiMarzo et al., 2002).

Endogenous anandamide is generally present for a short amount of time due to the action of the enzyme FAAH which breaks it down into arachidonic acid and ethanolamine. Since anandamide is degraded by the fatty acid amide hydrolase (FAAH) enzyme, inhibitors of FAAH will lead to elevated anandamide levels and can pursued for therapeutic use.

2-Arachidonoylglycerol (2-AG)

2-Arachidonoylglycerol (2 AG), the second endocannabinoid, was described by Shimon Ben-Shabat of Ben-Gurion University in 1994. 2AG is an endocannabinoid that stimulates the CB2 receptor, which is now well known for it’s anti-inflammatory effects.

2 AG is present in the central nervous system, where it exerts cannabinoid neuromodulatory effects. The discovery of 2AG established the existence of a cannabinoid neuromodulatory system in the nervous system. (Di Marzo, 2004). CB2 is the main receptor we will focus on due to it’s anti-inflammatory and immune modulating effects.

One of the most important takeaways here is that our bodies naturally produce these feel-good, self-regulating compounds anandamide (after the Sanskrit word for “bliss”) that binds to the CB1 receptor as well as anti-inflammatory compounds like 2AG that binds to CB2R.

Endocannabinoids, Inflammation and The Immune System

We now know that the endocannabinoid system, especially the CB2 receptor, is involved in immunoregulation and neuroprotection. The mechanisms of immune regulation by endocannabinoids include modulation of immune response, decrease in cytokines, induction of apoptosis in immune cells, and the downregulation of innate and adaptive immune response (Hicks., 2015).

The fact that CB1 and CB2 receptors have been found on immune cells suggests that cannabinoids play an important role in the regulation of the immune system. Due to the distribution on CB2 receptors in the immune system, CB2 receptor stimulation plays a major role in immune modulation and may prove important in autoimmune conditions.

CB2 receptor stimulation was shown to affect B-cell differentiation, and agonists (ligands that bind to CB2 receptors) were shown to suppress the proliferation of both B and T lymphocytes (Nargarkati et al., 2009). CB2 receptors stimulation can also suppress the activity of NK cells, which are the cells that lead to cell destruction and the proliferation of autoimmune diseases and neural inflammation. (Hicks., 2015). In addition, several studies showed that cannabinoids downregulate cytokine and chemokine production.
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and, in some models, upregulate T-regulatory cells (Tregs) as a mechanism to suppress inflammatory responses (Nagarkatti et al., 2009).

Cannabinoid receptor stimulation has also been shown to affect the number and function of T cells, B cells, natural killer cells, dendritic cells, microglia and macrophages in rodents and humans (Croxford and Yamamura, 2005).

Cannabinoid receptor stimulation can also suppress the production of proinflammatory cytokines including TNFα, IL-1β, IL-2, IL-6, IL-12 and IFN-γ, as well as cell proliferation, antigen presentation and trafficking into inflamed tissues (Rieder et al., 2010). Because the CB2 receptor is primarily expressed on immune cells many of these effects are mediated via the CB2 receptor (Mackie, 2005).

This is noteworthy for people with untamed immune cells in the case of autoimmune arthritis or other autoimmune reactions. Learning how to shore up endocannabinoid levels and stimulate the CB2 receptor may be the key to shutting down inflammation and balancing the immune system.

Since the CB2 receptor does not cause psychoactivity and is associated with decreased inflammation, insulin signaling/sensitivity, satiety, and energy balance, this receptor is the key target for its potential to treat chronic disease.

This research suggests that the use of CB2 receptor ligands, sourced from common foods and plants other than cannabis, may be a promising treatment for conditions ranging from Alzheimers to metabolic syndrome to autoimmune disease.

Research suggests that administration of endocannabinoids or the inhibitors of enzymes that breakdown the endocannabinoids, leads to immunosuppression and recovery from immune-mediated injury to organs. This manipulation of endocannabinoids in vivo may constitute a novel treatment modality against inflammatory disorders (Nagarkati, 2009).

The endocannabinoid system also provides antioxidant, anti-inflammatory and neuronal protection. (Jackson et al., 2005). Recently other endocannabinoids and related N-acyylethanolamines (NAEs) like PEA palmitoylethanolamide and OEA oleoylethanolamide have emerged as important regulators of metabolism and inflammation (Di Marzo et al., 2008).

PEA palmitoylethanolamide and OEA oleoylethanolamide possess anti-inflammatory and appetite stimulating effects, respectively. PPARα activation is responsible for mediating the anti-inflammatory actions of palmitoylethanolamide (Lo Verme J., 2005). All of these substances are now considered part of the greater ECS.

Endocannabinoid Effect on Neurotransmitters

Although they have a similar intercellular signaling role to neurotransmitters,
Endocannabinoids differ in that they use what has been referred to as retrograde signaling between neurons. That is, they are not stored in vesicles like neurotransmitters but are instead available in the cell membranes where they are synthesized as needed.

“Within the central nervous system, the endocannabinoid system acts as a negative feedback mechanism to dampen synaptic release of classic neurotransmitters” (McPartland, 2008). Endocannabinoids are thought of as retrograde transmitters because they are released from the postsynaptic cell to regulate neurotransmitter release at the presynaptic cells, where the target receptors are concentrated on axonal terminals, which is where neurotransmitters like dopamine, serotonin, acetylcholine, and gaba are released. This is likely how they exert their impact on mood.

**DIETARY CANNABINOIDS AKA PHYTOCANNABINOIDS**

Dietary cannabinoids, aka phytocannabinoids have been defined as plant-derived natural products capable of either interacting directly with cannabinoid receptors or sharing chemical similarity with cannabinoids or both. (Gertsch, et al., 2010). In light of this definition, Phytocannabinoids include N-acylethanolamines like PEA palmitoylethanolamide, OEA oleoylethanolamide, as well as terpene/dietary cannabinoid such as Beta-Caryophyllene (BCP) in common plants and their essential oils e.g. black pepper, cloves, cinnamon, hops and copaiba. All of these compounds work by either combining directly with a cannabinoid receptor (e.g. BCP that targets the CB2 receptor) or inhibiting the enzyme FAAH (e.g. oleamides in chocolate which activate PPARα), which in turn increases the levels of endocannabinoids, such as anandamide, produced by the body.

Since the ECS plays a major role in pain, immune function, inflammation, and hunger, we may experience illness when the ECS is out of balance. Because we now know that plant compounds can affect the ECS by interacting directly with cannabinoid receptors, inhibiting the enzymes that break down endocannabinoids, and/or influencing the availability of phospholipid precursors used to synthesize endocannabinoids (Gertsch et al., 2010), it makes sense to add in dietary cannabinoids to support and tone the ECS.

Dietary cannabinoids mimic endocannabinoids in the human body, which are a critical part of our ECS. We can use dietary intervention as an effective way of supporting the ECS and getting it into a more balanced state that supports and promotes healing. Knowing how to shore up the ECS, including how to stimulate CB2 naturally with BCP, will go a long way to decreasing inflammation and regulating immune function.

**Cannabinoid Receptors**

The term “cannabinoid receptors” was coined after it was recognized that THC from cannabis interacted with specific human receptors. Because we have endocannabinoid receptors everywhere, we respond to anything similar from an exogenous source (e.g, Beta-Caryophyllene in copaiba or even the stimuli from acupuncture needles) that stimulates the cannabinoid receptors (CB2) in the immune system.
Cannabinoid receptors are one of the most abundant receptors in the human brain and are expressed in nearly every tissue and cell. In fact, they are second only to endorphin receptors. Cannabinoid receptors are part of a family named G protein–coupled receptors (GPCRs) that have the capacity to sense molecules outside the cell and activate cellular responses accordingly (Reggio et al., 2014).

While there is now evidence of even more receptors, we will focus on CB1 and CB2, the two main types of cannabinoid receptors, with CB2 being the main (non-pyshoactive) target for decreasing inflammation and modulating the immune system.

As we move forward in our understanding of the endocannabinoid system, please consider how natural CB2 receptor stimulation along with foods that activate PPARs and turn off NFkB, can be a powerful combination for inflammation and autoimmune disease. Knowing how to combine these in a personalized program can lead to some remarkable results. For now, let’s understand more about our endocannabinoid receptors and how gentle stimulation adds to overall endocannabinoid tone.

**ENDOCANNABINOID RECEPTORS**
Although there is a lot of overlap, of the two main receptors, CB1 receptors are mostly located in the brain and central nervous system, while CB2 receptors are found mainly in the immune system. That being said, we need to pay close attention to supporting CB2 pathways for those with autoimmune reactions. Let’s now consider the location and function of these receptors and the plants that might increase their tone.

**Cannabinoid Receptor Type 1 (CB1)**
Because CB1 expression is found throughout the brain and central nervous system, in the basal ganglia, and the limbic system, including in the hippocampus and cerebellum, it has an influence on both excitatory and inhibitory neuronal circuits that regulate movement, memory, learning, cognition, neuroendocrine output, appetite, nausea, the regulation of body temperature, pain, and immune system modulation. (Croxford and Yamamura, 2005). This broad ability to regulate synaptic neurotransmission means that stimulating CB1 has great potential in treating a wide range of conditions.

**PLANTS THAT HAVE DIRECT ACTION ON THE CB1 RECEPTOR (CB1)**
The most well known plant constituent shown to interact directly with the CB1 receptor includes *Delta*-9-tetrahydrocannabinol (Δ⁹-THC, THC) from cannabis sativa. THC mimics the action of anandamide. THC produces its psychoactive effects by binding to the CB1 cannabinoid receptors in the brain and central nervous system. The Kava plant contains yangonin, a constituent that also acts as a ligand to stimulate the CB1 receptor (DiMarzo 2012). Absinthe contains thujone, a constituent of *Artemisia absinthium*, which also has a weak affinity for CB1. (Meschler et al., 1999). These plants add to the list of promising natural compounds that stimulate the CB1 receptor.
Cannabinoid Receptor Type 2 (CB2)

CB2 receptors are mainly found mainly in the immune system (in lymphocytes, macrophages, NK and microglial cells), but also found in the cerebral cortex in the orbital, visual, motor, and auditory areas as well as in the hippocampus, the corpus callosum, cerebellum, brain stem, and pineal gland. Given their global status throughout the body, CB2 receptors can modify brain function and immune function. I imagine researchers will soon discover the link between music and visualization and ECS tone. Interestingly, CB2 receptors are also found in the enteric nervous system, which modulates gastrointestinal contractility. In cases of immune, brain and gut issues, using natural CB2 agonists like Beta-Caryophyllene, may provide powerful relief.

PLANTS THAT HAVE DIRECT ACTION ON THE CB2 RECEPTOR

There are an increasing number of natural products that target the CB2 receptor. Plant products reported to target the CB2 receptor include rutamarin in Ruta graveolens L. (Rollinger et al., 2009) and 3,3′-diindolylmethane (DIM) commonly found in cruciferous vegetables. DIM has been shown to be a weak CB2 receptor partial agonist (Yin et al., 2009). There are also many common plants that contain Beta-Caryophyllene which also stimulates the CB2 receptor. Read on to understand more about the dual identity of Beta-Caryophyllene as both a terpene and dietary cannabinoid.

THE MOST PROMISING CB2 RECEPTOR STIMULANTS

Remember that CB2 is the main target for regulating inflammation, modulating the immune system, and improving endocannabinoid tone. Beta-Caryophyllene (BCP) is a sesquiterpene that also has the ability to bind to the CB2 receptor. Because it binds to the anti-inflammatory CB2 cannabinoid receptors, BCP is also categorized as a cannabinoid. BCP found in cannabis as well as many other herbs and common foods, is considered both a terpene and a dietary cannabinoid due to its ability to act directly on CB2.

Low Dose Beta-Caryophyllene Therapy

The fact that BCP is found in large amounts in the essential oils of commonly used herbs and spices (including cloves, basil, rosemary, oregano, lavender, cinnamon, copaiba and black pepper) suggests that low dose Beta-Caryophyllene stimulation of the CB2 receptor is available via diet and aromatherapy. In fact, it’s the BCP content in many herbs and essential oils that are responsible for the anti-inflammatory and neurohormonal modulating effects of these herbs and oils. (Bahi et al., 2014).

Since BCP does not bind to the CB1 receptor and therefore does not exert psychoactive effects, it has massive potential for treating pain, inflammation, autoimmune disease, and more. One human study showed that BCP selectively binds to the CB2 receptor and inhibits LPS-stimulated TNFα and IL-1b expression in peripheral blood (Gertsch et al., 2008). Another study found that β-Caryophyllene activation of both CB2 and PPARγ pathways; has the beneficial effect of reducing neuroinflammatory response in the treatment of Alzheimer’s disease (Cheng, 2014). Anxiolytic, and antidepressant, and anti-
alcoholism effects have also been reported (Bahi et al., 2014).

BCP has been shown to exert significant anti-inflammatory effects in mice. BCP from copaiba balsam was shown to be neuroprotective (Santos, 2012).

BCP is even an FDA-approved food additive and has been termed the “first dietary cannabinoid.” (Gertsch, 2010). Because BCP targets CB2 receptors without any psychoactivity, BCP offers an effective anti-inflammatory/analgesic without any alteration in perception or motor skills. Once people start realizing the multiple benefits of BCP, it will be a popular tool in the fight against any inflammatory, autoimmune, and/or metabolic disorder.

Some alkylamides from the Echinacea plant have also been shown to interact with the human CB2 receptor. Notably, the CB2 receptor-binding N-alkylamides from echinacea shows similar anti-inflammatory effects as anandamide (e.g., inhibition of TNF-α). Like anandamide and CBD, N-alkylamides also target PPARγ, a nuclear transcription protein that turns off TNF alpha and IL6, which explains their effect on inflammation. (Gertsch et al., 2010).

POLYPHENOLS AND THE ENDOCANNABINOID SYSTEM
Polyphenols such as trans-resveratrol in red wine, berries, and grape skins, curcumin in turmeric, Epigallocatechin-3-O-gallate (EGCG) in green tea all were shown to interact with the endocannabinoid system. Polyphenols are known to interact with multiple protein binding sites. Since most cannabinoid receptor ligands are highly lipophilic, hydrophilic polyphenols are considered atypical or indirect CB ligands. Studies on the catechin-derivatives in green tea can bind to human cannabinoid receptors non-selectively, which reflects nonspecific molecular denaturation of the protein surface rather than a functional binding interaction (Gertsch et al., 2009). In other words, polyphenols were found to be weak CB receptor agonists and instead shown to exert their impact through PPAR activation and altering enzymes like MAGL and FAAH which contributes to overall ECS tone.

INDIRECT CANNABINOID RECEPTOR LIGANDS
<table>
<thead>
<tr>
<th><strong>Name</strong></th>
<th><strong>Origin</strong></th>
<th><strong>CB receptor affinity</strong></th>
<th><strong>Function</strong></th>
<th><strong>In vivo efficacy</strong></th>
<th><strong>Other targets (ECS)</strong></th>
<th><strong>References</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>(N)-acylethanola mines</td>
<td>Widespread in plants</td>
<td>No affinity</td>
<td>FAAH inhibitors</td>
<td>Validated in CB1 and CB2 KO mice</td>
<td>GPR55</td>
<td>Maurelli et al., 1995; Di Tomaso et al., 1996; Di Marzo, 2008</td>
</tr>
<tr>
<td>Salvinorin A</td>
<td>Salvia divinorum</td>
<td>Insufficient affinity to CB receptors</td>
<td>Indirect cannabimimetic effects at CB1 (mechanism unknown)</td>
<td>No data</td>
<td>KOP agonist</td>
<td>Capasso et al., 2008; Fichna et al., 2009;</td>
</tr>
<tr>
<td>Pristimerin</td>
<td>Relatively widespread in the Celastraceae</td>
<td>No data</td>
<td>Potent reversible MAGL inhibitor (IC50 value &lt;100 nM)</td>
<td>No data</td>
<td>No data</td>
<td>King et al., 2009</td>
</tr>
<tr>
<td>Kaempferol</td>
<td>Widespread in plants</td>
<td>No affinity</td>
<td>FAAH inhibitor (IC50 value &lt;1 µM)</td>
<td>No data</td>
<td>No data</td>
<td>Thors et al., 2007; 2008</td>
</tr>
<tr>
<td>Trans-resveratrol</td>
<td>Relatively widespread in plants (e.g. Vitis vinifera L.)</td>
<td>Insufficient affinity</td>
<td>Insufficient effects</td>
<td>No data</td>
<td>No data</td>
<td>Prather et al., 2009</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Curcuma spp.</td>
<td>Insufficient affinity</td>
<td>Insufficient effects</td>
<td>No data</td>
<td>No data</td>
<td>Prather et al., 2009</td>
</tr>
<tr>
<td>Epigallocatechin-3-O-gallate</td>
<td>Relatively widespread in plants (e.g. Camellia sinensis L.)</td>
<td>Insufficient affinity</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>Korte et al., 2010</td>
</tr>
</tbody>
</table>
ECS, endocannabinoid system; FAAH, fatty acid amide hydrolase; MAGL, monoacylglycerol lipase.

**DIRECT CANNABINOID RECEPTOR LIGANDS**

<table>
<thead>
<tr>
<th>Name</th>
<th>Origin</th>
<th>CB receptor affinity</th>
<th>Function</th>
<th>In vivo efficacy</th>
<th>Other targets (ECS)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ⁹-THC</td>
<td>Cannabis sativa L.</td>
<td>Non-selective CB₁ and CB₂ affinity ($K_i$ values $&lt;$50 nM) (human)</td>
<td>Partial agonist $G_{i/o}$ Inhibition by SR141716 and SR144528</td>
<td>Validated in CB₁ and CB₂ KO mice</td>
<td>GPR55 PPARs Different ion channels</td>
<td>Mechoulam, 1986; Pertwee, 2006</td>
</tr>
<tr>
<td>N-alkylamide</td>
<td>Echinacea spp.</td>
<td>Selective CB₂ affinity ($K_i$ value $&lt;$100 nM) (human)</td>
<td>Partial agonist $[Ca^{2+}]_i$ Inhibition by SR144528</td>
<td>No data</td>
<td>PPAR-γ Inhibition of AEA transport Partial FAAH inhibition</td>
<td>Raduner et al., 2006; Chicca et al., 2009</td>
</tr>
<tr>
<td>β-caryophyllene</td>
<td>Widespread in plants</td>
<td>Selective CB₂ affinity ($K_i$ value $&lt;$200 nM) (human)</td>
<td>Full agonist $G_{i/o}$ $[Ca^{2+}]_i$</td>
<td>Validated in CB₂KO mice</td>
<td>No data</td>
<td>Gertsch et al., 2008</td>
</tr>
<tr>
<td>Falcarinol</td>
<td>Relatively widespread in Apiaceae (e.g. Daucus carota L.)</td>
<td>Non-selective CB₁ affinity ($K_i$ value $&lt;$1 μM) (human)</td>
<td>CB₁ receptor-selective inverse (covalent) agonist Inhibition of AEA/WIN552 12-2</td>
<td>No data</td>
<td>No data</td>
<td>Leonti et al., 2010</td>
</tr>
</tbody>
</table>
Δ⁹-THC is shown as the major phytocannabinoid from Cannabis sativa L. but there are several other structurally related cannabinoids that interact with CB receptors. Δ⁹-THC, Δ⁹-tetrahydrocannabinol; DIM, 3,3′-dindolylmethane; ECS, endocannabinoid system; FAAH, fatty acid amide hydrolase; PPAR, peroxisome proliferator-activated protein. Referenced from Gertsch, J., Pertwee, R. G. and Di Marzo, V. (2010), Phytocannabinoids beyond the Cannabis plant – do they exist?. British Journal of Pharmacology, 160: 523–529. doi: 10.1111/j.1476-5381.2010.00745.x

**POLYPHENOLS**

Every person with inflammation, from diabetes to mild arthritis to a full-blown autoimmune disease, is searching for the perfect balance of food and plant compounds that decrease inflammation and bring relief. The good news is that there are about 8000 other compounds with antioxidant properties in the polyphenol family, all with impressive health benefits. Since it is becoming clear that polyphenols also influence the ECS, it makes sense to include these in a program to support your ECS.

There are many other dietary choices that show similarities in influencing the ECS. Trans-resveratrol, curcumin and ECGC (in green tea), like cannabidiol act indirectly on the ECS via PPAR activation vs. cannabinoid receptor activation. Given this information, it seems appropriate to include other PPAR (and NFKB) ligands from polyphenols that have the potential to change gene transcription. Most of these ligands include common flavonoids (part of the polyphenol family) that can be found in our diet. While it’s obvious that polyphenols are found in abundance in nature, our next step is to hunt, gather, and be efficient with the active ingredients to yield significant results.

---

**POLYPHENOLS**

<table>
<thead>
<tr>
<th>Polyphenol Type</th>
<th>Dietary Source</th>
<th>Pharmacological Activity References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenolic Acids</td>
<td>Coffee (caffeic acid) Tea (gallic acid)</td>
<td>Anti-oxidative properties, cardio-protective properties associated with an enhanced anti-atherogenic function of</td>
</tr>
</tbody>
</table>
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Anne Angelone

<table>
<thead>
<tr>
<th>Lignans</th>
<th>Flax</th>
<th>Strawberries</th>
<th>Apricots</th>
<th>Sesame seeds</th>
<th>Broccoli</th>
<th>Kale</th>
<th>Cabbage</th>
<th>Soy</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Flavonoids Categories:</th>
<th>Fruits:</th>
<th>Vegetables:</th>
<th>Fruits:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flavonoids</td>
<td>Apples</td>
<td>Artichokes</td>
<td>Apples</td>
</tr>
<tr>
<td>Flavan-3-ols</td>
<td>Apricots</td>
<td>Broccoli</td>
<td>Apricots</td>
</tr>
<tr>
<td>Flavones</td>
<td>Blackberries</td>
<td>Cabbage</td>
<td>Blackberries</td>
</tr>
<tr>
<td>Flavonones</td>
<td>Blueberries</td>
<td>Carrot</td>
<td>Blueberries</td>
</tr>
<tr>
<td>Isoflavones</td>
<td>Cherries</td>
<td>Celery</td>
<td>Cherries</td>
</tr>
<tr>
<td>Anthocyanidins</td>
<td>Chokeberries</td>
<td>Eggplant</td>
<td>Chokeberries</td>
</tr>
<tr>
<td></td>
<td>Citrus</td>
<td>Fennel</td>
<td>Citrus</td>
</tr>
<tr>
<td></td>
<td>Cranberries</td>
<td>Garlic</td>
<td>Cranberries</td>
</tr>
<tr>
<td></td>
<td>Currants</td>
<td>Greens</td>
<td>Currants</td>
</tr>
<tr>
<td></td>
<td>Dates</td>
<td>Kohlrabi</td>
<td>Dates</td>
</tr>
<tr>
<td></td>
<td>Elderberries</td>
<td>Kale</td>
<td>Elderberries</td>
</tr>
<tr>
<td></td>
<td>Gooseberries</td>
<td>Leeks</td>
<td>Gooseberries</td>
</tr>
<tr>
<td></td>
<td>Grapes</td>
<td>Onions</td>
<td>Grapes</td>
</tr>
<tr>
<td></td>
<td>Kiwi</td>
<td>Black Olives</td>
<td>Kiwi</td>
</tr>
<tr>
<td></td>
<td>Lemon</td>
<td>Green Olives</td>
<td>Lemon</td>
</tr>
<tr>
<td></td>
<td>Ligonberries</td>
<td>Peppers</td>
<td>Ligonberries</td>
</tr>
<tr>
<td></td>
<td>Limes</td>
<td>Parsnips</td>
<td>Limes</td>
</tr>
<tr>
<td></td>
<td>Mangoes</td>
<td>Peas</td>
<td>Mangoes</td>
</tr>
<tr>
<td></td>
<td>Marionberries</td>
<td>Rutabagas</td>
<td>Marionberries</td>
</tr>
<tr>
<td></td>
<td>Nectarines</td>
<td>Scallions</td>
<td>Nectarines</td>
</tr>
<tr>
<td></td>
<td>Peaches</td>
<td>Shallots</td>
<td>Peaches</td>
</tr>
<tr>
<td></td>
<td>Pears</td>
<td>Spinach</td>
<td>Pears</td>
</tr>
<tr>
<td></td>
<td>Plums</td>
<td>Sweet potatoes</td>
<td>Plums</td>
</tr>
<tr>
<td></td>
<td>Prunes</td>
<td>Tomatoes</td>
<td>Prunes</td>
</tr>
<tr>
<td></td>
<td>Pomegranates</td>
<td>Watercress</td>
<td>Pomegranates</td>
</tr>
<tr>
<td></td>
<td>Quinces</td>
<td></td>
<td>Quinces</td>
</tr>
<tr>
<td></td>
<td>Raspberries</td>
<td></td>
<td>Raspberries</td>
</tr>
<tr>
<td></td>
<td>Rhubarb</td>
<td></td>
<td>Rhubarb</td>
</tr>
<tr>
<td></td>
<td>Raisins</td>
<td></td>
<td>Raisins</td>
</tr>
<tr>
<td></td>
<td>Strawberries</td>
<td></td>
<td>Strawberries</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Flavonols:</th>
<th>Onions</th>
<th>Kale</th>
<th>Leeks</th>
<th>Broccoli</th>
<th>Blueberries</th>
<th>Bok Choy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quercetin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaempferol</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Myricetin</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Quercitin suppresses brain inflammation. (Dajas F. et al 2015) Myricetin protects cells from carcinogenic mutations, inhibits viral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Flavan-3-ols aka Flavanols: Catechins and Proanthocyanidins (aka condensed tannins) | Napa Cabbage
Green Tea
Endive | activity, and protect neurons from oxidative stress. (Devi KP, et al 2015)
Kaempferol in all Brassica vegetables inhibits cancer, reduces heart disease risk, and has proven antimicrobial, neuroprotective, antidiabetic, anti-osteoporotic, anti-anxiety, pain-relieving, and anti-allergic properties. Calderón-Montaño JM, et al. Chem. 2011 |
| Flavones: Luteolin and Apigenin | Apricots
Red wine
Green tea
Grapes
Peaches
Berries
Pears
| Isoflavones and Phytoestrogens Genistein and Daidzein | Flax
Red Clover | Luteolin suppresses production of the inflammatory cytokines TNFα, IL-1b, and IL-6, actions that relate to a selective reduction in numbers of monocytes (Lee YS, et al 2015)
Luteolin protects against retinal oxidative stress (Hytti M, et al 2015)
Luteolin has neuroprotective effects Theoharides TC, et al 2015 |

**Isoflavone-induced inhibition of NFkB** is the mechanism by which isoflavones reduce the invasiveness of breast cancer and increase programmed cell death in various human cancer cell lines. (Uifalean A, et al 2015)

**Flavanones**
- Citrus
- Mint
- Tomato


**Anthocyanidins**
- Berries
- Cherries
- Grapes
- Red cabbage
- Eggplant


**ENDOCANNABINOID DEFICIENCY SYNDROME**

Since cannabinoid receptors and their endogenous lipid ligands were discovered via research on *Cannabis sativa*, scientists started to define the regulatory function of our internally produced endocannabinoids (or lack thereof).

Endocannabinoids are responsible for regulating many physiological functions by acting as anti-inflammatory and neurohormonal modulators. Human studies suggest that endocannabinoid deficiency syndrome may be the hidden etiology in migraine,
fibromyalgia, irritable bowel syndrome, schizophrenia, migraine, multiple sclerosis, Huntington's, Parkinson's, anorexia, and chronic motion sickness. (Russo et al, 2010).

Research has demonstrated alterations in the endocannabinoid system in chronic pain (Kaufmann et al., 2009) and in psychiatric patients (Koethe et al., 2007). Some studies show that serum levels of endocannabinoids are reduced in both depressed patients (Hill et al., 2009) and chronic pain patients (Fichna et al., 2013).

Interestingly, various polymorphisms of CB1 and CB2 receptors have been identified in patients with major depression and bipolar disorder (Mitjans et al., 2013). Similarly, genetic alterations in the CB1 receptor and the FAAH enzyme have also been identified in patients with pain associated with migraine, Parkinson's disease, and irritable bowel syndrome (Greenbaum et al., 2012).

Correcting endocannabinoid deficiency may be possible by enhancing endocannabinoid ligand synthesis, decreasing endocannabinoid ligand degradation, and augmenting or decreasing receptor density and function (Russo., 2009).

These findings support the idea of using small doses of dietary cannabinoids, polyphenols and terpenes regularly to support your ECS in cases of pain, inflammation, and mood disorders. Increasing endocannabinoid tone with dietary cannabinoids, terpenes, and polyphenols is equally promising for those with metabolic, inflammatory, and autoimmune disease. Studies show that when a person is deficient in endocannabinoids, certain fatty acids, terpenes, and polyphenols can be used to bolster endocannabinoid tone. (Russo, 2011).

**ENDOCANNABINOID TONE**

Now that we know more about the protective effects of our ECS, our goal should be to increase cannabinoid tone or plasticity. A great place to start is adding the potent members of the phytocannabinoid family (e.g., fatty acids, polyphenols and terpenes) to our diet. Many of the foods, herbs and essential oils presented in this guide work to increase endocannabinoid tone by acting either on PPAR’s, NFKB, CB2 or all three (as in the case of Beta-Caryophyllene).

As we have seen, polyphenols act on PPAR’s and NFKB to increase endocannabinoid tone. Dietary cannabinoids such as Beta-Caryophyllene increases endocannabinoid tone by stimulating the CB2 receptor and acting on PPARγ and NFKB. Studies also show that dietary levels of essential fatty acids affect the levels of anandamide and other endocannabinoids in the brain (Berger et al., 2001) thereby increasing endocannabinoid tone. EPA/DHA from fish oils also act on NFKB and PPAR’s.

Other natural non-food therapies that have been proven effective for increasing endocannabinoid tone include meditation, yoga, acupuncture, massage and spinal manipulation (McPartland et al., 2008).
For those with an endocannabinoid deficiency, regulating the levels of endocannabinoids with natural interventions, including dietary cannabinoids, terpenes, fatty acids, and polyphenols, as well as with acupuncture and other ways of communicating with the ECS, can be highly beneficial. All of these will go a long way to improving and maintaining endocannabinoid tone.

**ACHIEVING THE ENTOURAGE EFFECT**

Combining bioactive compounds such as terpenes, polyphenols, fatty acids, and cannabinoids can produce physiologic effects that have been referred to as “the entourage effect.” When combined, terpenes in essential oils, polyphenols, and dietary cannabinoids produce a synergistic entourage affect on the ECS, which basically means that the therapeutic impact is more effective as a result. For example, pine essential oil contains a high amount of the terpene pinene, which is known not only for its potent anti-inflammatory effects but also for being an acetylcholinesterase inhibitor (due to 1, 8 cineole) used for improved memory and recall (McPartland and Pruitti, 1999). This would be a great addition to an anti-inflammatory diet that prioritizes PPARγ ligands (e.g. fish oil) for anyone suffering with neuroinflammation, dementia or Alzheimer’s disease. By adding in specific anti-inflammatory foods and botanicals, you’ll enhance the benefits of the treatment via the entourage effect.

As we have seen, polyphenols are the potent plant compounds that have the power to bind to and turn “off” nuclear transcription factors (which turn “off” inflammatory genes and regulate glucose and lipid metabolism). In this way they may act indirectly to regulate endocannabinoid tone. Dietary cannabinoids, like BCP, work by binding directly to the anti-inflammatory CB2 receptor and by activating PPARγ. Terpenes, which are abundant in essential oils, vegetables, and fruit, represent yet another group of compounds that can also affect the ECS.

**TERPENES: THE ESSENTIAL OILS OF PLANTS**

Terpenes are the volatile oils of plants that are considered the chief compounds in essential oils. The terpenes studied in cannabis are also found in many other plants and edible foods and have been used medicinally for centuries in the practice of aromatherapy.

Terpenes are the building blocks that aid in the production of vitamins, hormones, pigments, resins, and cannabinoids. Terpenes in the essential oils of plants have been shown to interact with cannabinoid receptors in the immune, nervous, and gastrointestinal systems. Research also suggests that terpenes in combination with cannabinoids can alter the permeability of both cell membranes and the blood/brain barrier, causing phytocannabinoids to be more thoroughly absorbed (Russo., 2010).

The way this works is that the terpenes (volatile oil ligands) bind to odorant receptors (and likely CB receptors) in the nasal mucosa and other proximal olfactory structures
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(Friedrich, 2004). This is interesting since the sense of smell is a direct area of exchange and impacts on brain function via the quality of air and even the terpene profile we breathe.

Terpenoids are pharmacologically versatile: they are lipophilic, interact with cell membranes, neuronal and muscle ion channels, neurotransmitter receptors, G-protein coupled receptors, second messenger systems and enzymes (Buchbauer, 2010). To get clear on the terms, terpenoids is used to refer to the plant compounds before they are oxidized while terpenes refer to the volatile oils that comprise the scent of a plant. The terpene content in essential oils (EO’s) is what makes them so potent at a low dosage of a drop to a few drops/day. Terpenes have been shown to act as ligands to CB, NFKB and PPAR receptors, thereby halting inflammatory gene expression and being stellar candidates for any chronic disease.

A review of the literature on aromatherapy suggests that endocannabinoid tone can also be enhanced by exogenous terpenes in essential oils. The cannabis terpenoids: limonene, myrcene, α-pinene, linalool, β-caryophyllene, caryophyllene oxide, nerolidol and phytol are all phytotherapeutic agents in their own right and found in many other essential oils. “Terpenoids share a precursor with phytocannabinoids, and are all flavour and fragrance components common to human diets that have been designated Generally Recognized as Safe by the US Food and Drug Administration and other regulatory agencies. Terpenoids are quite potent, and affect animal and even human behaviour when inhaled from ambient air at serum levels in the single digits ng·mL⁻¹. They display unique therapeutic effects that may contribute meaningfully to the entourage effects of cannabis-based medicinal extracts”. (Russo, 2010).

It has been further pointed out that a combination of terpenoids and cannabinoids not only increase blood flow, enhance cortical activity, and have anti-inflammatory effects, but that cannabinoid-terpenoid interactions “could also produce synergy with respect to treatment of pain, inflammation, depression, anxiety, addiction, epilepsy, cancer, fungal, and bacterial infections.” (Russo et al., 2011).

It is well known in the field of aromatherapy that diffused terpenes in essential oils (e.g., linalool in lavender and limonene in citrus) are proven allies for treating anxiety and depression, respectively. Studies show serotoninergic effects at the 5HT and 5 HT receptors by specific terpenes like linalool, which explains lavender oil mediated analgesia and mood alteration (Guzman, et al., 2015). Limonene, the terpene in lemon, sweet orange, and grapefruit has proven antidepressant and anti-anxiety effects. (Carvalho-Freitas and Costa, 2002; Pultirini Ade et al., 2006 via 5-HT1A (Komiya et al., 2006).

Some terpenes, like BCP in copaiba, act both directly on the cannabinoid receptors (CB2) and via PPARγ activation while other terpenes act indirectly via PPARα activation (e.g. pinene), which affects enzymes that inhibit the breakdown of e.g. acetylcholinesterase. Myrcene (the terpene in hops, frankincense and black pepper) and other terpenes are
known to act as mixed agonist/antagonists of cannabinoid receptors, modulating the effects of anandamide and other endogenous ligands (McPartland et al., 2001).

Just as the selective use of high-terpenoid and high-phytocannabinoid-specific chemotypes has become the target of medical marijuana research for disorders such as depression, anxiety, and dementia, we can also use precise essential oils, such as lavender plus citrus oils to lift anxiety and depression and pine oil for mental clarity, along with our dietary cannabinoids, polyphenols and fatty acids that help keep anandamide and 2AG in circulation.

The use of terpenes in aromatherapy adds to the entourage effect to lift depression, calm irritable nerves, and generally encourage a better state of mind. Some terpenes and phytocannabinoids like BCP can be applied topically for anti-inflammatory effects. This practice can add to the entourage effect and increase endocannabinoid tone.

For more information on reproducing the entourage effect with essential oils, check out www.beyondcannabis.club.

Therapeutic terpenes can help you achieve the “Entourage Effect” with essential oils and aromatherapy.

<table>
<thead>
<tr>
<th>Terpene</th>
<th>Essential Oils</th>
<th>Pharmacological Activity</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limonene (Monoterpene)</td>
<td>Lemon, Black Pepper, Frankincense, Orange, Grapefruit, Lemongrass</td>
<td>Potent AD/immunostimulant via inhalation (Komori et al., 1995) Anxiolytic (Carvalho-Freitas and Costa, 2002; Pultirini Ade et al., 2006 via 5-HT1A (Komiya et al., 2006) Apoptosis of breast cancer cells (Vigushin et al., 1998) Active against acne bacteria (Kim et al., 2008) Dermatophytes (Sanguinetti et al., 2007; Singh et al., 2010) Gastro-oesophageal reflux (Harries, 2010)</td>
<td>Treats Acid Reflux Anti-anxiety Antidepressant Antiseptic Immune-modulating</td>
</tr>
<tr>
<td>Terpene</td>
<td>Common Plants</td>
<td>Properties</td>
<td>Uses</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------</td>
</tr>
<tr>
<td><strong>β-Caryophyllene</strong> (Sesquiterpene)</td>
<td>Black Pepper, Cloves, Rosemary, Cinnamon, Oregano, Thyme, Basil, Cannabis</td>
<td>Al via PGE-1 comparable phenylbutazone (Basile et al., 1988) Gastric cytoprotective (Tambe et al., 1996) Anti-malarial (Campbell et al., 1997) Selective CB&lt;sub&gt;2&lt;/sub&gt; agonist (100 nM) (Gertsch et al., 2008) Treatment of pruritus (Karsak et al., 2007) Treatment of addiction (Xi et al., 2010)</td>
<td>Anti-inflammatory Analgesic Protects the lining of the digestive tract Neuroprotective</td>
</tr>
<tr>
<td><strong>Caryophyllene Oxide</strong> (Sesquiterpene)</td>
<td>Eucalyptus, Lemon balm</td>
<td>Decreases platelet aggregation (Lin et al., 2003) Antifungal in onychomycosis comparable to</td>
<td>Antifungal Antiviral Antibacterial Antidepressant</td>
</tr>
<tr>
<td>Essential Oil Blends</td>
<td>Essential Oil Terpene Profile</td>
<td>Uses</td>
<td></td>
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<tr>
<td>Nerolidol (Sesquiterpene)</td>
<td>Orange Jasmine Lavender Tea Tree Lemongrass</td>
<td>Sedative (Binet et al., 1972) Skin penetrant (Cornwell and Barry, 1994) Potent antimalarial (Lopes et al., 1999, Rodrigues Goulart et al., 2004) Anti-leishmanial activity (Arruda et al., 2005)</td>
<td>Anti-anxiety Antianxiety Antifungal Antibacterial</td>
</tr>
<tr>
<td>Phytol (Diterpine)</td>
<td>Green tea Eucalyptus</td>
<td>Breakdown product of chlorophyll Prevents Vitamin A teratogenesis (Arnhold et al., 2002) ↑GABA via SSADH inhibition (Bang et al., 2002)</td>
<td>Antioxidant Antifungal Sleep aid Immune-modulating</td>
</tr>
</tbody>
</table>

5-HT, 5-hydroxytryptamine (serotonin); AD, antidepressant; AI, anti-inflammatory; CB1/CB2, cannabinoid receptor 1 or 2; GABA, gamma aminobutyric acid; PGE-1/PGE-2, prostaglandin E-1/prostaglandin E-2; SSADH, succinic semialdehyde dehydrogenase.

**Body Buzz**
Frankincense
Copaiba

For topical use

Frankincense: a-pinene, a-phellandrene, limonene, B-myrcene, B-pinene, B-caryophyllene (BCP), p-cymene, Terpinen-4-ol, Verbenone, Sabinene, Linalool

Copaiba: B-caryophyllene, pinene, sesquiterpenes, diterpenes, and terpenic acids

- Anti-inflammatory
- Anti-anxiety
- Pain reliever
- Anti-inflammatory
- Antifungal
- Antiseptic

**Calm**
Lavender
Bergamot

Best used with a diffuser

Lavender: a-pinene, limonene, camphor, linalool, caryophyllene, terpinen-4-ol

Bergamot: a-pinene, myrcene, limonene, a-bergaptene, b-bisabolene, linalool, nerol, geraniol, and a-terpineol

- Sleep Aid
- Muscle Relaxant
- Anti-inflammatory
- Analgesic
- Antispasmodic
- Antibiotic
- Digestive

**Mental Clarity**
Pine
Eucalyptus
Sage

Best used with a diffuser

Pine: borneol, a and b-phellandrene, a and b-pinene and 3-carene

Eucalyptus: a-pinene, b-pinene, a-phellandrene, limonene, terpinen-4-ol

Sage: a-pinene, camphene, b-pinene, myrcene, limonene, 1,8-cineole, a-thujone, b-thujone, camphor, linalool, bornyl acetate and borneol.

- Antifungal
- Antiviral
- Antibacterial
- Antidepressant
- Anti-anxiety
- Aids Memory
- Bronchodilator
- Aids Memory
- Anti-bacterial
- Anti-inflammatory
- Anti-inflammatory
- Antibacterial
- Antispasmodic
**FINAL THOUGHTS**

To halt chronic disease expression, we need to get a handle on the endocannabinoid system (ECS) and learn how best to interact with it. The research referenced in this guide demonstrates that our ECS is involved in multiple functions, and that modulating the activity of the ECS holds therapeutic promise in treating everything from diabetes, neuroinflammation and autoimmunity, to mood and movement disorders. Given the growing number of pre-clinical studies and clinical trials revealing compounds that modulate the ECS, we should further explore novel therapeutic approaches for treating chronic inflammatory and/or autoimmune disease.

As you learn more about your own ECS, you will learn how best to support it with the food you eat, the air you breathe, and the treatments, including acupuncture, yoga, running, osteopathy, and other body work, for ultimate endocannabinoid tone. All of these treatments are encouraged for synergistic results. Add to the targeted polyphenols, essential oils and dietary cannabinoids that also regulate inflammatory, sugar, and lipid genes and you have a dynamic way of approaching all inflammatory and autoimmune disease processes.

For those looking to support the ECS, you may find that with the right inputs you may not need a medical marijuana prescription.

These are exciting times in this field of study. We are learning so much about the ECS. That being said, we are also just beginning to discover more information about something we’ve had all along, which is a sensitive protective layer in our body that needs nurturance to stay intact and support better health.
This guide was written for informational purposes only with the following references.

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