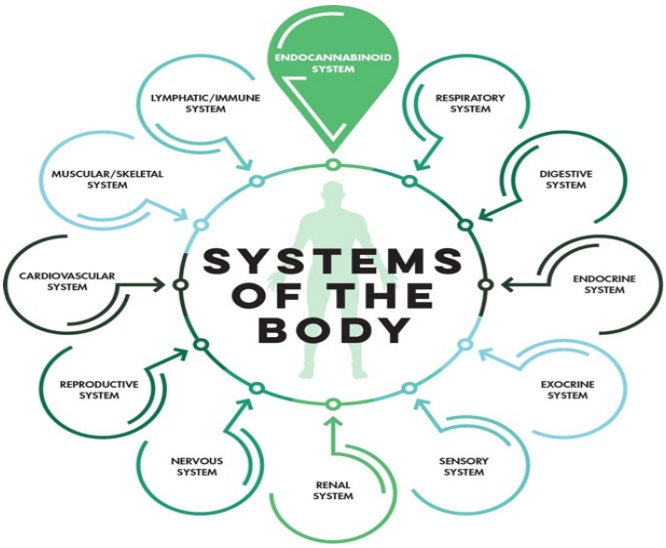
The Human Endocannabinoid System and Modulation of Pain and Inflammation.

ETI's Anti-pain and Anti-inflammatory Formulas *

In this review, we will be taking a scientific look at the human endocannabinoid system (ECS), with an emphasis on their role in inflammation and pain. Also, we will describe ETI's approach to decreasing bodily pain conditions and inflammatory states.

1. The Human Endocannabinoid System (ECS)

The endocannabinoid system (ECS) is a group of endogenous lipids, their receptors, and metabolic enzymes, which together synthesize and degrade endocannabinoids [1-2]. The purpose of the ECS is to maintain homeostasis in the organism; that is, to regulate stable energy and hormone levels, neurotransmitter concentrations, temperature, and more [3].



From https://emeraldhealthbio.com/pages/endocannabinoid-system-page

Also, manipulations of endocannabinoid enzymes, CB1 and CB2 receptors, and their endogenous ligands have shown potential in modulating numerous processes associated with neurodegenerative diseases [5,49], pain [13,20,35,37,39], and cancer [3,12,31]. In addition, the ECS is known to influence neuroplasticity [6,8,19], apoptosis [16], neuro-inflammation [34], and cerebrovascular breakdown associated with stroke and trauma [8].

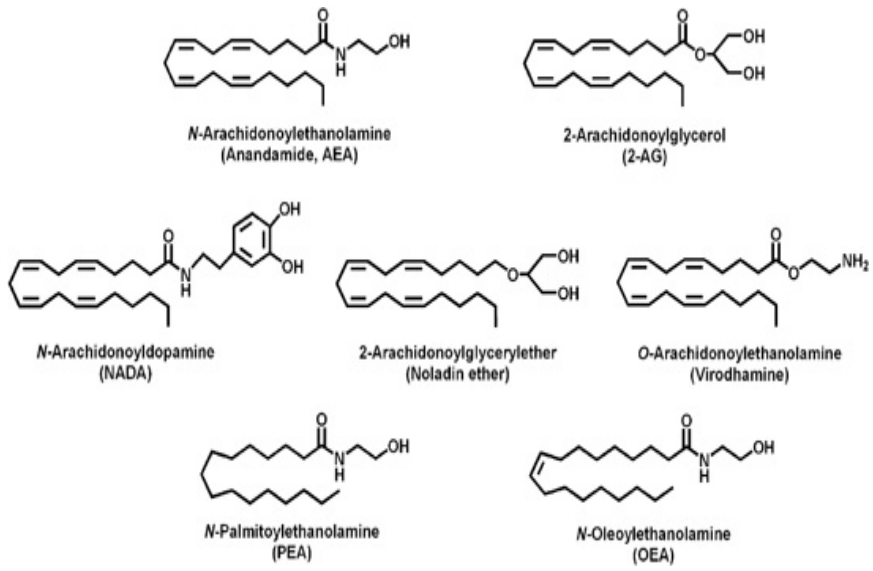
How disease manifests itself in the organism depends on a variety of genetic and environmental factors, but most conditions involve some dysfunction of the ECS [2,3,5,8,10,12,13,24,27,32,49,54,57,60]. It

makes sense, then, that by energetically enhancing the ECS, using natural ingredients that work with it, it is possible to efficiently and positively influence a wide variety of disorders.

Endocannabinoids

Endocannabinoids seem to be involved in many of the body's regulatory functions. Some examples are: regulator of sensorimotor and motivational aspects of behavior [(6)]; support of fertilized egg implantation [(7)]; hypotensive and bradycardia effects [(8)]; cognition and drug dependence [(9)]; interplay between the endocannabinoid system and the cytokine array that is involved in the control of human pregnancy [(10)]; sleep-wakefulness cycle, memory formation, locomotor activity, and pain perception [(11)]; modulation of the immune response [(12)]; and control of pain in parallel with endogenous opioids [(13)].

The human body produces a variation of endocannabinoids, including AE (anandamide) and 2-arachidonoyl glycerol (2-AG) at low levels [(4-5)]. Anandamide plays an important role in the regulation of appetite, hormonal balance, the reproductive system, and pleasure and reward processing. Elevated levels of it may increase the pleasure experienced in one's consumption of food. Anandamide may also be partly responsible for pain regulation and sleep patterns [(14-15)].



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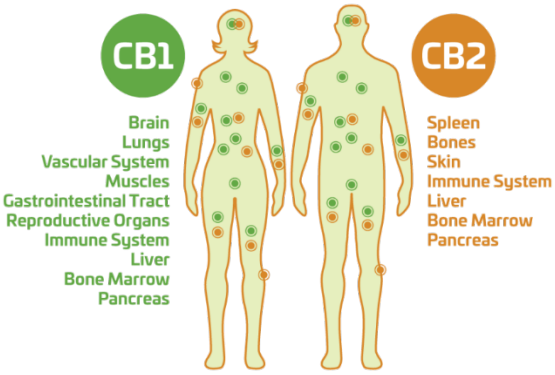
There are other endocannabinoid-like compounds and analogs that may work as endocannabinoids. These include 2-arachidonoyl glycerol ether (2-AGE), O-arachidonoyl ethanolamine (virodhamine), N-arachidonoyl dopamine, oleoylethanolamide and palmitoylethanolamide [(2)].

Cannabinoid Receptors

Cannabinoid receptors are expressed and functional from the very early mammalian developmental stages, when they regulate embryonic and trophoblast stem cell survival and

differentiation, and thus may affect the formation of various adult specialized tissues derived from the three different germ layers (ectoderm, mesoderm, and endoderm) [16].

Cannabinoid receptors are known as G protein-coupled receptors (GPCRs), because G (guanine nucleotide binding) proteins attach to them. Their biochemical pathways involve a series of second messengers that amplify the signal produced by the ligand and finally affect molecules producing a cellular response [17-18].
The primary cannabinoid receptors are CB1 and CB2 [1].



From http://www.plantscanchangeyourlife.com/your-endocannabinoid-system/

CB1 is the most abundant receptor in the mammalian brain, but is also found throughout the body in much lower concentrations. Its activation is responsible for the psychoactive effect of tetrahydrocannabinol (THC), one of the main compounds in cannabis. Distribution of CB1 is not constant; the highest concentrations are in the basal ganglia, hippocampus, cerebral cortex, cerebellum, and amygdaloid nucleus [2,5,19].

CB2 receptors are distributed widely in the major tissues responsible for immune cell production and regulation, including the spleen, tonsils, and thymus. These cell lines include B and T lymphocytes, natural killer cells, monocytes, macrophages, microglial cells, and mast cells. In smaller quantities, they are found in the brain, pancreas and liver. Activation of CB2 receptors can be extremely therapeutic, but unlike CB1, its stimulation does not cause psychoactivity. One of the main effects of CB2 activation is a reduction in inflammation [20-23].

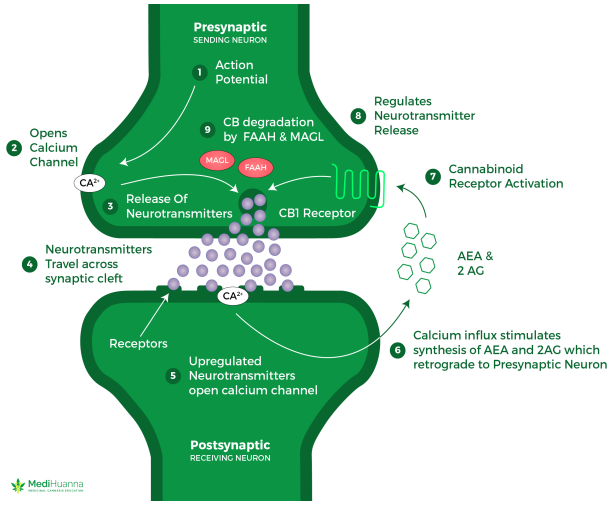
Although CB1 and CB2 are the most distinguished receptors in the ECS, endocannabinoids bind with other receptors, as well. The transient receptor potential vanilloid type 1 (TRPV1), which provides sensations of extreme heat and pain, as well as regulates body's temperature, interacts with anandamide [24].

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 2-AG and anandamide activate PPAR-gamma to converse anti-inflammatory effects. This receptor's activation can also cause vasorelaxation in isolated arteries [25].

There are a number of receptors whose endogenous ligands we do not distinguish. Several such organs' receptors may be the original cannabinoid receptors, including GPR55, GPR119, and GPR18 [26]. They may be involved in pain signaling and vasculature actions. Evidence suggests that GPR119 works in the pancreas to regulate energy balance. It is activated by OEA, and anandamide has a measurable affinity for it, too [27]. Palmitoylethanolamide (PEA), another compound with endocannabinoid-like effects, is weakly active at GPR119 [28]. One of GPR18's primary functions is to direct a microglial migration in the central nervous system. Microglia are immune cells in the brain that help protect neurons [29].

2. Maintaining Homeostasis

The ECS system's clear homeostatic role has been summarized as: "relax, eat, sleep, forget and protect" [30]. One of the key methods for endocannabinoids to maintain homeostasis is through decreasing feedback. For example, when neurons communicate, neurotransmitters are sent from the presynaptic neuron to the postsynaptic neuron. Binding of the neurotransmitters to their postsynaptic receptors causes a depolarization of the postsynaptic membrane and the accumulation of Ca^{2+}in the cytoplasm, stimulating the activation of the calcium-dependent enzymes in charge of the biosynthesis of endocannabinoids. After synthesis, the endocannabinoid ligands are released and diffuse within the synapse, acting locally as retrograde messengers to regulate the release of multiple presynaptic messengers. Endocannabinoids travel in the reverse direction, from the postsynapse to the presynapse, where they bind with presynaptic CB1 receptors to reduce neurotransmitter release [31-34].



From https://providahealth.com/2017/10/11/exploring-endocannabinoid-system-cbd/

Interestingly, while 2-AG and 2-AGE rely on the CB1 receptor to inhibit calcium channels and neurotransmitter release, anandamide can inhibit such channels through CB1 independent mechanisms [33]. This may be the case when one endocannabinoid cannot induce inhibition via a certain mechanism, another utilizes a different pathway as an alternative.

Similarly, in immune cells, CB2 activation has been shown to mediate an inhibitory effect on activation, cell motility and secretion of inflammatory mediators [35].

3. The ECS in Regulation of Pain and Inflammation

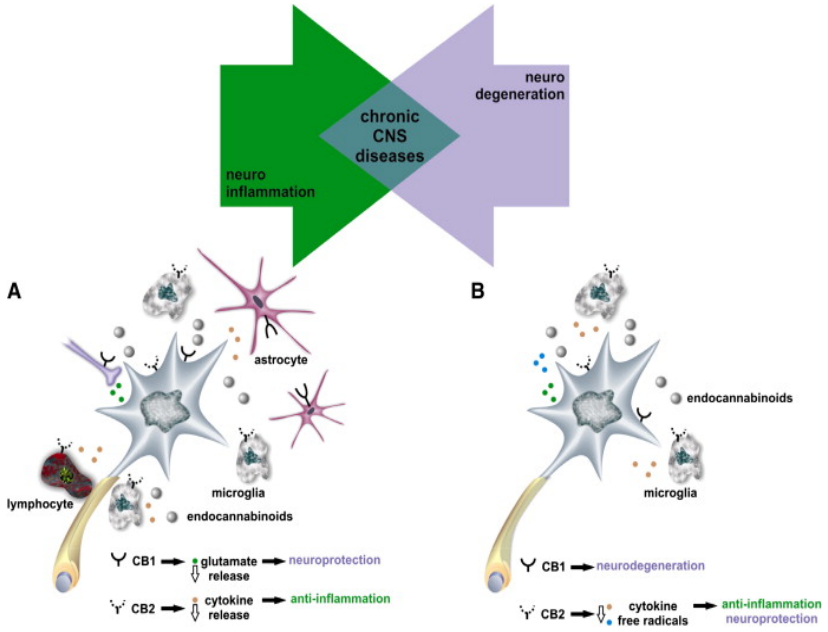
Analgesic Effect

Anti-nociception refers to the process of blocking the detection of painful stimuli by sensory neurons, thus reducing ones' sensitivity to pain. Under physiological conditions, potentially harmful stimuli are integrated by the nociceptors of primary afferent fibers and relayed for final processing in the supraspinal centers. In pathological states, the relaying of noxious input by the nervous system is corrupted, resulting in abnormal nociceptive signaling and an aberration in pain responses [36].

It is well recognized that endocannabinoids have anti-nociceptive effects [37-39]. CB1 receptors are distributed throughout areas of the central and peripheral nervous systems associated with pain [40]. CB1 was shown to be heavily accumulated within the frontal-limbic brain circuits that are a key in both the effective and emotional manifestations of human pain. CB1 inhibition of ascending nociceptive transmission, mainly at the thalamus level, has been shown to modify the emotional pain component acting at the limbic system and cortical areas [41-42]. At the level of the spinal cord, CB1 is densely expressed at the presynaptic terminals of primary afferents and excitatory neurons and regulates the transmission of noxious stimuli to the brain by inhibiting neurotransmitter release [43]. As well as these central effects, CB1 receptors localize on sensory terminals in the periphery, gating the propagation of pain signals, contributing to peripheral analgesia [44].

Anti-Inflammatory Effect

Endocannabinoids modulate the release of inflammatory mediators from many cell types (astrocytes, microglia, macrophages, lymphocytes, neutrophils and neurons) via CB1, CB2 and other receptors. Since excessive inflammation often leads to neurodegeneration, these mechanisms can be quite powerful.



From https://www.sciencedirect.com/science/article/pii/S0014488610001160

CB2 receptors are widely located on immune cells and therefore represent a target for influencing inflammatory pain processing. Specifically, cannabinoids modulate inflammatory cell signaling cytokines, like tumor necrosis factor-alpha and interleukin-6, as well as many other signaling molecules [45]. This data supports the concept that CB2-mediated effects may be regulated by a functional interplay between the endocannabinoid and μ-opioid systems, resulting in an indirect activation of opioid receptors expressed in primary afferent pathways [46].

There is increasing evidence showing that endocannabinoids regulate the immune response at both the innate (monocytes, macrophages, neutrophils, NK cells, eosinophils, basophils, mast cells) and adaptive immune levels [47]. Immune cells are not only able to be influenced, but are also able to generate and secrete endocannabinoids that lead to changes in immune-cell behavior, as well as the production of other inflammatory factors that subsequently influence tissue inflammation [48-49].

ECS State in Rheumatoid Arthritis (RA) and Osteoarthritis (OA)

Rheumatoid arthritis (RA) is a predominant pain condition that arises from chronic autoimmune inflammation. 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 [53].

Malfait et al. [50] have shown that endocannabinoids can block progression of joint inflammation in rodent models of arthritis. The anti-inflammatory potential of CB2 has been confirmed in mouse models of arthritis [50-51]. Further, elevated levels of AEA and 2-AG detected in the synovial fluid of RA and osteoarthritis (OA) patients, but absent in healthy controls, suggest that local endocannabinoid secretion may assist in minimizing inflammation in the arthritic joints [52].

ECS State in Multiple Sclerosis

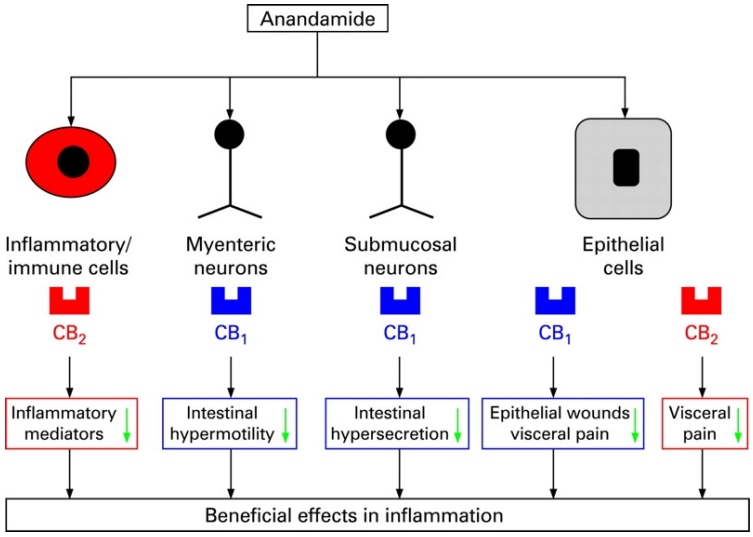
As a major component of the neurodegenerative disease multiple sclerosis (MS) is inflammation, treatment with cannabinoids has been an active area of investigation. Data have shown that CB1 and CB2 receptors influence spasticity and tremors, two common symptoms of MS, as well as bladder problems, and mobility issues [(54)]. In one research study, the levels of endocannabinoids in samples of cerebrospinal fluid from MS patients were compared with samples from healthy subjects; significant differences were observed [(55)]. In a group of 26 relapsing patients *vs.* 25 healthy controls, increased anandamide concentrations were seen.

ECS State in Eye Disorders and Glaucoma

Glaucoma is an irreversible eye disease that produces progressive retinal ganglion cell loss and involves abnormally high intraocular pressure (IOP), which eventually leads to blindness. CB1 receptors and endocannabinoids are found in many parts of the eye, including the retina, where their activation lowers IOP [(56-57)].

ECS State in Inflammatory Bowel Disease (IBD)

Several studies have shown the involvement of the ECS in the regulation of inflammatory and immune response in the digestive tract. The first scientific evidence came from CB1 and CB2 knockout mice, which showed a higher susceptibility to chemically induced colitis, suggesting that the ECS plays a key protective role against chronic inflammation [(58-60)].



From http://gut.bmj.com/content/57/8/1140/F5

Furthermore, in vitro experiments have shown that anandamide and 2-AG increased intestinal permeability when administered on Caco-2 cells, and an in vivo study in obese mice, a model of

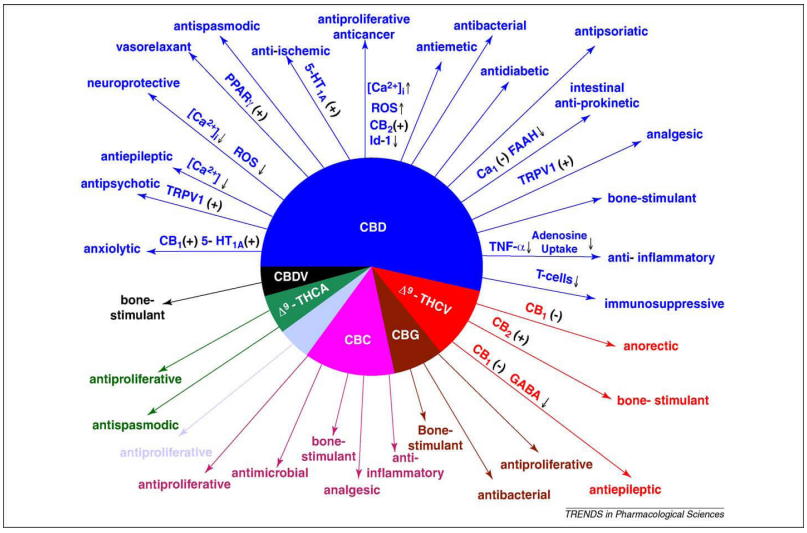
leaky gut, showed that the CB1 antagonist rimonabant was able to reduce plasmatic LPS level, confirming the role of the ECS in regulating the gut permeability [61-63].

ECS State in Celiac Disease

Celiac disease is an autoimmune disorder of the small intestine that occurs in genetically predisposed people of all ages and is caused by a reaction to gliadin, a gluten protein found in wheat. The only effective treatment, to date, is a life-long gluten-free diet; however, a recent study [64] was done to investigate a possible role for endocannabinoids as markers for the inflammatory phase of this disease. Anandamide and PEA concentrations were significantly elevated (100% and 90%, respectively) in active celiac patients, as were those of CB1 receptors. The levels returned to normal after remission with a gluten-free diet. Comparing the effects in CB1-deficient mice with those in wild-type littermates, a greater degree of inflammation was seen in the receptor-deficient mice.

4. Enhancing Your Endocannabinoid System

As you have just seen, the ECS is involved in many major diseases, and in most cases, a deficiency of the endocannabinoid activity contributes to the disease. In the remaining text, we will offer up facts regarding the use of natural substances that can support the ECS functioning and thereby possibly help anyone's return to true homeostasis**.**



From https://www.selfhacked.com/blog/the-lectin-sensitive-gene-cannabanoid-receptor-1-genes-cnr1-rs1049353/

Scientific Data on Cannabis for Modulation of Pain and Inflammation

The cannabis plant produces phytocannabinoids that are very similar in structure to the endocannabinoids made by our bodies. Evaluation of the consistent effects of cannabis on health or the ECS is difficult, because of the plant's complexity [65]. 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 CB1 and CB2 receptors, and CBD increases an anandamide level. CBD that is recognized as a nonpsychoactive phytocannabinoid has positive effects on decreasing psychotic, anxiety and depressive-like behaviors [66-68].

Mechanisms underlying the analgesic effects of cannabinoids likely include the inhibition of presynaptic neurotransmitter and neuropeptide release, modulation of postsynaptic neuronal excitability, activation of the descending inhibitory pain pathway, and reductions in neuro-inflammatory signaling [69-71].

One important mechanism used by the endocannabinoids system to maintain homeostasis is the activation of peroxisome proliferator-activated receptors (PPARs α, β, and γ). CBD, and to a lesser degree THC, can have both direct and indirect effects on isoforms of PPARs. Activation of PPAR, along with CB1 and CB2, mediates numerous analgesic, neuroprotective, neuronal function modulation, anti-inflammatory, metabolic, antitumor, gastrointestinal and cardiovascular effects, both in and outside the ECS. PPAR-γ decreases the inflammatory response of many cardiovascular cells, particularly endothelial cells, thereby reducing atherosclerosis [72].

Recent systematic review and meta-analysis of cannabinoids for medical use has examined 28 randomized trials among 2454 patients with chronic pain. They confirmed that, compared with a placebo, cannabinoids were associated with greater reduction in pain (37% vs. 31%; OR 1.41, 95% CI 0.99 to 2.00) and greater average reduction in numerical pain ratings (−0.46, 95% CI −0.80 to −0.11) [65].

Wilsey et al. conducted a randomized, placebo-controlled crossover trial utilizing vaporized cannabis among 42 participants with central neuropathic pain related to spinal cord injury and disease. Results indicated that vaporized cannabis flower reduced neuropathic pain scale ratings, but there was no evidence of a dose-dependent effect [73].

Interestingly, a group at Tel Aviv University has found in an in vivo experiment that a single ultralow dose of THC (0.002 mg/kg, several orders of magnitude lower than the conventional doses in mice) protects the brain from different insults, including inflammation, which cause cognitive deficits. Mice received a single injection of low-dose THC. Up to 7 days after treatment with lipopolysaccharide (LPS), THC protected the mice from the long-lasting cognitive deficits caused by LPS. The protective effect of THC was blocked by a CB1 receptor antagonist, but not by a CB2 receptor antagonist.

The study's authors suggest, "An ultralow dose of THC that lacks any psychotropic activity protects the brain from neuroinflammation-induced cognitive damage and might be used as an effective drug for the treatment of neuroinflammatory conditions, including neurodegenerative diseases" [74].
Some research found that the cannabinoid signaling system is functioning as a parallel, but distinct, mechanism from the opioids in modulating pain responses [75].

A current examination of Medicare claims data showed that the use of prescription pain medications, including opioids, was significantly reduced in states following the implementation of medical cannabis laws [76-77].

Collectively, current evidence supports the concept that cannabis can produce acute pain-inhibitory effects among individuals with chronic pain. This observation is consistent with determinations made by authors of the recent National Academies report on cannabis that there is "conclusive or substantial evidence" of benefit from cannabis or cannabinoids for chronic pain [78].

Cancer-Associated Pain

Several clinical trials examining the use of cannabinoid receptor agonists to relieve chronic cancer pain have been published. Ten patients were examined with various cancer diagnoses in a double-blind placebo-controlled trial. They found that the analgesic effect of THC at higher doses of 15 and 20 mg was significantly superior to a placebo, but with patients reporting substantial sedation at those doses [79].

The same group also completed another study of 36 patients comparing a placebo to THC at both 10 and 20 mg and to codeine at 60 and 120 mg. They reported that 10 mg of THC produced analgesic effects over a 7-hour observation period comparable to 60 mg of codeine, and 20 mg of THC induced similar effects to 120 mg of codeine [80].

A randomized, double-blind, placebo-controlled, graded-dose study was conducted of 360 randomized patients with advanced cancer and opioid-refractory pain. Patients received a placebo or nabiximols that contain the principal cannabinoids delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in a 1:1 ratio at a low dose (1-4 sprays/d), medium dose (6-10 sprays/d), or high dose (11-16 sprays/d). They found that low and medium doses of nabiximols had improved analgesia over the placebo after 5 weeks of treatment. Higher doses were not more effective than lower doses [81].

Another clinical trial examined the effects of cannabis extract preparations containing THC and CBD in 177 patients with advanced cancer and uncontrolled cancer pain, despite long-term opioid use. The study had 3 arms with THC:CBD extract (n = 60), THC extract (n = 58), and a placebo (n = 59). The results showed that pain relief was superior in the THC:CBD group, with twice as many patients experiencing a 30% reduction in pain when compared with the placebo [82].

Gastrointestinal Dysfunction and Inflammation

Cannabis has been used to treat gastrointestinal (GI) conditions that range from enteric infections and inflammatory conditions to disorders such as gastric ulcers, irritable bowel syndrome, ulcerative colitis, Crohn's disease, secretory diarrhea, paralytic ileus and gastroesophageal reflux disease [83-85]. There are a few controlled studies on medical cannabis that have shown that manipulating the endocannabinoid system can have beneficial effects in inflammatory bowel disease (IBD) [86].

Also, an observational study of 30 patients with Crohn's disease (CD) has shown that medical cannabis was associated with an improvement in disease activity and reduction in the use of other medications. In another placebo-controlled study involving 21 chronic CD patients, there was a demonstrated decrease in the CD activity index >100 in 10 of 11 subjects on cannabis, compared to 4 of 10 on the placebo. [87].

Glaucoma

Cannabinoids have the potential of becoming a useful treatment for glaucoma, as they seem to have neuroprotective properties and effectively reduce intraocular pressure. The converging evidence supporting their use for not only intraocular pressure, but also for their neuroprotective effects has prompted a number of recent reviews highlighting their promise for this eye disorder [88-89].

Multiple Sclerosis (MS)

Multiple data has confirmed that CBD might improve the severity of multiple sclerosis (MS) [90-92] by decreasing neuroinflammation [66,93] and axonal damage through its effect on oligodendrocyte progenitor cells (OPC), which can be used to differentiate into new myelinating oligodendrocytes [94].

Additionally, one research study has shown that both THC and CBD potently reduce the Th17 phenotype, which is known to be increased in inflammatory autoimmune pathologies, such as multiple sclerosis. They found that CBD and THC suppressed the production and secretion of both IL-17 and of IL-6, a key factor in Th17 induction [95].

5. Other Ways to Enhance the ECS

Essential Fatty Acids

Research has shown that adequate levels of dietary omega-3 fatty acids are required for proper endocannabinoids signaling. Mice supplemented with omega-3, compared to mice on a control diet, expressed greater levels of CB1 and CB2 mRNA [96]. Supplementation with omega-3 also modulated concentrations of the "backup compounds," such as PEA and OEA [97-98]. Using mice, the study found that a deficiency in Omega-3 caused presynaptic CB1 receptors to uncouple from their effector G proteins, essentially disabling them [99]. Foods like flax, hemp, and chia seeds, along with walnuts, are excellent vegetarian sources of Omega-3 [100].

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 several studies linking a probiotic consumption to improved cannabinoid signaling and corrected ECS imbalances [101-103]. Interestingly, depending on the situation, probiotics can either upregulate or downregulate cannabinoid receptors to optimally benefit their host [104].

Herbs

The following are specific plants and their constituents that can positively interact with the endocannabinoid system, besides *Cannabis spp.*:

- Yangonin, a kavalactone extracted from kava, *Piper methysticum*, shows affinity for CB1 [(105)].
- Copal incense, extracted from *Protium spp*. (family Burseraceae, the same family as *Boswellia serrata)* contains a pentacyclic triterpene with high affinity for CB1 and CB2 [(106)].
- Salvinorin A in *Salvia divinorum* produces CB1-mediated effects in the gastrointestinal tract of rodents [(107)].
- Flavonoids, such as biochanin A (from red clover, *Trifolium pretense*), develop some inhibition of fatty acid amide hydrolase (FAAH). Inhibitors of FAAH, the enzyme responsible for the metabolism of the endogenous cannabinoid (CB) receptor ligand anandamide, are active in a number of animal models of pain [(108)].
- Curcumin, extracted from curry powders, elevates endocannabinoids levels and brain nerve growth factor (NGF) in brain-specific regions [(109)].
- Alkamides from *Echinacea* species bind to CB2 and act as CB2 agonists with immunomodulatory effects [(110)]. Also, several constituents from the *Echinacea purpurea* root and herb produce synergistic, pleiotropic effects—they bind to CB2, as well as inhibit AEA uptake [(111)].
- The main terpenoid in black pepper, (E)-β-caryophyllene (BCP), binds to CB2 with nanomolar affinity and acts as an agonist. Its anti-inflammatory effects are reduced in CB2 knockout mice [(112)].

6. ETI Approach in Reducing Pain and Inflammation

At ETI, we understand that by energetically enhancing the endocannabinoid system, along with the use of natural ingredients that work within the system, we are able to efficiently influence a wide variety of disorders.

Vital360

Vital360 is formulated using energetically compatible patterns of different CBD oils. The main feature of this formula is its fast reduction of the discomfort caused by pain, along with a decrease of any inappropriate inflammatory response. A possible mechanism of its action might be due to the energetic interference with the intracellular signaling that regulates the body's energy homeostasis, as well as the energetic support of the multiple cytoprotective signaling pathways. Vital360 can help to:

- Decrease tension and discomfort, both on the mental and physical levels
- Support the body's normal response to inflammation initiated by various factors, such as acute or chronic infections, hormonal abnormalities or a pro-inflammatory dietary pattern

- Maintain an active lifestyle to support the body's normal processes of tissue repairing
- Relieve exercise-related musculoskeletal discomfort
- Strongly support the health of muscles and joints
- Promote a natural flow of energy within the body and tissues; strengthen and energize the body.

Suggested dosage:
Acute pain: 15-20 drops diluted in 2-4 oz. of water up to 4-5 times the first day.
After that: 10-15 drops 2-3 times per day.
Chronic pain: 10-15 drops 3-4 times per day.
Safety: Safe inside the recommended dosages.

Testimonial:

"I tried Vital360 with patients who I have seen for a very long time with rheumatoid arthritis with no pain relief from narcotics, CBD oil, etc. I was extraordinarily pleased to see the significant and rapid impact of Vital360 on my patient's outcome. One patient who I have seen for over 20 years with rheumatoid arthritis is in retractable, constant nagging pain. She went pain-free from the very first day using Vital380, for 2 solid weeks on 10-15 drops 3 times per day. Another young man in his 40's had a similar situation, including ankylosing spondylitis in the lower mid-cervical spine into the upper thoracic area, causing constant, chronic decreased range of motion and pain of varying degrees. With dosage of Vital360, about half of his pain went out using 25 drops. After testing, I increased the dosage by another 25 drops and got him to 90% pain-free. I was not satisfied, so I dosed him another 20 drops, so he had 70 drops over a 20-30-minute time period. Not only did he go pain-free, his range of motion dramatically increased. I have used it topically in combination with several sprays and had a wonderful outcome with that. It is also effective in scar therapy with surgical scars, and I've found very dramatic positive changes in sensitivity and released blocked energy from the area, as well as an increased range of motion in the musculoskeletal system." Jeffrey Marrongelle, DC, CCN

Vital360 Hemp Oil

Vital360 Hemp Oil has a more complicated energy pattern than Vital360, along with a full spectrum of the CBD extract from hemp. It is well known by those in the field that for general health, cannabis extracts with very high levels of CBD are ideal for the maintenance of one's well-being. With ETI's energetic formula Vital360 Hemp Oil, even a small amount of CBD is enough to possibly:

- Improve the body's homeostasis mechanism by supporting the endocannabinoid system and thus decreasing its dependence on genetic and environmental factors
- Create an adequate inflammatory response by improving coordination in the different cell types' integrated network

- Assist in the balancing of the entire ECS and thus decrease any exisiting chronic inflammatory state that contributes to obesity, arteriosclerosis, hypertension, cancer, depression or autism
- Help with chronic inflammatory disorders, such as rheumatoid arthritis, inflammatory bowel disease, eczema and others
- Reduce or relieve headaches, sore muscles after musculoskeletal injuries, as well as other aches and sharp or dull-pains
- Help with chronic pain caused by ongoing diseases, such as cancer, arthritis, fibromyalgia, carpal tunnel syndrome, IBS, etc.

Suggested Dosage:
One dropper (50 drops) under the tongue twice per day, or as recommended by your practitioner.
Safety: Safe inside the recommended dosages.

Testimonials:

"I'm a 50-year-old male and have had several surgeries, including back and hip surgery, plus an ankle fusion. There is not a day when I am not in pain. Due to my ankle fusion, I had to adapt the way I walk, which puts extreme strain on my back and neck. In the past, I was taking 800 mg of ibuprofen daily. I recently started taking Vital360 CBD oil and not only have I not taken any medication, I also have been pain-free." Ed, OR

"I started using Vital360 approximately 9 months ago and noticed an immediate difference in my pain levels. I was diagnosed with fibromyalgia many years ago and I've researched many dietary and herbal alternatives/remedies over the years. This product was the first I've used to give me almost instant results and over time, the longer I supplemented my regimen with it, the better I've felt. In addition to Vital360, I use the Arnica Cream as a topical in specific areas that are aggravated, and again, almost instant relief. The two in conjunction with one another are AMAZING! I'm excited, because ETI recently launched a new CBD product called Vital360 Hemp Oil. I've now replaced the use of my Vital360 with the Vital360 CBD. I've noticed for me, it works quicker and the relief lasts longer. I've been informed I can use both products together, as well, when my symptoms are more intense." Heidi, CA

Arnica Relief Cream

This ETI cream combines natural and organic ingredients, including therapeutic essential oils, an Arnica extract, along with MSM to create a nourishing and soothing cream. The beneficial qualities of these powerful ingredients have been enhanced through the Vital Force Technology proprietary process. The cream allows you to help manage the pain and improve flexibility. As well, it might be helpful with osteoarthritis or rheumatoid arthritis, osteoporosis, muscle cramps and premenstrual syndrome (PMS).

Usage:
Apply directly to the skin. Use as needed.

Warnings:
For external use only. Avoid contact with eyes and mucous membranes. If eye contact occurs, rinse thoroughly with water. Do not apply to open wounds or broken skin. Use only on adults and children over 12.

Testimonials:

"I had my first knee aspiration (removal of fluid) at 11 years of age. Over the years, I had my share of joint injuries, including ankles, knees, hips, shoulders and spine, as well as both my neck and lower back. I was forced to drop out of college football in my senior year, due to head, neck and shoulder injuries and pain. Twenty-five years ago, I was in a near head-on collision, which created two disc lesions with nerve entrapment in my neck, I had two disc lesions in my lumbar (lower back) with nerve entrapment and residual left-side sciatic nerve pain. I also had a meniscus tear of my left knee, a crushing injury to my left ankle, and right wrist carpal tunnel syndrome. I have tried hundreds of natural products, both lotions and rubs, externally, as well as, supplements orally. With all of this intro in mind, I can share that Energy Tools International's Arnica Relief Cream is a blessing. I use it 2-3 times a day for relief. It does just that! Pain relief, reducing swelling, muscle tension relief, nerve pain relief -- all of this without a narcotic feel!! The Arnica cream will take the pain from a 10 to a 7 in about 10-15 minutes. Later, in a half hour, if I apply it again to the pain region, the 7 pain typically drops to a 5, and so on. I have an active practice and have recommended this product to hundreds of patients. Patient satisfaction is nearly 100%." Steven C. Davis, DC, CTN, NMD, PScD

"I have suffered from MS for 30 years. Since I started using Arnica Relief Cream, the quality of my life has improved tremendously. I use the cream every day to help manage the pain and improve flexibility. For me, this cream is a godsend. I have never found anything like it." Bob, Orange County, CA

"I love sports, and getting hurt is part of the game. I have all kinds of remedies in my bag. I have found that Arnica Relief Cream is the best choice for contusions, strains and sprains. It takes the pain away and I have never healed so fast." Evan, Los Angles, CA.

"I was introduced to Arnica Relief Cream and could not believe the IMMEDIATE relief this product gave me. It was like a miracle product! I had to have this product. I have carpal tunnel syndrome and it helps me get through the day. I use it several times per day." Janet, San Bernardino County, CA

"For 25 years, I have been a karate instructor. I currently teach at the university level and play a lot of sports. I am always amazed at how fast Arnica Relief Cream relieves my pain, but most impressive is how fast I heal from injuries -- in days, instead of weeks! I think it is an athlete's best friend." Matt, Dayton, OH

"*I work in a very busy office with lots of stress every day. I used to have lots of tension in my neck and shoulders, until I started using Arnica Relief Cream. It is great! I keep it*

right at my desk and in my purse. I love it, because it takes the stress away, right away, and it does not smell or stain my clothes." Lynn, Portland, OR

"As a professional massage therapist, I have used many products, but I have never used a product that works so fast! The best part about using Arnica Relief Cream is that it makes my job easier, plus I can get better results for my clients. I love it and would not be without it." Ann, Portland, OR

"I wanted to let you know how wonderful your Arnica Relief Cream is. I dropped a 40 lb. piece of equipment on the front of my leg. WOW! It hurt! I grabbed your cream to put it to the ultimate test. It took the pain away! It is unbelievable how fast it works. Next great news is that I had no bruising. I could not believe it. Great product!" Connie, Yucca Valley, CA

MSM Aloe Spray

This product supports the body's structural integrity, decreases limitations in the range of motion of joints, and thereby supports regular life activity. This spray is beneficial for many skin conditions, and it works through well-known ingredients, like aloe vera and methyl-sulfonyl-methane (MSM). In nutrition circles, MSM is well known as a building block for collagen and connective tissues, making this spray an excellent approach to anti-aging skin care. Also, it can be used to soothe and relax any tensions arising from exercise.

Usage:
Spray directly on the skin. Use as needed.
Warnings:
For external use only. Avoid contact with eyes and mucous membranes. If eye contact occurs, rinse thoroughly with water. Do not apply to open wounds or broken skin. Use only on adults and children over 12.
Contraindications:
Hypersensitivity to aloe products.

ETI Formulation for Pain and Inflammatory Conditions

Practitioners can use these specific combinations of ETI formulas, as well as fine-tune dosage, frequency and proportions of each formula, to create a personalized approach for the individual client's support regarding pain and inflammatory conditions.

1. *Difficulty in falling asleep, when it is accompanied by pain*

Description: Helps to effectively, energetically support a person's normal sleep pattern by decreasing some nonspecific pain symptoms.
Formulation and Dosage:
During the day. Combine a dosage of Vital360 (10-20 drops) with Stress Relief (5-10 drops) in 2-4 oz. of water. Drink in the morning and in the middle of the day or when it is necessary to decrease the pain level.

At night. Combine a dosage of Goodnight (5 drops) and Stress Relief (5 drops), and Vital360 (5 drops) in 2-4 oz. of water. Drink before bed; continue up to two weeks.
Precautions: Increase the amount of water, up to 4-6 oz., for individuals with GI sensitivity to minerals in the solution.

2. *Difficulty in falling asleep, when it is accompanied with restless leg syndrome*

Formulation and Dosage:
At night. Combine a dosage of Goodnight (10 drops), Magnesium (3-5 drops) and Vital360 (10 drops) in 2-4 oz. of water. Drink before bedtime; continue up to two weeks.
Precautions: Increase the amount of water, up to 4-6 oz., for individuals with GI sensitivity to minerals in the solution.

3. *Gut dysfunction associated with any inflammatory state*

Description:
May be helpful in the spectrum of GI conditions associated with the increase of permeability and inflammation. This may be enhanced by using an oligo-antigenic diet, anti-inflammatory agents and factors that improve microbial balance.
Formulation and Dosage:
Combine a dosage of Healthy Mouth (5 drops), GI Aid (3-5 drops) and Vital360 (5 drops) in 2-4 oz. of water. Drink 3 times per day after food intake; continue up to two weeks.
Precautions: Always increase the amount of water up to 4-6 oz. for individuals with GI sensitivity to minerals in the solution.

4. *Healthy Teeth and Gums*

Description:
The following combination effectively supports you against pain and inflammation after dental procedures, as well as in the spectrum of conditions associated with gum problems. You may want to add it to your personal dental-care regimen, too.
Formulation and Dosage:
Combine a dosage of Healthy Mouth (10 drops) and Vital360 (10 drops). Add several drops to your toothbrush and gently apply to your gums and teeth.
Safety: Safe inside the recommended dosage.

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