Endocannabinoid System and Chronic Illness

Greg Abernathy, LMSW
GregAbernathyAnandConsulting@gmail.com
505-675-0692

1

The Endocannabinoid System (ECS):

- Biological regulatory system that regulates every other regulatory system in our bodies.
- Involved in our perception of the world.
- Helps connect us to our internal experiences.
- Associated with how we think and feel about ourselves.
- Is an aspect of our social interactions with people.
- Goal of the endocannabinoid system: Homeostasis–Balance.

2

ECS Function:

- ECS is involved in protection, food behaviors, rest and relaxation, repair of biological systems, sleep, eat, forget & protect, along with being integral in gut-health and the microbiome.
- Regulates pleasure, well-being, cellular homeostasis, pain perception, and immunological function.
- ECS protects against cancer cell proliferation, nerve damage, neurological disorders, and autoimmune disorders.

3

How the ECS Functions:

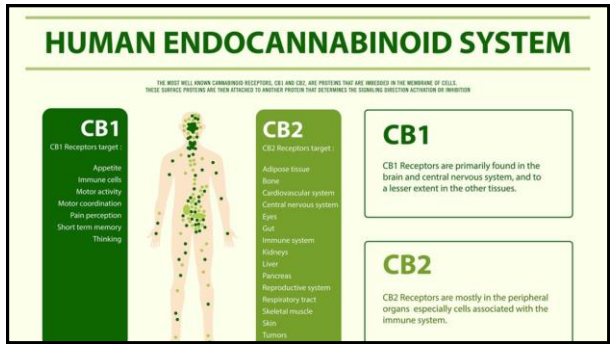
- The endocannabinoid system interacts via the CB1, CB2 & a variety of TRPV receptors in the body and brain to help regulate receptor functions via chemical messengers–Neurotransmitters.
- CB1 receptors work more with Central Nervous System (CNS) and are abundant in the brain.
- CB2 receptors are more associated with peripheral systems and immune function.
- TRPV1 receptors modulate pain perception.

4

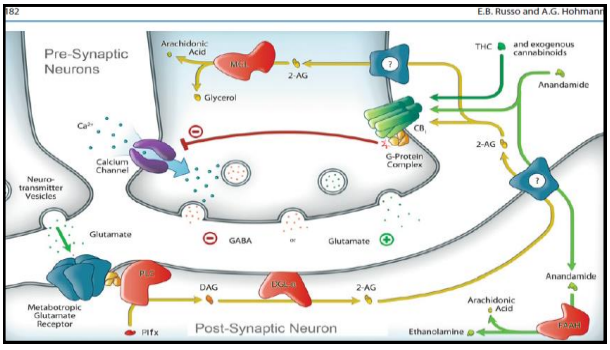
ECS Function:

- Primary endocannabinoids are anadamide (AEA) and 2-arachydonal glycerol (2-AG).
- AEA works on CB1 primarily and 2-AG works on CB2 primarily and can also be seen in the brain with TBI's.
- Endocannabinoids are produced and broken down on demand & travel in a retrograde fashion to inhibit neurotransmitter release from the post-synaptic neuron to the pre-synaptic neuron.

5



6



7

CB1 Expression in the Brian

- CB1 is highly expressed in nociceptive (pain sensing) areas, cerebellum (coordinated movement, equilibrium, posture, and motor learning), limbic system (reward, memory, emotions), basal ganglia (voluntary movement, procedural learning, eye-movements, cognition, and emotions).
- Though prominent in the substantia nigra (part of midbrain & basal ganglia important for reward and movement high in dopaminergic neurons), and periaqueductal grey matter (critical in autonomic function, motivated behavior, behavioral responses to threats, and primary control center for descending pain); distributed in a limited capacity in the brain stem—and not in medullary respiratory centers; harm reduction compared to opiates.

8

CB1 Receptors:

- CB1 is the most abundant G-protein-coupled receptor in the brain, with a major neuromodualry function; Role in "relax, eat, sleep, forget and protect." (Di Marzo, 1998).
- CB1 receptors modulate pain, memory, movement, emotion, appetite, emesis (vomiting), seizure threshold, GI motility/secretion.

9

CB2 Receptors:

- CB2 is a mainly peripheral (body, organs, etc.), immunomodulary receptor with an important role in pain, inflammation, and physiological defense (Pacher, 2011).
- CB2 agonists are currently being studied for the treatment of hepatic (liver) fibrosis and several other autoimmune disorders.

10

CB1 & CB2 Receptors in Skin:

- Cannabidiol (CBD) works on both CB1 and CB2 receptors which along with their effect on inflammation has anti-bacterial properties and is a TRPV4 agonist which can reduce acne (Olah, 2014).
- Topical THC is good for muscle pain and soreness provided the topical has other ingredients that help it absorb in the skin.
- CBD as a topical works best for conditions like eczema or psoriasis.

11

ECS Stimulation:

- The ECS is active in cardiac and bone physiology.
- Cannabis typically lowers blood pressure and raises heart rate, especially THC.
- Using cannabis in excess increases tachycardia (rapid heart rate), and postural hypotension (blood pressure), (Mittleman et al., 2001).
- CBD has been shown to stimulate bone fracture healing (Kogan et al., 2015).

12

Mechanisms of pain control by Cannabinoids: These effects take place whether they are endogenous or exogenous cannabinoids.

- Sertonergic
- Dopaminergic
- Anti-Inflammitory
- Cannabinoid-Opioid Interactions
- Periaqueductal Gray Matter
- NMDA/Gtluamate Receptors
- Substance P (vasodilation & neuromodulator)
- Synergy/Entourage Effect

13

ECS Tone:

- ECS tone is the baseline production of endocannabnoids and can be influenced by many factors e.g., trauma.
- ECS tone in certain brain regions (PAG) work in the control of pain (Walker, 1999).
- PAG is known as the source of migraines
- Cannabinoids are also located in the thalamus (relay for motor and sensory signals) and when tested in this region, cannabinoids were shown to be 10 times more effective than morphine (Russo, 2008).

14

Cannabis and Muscle Spasticity:

- Muscle tone is under tonic control of the ECS.
- CB1 agonists reduce spasticity while antagonist exacerbate it (Baker et al., 2000).
- CB1 Receptors are densely represented in cortical and basal ganglia areas (Parkinson's & Multiple Sclerosis), (Glass et al., 1997).
- Endocannabinoid functions are prominent in interneurons of the spinal cord (Farquhar-Smith et al., 2000).
- Cannabis based medications are clinically effective treatments for spasticity in multiple sclerosis (Novotna et al., 2011).

15

16

That our endocannabinoid system is integral to our physical and mental health, and overall wellbeing!

17

Clinical Endocannabinoid Deficiency:

- Proposed by neurologist and cannabis researcher, Dr. Ethan Russo, MD., in 2004.
- **Hypothesis**: All humans have an underlying "endocannabinoid tone" that is a reflection of levels of AEA & 2-AG, their production, metabolism, and relative abundance and state of cannabinoid receptors.
- **Theory**: In certain conditions, whether congenital or acquired, endocannabinoid tone becomes deficient, and productive of pathophysiological–and mental–syndromes.

18

Clinical Endocannabinoid Deficiency (CED) and other conditions:

- Migraine
- Fibromyalgia
- Irritable bowl syndrome (IBS)
- Causalgia/allodynia/brachial plexopathy/phantom limb pain
- Infantile colic
- Glaucoma
- Dysenorrhea (menstrual cramps)
- Hyeremesis Gravidarum (severe nausea and vomiting during pregnancy)
- Post-traumatic stress (PTS)
- Bipolar

19

CED Comorbidity: Migraine, Fibromyalgia, IBS:

All are hyperalgesic states: Pain perception with no apparent cause.

Primary headache in 97% of 201 fibromyalgia patients (Nicoldi, 1996).

35.6% of 101 migraine/coronary heart disease subjects had fibromyalgia (Peres, 2001).

31.6% of IBS patients had fibromyalgia; 32% of fibromyalgia patients had IBS (Sperber, 1999).

20

Adverse Childhood Experiences (ACE):

- Developed by the CDC and Kaiser Permanente in 1995 (Felitti et al., 1998).
- 10 question assessment surrounding childhood experiences over 3 domains: Physical Abuse, Physical Neglect, and Environmental factors.
- ACE scores of 3 and higher are shown to have higher incidences of heart disease and autoimmune disorders later in life.

21

ACE and CED and Mental Health:

- It has been shown that those who have developmental trauma and aversive experiences in childhood experience are prone to have higher reported symptoms associated with anxiety, depression, bipolar, BPD, ADHD, substance use, and other mental health concerns.
- Just as with physical conditions, the ECS influences mental health as well.
- The more we can understand the underlying mechanisms of these conditions, and how to appropriately apply medical cannabis for symptom management, helps us guide clients in ways that improve their well-being and quality of life.

22

Cannabis Overview

- It is critical to understand that cannabis is a plant that modulates the ECS, an innate homeostatic regulator of human physiology. CBD is a promising therapeutic ECS modulator.
- The ECS can also be influenced by lifestyle and dietary factors beyond cannabis, such as low-impact aerobic exercise and an anti-inflammatory/antioxidant diet.

23

Cannabis Plant:

There are three cannabis plant types, depending on who you ask.

Type I: High THC

Type II: Mixed THC/CBD

Type III: CBD Dominant

24

25

Cannabinoids:

- THC and CBD are the primary cannabinoids the plant produces.
- There are over 120 different cannabinoids in cannabis and each one has its own specific pharmacology.
- Research is currently being done on the various cannabinoids, and flavonoids, and many other constituents that have promising therapuetic effects.

26

Tetrahydrocannabinol (THC):

- Isolated in 1964 (Gaoni & Mechoulam, 1964).
- Delta-9 THC is what most people are familiar with.
- THC is produced in high amounts and is selectively bred to produce higher amounts of THC.
- There are several types of THC in the plant: THC-A, THCV, THCP, Delta-8 THC, and others.

27

THC:

- THC selectively binds to CB1 receptors and binds endogenous cannabinoids AEA and 2-AG (Patcher et al., 2006).
- THC mimics AEA and is responsible for the psychoactive intoxicating side-effect of cannabis.
- THC has many therapeutic benefits.

28

THC Benefits:

- THC is a muscle relaxant and reduces muscle spasticity of MS.
- Works as an antiemetic–prevents vomiting.
- THC does not inhibit COX-1 or COX-2 (Stott, 2005), like many other pain medications do; which can cause ulcers, heart attacks, and strokes as possible side-effects.
- Can reduce Beta-amyloid production (Eubanks, 2006); which is a component of Alzheimer's disease.

29

THC Benefits:

- THC is a bronchodilator (Williams, 1976).
- Analgesic and antipruritic (itching), (Neff, 2002).
- Neuroprotective antioxidant & prevents brain damage (Hampson, 1998; Magid et al., 2019).
- THC has 20 times the anti-inflammatory power than Aspirin and 2 times the anti-inflammatory power of hydrocortisone (Evans, 1991).

30

Cannabidiol (CBD):

- CBD was positively identified in 1963 by Mechoulam & Shvo.
- CBD is psychoactive but not intoxicating (Russo, 2017).
- CBD hardly binds to CB1 receptors.
- CBD binds to CB2 receptors and mimics 2-AG.
- Works as a negative allosteric modulator on CB1; which is why is can counter act the negative intoxicating side-effects of THC (Laprairie, 2015).

31

CBD Benefits:

CBD is neuroprotective anti-oxidant, strongly inhibits glutamate excitotoxicity (Hampson et al., 1998).

Known as a TRPV1 agonist like AEA and desensitize it (Bisogno et al., 2001).

Inhibits uptake of AEA and weakly inhibits the breakdown of AEA.

32

CBD Benefits:

- CBD is an alerting molecule compared to THC (Nicholson, 2004).
- CBD is an anticonvulsant (Cunha, 1980; Jones, 2010).
- Anti-anxiety (Crippa, 2010).
- CBD is cytotoxic in high concentrations for certain types of breast cancer while being preservative to other cells (Ligresti, 2006).

33

CBD Benefits:

- Antagonizes tumor necrosis factor alpha (tnf-a) in rheumatoid arthritis (Malfait, 2000).
- Agonist for 5-HT1a (serotonin) as anti-anxiety (Russo & Parker, 2005).
- Reduces brain damage from stroke and liver damage due to hepatic encephalopathy (Magen, 2010).
- CBD stimulates bone fracture healing (Kogan, 2015).

34

CBD Misconceptions:

- Small amounts are enough: Studies are showing that more CBD is better—especially with schizophrenia.
- CBD is sedative: CBD is an alerting molecule and sedation is typically due to drug-drug interactions or interactions with terpenoids like myrcene (Russo, 2017).
- CBD can turn into THC in the body: Humans don't have the enzymes to make this possible, and it upregulates AEA and ECS (Crippa et al., 2012).

35

Other Cannabinoids in the Plant:

- Cannabichromene (CBC)
- Cannabigerol (CBG)
- Tetrahydrocannabivarin (THCV)
- Cannabidivarin (CBDV)
- Cannabidolic Acid (CBD-A)
- Cannabinol (CBN)

36

Cannabigerol (CBG):

- GABA uptake inhibitor more so than THC & CBD (Banerjee et al., 1975).
- Antidepressant (Musty-Deyo, 2006).
- Lowers blood pressure and interocular pressure.
- Strong antispectic and antibiotic properties and is powerful against MRSA (Appendino, 2008).
- Stimulates several TRP channels (de Petrocellis, 2010; 2011).

37

Cannabichromene (CBC):

- Anti-inflammatory (Wirth et al., 1980).
- Pain relief, although less potent than THC (Davis & Hatoum, 1983).
- Antibiotic & Antifungal (ElSohly, 1982; McPartland & Russo, 2001).
- Destroys cancer cells (Ligresti et al., 2006).
- Demonstrates FAAH-inhibition (fatty acid amide hydrolase) that breaks down endocannabinoids and boosts AEA levels (Bisogno, 2001).

38

Tetrahydrocannabivarin (THCV):

- CB1 antagonist at low concentrations (Thomas et al., 2005), but becomes an agonist at higher doses (Pertwee, 2007).
- Helps with weight loss and blood sugar control for type II diabetics (Cawthorne, 2007; Riedel, 2009).
- Anticonvulsant (Hill et al., 2010).
- Decreases edema (fluid retention) and hyperalgesia (increased sensitivity to pain), (Bolognini, 2010).
- High in chemovars (strains) from South Africa (Durban Poison, Wowie Gold).

39

Cannabidivarin (CBDV):

- Under investigation as an anticonvulsant for partial onset seizures and is promising as a therapeutic for seizure control (Hill et al., 2010).
- Phase II human trials show around a 40% decrease in focal seizures when treated with CBDV (Brodie et al., 2021).

40

Tetrahydrocannabinolic Acid (THC-A):

- THC-A is the unheated cannabis flower and when decarboxylated converts to active THC.
- Anti-inflammatory and anti-TNF-alpha (Verhoeckx, 2006), and potentially good for autoimmune disorders.
- Anticonvulsant (Russo, 2016).
- Can stimulate appetite and reduce pain.
- I consider this a cannabenzo because it is great for anxiety relief without the negative side-effects.
- THC-A is psychoactive but not intoxicating.

41

Cannabidiolic Acid (CBD-A):

- Prominent phytocannabinoid in fresh hemp.
- Natural herbicide (Shoyama, 2008).
- Produces COX-inhibition at high doses (Takeda, 2008).
- Powerful antiemetic via 5-HT1a stimulation (Bolognini, 2013; Rock, 2013).

42

Cannabinol (CBN):

- CBN is a non-enzymatic byproduct of THC oxidation (Jin et al., 2019).
- Mildly sedative (Musty, 1976).
- Anticonvulsant (Turner, 1980).
- Anti-inflammatory (Evans, 1991).
- Antibiotic (McPartland & Russo, 2001).

43

Cannabis Constituents:

- Friedelin
- Epifridelanol
- (+)-Cannabisativine
- Anhydrocannabisativine
- Canniprene
- Cannflavin A
- Cannabisin B
- N-Trans-Caffeoytyramine

44

Terpenes the true heroes of Cannabis:

Terpenes are plant oils that give cannabis its unique flavor and aroma.

Most of the medical benefits of cannabis are mediated by terpene and cannabinoid interactions with each one having its own pharmacology and mechanism of action.

There are hundreds of terpenoids in the cannabis plant.

45

Common Cannabis Terpenes:

- Alpha-Pinene
- Beta-Myrcene
- D-Limonene
- D-Linalool
- Ocimene
- Terpinolene
- B-Caryophyllene
- Humulene
- Nerolidol

46

Alpha-Pinene Benefits:

- Most widely produced terpene in nature; pine trees (Noma, 2010).
- Anti-inflammatory (Gil et al., 1989).
- 60% bioavailability via inhalation (Falk, 1990), and is a bronchodilator.
- Wide spectrum antibiotic (Nissen, 2010).
- Acetylcholinesterase; prevents the breakdown of acetylcholine and reduces that short-term memory loss due to THC (Perry et al., 2000; Miyazawa, 2005); and can modulate the effect of too much THC (Russo, 2011).
- Good for mood uplift and concentration.

47

Beta-Myrcene Benefits:

- Found in mangos, hops, lemongrass, thyme.
- Sedative (Wichtl, 2004), and muscle relaxing (do Vale et al., 2002) and contributes to the "couch lock" associated with relaxing chemovars (Russo, 2011).
- Pain management and is shown to reduce pain for longer than morphine (Paula-Freire, 2012).

48

D-Limonene Benefits:

- Strong antidepressant (Komori et al., 1995).
- Breast cancer cell death in Phase II trials (Vigushin et al., 1998); and works against Bcl-2 colon cancer (Chidambara Murthy, 2012).
- Reduces inflammation and decreased IL-6 inflammatory markers in humans (d'Alessio, 2013).
- Agonist for adenosine A2a receptors (regulates release of glutamate and dopamine), and synergizes with THC and CBD (Carrier, 2006) for treatment of pain, depression, and Parkinson's.

49

D-Linalool Benefits:

- Found in lavender.
- Sedative via inhalation (Buchbauer et al., 1993).
- Anticonvulsant & anti-glutamaneric (Elisabetsky et al., 1995).
- Anti-anxiety (Russo, 2001).

50

Ocimene Benefits:

- Found commonly in West Coast and Dutch chemovars.
- Found in basil.
- Antifungal, anticonvulsant, and can act as an expectorant.
- Low boiling point (more on that later).

51

Terpinolene Benefits:

- Can reduce pain perception and inflammatory markers for rheumatoid arthritis (Macedo, 2016).
- Reduced short-term memory loss associated with THC and can be more stimulating in cannabis (Bonesi, 2010).
- Antifungal (Aydin, 2013).

52

Beta-Caryophyllene Benefits:

- Acts also as a cannabinoid due to selectively binding to CB2 receptors (Gertsch, 2008).
- Gastro-protective (Tambe et al., 1996).
- Decreased cocaine administration (Bahi, 2014), and is the best terpene cannabis has to offer in reducing cravings and drug-seeking behavior.

53

Humulene Benefits:

- Found in hops
- Anti-inflammatory (Fernandes et al., 2007)
- Works as an appetite suppressant and can reduce THC induced munchies.

54

Nerolidol Benefits:

- Found in ginger, jasmine, lavender, and lemongrass.
- Sedative and good for insomnia (Musty et al., 1976).
- Anti-anxiety.
- Antimicrobial, anti-parasitic, anti-oxidant, and pain relieving (Chan et al., 2016).

55

Here is a picture of a ninja-unicorn riding a T-Rex:

56

The Entourage Effect

- The "entourage effect", is the suggested positive contribution derived from the addition of terpenes to the effect of cannabinoids (Russo, 2017). Meaning that the entirety of effect is greater than the sum of its contributing parts (Ferber et al., 2020).
- Russo, 2019 described the concept of botanical synergy, in which a dominant molecule is supported by other plant derivatives – cannabinoids, terpenes, flavonoids and other inactive substances, to achieve a maximal pharmacological effect
- Simply put, the specific mixture of cannabinoids and terpenes can contribute to the positive benefits of cannabis-based medications.

57

Methods of Consumption:

Combustion by way of joint, pipe, water pipe.	Vaporization: Preferred method of inhalation.	Topical
Edible via chocolate, candy, beverages.	Tincture based: Best for full-spectrum CBD use.	Concentrates: Cannabis oil, wax, shatter.

58

Differences between Recreational and Medical Cannabis:

- Recreational is primary focused on levels of THC and less on the Entourage Effect and terpenes.
- Medical cannabis tests for cannabinoids and terpenes to provide more accurate information for patient health management.
- Medical more focused on symptom relief and recreational more on social or relaxing effects.

59

New Mexico Qualifying Conditions:

- Alzheimer's Disease
- Amyotrophic Lateral Sclerosis (ALS)
- Autism Spectrum Disorder
- Cancer
- Crohn's Disease
- Damage to the Nervous Tissue of the Spinal Cord (with objective neurological indication of intractable spasticity).
- Epilepsy/Seizure Disorder
- Friedreich's Ataxia
- Glaucoma
- Hepatitis C Infection currently receiving antiviral therapy
- HIV/AIDS
- Hospice Care
- Huntington's disease
- Inclusion Body Myositis
- Intractable Nausea/Vomiting
- Inflammatory Autoimmune-mediated Arthritis
- Lewy Body Disease
- Multiple Sclerosis
- Obstructive Sleep Apnea
- Opioid Use Disorder
- Painful Peripheral Neuropathy
- Parkinson's disease
- Post-Traumatic Stress Disorder
- Severe Anorexia/Cachexia
- Severe Chronic Pain
- Spasmodic Torticollis (Cervical Dystonia)
- Spinal Muscular Atrophy
- Ulcerative Colitis

60

Cannabis and Medication Interactions:

- CBD has been shown to affect in vivo and in vitro metabolism of drugs by inhibiting hepatic P450s in the 2C and 3A subtypes (Jaeger et al., 1996; Bornheim & Grillo, 1998).
- If a cannabinoid inhibits a CYP enzyme, then the metabolism of other drugs will be delayed, and their levels may increase. If a cannabinoid induces a CYP enzyme, causing more the the enzyme to be made, this will shorten the lifespan of another drug that is a substrate for the same CYP (Devitt-Lee, 2018).

61

Cannabinoid Drug Interactions:

- Warfarin: Cannabinoids inhibit CYP2C9- mediated metabolism of Warfarin and can cause elevated international normalized ratio (INR) and bleeding (Damkier et al., 2018).
- Cannabinoids can mix to various effects with other drugs causing a multitude of potential side-effects (Antoniou et al., 2020; Cox et al., 2019).
- Gabapentin: Gabapentin and cannabis have similar mechanism of action by way of affecting the action potential of neurons (Atwal et al., 2018), and for some people may experience unpleasant side-effects.

62

References:

- Antoniou, T., Bodkin, J., & Ho, J. M. (2020). Drug interactions with cannabinoids. *Canadian Medical Association Journal, 192*(9), E206. doi:10.1503/cmaj.191097
- Appendino, G., Gibbons, S., Giana, A., Pagani, A., Grassi, G., Stavri, M., . . . Rahman, M. M. (2008). Antibacterial cannabinoids from cannabis sativa: A structure−activity study. *Journal of Natural Products, 71*(8), 1427-1430. doi:10.1021/np8002673
- Atwal, N., Casey, S. L., Mitchell, V. A., & Vaughan, C. W. (2019). THC and gabapentin interactions in a mouse neuropathic pain model. *Neuropharmacology, 144*, 115-121. doi:10.1016/j.neuropharm.2018.10.006
- Aydin, E., Türkez, H., & Taşdemir, Ş. (2013). Anticancer and antioxidant properties of terpinolene in rat brain cells. *Archives of Industrial Hygiene and Toxicology, 64*(3), 415-424. doi:10.2478/10004-1254-64-2013-2365
- Bahi, A., Al Mansouri, S., Al Memari, E., Al Ameri, M., Nurulain, S. M., & Ojha, S. (2014). B-caryophyllene, a CB2 receptor agonist produces multiple behavioral changes relevant to anxiety and depression in mice. *Physiology & Behavior, 135*, 119-124. doi:10.1016/j.physbeh.2014.06.003
- Baker, D., Pryce, G., Croxford, J. L., Brown, P., Pertwee, R. G., Huffman, J. W., & Layward, L. (2000). Cannabinoids control spasticity and tremor in a multiple sclerosis model. *Nature, 404*(6773), 84-87. doi:10.1038/35003583
- Banerjee, S. P. (1975). Cannabinoids: Influence on neurotransmitter uptake in rat brain synaptosomes. *Journal of Pharmacology and Experimental Therapeutics, 194*(1), 74-81.

63

References:

- Bermudez-Silva, F. J., Cardinal, P., & Cota, D. (2011). The role of the endocannabinoid system in the neuroendocrine regulation of Energy Balance. *Journal of Psychopharmacology, 26*(1), 1-11. doi:10.1177/0269881111408458
- Bisogno, T., Hanuš, L., De Petrocellis, L., Tchilibon, S., Ponde, D. E., Brandi, I., . . . Di Marzo, V. (2001). Molecular targets for Cannabidiol and its synthetic analogues: Effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *British Journal of Pharmacology, 134*(4), 845-852. doi:10.1038/sj.bjp.0704327
- Bolognini, D., Costa, B., Maione, S., Comelli, F., Marini, P., Di Marzo, V., . . . Pertwee, R. G. (2010). The plant cannabinoid Δ9-tetrahydrocannabivarin can decrease signs of inflammation and inflammatory pain in mice. *British Journal of Pharmacology, 160*(3), 677-687. doi:10.1111/j.1476-5381.2010.00756.x
- Bolognini, D., Rock, E., Cluny, N., Cascio, M., Limebeer, C., Duncan, M., . . . Pertwee, R. (2013). Cannabidiolic acid prevents vomiting in*suncus murinus*and nausea-induced behaviour in rats by enhancing 5-HT1a receptor activation. *British Journal of Pharmacology, 168*(6), 1456-1470. doi:10.1111/bph.12043
- Bonesi, M., Menichini, F., Tundis, R., Loizzo, M. R., Conforti, F., Passalacqua, N. G., . . . Menichini, F. (2010). Acetylcholinesterase and butyrylcholinesterase inhibitory activity of pinus species essential oils and their constituents. *Journal of Enzyme Inhibition and Medicinal Chemistry, 25*(5), 622-628. doi:10.3109/14756360903389856
- Bornheim, L. M., & Grillo, M. P. (1998). Characterization of cytochrome P450 3A inactivation by cannabidiol: possible involvement of Cannabidiol-hydroxyquinone as a P450 inactivator. *Chemical Research in Toxicology, 11*(10), 1209-1216. doi:10.1021/tx9800598

64

References:

- Brodie, J. F., Lieberman, S., Moehrenschlager, A., Redford, K. H., Rodríguez, J. P., Schwartz, M., . . . Watson, J. E. (2021). Global policy for assisted colonization of species. *Science, 372*(6541), 456-458. doi:10.1126/science.abg0532
- Buchbauer, G., Jirovetz, L., Jäger, W., Plank, C., & Dietrich, H. (1993). Fragrance compounds and essential oils with sedative effects upon inhalation. *Journal of Pharmaceutical Sciences, 82*(6), 660-664. doi:10.1002/jps.2600820623
- Carrier, E. J., Auchampach, J. A., & Hillard, C. J. (2006). Inhibition of an equilibrative nucleoside transporter by Cannabidiol: A mechanism of cannabinoid immunosuppression. *Proceedings of the National Academy of Sciences, 103*(20), 7895-7900. doi:10.1073/pnas.0511232103
- Chidambara Murthy, K. N., Jayaprakasha, G. K., & Patil, B. S. (2012). D-limonene rich volatile oil from blood oranges inhibits angiogenesis, metastasis and cell death in human colon cancer cells. *Life Sciences, 91*(11-12), 429-439. doi:10.1016/j.lfs.2012.08.016
- Cox, E. J., Maharao, N., Patilea-Vrana, G., Unadkat, J. D., Rettie, A. E., McCune, J. S., & Paine, M. F. (2019). A marijuana-drug interaction primer: Precipitants, pharmacology, and pharmacokinetics. *Pharmacology & Therapeutics, 201*, 25-38. doi:10.1016/j.pharmthera.2019.05.001
- Crippa, J. S., Derenusson, G. N., Ferrari, T. B., Wichert-Ana, L., Duran, F. L., Martin-Santos, R., . . . Hallak, J. E. (2010). Neural basis of anxiolytic effects of cannabidiol (CBD) in Generalized Social Anxiety Disorder: A preliminary report. *Journal of Psychopharmacology, 25*(1), 121-130. doi:10.1177/0269881110379283

65

References:

- Cunha, J. M., Carlini, E., Pereira, A. E., Ramos, O. L., Pimentel, C., Gagliardi, R., . . . Mechoulam, R. (1980). Chronic administration of Cannabidiol to healthy volunteers and epileptic patients. *Pharmacology, 21*(3), 175-185. doi:10.1159/000137430
- D'Alessio, P. A., Ostan, R., Bisson, J., Schulzke, J. D., Ursint, M. V., & Béné, M. C. (2013). Oral administration of D-limonene controls inflammation in rat colitis and displays anti-inflammatory properties as diet supplementation in humans. *Life Sciences, 92*(24-26), 1151-1156. doi:10.1016/j.lfs.2013.04.013
- Damkier, P., Lassen, D., Christensen, M. M., Madsen, K. G., Hellfritzsch, M., & Pottegård, A. (2018). Interaction between warfarin and Cannabis. *Basic & Clinical Pharmacology & Toxicology, 124*(1), 28-31. doi:10.1111/bcpt.13152
- Davis, W., & Hatoum, N. S. (1983). Neurobehavioral actions of cannabichromene and interactions with Δ9-tetrahydrocannabinol. *General Pharmacology: The Vascular System, 14*(2), 247-252. doi:10.1016/0306-3623(83)90004-6
- De Petrocellis, L., Ligresti, A., Moriello, A. S., Allarà, M., Bisogno, T., Petrosino, S., . . . Di Marzo, V. (2011). Effects of cannabinoids and cannabinoid-enriched cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. *British Journal of Pharmacology, 163*(7), 1479-1494. doi:10.1111/j.1476-5381.2010.01166.x
- Di Marzo, V., Melck, D., Bisogno, T., & De Petrocellis, L. (1998). Endocannabinoids: Endogenous cannabinoid receptor ligands with neuromodulatory action. *Trends in Neurosciences, 21*(12), 521-528. doi:10.1016/s0166-2236(98)01283-1
- Elisabetsky, E., Marschner, J., & Onofre Souza, D. (1995). Effects of linalool on glutamatergic system in the rat cerebral cortex. *Neurochemical Research, 20*(4), 461-465. doi:10.1007/bf00973103

66

References:

- Elsohly, H. N., Turner, C. E., Clark, A. M., & Elsohly, M. A. (1982). Synthesis and antimicrobial activities of certain cannabichromene and cannabigerol related compounds. *Journal of Pharmaceutical Sciences*, *71*(12), 1319-1323. doi:10.1002/jps.2600711204
- Eubanks, L. M., Rogers, C. J., Beuscher IV, A. E., Koob, G. F., Olson, A. J., Dickerson, T. J., & Janda, K. D. (2006). A molecular link between the active component of marijuana and alzheimer's disease pathology. *Molecular Pharmaceutics*, *3*(6), 773-777. doi:10.1021/mp060066m
- Evans, F. J. (1991). Cannabinoids: The separation of central from peripheral effects on a structural basis. *Planta Medica*, *57*(7), S60-67. doi:10.1055/s-2006-960231
- Falk, A. A., Hagberg, M. T., Lof, A. E., Wigaeus-Hjelm, E. M., & Wang, Z. P. (1990). Uptake, distribution and elimination of alpha-pinene in man after exposure by inhalation. *Scandinavian Journal of Work, Environment & Health*, *16*(5), 372-378. doi:10.5271/sjweh.1771
- Fanqahar-Smith, W., Egerová, M., Bradbury, E. J., McMahon, S. B., Rice, A. S., & Elphick, M. R. (2000). Cannabinoid CB1 receptor expression in rat spinal cord. *Molecular and Cellular Neuroscience*, *15*(6), 510-521. doi:10.1006/mcne.2000.0844
- Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., . . . Marks, J. S. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. *American Journal of Preventive Medicine*, *14*(4), 245-258. doi:10.1016/s0749-3797(98)00017-8

67

References:

- Ferber, S. G., Namdar, D., Hen-Shoval, D., Eger, G., Koltai, H., Shoval, G., . . . Weller, A. (2020). The "entourage effect": Terpenes coupled with cannabinoids for the treatment of mood disorders and anxiety disorders. *Current Neuropharmacology*, *18*(2), 87-96. doi:10.2174/1570159x17666190903103923
- Fernandes, E. S., Passos, G. F., Medeiros, R., Da Cunha, F. M., Ferreira, J., Campos, M. M., . . . Calixto, J. B. (2007). Anti-inflammatory effects of compounds alpha-humulene and (−)-Trans-caryophyllene isolated from the essential oil of Cordia Verbenacea. *European Journal of Pharmacology*, *569*(3), 228-236. doi:10.1016/j.ejphar.2007.04.059
- Gaetani, S., Dipasquale, P., Romano, A., Righetti, L., Cassano, T., Piomelli, D., & Cuomo, V. (2009). Chapter 5 the endocannabinoid system as a target for novel anxiolytic and antidepressant drugs. *International Review of Neurobiology*, *85*, 57-72. doi:10.1016/s0074-7742(09)85005-8
- Gallily, R., Yekhtin, Z., & Hanuš, L. O. (2015). Overcoming the Bell-Shaped Dose-Response of Cannabidiol by Using Cannabis Extract Enriched in Cannabidiol. *Pharmacology & Pharmacy*, *06*(02), 75-85. doi:10.4236/pp.2015.62010
- Gaoni, Y., & Mechoulam, R. (1964). Isolation, structure, and partial synthesis of an active constituent of hashish. *Journal of the American Chemical Society*, *86*(8), 1646-1647. doi:10.1021/ja01062a046
- Gertsch, J., Leonti, M., Raduner, S., Racz, I., Chen, J., Xie, X., . . . Zimmer, A. (2008). Beta-caryophyllene is a dietary cannabinoid. *Proceedings of the National Academy of Sciences*, *105*(26), 9099-9104. doi:10.1073/pnas.0803601105

68

References:

- Glass, M., Faull, R., & Dragunow, M. (1997). Cannabinoid receptors in the human brain: A detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. *Neuroscience*, *77*(2), 299-318. doi:10.1016/s0306-4522(96)00428-9
- Gargel do Vale, T., Couto Furtado, E., Santos Jr., J., & Viana, G. (2002). Central effects of citral, myrcene and limonene, constituents of essential oil chemotypes from Lippia Alba (mill.) N.E. Brown. *Phytomedicine*, *9*(8), 709-714. doi:10.1078/094471102321621304
- Hampson, A. J., Grimaldi, M., Axelrod, J., & Wink, D. (1998). Cannabidiol and (−)Δ 9-tetrahydrocannabinol are neuroprotective antioxidants. *Proceedings of the National Academy of Sciences*, *95*(14), 8268-8273. doi:10.1073/pnas.95.14.8268
- Hill, A. J., Weston, S. E., Jones, N. A., Smith, I., Bevan, S. A., Williamson, E. M., . . . Whalley, B. J. (2010). Δ9-tetrahydrocannabivarin suppresses in vitro epileptiform and in vivo seizure activity in adult rats. *Epilepsia*, *51*(8), 1522-1532. doi:10.1111/j.1528-1167.2010.02523.x
- Huestis, M. A. (2005). Pharmacokinetics and metabolism of the plant cannabinoids, Δ9-tetrahydrocannabinol, Cannabidiol and Cannabinol. *In: Pertwee, R.G. (eds) Handbook of Experimental Pharmacology*, *168*, 657-690. doi:10.1007/3-540-26573-2_23
- Jaeger, W., Benet, L. Z., & Bornheim, L. M. (1996). Inhibition of cyclosporine and tetrahydrocannabinol metabolism by cannabidiol in mouse and human microsomes. *Xenobiotica*, *26*(3), 275-284. doi:10.3109/00498259609046707
- Jin, D., Jin, S., & Chen, J. (2019). Cannabis indoor growing conditions, management practices, and Post-Harvest Treatment: A Review. *American Journal of Plant Sciences*, *10*(06), 925-946. doi:10.4236/ajps.2019.106067

69

References:

- Jones, N. A., Hill, A. J., Smith, I., Bevan, S. A., Williams, C. M., Whalley, B. J., & Stephens, G. J. (2010). Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. *Journal of Pharmacology and Experimental Therapeutics*, *332*(2), 569-577. doi:10.1124/jpet.109.159145
- Kaminol, I. G., Shirakawa, I., Takahashi, R. N., Knobel, E., & Musty, R. E. (1975). Effects of delta9-tetrahydrocannabinol and cannabinol in man. *Pharmacology*, *13*(6), 502-512. doi:10.1159/000136944
- Kilaru, A., & Chapman, K. (2020). The endocannabinoid system. *Essays in Biochemistry*, *64*(3), 485-499. doi:10.1042/ebc20190086
- Kogan, N. M., Melamed, E., Wasserman, E., Raphael, B., Breuer, A., Stok, K. S., . . . Bab, I. (2015). Cannabidiol, a major non-psychotropic cannabis constituent enhances fracture healing and stimulates lysyl hydroxylase activity in osteoblasts. *Journal of Bone and Mineral Research*, *30*(10), 1905-1913. doi:10.1002/jbmr.2513
- Komori, T., Fujiwara, R., Tanida, M., Nomura, J., & Yokoyama, M. M. (1995). Effects of citrus fragrance on immune function and depressive states. *Neuroimmunomodulation*, *2*(3), 174-180. doi:10.1159/000096889
- Lapaire, R. B., Bagher, A. M., Kelly, M. E., & Denovan-Wright, E. M. (2015). Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. *British Journal of Pharmacology*, *172*(20), 4790-4805. doi:10.1111/bph.13250
- Ligresti, A., Moriello, A. S., Starowicz, K., Matias, I., Pisanti, S., De Petrocellis, L., . . . Di Marzo, V. (2006). Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. *Journal of Pharmacology and Experimental Therapeutics*, *318*(3), 1375-1387. doi:10.1124/jpet.106.105247

70

References:

- Macedo, E., Santos, W., Sousa Neto, B., Lopes, E., Piauilino, C., Cunha, F., . . . Almeida, F. (2016). Association of terpinolene and diclofenac presents antinociceptive and anti-inflammatory synergistic effects in a model of chronic inflammation. *Brazilian Journal of Medical and Biological Research*, *49*(7), E5103. doi:10.1590/1414-431x20165103
- Magen, I., Avraham, Y., Ackerman, Z., Vorobiev, L., Mechoulam, R., & Berry, E. (2010). Cannabidiol ameliorates cognitive and motor impairments in bile-duct ligated mice via 5-HT1A receptor activation. *British Journal of Pharmacology*, *159*(4), 950-957. doi:10.1111/j.1476-5381.2009.00589.x
- Magid, L., Heymann, S., Elgali, M., Avram, L., Cohen, Y., Liraz-Zaltsman, S., . . . Shohami, E. (2019). Role of CB2 receptor in the recovery of mice after traumatic brain injury. *Journal of Neurotrauma*, *36*(11), 1836-1846. doi:10.1089/neu.2018.6063
- Malfait, A. M., Gallily, R., Sumariwalla, P. F., Malik, A. S., Andreakos, E., Mechoulam, R., & Feldmann, M. (2000). The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. *Proceedings of the National Academy of Sciences*, *97*(17), 9561-9566. doi:10.1073/pnas.160105897
- Martin-Santos, R., A. Crippa, J., Batalla, A., Bhattacharyya, S., Atakan, Z., Borgwardt, S., . . . K. McGuire, P. (2012). Acute effects of a single, oral dose of D9-tetrahydrocannabinol (THC) and cannabidiol (CBD) administration in Healthy Volunteers. *Current Pharmaceutical Design*, *18*(32), 4966-4979. doi:10.2174/138161212802884780
- McPartland, J. M., & Russo, E. B. (2001). Cannabis and cannabis extracts. *Journal of Cannabis Therapeutics*, *1*(3-4), 103-132. doi:10.1300/j175v01n03_08
- Mechoulam, R., & Shvo, Y. (1963). Hashish. I. The structure of cannabinol. *Tetrahedron*, *19*(12), 2073-2078. doi:10.1016/0040-4020(63)85022-x

71

References:

- Mitlleman, M. A., Lewis, R. A., Maclure, M., Sherwood, J. B., & Muller, J. E. (2001). Triggering myocardial infarction by marijuana. *Circulation*, *103*(23), 2805-2809. doi:10.1161/01.cir.103.23.2805
- Miyazawa, M., & Yamakiji, C. (2005). Inhibition of acetylcholinesterase activity by bicyclic monoterpenoids. *Journal of Agricultural and Food Chemistry*, *53*(5), 1765-1768. doi:10.1021/jf040019b
- Neff, G. W., O'Brien, C. B., Reddy, K. R., Bergasa, N. V., Regev, A., Molina, E., . . . Schiff, E. (2002). Preliminary observation with dronabinol in patients with intractable pruritus secondary to cholestatic liver disease. *The American Journal of Gastroenterology*, *97*(8), 2117-2119. doi:10.1111/j.1572-0241.2002.05852.x
- Nicholson, A. N., Turner, C., Stone, B. M., & Robson, P. J. (2004). Effect of Δ-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. *Journal of Clinical Psychopharmacology*, *24*(3), 305-313. doi:10.1097/01.jcp.0000125688.05091.8f
- Nicoloff, M. (1996). Differential sensitivity to morphine challenge in migraine sufferers and headache-exempt subjects. *Cephalalgia*, *16*(5), 297-304. doi:10.1046/j.1468-2982.1996.1605297.x
- Nissen, L., Zatta, A., Stefanini, I., Grandi, S., Sgorbati, B., Biavati, B., & Monti, A. (2010). Characterization and antimicrobial activity of essential oils of industrial hemp varieties (cannabis sativa L.). *Fitoterapia*, *81*(5), 413-419. doi:10.1016/j.fitote.2009.11.010
- Noma, Y., & Asakawa, Y. (2016). Biotransformation of monoterpenoids by microorganisms, insects, and mammals. In 1948883215 1359571704 B. K. Can & 1948883216 1359571704 G. Buchbauer (Authors), *Handbook of Essential Oils: Science, technology, and applications* (3rded., pp. 585-736). Boca Raton, FL: CRC Press.

72

References:

- Novotna, A., Mares, J., Ratcliffe, S., Novakova, I., Vachova, M., Zapletalova, O., . . . Davies, P. (2011). A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. *European Journal of Neurology, 18*(8), 1122-1131. doi:10.1111/j.1468-1331.2010.03328.x
- Oláh, A., Tóth, B. I., Borbíró, I., Sugawara, K., Szöllősi, A. G., Czifra, G., . . . Bíró, T. (2014). Cannabidiol exerts sebostatic and antiinflammatory effects on human sebocytes. *Journal of Clinical Investigation, 124*(9), 3713-3724. doi:10.1172/jci64628
- Pacher, P., Bátkai, S., & Kunos, G. (2006). The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacological Reviews, 58*(3), 389-462. doi:10.1124/pr.58.3.2
- Paula-Freire, L. I., Andersen, M. L., Molska, G. R., Köhn, D. O., & Carlini, E. L. (2012). Evaluation of the antinociceptive activity of ocimum gratissimum L. (Lamiaceae) essential oil and its isolated active principles in mice. *Phytotherapy Research, 27*(8), 1220-1224. doi:10.1002/ptr.4845
- Peres, M. F., Young, W. B., Kaup, A. O., Zukerman, E., & Silberstein, S. D. (2001). Fibromyalgia is common in patients with transformed migraine. *Neurology, 57*(7), 1326-1328. doi:10.1212/wnl.57.7.1326
- Perry, N. S., Houghton, P. J., Theobald, A., Jenner, P., & Perry, E. K. (2000). In-vitro inhibition of human erythrocyte acetylcholinesterase by salvia lavandulaefolia essential oil and constituent terpenes. *Journal of Pharmacy and Pharmacology, 52*(7), 895-902. doi:10.1211/0022357001774598

73

References:

- Pertwee, R. G. (2007). GPR55: A new member of the Cannabinoid Receptor Clan? *British Journal of Pharmacology, 152*(7), 984-986. doi:10.1038/sj.bjp.0707464
- Riedel, G., Fadda, P., McKillop-Smith, S., Pertwee, R. G., Platt, B., & Robinson, L. (2009). Synthetic and plant-derived cannabinoid receptor antagonists show hyperphagic properties in fasted and non-fasted mice. *British Journal of Pharmacology, 156*(7), 1154-1166. doi:10.1111/j.1476-5381.2008.00107.x
- Rock, E., & Parker, L. (2013). Effect of low doses of cannabidiolic acid and ondansetron on LiCl-induced conditioned gaping (a model of nausea-induced behaviour) in rats. *British Journal of Pharmacology, 169*(3), 685-692. doi:10.1111/bph.12162
- Russo, E. B. (2004). Clinical Endocannabinoid Deficiency (CECD): Can this Concept Explain Therapeutic Benefits of Cannabis in Migraine, Fibromyalgia, Irritable Bowel Syndrome and other Treatment-Resistant Conditions? *Neuroendocrinology Letters, 25*(1-2), 31-39.
- Russo, E. B. (2008). Cannabinoids in the management of difficult to treat pain. *Therapeutics and Clinical Risk Management, 4*(1), 245-259. doi:10.2147/tcrm.s1928
- Russo, E. B. (2011). Taming THC: Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *British Journal of Pharmacology, 163*(7), 1344-1364. doi:10.1111/j.1476-5381.2011.01238.x
- Russo, E. B. (2016). Clinical endocannabinoid deficiency reconsidered: Current research supports the theory in migraine, fibromyalgia, irritable bowel, and other treatment-resistant syndromes. *Cannabis and Cannabinoid Research, 1*(1), 154-165. doi:10.1089/can.2016.0009
- Russo, E. B. (2017). Cannabidiol claims and misconceptions. *Trends in Pharmacological Sciences, 38*(3), 198-201. doi:10.1016/j.tips.2017.03.006

74

References:

- Russo, E. B., Burnett, A., Hall, B., & Parker, K. K. (2005). Agonistic properties of cannabidiol at 5-HT1A receptors. *Neurochemical Research, 30*(8), 1037-1043. doi:10.1007/s11064-005-6978-1
- Shoyama, Y., Sugawa, C., Tanaka, H., & Morimoto, S. (2008). Cannabinoids act as necrosis-inducing factors in cannabis sativa. *Plant Signaling & Behavior, 3*(12), 1111-1112. doi:10.4161/psb.3.12.7011
- Sperber, A. D., Atzmon, Y., Neumann, L., Weisberg, I., Shalit, Y., Abu-Shakrah, M., . . . Baskila, D. (1999). Fibromyalgia in the irritable bowel syndrome: Studies of prevalence and clinical implications. *American Journal of Gastroenterology, 94*(12), 3541-3546. doi:10.1111/j.1572-0241.1999.01643.x
- Takeda, S., Misawa, K., Yamamoto, I., & Watanabe, K. (2008). Cannabidiolic acid as a selective cyclooxygenase-2 inhibitory component in Cannabis. *Drug Metabolism and Disposition, 36*(9), 1917-1921. doi:10.1124/dmd.108.020909
- Tambe, Y., Tsujiuchi, H., Honda, G., Ikeshiro, Y., & Tanaka, S. (1996). Gastric cytoprotection of the non-steroidal anti-inflammatory sesquiterpene, β-caryophyllene. *Planta Medica, 62*(05), 469-470. doi:10.1055/s-2006-957942
- Thomas, A., Stevenson, L. A., Wease, K. N., Price, M. R., Baillie, G., Ross, R. A., & Pertwee, R. G. (2005). Evidence that the plant cannabinoid Δ9-tetrahydrocannabivarin is a cannabinoid CB1 and CB2 receptor antagonist. *British Journal of Pharmacology, 146*(7), 917-926. doi:10.1038/sj.bjp.0706414
- Turner, C. E., Elsohly, M. A., & Boeren, E. G. (1980). Constituents of Cannabis sativa L. XVII. A review of the natural constituents. *Journal of Natural Products, 43*(2), 169-234. doi:10.1021/np50008a001

75

References:

- Verhoeckx, K. C., Korthout, H. A., Van Meeteren-Kreikamp, A., Ehlert, K. A., Wang, M., Van der Greef, J., . . . Witkamp, R. F. (2006). Unheated Cannabis sativa extracts and its major compound THC-acid have potential immuno-modulating properties not mediated by CB1 and CB2 receptor coupled pathways. *International Immunopharmacology, 6*(4), 656-665. doi:10.1016/j.intimp.2005.10.002
- Vigushin, D. M., Poon, G. K., Boddy, A., English, J., Halbert, G. W., Pagonis, C., . . . Coombes, R. C. (1998). Phase I and pharmacokinetic study of D -limonene in patients with advanced cancer. *Cancer Chemotherapy and Pharmacology, 42*(2), 111-117. doi:10.1007/s002800050793
- Walker, J. M., Huang, S. M., Strangman, N. M., Tsou, K., & Sañudo-Peña, M. C. (1999). Pain modulation by release of the endogenous cannabinoid anandamide. *Proceedings of the National Academy of Sciences, 96*(21), 12198-12203. doi:10.1073/pnas.96.21.12198
- Williams, S. J., Hartley, J. P., & Graham, J. D. (1976). Bronchodilator effect of delta1-tetrahydrocannabinol administered by aerosol of asthmatic patients. *Thorax, 31*(6), 720-723. doi:10.1136/thx.31.6.720
- Wirth, P. W., Sue Watson, E., ElSohly, M., Turner, C. E., & Murphy, J. C. (1980). Anti-inflammatory properties of cannabichromene. *Life Sciences, 26*(23), 1991-1995. doi:10.1016/0024-3205(80)90631-1

76