

Understanding the Endocannabinoid System

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The Endocannabinoid System

The endocannabinoid system (ECS) was discovered by Dr. Rafael Mechoulam: the father of cannabis-based medicines.

The endocannabinoid system (ECS) – composed of cannabinoid receptors, endocannabinoids, and metabolic enzymes – serves an essential function in the human body: restoring homeostasis via various physiological and regulatory mechanisms.

In 1992, at the Hebrew University in Jerusalem, Dr. Lumir Hanus along with American researcher Dr. William Devane, discovered the first endocannabinoid anandamide.



WholisticMatters. (October 2018). The Role of the Endocannabinoid System in Human Health. Retrieve July 16, 2020 from <https://wholisticmatters.com/the-role-of-the-endocannabinoid-system-in-human-health/>

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The Endocannabinoid System

Components of the ECS are present and vital in nearly every area of the human body. Thus, disruption of the ECS has a serious, negative impact on human health.

The ECS is responsible for homeostatic roles:

- Relaxation
- Metabolism
- Sleep
- Memory
- Neuroprotection
- Immunity and inflammation
- Pain and emotional memory



Aizpurua-Olaizola, O., Elezgarai, I., Rico-Barrio, I., Zaramona, I., Etxebarria, N., & Usobiaga, A. (2017). Targeting the endocannabinoid system: future therapeutic strategies. *Drug Discovery Today*, 22(1), 105-110. doi:<https://doi.org/10.1016/j.drudis.2016.08.005>

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The Endocannabinoid System

Deemed the “endocannabinoid tone,” the proper functioning of the ECS depends on the density, functional status, and availability of endocannabinoids (eCBs): endogenous, tightly regulated, lipid-signaling molecules synthesized as needed in neurons. These signaling molecules bind cannabinoid receptors (CBs) to inhibit the release of certain neurotransmitters.

Endocannabinoid tone is influenced by multiple external factors, such as physical activity, eating a well-balanced diet of macronutrients, micronutrients, and phytonutrients, and stress modification. Whatever the reason, endocannabinoid deficiency prevents the ECS from properly regulating homeostasis in the body, but supplementation with phytocannabinoids can resolve some of these issues.

Aizpurua-Olaizola, O., Elezgarai, I., Rico-Barrio, I., Zaramona, I., Etxebarria, N., & Usobiaga, A. (2017). Targeting the endocannabinoid system: future therapeutic strategies. *Drug Discovery Today*, 22(1), 105-110. doi:<https://doi.org/10.1016/j.drudis.2016.08.005>

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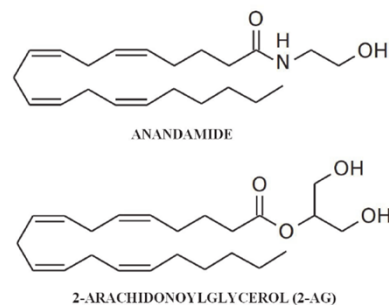
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Cannabinoids - Endocannabinoids

The endogenous arachidonate-based lipids, anandamide (N-arachidonylethanolamide, AEA) and 2-arachidonoylglycerol (2-AG); these are known as "endocannabinoids" and are physiological ligands for the cannabinoid receptors. Endocannabinoids are all eicosanoids.

The enzymes that synthesize and degrade the endocannabinoids, such as FAAH or MAGL.



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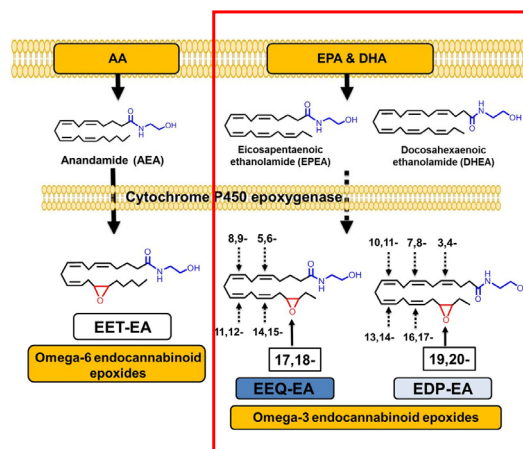
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Cannabinoids - Endocannabinoids

The endogenous EPA/DHA -based lipids, EPEA and DHEA, are known as "endocannabinoids" and are physiological ligands for the cannabinoid receptors.

The endocannabinoid epoxides derived from endocannabinoids via cytochrome P450 epoxigenase act as endocannabinoids.



McDougle, Daniel R., Josephine E. Watson, Amr A. Abdeen, Reheem Adili, Megan P. Caputo, John E. Krampf, Rodney W. Johnson, Kristopher A. Kilian, Michael Holinstat, and Aditi Das. 2017. "Anti-inflammatory ω-3 endocannabinoid epoxides". *Proceedings of the National Academy of Sciences*, 114: E6034-E43.

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Anti-inflammatory ω -3 endocannabinoid epoxides

“... the ω -3 endocannabinoid epoxides are found at concentrations comparable to those of other endocannabinoids and are expected to play critical roles during inflammation in vivo; thus their identification may aid in the development of therapeutics for neuroinflammatory and cerebrovascular diseases.”

McDougle, Daniel R., Josephine E. Watson, Amr A. Abdeen, Rehem Adili, Megan P. Caputo, John E. Krapf, Rodney W. Johnson, Kristopher A. Kilian, Michael Holinstat, and Aditi Das. 2017. 'Anti-inflammatory ω -3 endocannabinoid epoxides'. *Proceedings of the National Academy of Sciences*, 114: E6034-E43.

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Polyunsaturated fatty acids and endocannabinoids in health and disease

“Polyunsaturated fatty acids (PUFAs) are lipid derivatives of omega-3 (docosahexaenoic acid, DHA, and eicosapentaenoic acid, EPA) or of omega-6 (arachidonic acid, ARA) synthesized from membrane phospholipids and used as a precursor for endocannabinoids (ECs). ... Western diet — as well as restriction of micronutrients and fatty acids, such as DHA — could be related to altered production of pro-inflammatory mediators (e.g. eicosanoids) and ECs, contributing to the progression of cardiovascular diseases, diabetes, obesity, depression or impairing conditions, such as Alzheimer's disease.”

McDougle, Daniel R., Josephine E. Watson, Amr A. Abdeen, Rehem Adili, Megan P. Caputo, John E. Krapf, Rodney W. Johnson, Kristopher A. Kilian, Michael Holinstat, and Aditi Das. 2017. 'Anti-inflammatory ω -3 endocannabinoid epoxides'. *Proceedings of the National Academy of Sciences*, 114: E6034-E43.

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Cannabinoids - Phytocannabinoids

Plant-based compounds for which our bodies respond similarly to cannabinoids that we produce.

Plants that contain compounds that interact with the ECS system:

- Hemp
- Carrot
- Echinacea



Russo, Ethan B. 2016. 'Beyond Cannabis: Plants and the Endocannabinoid System'. *Trends in Pharmacological Sciences*, 37: 594-605.

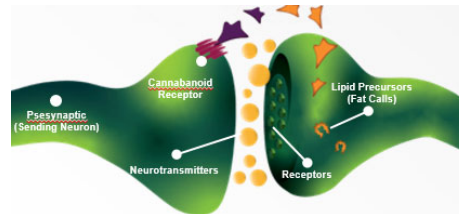
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Endocannabinoid Receptors

A “receptor” is typically defined as an intracellular protein molecule that receives and responds to extracellular chemical signals, ultimately producing a cellular cascade of events. Cannabinoid receptors (CBs) are the primary targets of the ECS, bound by lipid-signaling molecules called endocannabinoids (eCBs) that are produced on demand in response to elevated intracellular calcium levels in neurons. After eCBs bind a receptor to inhibit the release of neurotransmitters and exert a particular effect on the body, they are degraded via metabolic enzymes in a process called hydrolysis.



WholisticMatters. (October 2018). Cannabinoid Receptors: CB1 and CB2. Retrieved July 16, 2020 from <https://wholisticmatters.com/cb2-to-the-rescue-understanding-cb1-and-cb2-receptors/>.

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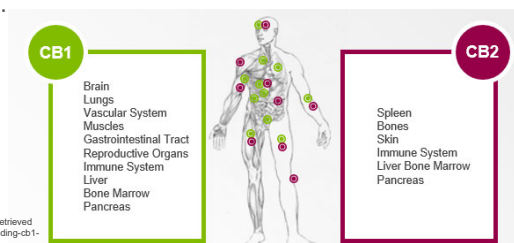
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Endocannabinoid Receptors: CB1 & CB2

Cannabinoid Receptor 1 (CB1) is associated with psychoactive, neuromodulatory, and analgesic effects due to its activation by a lipid called tetrahydrocannabinol (THC). CB1 is mostly expressed in the brain, adipocytes (fat cells), hepatocytes (liver cells), and musculoskeletal tissues.

Cannabinoid Receptor 2 (CB2) is associated with anti-inflammatory and immunomodulatory effects, but delivers no psychoactive effects. CB2 is expressed in body cells that control immune function and (potentially) the central nervous system (CNS). Additionally, research suggests that secondary metabolites from phytonutrients in plant-based foods enhance the activity of CB2 receptors and confer healthy inflammatory responses.



WholisticMatters. (October 2018). Cannabinoid Receptors: CB1 and CB2. Retrieved July 16, 2020 from <https://wholisticmatters.com/cb2-to-the-rescue-understanding-cb1-and-cb2-receptors/>.

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ECS Ligands

2-arachidonoyl glycerol (2-AG) has been linked to our emotional states, protection from seizures, and maintaining cardiovascular health.

Anandamide, or the bliss molecule, plays a role in the neural generation of pleasure and motivation so it's appropriate that its name is derived from "ananda," a Sanskrit word meaning bliss. It has been linked to that post exercise "high" after intense activity.

Di Marzo, V., & De Petrocellis, L. (2012). Why do cannabinoid receptors have more than one endogenous ligand?. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, 367(1607), 3216–3228. <https://doi.org/10.1098/rstb.2011.0382>

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Anandamide (AEA) & 2-AG (2-Arachidonoyl Glycerol)

Endocannabinoid ligands such as anandamide [N-arachidonylethanolamine (AEA)] and 2-arachidonoyl glycerol (2-AG) are known orexigenic mediators that act via CB₁ receptors in hypothalamus and limbic forebrain to induce appetite and stimulate food intake.

Yoshida R, Ohkuni T, Jyotaki M, et al. Endocannabinoids selectively enhance sweet taste. *Proc Natl Acad Sci U S A*. 2010;107(2):935-939.

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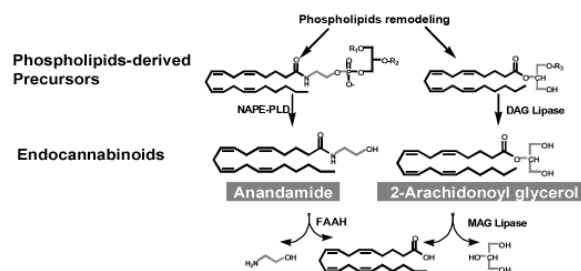


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Anandamide: FAAH Enzyme

CBD is known to interfere with the FAAH enzyme that degrades anandamide and, therefore, keeps levels high (endocannabinoid tone).¹

Endocannabinoids Formation and Inactivation



Ibeas Bih, Clementino, Tong Chen, Alistair V. W. Nunn, Michaël Bazelot, Mark Dallas, and Benjamin J. Whalley. 2015. 'Molecular Targets of Cannabidiol in Neurological Disorders'. *Neurotherapeutics*, 12: 699-730.

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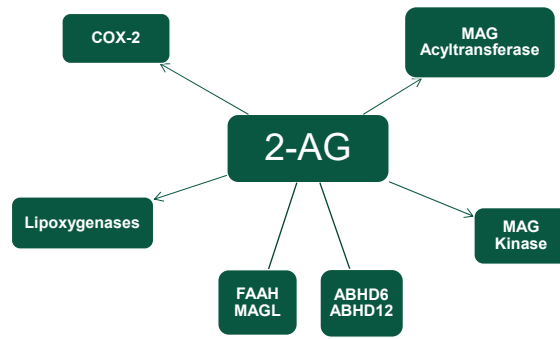
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2-Arachidonoylglycerol (2-AG)

2-Arachidonoylglycerol (2-AG) is an endocannabinoid, an endogenous agonist of the CB1 receptor and the primary endogenous ligand for the CB2 receptor. It is an ester formed from the omega-6 fatty acid arachidonic acid and glycerol.

It is present at relatively high levels in the central nervous system, with cannabinoid neuromodulatory effects.

2-AG is susceptible to degradation primarily by an enzyme in the body called MAGL



Ueda, Natsuo, Kazuhito Tsuboi, Toru Uyama, and Taira Ohnishi. 2011. 'Biosynthesis and degradation of the endocannabinoid 2-arachidonoylglycerol', *Biofactors*, 37: 1-7.

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2-Arachidonoylglycerol (2-AG): The Work Horse

2-AG acts as a full CB2 agonist and exhibits a variety of activities throughout the body

When 2-AG activates CB1 and CB2 receptors, many physiological processes are

influenced including:

- Immunity¹
- Reduced inflammation¹
- Insulin sensitivity²
- Pain signaling¹
- Bone remodeling³
- Reduced COX-2 activity in the brain (protect neurons) and throughout the body¹

1. Turcotte, Caroline, Francois Chouinard, Julie S. Lefebvre, and Nicolas Flamand. 2015. 'Regulation of inflammation by cannabinoids, the endocannabinoids 2-arachidonoylglycerol and arachidonoyl-ethanolamide, and their metabolites'. *Journal of Leukocyte Biology*, 97: 1049-70.

2. Motlaghed, Roya, and Timothy E. McGraw. 2008. 'The CB1 Endocannabinoid System Modulates Adipocyte Insulin Sensitivity', *Obesity*, 16: 1727-34.

3. Elefteriou, Florent. 2008. 'Regulation of bone remodeling by the central and peripheral nervous system', *Archives of Biochemistry and Biophysics*, 473: 231-36.

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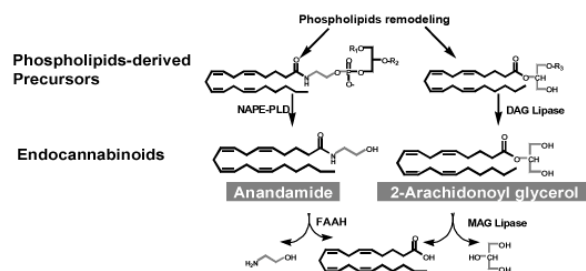
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2-AG - MAGL Enzyme

An active component of Boswellia called b-amyryn has shown to inhibit MAGL which can result in increasing 2-AG tone.^{1,2}

Endocannabinoids Formation and Inactivation



1. Chica, A, J Marazzi, and J Gertsch. 2012. 'The antinociceptive triterpene β -amyryn inhibits 2-arachidonoylglycerol (2-AG) hydrolysis without directly targeting cannabinoid receptors', British journal of pharmacology, 167: 1596-608.
2. Bekana, Derbachew, Tesfahun Kebede, Mulugeta Assefa, and Habtemariam Kassa. 2014. 'Comparative phytochemical analyses of resins of Boswellia species (B. papyrifera (Del.) Hochst., B. neglecta S. Moore, and B. rivae Engl.) from Northwestern, Southern, and Southeastern Ethiopia', ISRN Analytical Chemistry, 2014.

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CB1 Links to Sweet Taste

Linked to both motivation and reward, CB1 receptor signaling encourages sugar consumption by enhancing neural responses to sweet flavors.



Yoshida R, Ohkuni T, Jyotaki M, et al. Endocannabinoids selectively enhance sweet taste. Proc Natl Acad Sci U S A. 2010;107(2):935-939.

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CB1 Receptor & Insulin Resistance

Activation of hepatic CB1R is associated with obesity, insulin resistance, and impaired metabolic function, owing to increased energy intake and storage, impaired glucose and lipid metabolism, and enhanced oxidative stress and inflammatory responses.

Additionally, blocking peripheral CB1R improves insulin sensitivity and glucose metabolism and also reduces hepatic steatosis and body weight (in obese mice).

Nageppan A, Shin J, Jung MH. Role of Cannabinoid Receptor Type 1 in Insulin Resistance and Its Biological Implications. *Int J Mol Sci*. 2019;20(9):2109. Published 2019 Apr 29.

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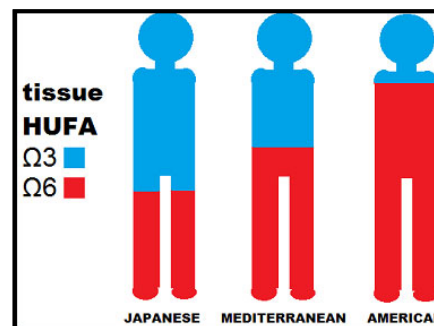


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PUFA's Role in the Endocannabinoid System

Studies have revealed that omega-3 deficiency reduces endocannabinoid production and receptor activity in the body.

Maintaining a healthier O3 to O6 ratio along with phytocannabinoid supplementation from hemp extracts will help to support proper functioning of ECS tone.



Lafourcade, Mathieu, Thomas Larnieu, Susana Mato, Anais Duffaud, Marja Sepers, Isabelle Matias, Veronique De Smedt-Peyussse, Virginie F. Labrousse, Lionel Breillon, Carlos Matute, Rafael Rodriguez-Puertas, Sophie Laye, and Olivier J. Manzoni. 2011. 'Nutritional omega-3 deficiency abolishes endocannabinoid-mediated neuronal functions'. *Nature Neuroscience*, 14, 245-50.

McPartland, John M, Geoffrey W Guy, and Vincenzo Di Marzo. 2014. 'Care and feeding of the endocannabinoid system: a systematic review of potential clinical interventions that upregulate the endocannabinoid system'. *PLOS ONE*, 9: e89566.

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ECS in Pain & Inflammation

Globally, it is estimated that about one in five — or about 1.5 billion people — suffer from chronic pain.

Sleep disturbances, depression, and fatigue are common mutually reinforcing problems for people with chronic pain.



BU School of Public Health. (September 2017). Chronic Pain and the Health of Populations. Retrieved July 16, 2020 from <https://www.bu.edu/sph/2017/09/24/chronic-pain-and-the-health-of-populations/>.

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ECS in Pain & Inflammation

The CNS-brain, spinal cord, and peripheral nerves play a central role in generation of pain.

The nervous system acts with the immune system to regulate chemical messengers that cause pain.

When these systems are in balance, both organs are capable of producing chemicals that reduce pain.



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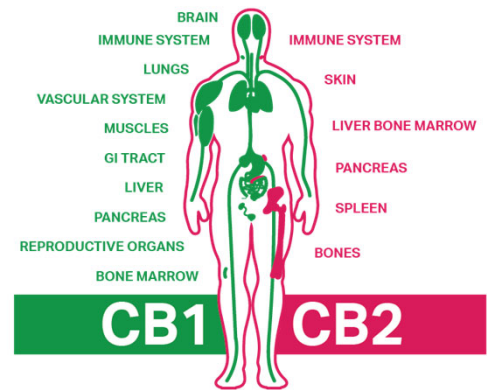
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ECS in Pain & Inflammation

CB1 receptors are densely located in the limbic area of the brain, which is key in the emotional expression of pain. In the spinal cord, CB1 receptors help regulate the transmission of pain to the brain by inhibiting neurotransmitters associated with pain sensation.

CB2 receptors are widely located on immune cells, and are a perfect target for influencing inflammatory pain processing.



Banik, N., & Manolagas, S. C. (2017). The endocannabinoid system in pain and inflammation: Its relevance to rheumatic disease. *European journal of rheumatology*, 4(3), 210-218. <https://doi.org/10.5152/eurjrheum.2017.17025>

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Cannabinoids, endocannabinoids, and related analogs in inflammation

“...A possible mechanism for these actions is suggested involving increased production of eicosanoids that promote the resolution of inflammation. This differentiates these cannabinoids from cyclooxygenase-2 inhibitors that suppress the synthesis of eicosanoids that promote the induction of the inflammatory process.”

Burstein, S. H., & Zurier, R. B. (2009). Cannabinoids, endocannabinoids, and related analogs in inflammation. *The AAPS journal*, 11(1), 109-119. doi:10.1208/s12248-009-9084-5

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ECS & Sleep

- 50 to 70 million people in the U.S. suffer from one or several sleep disorders.
- 75 to 90% of insomnia sufferers have an increased risk of medical disorders such as hypoxemia, GSD, and pain conditions.
- 9 million Americans take prescription drugs to help them fall asleep.



Sleep Advisor. (January 2020). 54 Shocking Sleep Statistics and Trends for 2020. Retrieved July 16, 2020 from <https://www.sleepadvisor.org/sleep-statistics/>

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ECS & Sleep

- AEA and 2-AG are endocannabinoids that bind to CB receptors in the brain.
- CB1 receptors may be localized in sleep-inducing areas in the brain.
- Pre-clinical data indicates the activation of the CB1 receptor (i.e. by AEA) may lead to an induction of sleep.
- eCBs have been shown to influence melanin-concentrating hormone(MCH), located in the hypothalamus, which promotes REM sleep and helps restore sleep in animals with insomnia.

Pava, M. J., Makrygiannis, A., & Lovinger, D. M. (2016). Endocannabinoid Signaling Regulates Sleep Stability. *PLoS one*, 11(3), e0152473. <https://doi.org/10.1371/journal.pone.0152473>

Prospéro-García, O., Amancio-Belmont, O., Becerril Meléndez, A. L., Ruiz-Contreras, A. E., & Méndez-Díaz, M. (2016). Endocannabinoids and sleep. *Neuroscience and biobehavioral reviews*, 71, 671–679. <https://doi.org/10.1016/j.neubiorev.2016.10.005>

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Endocannabinoids and sleep

“...Studies suggested 1. eCBs and NAEs are under circadian control. 2. NAEs promote wake. 3. eCBs promote non-rapid-eye movement. 4. eCBs also promote rapid-eye-movement sleep by interacting with melanin-concentrating hormone neurons in the lateral hypothalamus. 5. The pharmacological blockade of the CB1R reduces sleep while increasing wake. 6. eCBs restore sleep in a model of insomnia in rats.”

Prospero-Garcia, O., O. Amancio-Belmont, A. L. Becerril Melendez, A. E. Ruiz-Contreras, and M. Mendez-Diaz. 2016. 'Endocannabinoids and sleep', *Neurosci Biobehav Rev*, 71: 671-79.

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2-AG into the lateral hypothalamus increases REM sleep and cFos expression in melanin concentrating hormone neurons in rats.

“...results suggest that endocannabinoid activation of the CB1R in the lateral hypothalamus, which activates MCH neurons, is one mechanism by which REMS is triggered.”

Perez-Morales, M., A. K. De La Herran-Arita, M. Mendez-Diaz, A. E. Ruiz-Contreras, R. Drucker-Colin, and O. Prospero-Garcia. 2013. '2-AG into the lateral hypothalamus increases REM sleep and cFos expression in melanin concentrating hormone neurons in rats', *Pharmacol Biochem Behav*, 108: 1-7.

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ECS & Stress/Anxiety

An estimated 19.1% of U.S. adults had any anxiety disorder in the past year.

Past year prevalence of any anxiety disorder was higher for females (23.4%) than for males (14.3%).

An estimated 31.1% of U.S. adults experience any anxiety disorder at some time in their lives.



National Institute of Mental Health. (November 2017). Any Anxiety Disorder. Retrieved July 16, 2020 from <https://www.nimh.nih.gov/health/statistics/any-anxiety-disorder.shtml>.

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ECS & Stress/Anxiety

Central anandamide deficiency predicts stress-induced anxiety in animal studies.

Preclinical studies show animals with genetic deficiencies of 2-AG induce both anxiety and depression states while increasing 2-AG reduces anxiety and stress behavior.

Faraji, N., Komaki, A., & Salehi, L. (2017). Interaction Between the Cannabinoid and Vanilloid Systems on Anxiety in Male Rats. *Basic and clinical neuroscience*, 8(2), 129–137. <https://doi.org/10.18869/nirp.bcn.8.2.129>

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The endocannabinoid system in guarding against fear, anxiety and stress.

“... eCB signaling seems to determine the value of fear-evoking stimuli and to tune appropriate behavioral responses, which are essential for the organism's long-term viability, homeostasis and stress resilience; and dysregulation of eCB signaling can lead to psychiatric disorders.... ”

Lutz, B., Marsicano, G., Maldonado, R., & Hillard, C. J. (2015). The endocannabinoid system in guarding against fear, anxiety and stress. *Nature reviews Neuroscience*, 16(12), 705–715. doi:10.1038/nrn4036

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Regulation of endocannabinoid signaling by stress: implications for stress-related affective disorders.

“...Disrupted endocannabinoid signaling, on the other hand, is associated with an inability to adapt to chronic stress.”

Gorzalka, B. B., Hill, M. N., & Hillard, C. J. (2008). Regulation of endocannabinoid signaling by stress: implications for stress-related affective disorders. *Neuroscience & Biobehavioral Reviews*, 32(6), 1152-1160.

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Endocannabinoid signaling in psychiatric disorders: a review of positron emission tomography studies.

“... the synthesis of new radiotracers targeting enzymes involved in endocannabinoid degradation, such as fatty acid amide hydrolase, will allow for other facets of endocannabinoid signaling to be evaluated in future studies.”

Sloan, M. E., C. W. Grant, J. L. Gowin, V. A. Ramchandani, and B. Le Foll. 2019. 'Endocannabinoid signaling in psychiatric disorders: a review of positron emission tomography studies'. *Acta Pharmacol Sin*, 40: 342-50.

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ECS & Bone Health

Worldwide, 1 in 3 women over age 50 will experience osteoporotic fractures, as will 1 in 5 men aged over 50.

By 2050, the worldwide incidence of hip fracture in men is projected to increase by 310% and 240% in women, compared to rates in 1990.

In women over 45 years of age, osteoporosis accounts for more days spent in the hospital than many other diseases, including diabetes, myocardial infarction, and breast cancer.



International Osteoporosis Foundation. (2017). Facts and Statistics. Retrieved July 16, 2020, from <https://www.iobonehealth.org/facts-statistics>

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ECS & Bone Health

Both 2-AG and anandamide — and their receptors, CB1 and CB2 — are present in osteoblast and osteoclasts.

The communication between the CNS and our bones is vital to the proper building of healthy bone tissue.

Anandamide stimulates CB1 receptors in bone, which sends signals to suppress the release of norepinephrine: a hormone that inhibits bone formation.

Bab, I., & Zimmer, A. (2008). Cannabinoid receptors and the regulation of bone mass. *British journal of pharmacology*, 153(2), 182–188. <https://doi.org/10.1038/sj.bjp.0707593>

Idris, A. I., & Ralston, S. H. (2012). Role of cannabinoids in the regulation of bone remodeling. *Frontiers in endocrinology*, 3, 136. <https://doi.org/10.3389/fendo.2012.00136>

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ECS & Bone Health

It is well established that 2-AG stimulation of CB2 receptors reduces both the number and activity of bone breaking osteoclast

Studies show that activating CB2 receptors also increases bone mass by increasing the number and activity of bone building osteoblast

Rossi, F., Tortora, C., Purzo, F., Bellini, G., Argenziano, M., Di Paola, A., Torella, M., & Perrotta, S. (2019). The Endocannabinoid/Endovanilloid System in Bone: From Osteoporosis to Osteosarcoma. *International journal of molecular sciences*, 20(8), 1919. <https://doi.org/10.3390/ijms20081919>

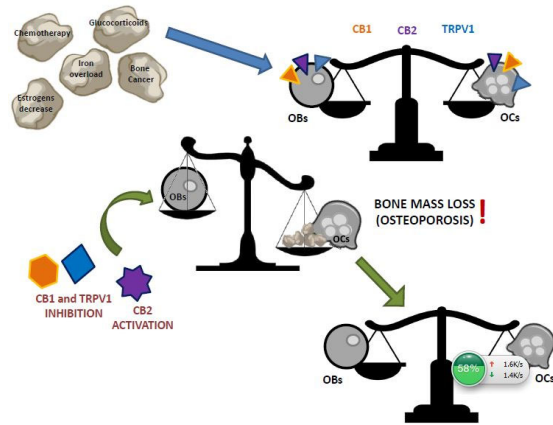
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ECS & Bone Health

- Bone homeostasis is controlled by a balance between Osteoclast (OC) and Osteoblast (OB) Activity. Various factors influence bone density in individuals positively or negatively acting through OCs and Obs.¹
- Recently the Endocannabinoid/endovanilloid (EC/EV) system's receptors – cannabinoid receptor type 1 (CB1), the cannabinoid receptor type 2 (CB2), and the transient receptor potential cation channel subfamily V member 1 (TRPV1) – have been identified as influencers for bone formation and bone resorption.¹
- Lower bone density has been associated with OCs expressing low levels of CB2 receptors and high levels of CB1 and stimulation of TRPV1.¹
- CB2 represents the counterpart for bone mineralization and remodeling via osteoclast inhibition.¹



1. Rossi, Tortora, Punzo, Bellini, Argenziano, Di Paola, ... Perrotta. (2019). The Endocannabinoid/Endovanilloid System in Bone: From Osteoporosis to Osteosarcoma. *International Journal of Molecular Sciences*, 20(8), 1919. doi:10.3390/ijms20081919

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A collaboration investigating endocannabinoid signaling in brain and bone.

“...activation of CB2 stimulates bone formation and represses bone resorption, whereas the genetic disruption of CB2 results in an osteoporosis-like phenotype.”

Zimmer, A. (2016). A collaboration investigating endocannabinoid signaling in brain and bone. *Journal of basic and clinical physiology and pharmacology*, 27(3), 229-235.

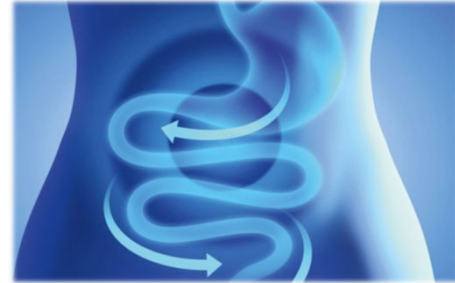
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ECS & Digestive Health

- According to a 2013 survey, 74 percent of Americans are living with digestive symptoms like diarrhea, gas, bloating, and abdominal pain.
- Increased intestinal permeability plays a role in certain gastrointestinal conditions such as celiac disease, Crohn’s disease, and IBS.
- Some studies show that leaky gut may be associated with other autoimmune diseases such as, chronic fatigue, fibromyalgia, arthritis, allergies and obesity.



Fox News. (2015, January 09). Survey shows 74 percent of Americans living with GI discomfort. Retrieved July 16, 2020, from <https://www.foxnews.com/health/survey-shows-74-percent-of-americans-living-with-gi-discomfort>
 Marcelo Campos, M. (2019, October 24). Leaky gut: What is it, and what does it mean for you? Retrieved July 16, 2020, from <https://www.health.harvard.edu/blog/leaky-gut-what-is-it-and-what-does-it-mean-for-you-2017092212451>

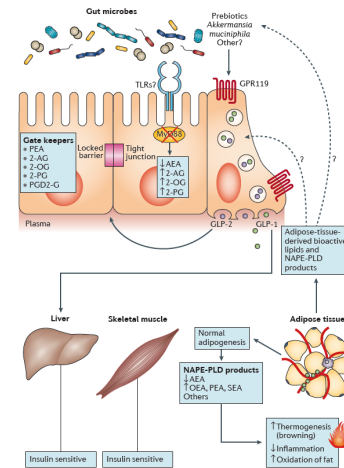
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ECS & Digestive Health

Several studies demonstrate gut bacteria activates GPCR receptors that are also targeted by the ECS.

In addition, specific gut microbes have been shown to have a regulatory role in increasing or decreasing ECS activity and collectively are involved in obesity, type 2 diabetes, and inflammation.



Cani, P. D., Plovier, H., Van Hul, M., Geurts, L., Delzenne, N. M., Druart, C., & Everard, A. (2016). Endocannabinoids—at the crossroads between the gut microbiota and host metabolism. *Nature Reviews Endocrinology*, 12(3), 133.

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The Important Role of the Endocannabinoid System and the Endocannabinoidome in Gut Health.

“A dysregulated endocannabinoid system may lead to inflammatory bowel disease and colon cancer.”

Meletis, C. (2019). The Important Role of the Endocannabinoid System and the Endocannabinoidome in Gut Health. *ALTERNATIVE THERAPIES*, 224

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Nutritional Support for the ECS: Hemp vs Marijuana

While both are considered *Cannabis sativa*, there has been a great deal of confusion about hemp products and many people don't understand the distinction between hemp and marijuana.¹

In simplest terms, marijuana contains significant amounts of the psychoactive phytocannabinoid known as THC.²

Industrial Hemp is cultivated very differently and has very little if any THC after extraction.²

Hemp stalk in particular is also a source of many beneficial components called phytocannabinoids.²



1. Malone, Trey, and Kevin Gomez. 2019. 'Hemp in the United States: A Case Study of Regulatory Path Dependence', *Applied Economic Perspectives and Policy*, 41: 199-214.
2. Fike, John. 2016. 'Industrial Hemp: Renewed Opportunities for an Ancient Crop', *Critical Reviews in Plant Sciences*, 35: 406-24.

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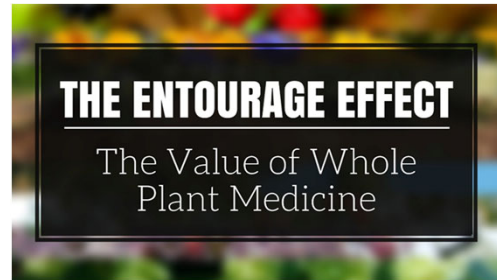


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Nutritional Support for the ECS: Isolate vs. Full Spectrum

Phytocannabinoids (CBN, CBG, CBC, CBD, etc.) and Terpenoids (limonene, α -pinene, linalool, β -caryophyllene, etc.) are reported to have unique properties that may contribute meaningfully to the entourage of hemp

Synergistic effects of all the phytocannabinoids and terpenes are greater than the single magic bullet approach



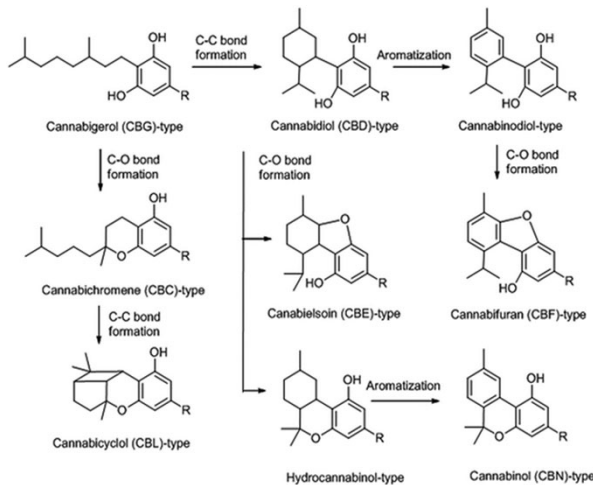
Russo E. B. (2011). Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *British journal of pharmacology*, 163(7), 1344–1364. <https://doi.org/10.1111/j.1476-5381.2011.01238.x>

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Wisdom in Nature: Full Spectrum Hemp



- Cannabigerol (CBG)
- Cannabichromene (CBC)
- Cannabidiol (CBD)
- Cannabinol (CBN)
- Cannabinodiol (CBDL)
- Cannabicyclol (CBL)
- Cannabielsoin (CBE)
- Cannabitrinol (CBT)
- Cannabivarin (CBV)
- Tetrahydrocannabivarin (THCV)
- Cannabidivarin (CBDV)
- Cannabichromevarin (CBCV)
- Cannabigerovarin (CBGV)
- Cannabigerol Monoethyl Ether (CBGM)
- Beta Caryophyllene

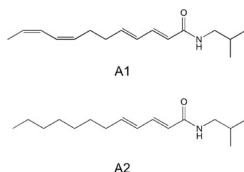
Russo E. B. (2011). Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *British journal of pharmacology*, 163(7), 1344–1364. <https://doi.org/10.1111/j.1476-5381.2011.01238.x>

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Alkylamides (coneflower *Echinacea purpurea*)



- It is generally believed that Echinacea affords its benefits through interactions with the immune system
- Alkylamides dodeca-2E,4E,8Z,10Z-tetraenoic acid isobutylamide (A1) and dodeca-2E,4E-dienoic acid isobutylamide (A2) bind to the CB2 receptor
- The K_i values of A1 and A2 (CB2 ~60 nM; CB1 >1500 nM)
- Both partial and inverse agonist compounds for cannabinoid (CB1) receptors were identified among the metabolites, characterized by weak to moderate interactions

Raduner S, Majewska A, Chen JZ, Xie XQ, Hamon J, et al. (2006) Alkylamides from Echinacea are a new class of cannabinomimetics - cannabinoid type 2 receptor-dependent and -independent immunomodulatory effects. *Journal of Biological Chemistry* 281: 14192-14206

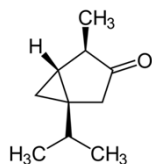
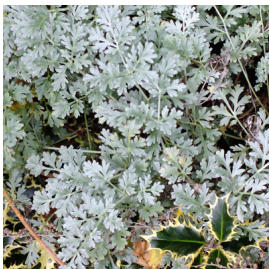
Hohmann J, Redel D, Forgo P, Szabo P, Freund TF, et al. (2011) Alkylamides and a neolignan from *Echinacea purpurea* roots and the interaction of alkylamides with G-protein-coupled cannabinoid receptors. *Phytochemistry* 72: 1848-1853

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Thujone (wormwood *Artemisia absinthium*)



- Absinthe, an abused drug in the early 1900s
- A ketone and a monoterpene that occurs naturally in two epimeric forms: (-)- α -thujone and (+)- β -thujone
- Thujone showed low affinity towards CB1 and CB2 receptors only at concentrations above 10 μ M
- In the USA, the addition of thujone to foods is not permitted, which in practice means <10 mg/l thujone, but...
- Sage oil (which can be up to 50% thujone) is on the FDA list of generally recognized as safe (GRAS) substances

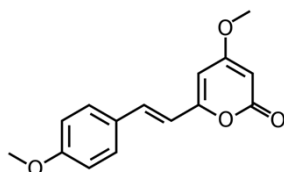
Meschler JP, Howlett AC (1999) Thujone exhibits low affinity for cannabinoid receptors but fails to evoke cannabinomimetic responses. *Pharmacology Biochemistry and Behavior* 62: 473-480

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Yangonin (kava *Piper methysticum*)



- Kava consists of sterile cultivars cloned from its wild ancestor, *Piper wichmanii*
- The mature roots of the kava plant are harvested after a minimum of four years (at least five years ideally) for peak kavalactone content
- Yangonin exhibited affinity for the human recombinant CB₁ receptor with a K_i=0.72 μM and selectivity vs. the CB₂ receptor K_i>10 μM

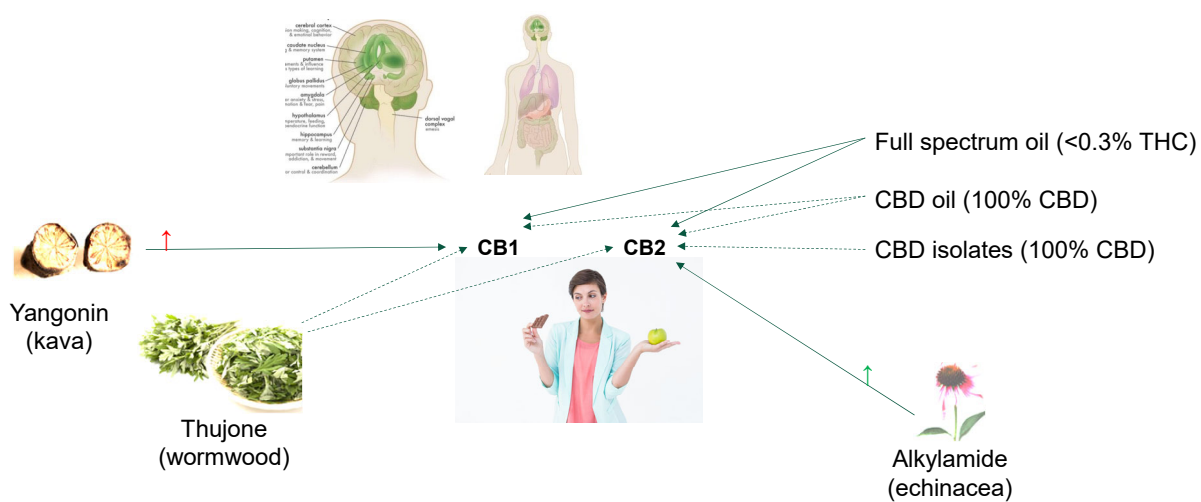
Ligresti A, Villano R, Allara M, Ujvary I, Di Marzo V (2012) Kavalactones and the endocannabinoid system: the plant-derived yangonin is a novel CB₁ receptor ligand. *Pharmacological Research* 66: 163–169

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How to Tune the ECS



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