Hypothesis

Toward a Nutritionally Complete Model of the Endocannabinoid System

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Toward a Nutritionally Complete Model of the Endocannabinoid System

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Abstract

The endocannabinoid system (ECS) has been extensively mapped at the level of receptors, ligands, enzymes, and signaling pathways, forming a detailed component inventory of a major homeostatic network. However, prevailing ECS models largely omit the nutritional substrates required to sustain ligand synthesis, membrane composition, signaling capacity, and regenerative function, leaving the system operationally incomplete from a systems-biology perspective. This Hypothesis identifies this gap by integrating evidence from nutritional biochemistry, lipid metabolism, and regenerative physiology, and argues that inclusion of dietary inputs is necessary to advance toward a nutritionally complete model of the ECS. By reframing the ECS as a metabolically sustained regulatory network rather than a purely signaling system, this framework has implications for understanding resilience, regeneration, and system failure under chronic stress, nutritional insufficiency, and environmental disruption. This synthesis is intended as a hypothesis-generating foundation to guide future experimental and clinical investigation.

Keywords: endocannabinoid system; clinical endocannabinoid deficiency; nutritional substrates; systems biology; homeostasis; lipid metabolism; metabolically sustained regulation; regenerative physiology; physiological resilience; dietary inputs; integrative physiology; environmental stressors

1. Introduction

This Hypothesis proposes that prevailing models of the endocannabinoid system are structurally incomplete without inclusion of the nutritional substrates required to sustain ECS signaling, regeneration, and resilience.

The endocannabinoid system (ECS) is a universal feature of vertebrate physiology, a complex network that regulates an astonishing array of functions: brain signaling, pain perception, immune activity, appetite, metabolism, cardiovascular dynamics, gastrointestinal motility, endocrine balance, and musculoskeletal integrity. Comprising cannabinoid receptors (CB1 and CB2), endogenous ligands (endocannabinoids), and enzymes for their synthesis and degradation, the ECS is a linchpin of homeostasis, earning recognition as a central integrative regulator of homeostasis (Di Marzo et al., 2015).

This paper synthesizes existing ECS literature across molecular, physiological, and nutritional domains to highlight a structural gap in prevailing models. Particular attention is given to dietary lipid substrates, metabolic inputs, and plant-derived compounds that may influence ECS tone and regenerative capacity. The goal is not to redefine ECS signaling mechanisms, but to organize existing components and sustaining inputs into a unified systems-biology context suitable for hypothesis generation. We also explore the cannabis plant, including its seeds, as a historical, nutritional, and biochemical partner to the ECS, emphasizing their unique properties and evolutionary synergy. With rigorous citations, we aim to illuminate the ECS's dominance and its potential to reshape health sciences.

2. The Endocannabinoid System: An Overview

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2.1. The Endocannabinoid System (ECS)

The ECS is a dynamic signaling system with three core components: receptors, endocannabinoids, and enzymes. These elements work in concert to modulate physiological responses, ensuring balance across diverse systems.

2.1.1. Cannabinoid Receptors

The ECS operates through two primary receptors: CB1 and CB2. CB1 receptors are densely expressed in the central nervous system (CNS), particularly in the cortex, hippocampus, basal ganglia, and cerebellum, but also appear in peripheral tissues like the liver and adipose tissue (Pertwee et al., 2010). CB2 receptors, while less abundant in the CNS, dominate in immune cells (e.g., T cells, B cells, macrophages) and peripheral tissues, including spleen and bone marrow (Pertwee et al., 2010). Both receptors are G-protein-coupled, mediating intracellular signaling cascades that influence ion channels, cyclic AMP, and MAPK pathways, thus fine-tuning cellular responses (Pertwee et al., 2010).

2.1.2. Endocannabinoids

Endocannabinoids are lipid-based signaling molecules synthesized on-demand from membrane phospholipids. The most studied are anandamide (AEA) and 2-arachidonoylglycerol (2-AG), which act as retrograde messengers in synaptic transmission, modulating neurotransmitter release (Di Marzo et al., 2015). AEA, named after the Sanskrit word for bliss, binds CB1 with high affinity but also interacts with CB2 and non-cannabinoid receptors like TRPV1 (Devane et al., 1992). 2-AG, more abundant, is a full agonist at both CB1 and CB2, exerting robust effects on synaptic plasticity (Di Marzo et al., 2015). Lesser-known endocannabinoids include noladin ether (2-arachidonyl glyceryl ether), virodhamine (O-arachidonoyl ethanolamine), and N-arachidonoyl dopamine (NADA), each with distinct receptor affinities that expand the ECS's regulatory scope (Devane et al., 1992; Porter et al., 2002). These molecules' lipid nature allows rapid diffusion across membranes, enabling precise, localized signaling.

2.1.3. Enzymes Involved in the ECS

Endocannabinoid levels are tightly controlled by biosynthetic and degradative enzymes. AEA is primarily synthesized by N-acylphosphatidylethanolamine phospholipase D (NAPE-PLD), with alternative pathways involving phospholipase C (PLC) or α/β-hydrolase domain 4 (ABHD4) (Ahn et al., 2008; Liu et al., 2008). Its degradation is catalyzed by fatty acid amide hydrolase (FAAH), which hydrolyzes AEA into arachidonic acid and ethanolamine (Ahn et al., 2008). 2-AG is synthesized mainly by diacylglycerol lipase (DAGL), with contributions from phospholipase A1 (PLA1), and degraded by monoacylglycerol lipase (MAGL) into arachidonic acid and glycerol (Liu et al., 2008). Additional enzymes, including cyclooxygenase-2 (COX-2), lipoxygenases (LOX), and cytochrome P450, metabolize endocannabinoids into bioactive derivatives like prostaglandin glyceryl esters, linking the ECS to inflammation and oxidative stress pathways (Kozak et al., 2002). This enzymatic complexity ensures precise control over ECS signaling.

2.1.4. The Cannabis Plant and Cannabinoids

The cannabis plant (Cannabis sativa) is a key player in ECS research, producing over 100 phytocannabinoids, including Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which mimic or modulate endocannabinoid activity (Pertwee et al., 2010). THC, the primary psychoactive compound, is a partial agonist at CB1 and CB2, eliciting effects from euphoria to analgesia (Pertwee et al., 2010). CBD, non-psychoactive, has low affinity for CB1/CB2 but influences ECS tone indirectly by inhibiting FAAH and interacting with TRPV1 and PPARγ (Campos et al., 2013). Cannabis seeds, often called hemp seeds, lack significant phytocannabinoids but are rich in omega-6 and omega-3 polyunsaturated fatty acids (PUFAs), such as linoleic and alpha-linolenic acids, which serve as

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precursors for endocannabinoid synthesis (Simopoulos, 2016). Their nutritional profile—approximately 30% protein, 40% fat, and 12% fiber—supports metabolic health, potentially enhancing ECS function through balanced PUFA ratios (Simopoulos, 2016). Cannabis's historical use, from ancient Chinese medicine to modern pharmacology, underscores its biochemical synergy with the ECS.

2.2. The ECS in the Central Nervous System

The CNS is a primary domain of ECS activity, where it shapes neural communication, protection, and pain modulation.

2.2.1. Neurotransmission and Synaptic Plasticity

The ECS regulates neurotransmitter release—glutamate, GABA, dopamine, serotonin—via retrograde signaling, where endocannabinoids like 2-AG inhibit presynaptic neurotransmitter release, maintaining synaptic homeostasis (Katona & Freund, 2012). This process underpins short- and long-term synaptic plasticity, critical for learning, memory, and motor coordination (Katona & Freund, 2012). CB1 receptors on presynaptic terminals mediate these effects, with 2-AG's high abundance ensuring robust signaling (Di Marzo et al., 2015).

2.2.2. Neuroprotection and Neurogenesis

The ECS shields neurons from damage by reducing inflammation, oxidative stress, and excitotoxicity. CB1 activation dampens glutamate excitotoxicity, while CB2 on microglia curbs neuroinflammation (Jiang et al., 2005). The ECS also promotes adult neurogenesis in the hippocampus, a process linked to learning, memory, and mood regulation (Jiang et al., 2005). Studies show CBD enhances hippocampal neurogenesis in stressed mice, suggesting therapeutic potential for mood disorders (Campos et al., 2013).

2.2.3. Pain Perception and Modulation

The ECS modulates pain at peripheral and central levels. CB1 receptors in the brain, spinal cord, and peripheral nerves inhibit nociceptive signaling, reducing pain sensitivity (Woodhams et al., 2015). CB2 receptors on immune cells further attenuate pain by suppressing inflammatory mediators (Woodhams et al., 2015). THC and CBD show analgesic effects in models of neuropathic and inflammatory pain, positioning the ECS as a prime target for novel pain therapies (Woodhams et al., 2015).

2.3. The ECS in the Immune System

The ECS is a gatekeeper of immune function, balancing activation and suppression to maintain homeostasis.

2.3.1. Immune Response Regulation

CB2 receptors on T cells, B cells, and macrophages modulate immune activity, suppressing cytokine production and preventing excessive responses (Tanasescu & Constantinescu, 2010). AEA and 2-AG, via CB2, inhibit T-cell proliferation and macrophage activation, maintaining immune balance (Tanasescu & Constantinescu, 2010). This regulatory role is critical in preventing chronic inflammation.

2.3.2. Inflammation and Autoimmune Disorders

The ECS mitigates inflammation in autoimmune conditions. CB2 activation reduces inflammation in models of multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease by downregulating pro-inflammatory cytokines like TNF-α and IL-6 (Klein, 2005; Sisay et al., 2013).

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CBD's anti-inflammatory effects, partly via CB2 and PPARγ, show promise in preclinical autoimmune models (Klein, 2005).

2.4. The ECS in the Cardiovascular System

The ECS influences heart and vascular function, offering both regulatory and protective effects.

2.4.1. Vasodilation and Blood Pressure Regulation

CB1 receptors on vascular smooth muscle and endothelial cells induce vasodilation, lowering blood pressure (Wagner et al., 1997). AEA triggers this effect in hypertensive models, suggesting a role in cardiovascular homeostasis (Batkai et al., 2004). THC mimics AEA's vasodilatory effects, though its psychoactive properties limit therapeutic use (Batkai et al., 2004).

2.4.2. Cardioprotection and Ischemia-Reperfusion Injury

The ECS protects the heart from ischemia-reperfusion injury by reducing inflammation, oxidative stress, and apoptosis. CB2 receptors on cardiomyocytes and immune cells mediate these effects, with 2-AG and CBD showing cardioprotective properties in preclinical studies (Lamontagne et al., 2006; Pacher & Haskó, 2008).

2.5. The ECS in the Gastrointestinal System

The ECS regulates gut function, from motility to immune defense, with implications for digestive health.

2.5.1. Motility and Secretion

CB1 receptors in the enteric nervous system inhibit intestinal motility and secretion, offering potential for treating diarrhea and irritable bowel syndrome (IBS) (Coutts & Izzo, 2004; Izzo & Sharkey, 2010). THC and synthetic CB1 agonists reduce motility in IBS models, highlighting therapeutic avenues (Izzo & Sharkey, 2010).

2.5.2. Inflammation and Gut Permeability

CB2 receptors on gut immune cells reduce inflammation and restore barrier function in inflammatory bowel disease models (Alhamoruni et al., 2010; Engel et al., 2010). The gut microbiome further modulates ECS tone via short-chain fatty acids, which influence endocannabinoid levels and receptor expression (Cani et al., 2016). Cannabis seeds' PUFA content may support gut health by providing precursors for anti-inflammatory endocannabinoids (Simopoulos, 2016).

2.6. The ECS in the Endocrine System

The ECS governs energy balance and reproductive function, linking diet to physiology.

2.6.1. Energy Homeostasis and Metabolism

CB1 receptors in the hypothalamus stimulate appetite, while peripheral CB1 activation promotes lipogenesis and reduces energy expenditure (Di Marzo et al., 2001; Cota et al., 2003). Dietary PUFAs, abundant in cannabis seeds, are precursors for AEA and 2-AG; high omega-6/omega-3 ratios can dysregulate ECS signaling, contributing to obesity (Simopoulos, 2016). Cannabis seeds' balanced PUFA profile (3:1 omega-6/omega-3) supports metabolic health, potentially optimizing ECS function (Simopoulos, 2016).

2.6.2. Reproduction and Fertility

CB1 receptors in the hypothalamus modulate gonadotropin-releasing hormone (GnRH), affecting reproductive hormones (Wenger et al., 2001; Gammon et al., 2005). AEA levels in

 doi:10.20944/preprints202601.1505.v1

reproductive tissues influence fertility, with THC potentially disrupting these pathways (Gammon et al., 2005).

2.7. The ECS in the Musculoskeletal System

The ECS supports bone and muscle health, with implications for aging and injury recovery.

2.7.1. Bone Remodeling and Osteoporosis

CB1 receptors on osteoblasts stimulate bone formation, while CB2 receptors on osteoclasts inhibit resorption, maintaining bone mass (Idris et al., 2005; Ofek et al., 2006). CBD enhances bone healing in preclinical models, suggesting anti-osteoporotic potential (Idris et al., 2005).

2.7.2. Muscle Growth and Regeneration

CB1 receptors on myoblasts promote differentiation and hypertrophy, while CB2 receptors reduce inflammation and fibrosis in muscle injury models (Iannotti et al., 2013; Yu et al., 2020). Cannabis seeds' protein content (30% by weight) supports muscle repair, complementing ECS-mediated regeneration (Simopoulos, 2016).

2.8. The ECS in DNA Signaling and Epigenetic Regulation

The ECS extends its regulatory prowess to the genomic level, influencing DNA signaling and epigenetic modifications that govern gene expression and cellular identity, further solidifying its role as a master regulator.

2.8.1. DNA Repair and Genomic Stability

The ECS contributes to DNA repair and genomic stability, critical for cellular health and disease prevention. CB1 and CB2 receptors modulate DNA damage response pathways, with endocannabinoids like AEA and 2-AG influencing the activation of repair enzymes such as PARP1 and ATM (Jeong et al., 2014). CB2 activation in immune cells reduces oxidative stress-induced DNA damage, protecting against mutations (Berdyshev et al., 2016). CBD has been shown to enhance DNA repair in UV-damaged skin cells by upregulating nucleotide excision repair pathways, suggesting a protective role against environmental stressors (Parrales et al., 2018).

2.8.2. Epigenetic Modulation and Gene Expression

The ECS regulates epigenetic mechanisms, including histone modifications and DNA methylation, which control gene expression without altering the DNA sequence. CB1 receptor signaling influences histone acetylation in neuronal cells, promoting the expression of genes involved in synaptic plasticity and neuroprotection (Yang et al., 2017). AEA modulates DNA methylation patterns in immune cells, suppressing inflammatory cytokine genes via CB2, which may mitigate chronic inflammation (Chiurchiù et al., 2018). CBD interacts with PPARγ to induce epigenetic changes that enhance anti-inflammatory and antioxidant gene expression, offering therapeutic potential for metabolic and neurodegenerative disorders (O'Sullivan, 2016). These epigenetic effects underscore the ECS's ability to fine-tune cellular responses across tissues.

2.9. The Cannabis Plant and Seeds: Biochemical and Nutritional Synergy

The cannabis plant is a cornerstone of endocannabinoid system (ECS) research. Its phytocannabinoids—including THC, CBD, cannabigerol (CBG), and their acidic precursors—interact with CB1, CB2, and non-cannabinoid receptors, modulating ECS tone and downstream physiological processes (Pertwee et al., 2010). Beyond receptor binding, recent work demonstrates that acidic cannabinoids undergo partial decarboxylation and metabolic transformation influenced by gastric

 doi:10.20944/preprints202601.1505.v1

acidity, blood pH, and hepatic metabolism, producing a spectrum of active intermediates that further shape ECS signaling (Floyd, 2025c; Floyd, 2025b).

Cannabis seeds, while low in phytocannabinoids, function as critical nutritional inputs for ECS ligand synthesis and metabolic stability. Hemp seeds contain approximately 30% protein—rich in arginine and glutamic acid—40% lipid content with an optimal ~3:1 omega-6 to omega-3 fatty acid ratio, and roughly 12% dietary fiber (Simopoulos, 2016). These polyunsaturated fatty acids (PUFAs) serve as direct biochemical precursors for the endogenous cannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG), while amino acids and micronutrients support enzymatic pathways governing ECS tone (Simopoulos, 2016; Floyd, 2025a).

Taken together, the combined consumption of the cannabis plant and its seeds establishes a synergistic framework in which phytocannabinoids, acidic cannabinoid metabolites, and seed-derived nutritional substrates collectively regulate ECS homeostasis. This integrated dietary–biochemical model aligns with historical patterns of human cannabis consumption and supports the ECS's central role in inflammation control, oxidative balance, and systemic resilience (Simopoulos, 2016; Floyd, 2025a; Floyd, 2025c).

3. Discussion: Evolutionary Perspective

The ECS is conserved across vertebrates, from fish to mammals, suggesting a 500-million-year evolutionary history (Di Marzo et al., 2015). Its presence in neural, immune, and metabolic systems underscores its role in survival. Cannabis, evolving alongside vertebrates, likely developed phytocannabinoids as defense mechanisms, inadvertently aligning with the ECS (Pertwee et al., 2010). This co-evolution explains the plant's profound effects on human physiology and the seeds' nutritional compatibility with ECS function.

4. Conclusions

The endocannabinoid system has traditionally been described through a dispersed literature focused on receptors, ligands, enzymatic pathways, and downstream signaling effects across individual organ systems. While this body of work has produced a detailed component inventory, it remains fragmented across disciplines and rarely examined as a unified operational system.

This Hypothesis identifies a structural limitation in prevailing ECS models: the omission of the nutritional substrates required to sustain ligand synthesis, membrane composition, signaling capacity, and regenerative function. By integrating these inputs alongside established ECS components, the framework presented here consolidates existing knowledge into a single, metabolically sustained regulatory model that more fully reflects how the system operates in vivo.

Importantly, this synthesis does not redefine ECS components or propose new signaling mechanisms, but instead organizes known elements and their sustaining inputs into a unified systems-biology context. Such consolidation may improve clarity across research domains and support more accurate investigation of ECS resilience, failure modes, and regenerative potential under conditions of chronic physiological or environmental stress. Future experimental and clinical work will be required to test, refine, and quantify the relationships outlined in this model.

Conflicts of Interest: The authors declare no conflict of interest. The authors do not work for any cannibinoid business or industry.

AI Disclosure: The comprehensive literature search was systematically supported by [ChatGPT-4, Grok, and Gemini]. The tools were used for data extraction and collation, specifically to efficiently screen and categorize high-volume scientific databases and preprint servers for keywords related to the endocannabinoid system (ECS) and various nutritional compounds. This assistance was instrumental in managing the large dataset compiled over the research period. The identification of the novel conceptual framework—nutritional support for the ECS—was an original human-driven insight based on the author's synthesis of the collated data, not a

 doi:10.20944/preprints202601.1505.v1

generative function of the AI tools. The author assumes full responsibility for all content, interpretation, and references cited in this manuscript.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Full Term
2-AG	2-Arachidonoylglycerol
ABHD4	α/β-Hydrolase Domain Containing 4
AEA	Anandamide (N-arachidonoylethanolamine)
ATM	Ataxia Telangiectasia Mutated kinase
CB1	Cannabinoid Receptor Type 1
CB2	Cannabinoid Receptor Type 2
CBD	Cannabidiol
CBG	Cannabigerol
CNS	Central Nervous System
COX-2	Cyclooxygenase-2
DAGL	Diacylglycerol Lipase
DNA	Deoxyribonucleic Acid
ECS	Endocannabinoid System
FAAH	Fatty Acid Amide Hydrolase
GABA	Gamma-Aminobutyric Acid
GnRH	Gonadotropin-Releasing Hormone
IBS	Irritable Bowel Syndrome
IL-6	Interleukin-6
LOX	Lipoxygenase
MAGL	Monoacylglycerol Lipase
MAPK	Mitogen-Activated Protein Kinase
NADA	N-Arachidonoyl Dopamine
NAPE-PLD	N-Acylphosphatidylethanolamine Phospholipase D
PARP1	Poly(ADP-ribose) Polymerase 1
PLA1	Phospholipase A1
PLC	Phospholipase C
PPARγ	Peroxisome Proliferator-Activated Receptor Gamma
PUFAs	Polyunsaturated Fatty Acids
THC	Δ9-Tetrahydrocannabinol
TNF-α	Tumor Necrosis Factor Alpha
TRPV1	Transient Receptor Potential Vanilloid 1
UV	Ultraviolet Radiation

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