

Review

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Review

Hemp Seeds: The Nutritional Support for the Endocannabinoid System (ECS)

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Abstract

The endocannabinoid system (ECS) is a lipid-based, on-demand signaling network essential for maintaining physiological homeostasis across metabolic, immune, cardiovascular, and neurological domains. Proper ECS function is contingent upon the availability of specific dietary nutrients that serve as biochemical precursors, structural components, enzymatic cofactors, and receptor modulators. This analysis examines hemp seeds as a uniquely complete nutritional substrate for ECS support, organizing their contributions according to the three functional pillars of the ECS: endogenous ligands, cannabinoid receptors, and enzymatic machinery. Hemp seeds provide an optimal omega-6 to omega-3 fatty acid ratio, supplying precursors for both arachidonic acid–derived endocannabinoids and anti-inflammatory omega-3 ethanolamides, thereby supporting balanced endocannabinoid tone. Their inclusion of gamma-linolenic acid enables bypass metabolism that further modulates inflammatory signaling. In addition, hemp seeds deliver complete, highly digestible proteins rich in L-arginine, facilitating nitric oxide–mediated vascular responses that intersect with ECS signaling. Essential micronutrients such as magnesium, zinc, and vitamin E support enzymatic function and protect lipid substrates from oxidative degradation. Finally, bioactive phytochemicals including beta-caryophyllene and phytosterols directly influence cannabinoid receptor activation and membrane dynamics. Collectively, these findings position hemp seeds as a functional food capable of supporting ECS integrity through multiple, convergent biochemical pathways.

Keywords: endocannabinoid system; endocannabinoidome; dietary cannabinoids; whole plant cannabis; Hemp seed nutrition; Hemp seed endocannabinoid modulation; omega-3 fatty acids endocannabinoid; polyunsaturated fatty acids ECS; clinical endocannabinoid deficiency; entourage effect

1. Introduction

The endocannabinoid system (ECS) is a lipid-based, on-demand signaling network essential for maintaining physiological homeostasis across metabolic, immune, cardiovascular, and neurological domains. It requires nutritional support like any other system in the body.

This preprint is part of a three-work integrated series examining (1) dietary inputs from the seeds of the hemp plant, (2) and the dietary inputs from the phytocannabinoids from the plants, (3) the mechanistic ECS pathways they activate, and the physiological outcomes.

2. Materials and Methods

This review series is a narrative synthesis of existing peer-reviewed literature on dietary inputs from Cannabis sativa L. (whole plant and seeds), endocannabinoid system (ECS) mechanisms, and physiological outcomes. No primary experimental data were generated.

A comprehensive literature search was conducted using PubMed, Google Scholar, Scopus, and Web of Science databases from inception through December 2025, with keywords including but not

limited to: "hemp seed nutrition," "acidic cannabinoids," "THCA/CBDA/CBGA pharmacokinetics," "endocannabinoid precursors," "PUFA ECS modulation," "raw cannabis consumption," "entourage effect," "clinical endocannabinoid deficiency," and organ-specific terms (e.g., "hemp seed cardiovascular," "cannabis neuroprotection").References were selected for relevance, methodological rigor, and recency, prioritizing human studies, clinical trials, and mechanistic reviews where available, supplemented by preclinical and in vitro evidence. Inclusion focused on studies demonstrating direct links between cannabis/hemp constituents and ECS pathways or homeostasis outcomes.

Metabolite pathways (e.g., "The Acidic Cannabinoid Metabolome") were constructed by integrating established pharmacokinetic data with logical chemical extensions based on known CYP450, UGT, and oxidative transformations. Speculative or trace compounds/metabolites were explicitly labeled as such, derived from structural analogy and rare reported pathways.

All claims are supported by cited sources; synthesis connects established findings to propose integrative models for dietary ECS modulation.

3. AI Disclosure

The comprehensive literature search spanning the past 13 years 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. The multiple AIs were then pitted against each other to test and validate the scientific data and theories.

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

4. Hemp Seeds: The Nutritional Support for the Endocannabinoid System (ECS)

Analysis details the biochemical interactions between hemp seed nutrients and the Endocannabinoid System (ECS), categorized by the three pillars of ECS function: Ligands (Endocannabinoids), Receptors, and Enzymatic Machinery.

1. Fatty Acid Precursors: The Building Blocks of "Endocannabinoid Tone"

The ECS is a unique "on-demand" system; lipids are not stored but are synthesized from the cell membrane's phospholipid bilayer when needed. Hemp seeds are the most efficient botanical source for these specific lipid precursors.

The Omega-3/6 Synergy and Competitive Inhibition

Hemp seeds provide a specific 3:1 ratio of Linoleic Acid (LA, Omega-6) to Alpha-Linolenic Acid (ALA, Omega-3). This ratio is vital for establishing "endocannabinoid tone":

Anandamide (AEA) & 2-AG Synthesis: These primary ligands are derived from Arachidonic Acid (AA). While the body needs AA for baseline ECS function, an excess of Omega-6 (typical in Western diets) can lead to overproduction of AA-derived endocannabinoids, which is linked to metabolic dysregulation and chronic inflammation.

Omega-3 Derivatives: The ALA in hemp seeds is converted into EPA and DHA, which serve as precursors for EPEA (Eicosapentaenoyl ethanolamide) and DHEA (Docosahexaenoyl ethanolamide). These "omega-3 endocannabinoids" act as anti-inflammatory counterparts to AEA. They compete for the same metabolic enzymes (FAAH and MAGL), effectively "diluting" the inflammatory potential of an overactive Omega-6-driven system.

Gamma-Linolenic Acid (GLA) and Bypass Metabolism

Unlike other seeds, hemp contains GLA. In the body, GLA is rapidly converted to Dihomo-gamma-linolenic acid (DGLA). DGLA-derived metabolites interact with the ECS to inhibit the synthesis of pro-inflammatory leukotrienes. This adds a layer of indirect ECS support by reducing the "inflammatory noise" that the ECS would otherwise have to work to suppress.

2. Protein & Amino Acids: Supporting Receptor Integrity

Hemp seeds are a complete protein source, specifically rich in Edestin and Albumin, which are highly digestible and provide the structural amino acids for GPCR (G-protein coupled receptor) synthesis.

The L-Arginine / Nitric Oxide (NO) Axis

Hemp seeds contain exceptionally high levels of L-arginine, the direct precursor to Nitric Oxide.

Crosstalk Mechanism: Research shows a significant "crosstalk" between the ECS and the nitrenergic system. Activation of the CB1 receptor often triggers the release of Nitric Oxide via the activation of Nitric Oxide Synthase (NOS).

Vascular Homeostasis: NO serves as a primary signal for vasodilation. By providing ample L-arginine, hemp seeds ensure that the "downstream" messages sent by the ECS—particularly regarding blood pressure and cardiovascular tension—can be successfully executed by the body's hardware.

3. Micronutrients: Enzymatic Cofactors and Protection

The "metabolic lifecycle" of an endocannabinoid involves its creation (by NAPE-PLD or DAGL) and its destruction (by FAAH or MAGL). These enzymes are highly sensitive to mineral status.

Magnesium and Zinc: These minerals, abundant in hemp, are essential cofactors for over 300 enzymatic reactions. In the ECS context, Magnesium is required for the production of cAMP (cyclic Adenosine Monophosphate). When an endocannabinoid binds to a CB1 receptor, it typically inhibits cAMP; however, the receptor's ability to signal and the cell's ability to reset require stable Magnesium levels.

Vitamin E (Tocopherols): Because endocannabinoids are lipids, they are highly susceptible to lipid peroxidation (oxidative damage). The high Vitamin E content in hemp seeds acts as a biological shield, protecting the delicate long-chain fatty acids in the cell membrane from free radical damage, thereby preserving the "pool" of available precursors for ECS signaling.

4. Bioactive Phytochemicals: Direct Receptor Interaction

While hemp seeds do not contain significant THC/CBD, they contain "minor" compounds that act as functional ligands.

Beta-Caryophyllene (BCP) as a Dietary Cannabinoid

BCP is a terpene found in hemp seeds that acts as a selective CB2 receptor agonist.

Immune Regulation: Unlike THC, BCP does not bind to CB1 (the psychoactive receptor) but fits perfectly into the CB2 receptor, which is found primarily on immune cells. This direct binding triggers anti-inflammatory pathways, making hemp seeds a rare food source that contains a literal "dietary cannabinoid."

Phytosterols and Membrane Fluidity

Hemp seeds are rich in beta-sitosterol. These plant sterols integrate into the cell's lipid bilayer.

GPCR Dynamics: Cannabinoid receptors are "embedded" in the membrane. If the membrane is too rigid (due to saturated fats) or too fluid, the receptor cannot change shape properly to send a

signal. Phytosterols help optimize membrane fluidity, ensuring that the CB1 and CB2 receptors remain in a "high-affinity" state, ready to bind with ligands.

4. Discussion

This body of work demonstrates that ECS functionality is not determined solely by receptor presence or endogenous ligand synthesis, but by a broader nutritional architecture that governs substrate availability, membrane composition, enzymatic efficiency, and signal resolution. Hemp seeds emerge as a rare dietary input that simultaneously addresses all three pillars of ECS operation.

A central finding is the importance of fatty acid balance in establishing endocannabinoid tone. While arachidonic acid-derived ligands such as anandamide and 2-AG are indispensable for baseline signaling, excessive omega-6 intake—characteristic of modern diets—skews ECS activity toward pro-inflammatory and metabolically dysregulated states. Hemp seeds counter this imbalance by providing alpha-linolenic acid alongside linoleic acid in a physiologically favorable ratio, enabling the endogenous production of EPA- and DHA-derived ethanolamides that compete for the same degradative enzymes. This competitive inhibition represents a nutritional mechanism for moderating ECS signaling intensity rather than suppressing it outright.

The presence of gamma-linolenic acid further distinguishes hemp seeds from other botanical fat sources. By feeding into DGLA pathways that suppress leukotriene synthesis, GLA reduces inflammatory signaling upstream of ECS engagement. This effectively lowers the regulatory burden placed on the ECS, allowing it to function as a fine-tuning system rather than a chronic compensatory mechanism.

Beyond lipid substrates, this analysis highlights the often-overlooked role of protein and amino acid sufficiency in ECS signaling. Cannabinoid receptors are G-protein coupled receptors whose synthesis, maintenance, and conformational flexibility depend on adequate amino acid availability. The high L-arginine content of hemp seeds is particularly relevant, as nitric oxide signaling represents a documented point of convergence between ECS activation and vascular response. Without sufficient nitric oxide production, ECS-mediated instructions related to blood flow and vascular tone cannot be effectively executed.

Micronutrient sufficiency emerges as another critical determinant of ECS efficiency. Enzymes responsible for endocannabinoid synthesis and degradation operate within narrow mineral and redox tolerances. Magnesium and zinc availability directly influence signaling fidelity and receptor reset capacity, while vitamin E preserves the integrity of membrane-bound lipid precursors. In this context, oxidative stress and mineral depletion may be understood not merely as pathological states, but as conditions that structurally impair ECS signaling capacity.

Finally, the identification of beta-caryophyllene as a selective CB2 agonist underscores the relevance of dietary phytochemicals as direct ECS modulators. Unlike isolated phytocannabinoids, BCP operates within a nutritional matrix that simultaneously supports receptor environment, ligand availability, and enzymatic control. Phytosterols further stabilize this system by optimizing membrane fluidity, a prerequisite for GPCR activation and signal transduction.

Taken together, these findings support a model in which ECS dysfunction may arise as a consequence of nutritional insufficiency or imbalance, and conversely, where targeted whole-food nutrition can restore ECS efficiency without pharmacological intervention.

5. Conclusions

The endocannabinoid system functions as a master regulatory network whose effectiveness depends on continuous access to specific nutritional inputs. This analysis demonstrates that hemp seeds provide a comprehensive array of ECS-supportive nutrients, supplying fatty acid precursors for ligand synthesis, amino acids for receptor integrity and vascular signaling, micronutrients for enzymatic control, and phytochemicals capable of direct receptor interaction. Rather than acting through a single pathway, hemp seeds support ECS function through convergent biochemical

mechanisms that collectively stabilize signaling tone, reduce inflammatory load, and preserve membrane and enzymatic integrity. These findings reinforce the concept of the ECS as a nutrition-dependent system and position hemp seeds as a foundational food for maintaining endocannabinoid homeostasis. Future research should further explore dietary patterns that prioritize ECS substrate sufficiency as a preventative and regenerative strategy in human health.

Conflicts of Interest: The authors declare no conflict of interest. The author does not work for any cannabinoid business or industry.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Full Term
2-AG	2-Arachidonoylglycerol
AA	Arachidonic Acid
AEA	Anandamide (N-arachidonoylethanolamine)
ALA	Alpha-Linolenic Acid
BCP	Beta-Caryophyllene
CB1	Cannabinoid Receptor Type 1
CB2	Cannabinoid Receptor Type 2
cAMP	Cyclic Adenosine Monophosphate
DAGL	Diacylglycerol Lipase
DGLA	Dihomo-Gamma-Linolenic Acid
DHA	Docosahexaenoic Acid
DHEA	Docosahexaenoyl Ethanolamide
ECS	Endocannabinoid System
EPA	Eicosapentaenoic Acid
EPEA	Eicosapentaenoyl Ethanolamide
FAAH	Fatty Acid Amide Hydrolase
GLA	Gamma-Linolenic Acid
GPCR	G-Protein Coupled Receptor
LA	Linoleic Acid
MAGL	Monoacylglycerol Lipase
NAPE-PLD	N-Acylphosphatidylethanolamine-Specific Phospholipase D
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
THC	Δ^9 -Tetrahydrocannabinol
CBD	Cannabidiol

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