

Hypothesis

Not peer-reviewed version

Acidic Phytocannabinoids as Potential ECS Vitamers: A Formal Nutritional Hypothesis Requiring Clinical Validation

[Keith Floyd](#)^{*} and Jeffrey Benjamin^{*}

Posted Date: 13 February 2026

doi: 10.20944/preprints202602.1085.v1

Keywords: acidic phytocannabinoids; endocannabinoid system; endocannabinoidome; ECS tone; nutritional hypothesis; conditional micronutrients; vitamers; THCA; CBDA; lipophilic bioactives; homeostasis; clinical endocannabinoid deficiency; metabolic activation; antioxidant modulation; translational nutrition research; micronutrient classification; nutritional biochemistry; adipose tissue storage; provitamin framework



Preprints.org is a free multidisciplinary platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This open access article is published under a [Creative Commons CC BY 4.0 license](#), which permit the free download, distribution, and reuse, provided that the author and preprint are cited in any reuse.

Hypothesis

Acidic Phytocannabinoids as Potential ECS Vitamers: A Formal Nutritional Hypothesis Requiring Clinical Validation

Keith Floyd and Jeffrey Benjamin

Independent Researcher, USA

* Correspondence: 420elder@gmail.com (K.F.); jbenjaminaz@gmail.com (J.B.)

Abstract

This manuscript advances a formal nutritional hypothesis proposing that acidic phytocannabinoids (e.g., THCA, CBDA, CBGA) may function as conditional endocannabinoid system (ECS)–supportive micronutrients, provisionally termed “ECS vitamers.” The endocannabinoid system plays a central role in maintaining physiological homeostasis, and age- and stress-associated declines in ECS tone have been reported. Acidic phytocannabinoids exhibit structural relatedness, lipophilicity, metabolic transformation, antioxidant capacity, and biological activity in ECS-related pathways—characteristics that parallel certain properties of established vitamin families. These similarities do not establish essentiality. Rather, they provide a rationale for structured investigation. This manuscript formalizes a testable framework outlining the criteria, experimental designs, and clinical validation steps required to determine whether acidic phytocannabinoids meet accepted definitions of micronutrients or vitamers.

Keywords: acidic phytocannabinoids; endocannabinoid system; endocannabinoidome; ECS tone; nutritional hypothesis; conditional micronutrients; vitamers; THCA; CBDA; lipophilic bioactives; homeostasis; clinical endocannabinoid deficiency; metabolic activation; antioxidant modulation; translational nutrition research; micronutrient classification; nutritional biochemistry; adipose tissue storage; provitamin framework

1. Vitamins: Foundational Criteria for Nutritional Classification

1.1. Definition of Vitamin

A vitamin is defined as an organic compound required in the human diet for normal health, growth, and survival (Fitzpatrick et al., 2012; Mozaffarian et al., 2018). These compounds are categorized as micronutrients because they are required in small quantities—typically milligrams or micrograms—yet are indispensable for specific physiological functions (Norbitt et al., 2022; Sugandhi et al., 2023).

Unlike macronutrients, vitamins do not serve as direct energy substrates but instead function primarily as cofactors, coenzymes, or regulators of essential biochemical pathways (Bellazzi, 2022; Fitzpatrick et al., 2012). A defining feature of vitamins in human biology is the loss of endogenous synthetic capacity, necessitating dietary acquisition (Fitzpatrick et al., 2012).

Historically, the term “vitamin” was introduced by Casimir Funk in 1912, initially under the mistaken assumption that all such compounds were “vital amines,” a designation later refined as biochemical understanding evolved (Ridgway et al., 2019; Semba, 2012).

These criteria—organic nature, trace-level requirement, essential physiological function, and dietary dependence—form the evaluative framework within which any proposed micronutrient must be assessed.

2. Vitamers and Functional Families

2.1. Definition of Vitamers

Most vitamins do not exist as singular molecular entities but as families of structurally related compounds termed vitamers (Arachchige et al., 2022; Rafeeq et al., 2020). Vitamers share a common biological function yet may differ substantially in potency, bioavailability, stability, and metabolic fate (Bittner et al., 2024; Sugandhi et al., 2023).

For example, vitamin E comprises multiple tocopherols and tocotrienols, with varying antioxidant activities (Rafeeq et al., 2020). Vitamin B12 similarly includes several structurally related forms unified by a central cobalt-corrin complex (Bellazzi, 2022).

Importantly, classification as a vitamer family depends not solely on structural similarity but on shared contribution to a defined physiological requirement.

3. The Endocannabinoid System and Nutritional Inquiry

The endocannabinoid system (ECS) functions as a regulatory network influencing immune balance, redox status, metabolism, neural signaling, and gastrointestinal integrity (Di Marzo & Piscitelli, 2015; Bilkei-Gorzo, 2012). Age-related and stress-associated reductions in endocannabinoid tone have been documented, including declines in AEA, 2-AG, and CB1 receptor density (Bilkei-Gorzo, 2012; Piyanova et al., 2015; Piyanova et al., 2022).

The classical endocannabinoid system has more recently been expanded into the concept of the “endocannabinoidome,” encompassing a broader lipid signaling network that includes endocannabinoid-like mediators, metabolic enzymes, receptor subtypes, and microbiome interactions that collectively influence systemic homeostasis (Di Marzo & Piscitelli, 2015).

Experimental evidence suggests that modulation of ECS signaling may influence inflammatory pathways, metabolic resilience, and cognitive function (Bilkei-Gorzo et al., 2017; Mathew et al., 2025). These observations raise a broader question: could certain dietary compounds serve as conditional contributors to ECS tone under specific physiological contexts?

This question forms the basis of the present hypothesis.

4. Acidic Phytocannabinoids: Structural and Functional Considerations

4.1. Structural Relatedness

Acidic phytocannabinoids such as THCA, CBDA, CBGA, and CBGVA share a resorcinol core and carboxylic acid moiety and arise from common biosynthetic pathways within *Cannabis sativa* (Gülck & Möller, 2020). This structural organization resembles the family-based architecture seen in classical vitamin systems.

However, structural relatedness alone does not establish micronutrient status and must be evaluated in the context of biological necessity.

4.2. Antioxidant and Regulatory Activity

Acidic phytocannabinoids and related compounds demonstrate antioxidant properties, including radical scavenging and modulation of oxidative pathways (Borges & da Silva, 2021; Dawidowicz et al., 2021). Such activity parallels known antioxidant functions of vitamin E and other fat-soluble vitamins (Rafeeq et al., 2020).

They have also been shown to influence adipocyte function, glucose utilization, and inflammatory signaling in experimental models (Fellous et al., 2020; Adejumo et al., 2022; Bielawiec et al., 2021).

While these findings support bioactivity, they do not demonstrate essentiality. Many bioactive phytochemicals exert physiological effects without meeting criteria for vitamin classification.

4.3. Lipophilicity and Tissue Storage

Acidic phytocannabinoids are lipophilic and accumulate in adipose tissue and liver following exposure (Grotenhermen, 2003; Huestis, 2005). Fat-soluble vitamins (A, D, E, K) share similar storage dynamics, enabling reservoir-based regulation (Arachchige et al., 2022; Sugandhi et al., 2023).

The hypothesis proposes that adipose sequestration may function as a potential ECS reserve system. However, demonstration of regulated mobilization during physiological demand remains unproven and requires metabolic tracer studies.

4.4. Metabolic Transformation and Activation

Acidic phytocannabinoids undergo partial decarboxylation and hepatic metabolism via CYP enzymes, yielding neutral cannabinoids and conjugated metabolites (Hlozek et al., 2017; Ujvary & Hanus, 2016; Floyd, 2025).

This transformation bears conceptual resemblance to provitamin activation pathways such as vitamin D hydroxylation or carotenoid conversion to retinol (Fitzpatrick et al., 2012; Rafeeq et al., 2020).

However, the provitamin analogy remains hypothetical unless deficiency states and functional correction through intake are demonstrated.

5. Breast Milk, Development, and Age-Related ECS Decline

Human breast milk contains endogenous cannabinoids such as AEA and 2-AG, which contribute to early neurodevelopment and feeding regulation (Fride et al., 2009; Harkany et al., 2008). Exogenous cannabinoids can transfer into breast milk under maternal exposure (Wymore et al., 2021; Wysocka et al., 2025).

Age-related decline in ECS tone has been observed in both animal and human studies (Bilkei-Gorzo, 2012; Piyanova et al., 2022; Sorkhou et al., 2025).

The hypothesis suggests that if ECS tone decline contributes to physiological vulnerability, dietary acidic phytocannabinoids could be investigated as conditional modulators. This remains speculative and demands controlled human trials.

6. Proposed Research Framework

To evaluate whether acidic phytocannabinoids qualify as conditional ECS vitamers, the following research domains are required:

1. **Deficiency Modeling:** Identification of measurable ECS insufficiency biomarkers reversible through controlled acidic cannabinoid administration.
2. **Randomized Controlled Trials:** Placebo-controlled dose-response studies evaluating functional endpoints.
3. **Metabolic Tracing:** Quantification of adipose storage, mobilization kinetics, and enterohepatic recycling.
4. **Safety Profiling:** Determination of tolerable upper intake levels and long-term toxicity risk.
5. **Population Studies:** Epidemiological analysis correlating dietary exposure with ECS-related outcomes.

Falsification would occur if supplementation fails to modify validated ECS biomarkers beyond placebo or if no deficiency phenotype is reproducibly identified.

7. Conclusions

This manuscript does not assert that acidic phytocannabinoids are vitamins. It advances a structured, falsifiable nutritional hypothesis proposing that these compounds may represent a candidate class of conditional ECS-supportive micronutrients.

Parallels to vitamin systems—family structure, lipophilicity, metabolic activation, antioxidant activity, and age-associated physiological relevance—provide justification for systematic investigation. However, essentiality, deficiency syndromes, and intake-dependent correction remain to be demonstrated through rigorous clinical research.

Until such validation occurs, acidic phytocannabinoids should be regarded as investigational dietary bioactives.

The contribution of this work lies in formalizing the research question and defining the experimental path necessary to answer it.

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

AI Disclosure: The comprehensive literature search was systematically supported by [ChatGPT-4, Grok, and Gemini]. The identification of the novel conceptual framework—acidic cannabinoids as a class of vitamin family for endocannabinoid tone and baseline function—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.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Full Term
AEA	Anandamide (N-arachidonylethanolamine)
2-AG	2-Arachidonoylglycerol
CB1	Cannabinoid receptor type 1
CB2	Cannabinoid receptor type 2
CBDA	Cannabidiolic acid
CBGA	Cannabigerolic acid
CBGVA	Cannabigerovarinic acid
CED	Clinical Endocannabinoid Deficiency
CNS	Central nervous system
CYP	Cytochrome P450 enzymes
ECS	Endocannabinoid system
FAAH	Fatty acid amide hydrolase
GI	Gastrointestinal
THC	Δ^9 -Tetrahydrocannabinol
THCA	Δ^9 -Tetrahydrocannabinolic acid
TPP	Thiamine pyrophosphate

References

- Fitzpatrick, T. B., Basset, G. J. C., Borel, P., Carrari, F., DellaPenna, D., Fraser, P. D., Hellmann, H., Osorio, S., Rothan, C., Valpuesta, V., Caris-Veyrat, C., & Fernie, A. R. (2012). Vitamin deficiencies in humans: Can plant science help? *The Plant Cell*, 24(2), 395–414. <https://doi.org/10.1105/tpc.111.093120>
- Mozaffarian, D., Rosenberg, I., & Uauy, R. (2018). History of modern nutrition science—Implications for current research, dietary guidelines, and food policy. *BMJ*, 361, k2392. <https://doi.org/10.1136/bmj.k2392>
- Norbitt, C. F., Kimita, W., Bharmal, S. H., Ko, J., & Petrov, M. S. (2022). Relationship between habitual intake of vitamins and new-onset prediabetes/diabetes after acute pancreatitis. *Nutrients*, 14(7), 1480. <https://doi.org/10.3390/nu14071480>
- Sugandhi, V. V., Pangeni, R., Vora, L. K., Poudel, S., Nangare, S., Jagwani, S., Gadhave, D., Qin, C., Pandya, A., Shah, P., Jadhav, K., Mahajan, H. S., & Patravale, V. (2023). Pharmacokinetics of vitamin dosage forms: A complete overview. *Food Science & Nutrition*, 12(1), 48–83. <https://doi.org/10.1002/fsn3.3787>
- Bellazzi, F. (2022). Biochemical functions. *The British Journal for the Philosophy of Science*, 76(4). <https://doi.org/10.1086/723241>
- Ridgway, E., Baker, P., Woods, J., & Lawrence, M. (2019). Historical developments and paradigm shifts in public health nutrition science, guidance and policy actions: A narrative review. *Nutrients*, 11(3), 531. <https://doi.org/10.3390/nu11030531>
- Semba, R. D. (2012). The discovery of the vitamins. *International Journal for Vitamin and Nutrition Research*, 82(5), 310–315. <https://doi.org/10.1024/0300-9831/a000124>
- Arachchige, G. R. P., Pook, C. J., Jones, B., Coe, M., Saffery, R., Wake, M., Thorstensen, E. B., & O'Sullivan, J. M. (2022). Fat-soluble vitamins: Parent-child concordance and population epidemiology in the longitudinal study of Australian children. *Nutrients*, 14(23), 4990. <https://doi.org/10.3390/nu14234990>
- Rafeeq, H., Ahmad, S., Burhan Khan Tareen, M., Shahzad, K. A., Bashir, A., Jabeen, R., Tariq, S., & Shehzadi, I. (2020). Biochemistry of fat soluble vitamins, sources, biochemical functions and toxicity. *Haya: The Saudi Journal of Life Sciences*, 5(9), 188–196.
- Bittner, M. J., Bannon, C. C., Rowland, E., Sundh, J., Bertrand, E. M., Andersson, A. F., Paerl, R. W., & Riemann, L. (2024). New chemical and microbial perspectives on vitamin B1 and vitamin dynamics of a coastal system. *ISME Communications*, 4(1). <https://doi.org/10.1093/ismeco/ycad016>
- Di Marzo, V., & Piscitelli, F. (2015). The endocannabinoid system and its modulation by phytocannabinoids. *Neurotherapeutics*, 12(4), 692–698.
- Bilkei-Gorzo, A. (2012). The endocannabinoid system in normal and pathological brain ageing. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 367(1607), 3326–3341. <https://doi.org/10.1098/rstb.2011.0388>
- Piyanova, A., et al. (2015). Age-related changes in the endocannabinoid system in the mouse hippocampus. *Mechanisms of Aging and Development*, 150, 20–32. <https://doi.org/10.1016/j.mad.2015.08.005>
- Piyanova, A., et al. (2022). Dynamic changes in the endocannabinoid system during the aging process: Focus on the middle-age crisis. *International Journal of Molecular Sciences*, 23(18), 10254. <https://doi.org/10.3390/ijms231810254>
- Bilkei-Gorzo, A., et al. (2017). A chronic low dose of Δ^9 -tetrahydrocannabinol restores cognitive function in old mice. *Nature Medicine*, 23(6), 782–787. <https://doi.org/10.1038/nm.4311>
- Mathew, R. J., et al. (2025). Cannabidiol (CBD) and cognitive function in older adults: A mini review. *Frontiers in Psychiatry*, 16, 1646151. <https://doi.org/10.3389/fpsy.2025.1646151>
- Gülck, T., & Møller, B. L. (2020). Phytocannabinoids: Origins and biosynthesis. *Trends in Plant Science*, 25(10), 985–1004. <https://doi.org/10.1016/j.tplants.2020.05.005>
- Borges, R. S., & da Silva, A. B. F. (2021). Cannabidiol as an antioxidant. *Handbook of Experimental Pharmacology*, 268, 67–96. https://doi.org/10.1007/164_2020_397
- Dawidowicz, A. L., et al. (2021). Cannabis sativa L. bioactive compounds and their protective role in oxidative stress and inflammation. *Antioxidants*, 10(4), 660. <https://doi.org/10.3390/antiox10040660>
- Fellous, T., et al. (2020). Phytocannabinoids promote viability and functional adipogenesis of bone marrow-derived mesenchymal stem cells through different molecular targets. *Biochemical Pharmacology*, 175, 113859. <https://doi.org/10.1016/j.bcp.2020.113859>

- Adejumo, A. C., et al. (2022). Cannabidiol improves glucose utilization and modulates glucose-induced dysmetabolic activities in isolated rats' peripheral adipose tissues. *Biomedicine & Pharmacotherapy*, 149, 112752. <https://doi.org/10.1016/j.biopha.2022.112752>
- Bielawiec, P., et al. (2021). Cannabis sativa as a treatment for obesity. *Cannabis and Cannabinoid Research*, 7(4), 433–440. <https://doi.org/10.1089/can.2021.0016>
- Grotenhermen, F. (2003). Pharmacokinetics and pharmacodynamics of cannabinoids. *Clinical Pharmacokinetics*, 42(4), 327–360.
- Huestis, M. A. (2005). Pharmacokinetics and metabolism of cannabinoids. *Chemistry & Biodiversity*, 2(12), 1770–1804.
- Hlozek, T., et al. (2017). Pharmacokinetic and behavioural profile of THCA in rats. *British Journal of Pharmacology*, 174(23), 4264–4279.
- Ujvary, I., & Hanus, L. (2016). Human metabolites of cannabidiol: A review. *Cannabis and Cannabinoid Research*, 1(1), 90–101.
- Floyd, K. (2025). The interaction of stomach acid, blood pH, and liver metabolism with acidic cannabinoids. *Preprints*, 202512.1465.
- Fride, E., et al. (2009). The endocannabinoid system and infant feeding. *Neuroendocrinology Letters*, 30(3), 303–310.
- Harkany, T., et al. (2008). Endocannabinoid signaling in brain development. *Trends in Pharmacological Sciences*, 29(2), 83–92.
- Wymore, E. M., et al. (2021). Persistence of Δ^9 -tetrahydrocannabinol in human breast milk. *JAMA Pediatrics*, 175(7), 692–699. <https://doi.org/10.1001/jamapediatrics.2021.0175>
- Wysocka, A., et al. (2025). Maternal cannabis use during lactation and potential effects on human milk composition and production: A narrative review. *Advances in Nutrition*, 16(3), 100234.
- Sorkhou, M., et al. (2025). Age differences in endocannabinoid tone are ameliorated after recent cannabis use. *Cannabis and Cannabinoid Research*, 10(1), 41–50.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.