

Review

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Review

The Mapping of Physiological Conversion Pathways from the Major Acidic Cannabinoids

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Abstract

The acidic cannabinoids tetrahydrocannabinolic acid (THCA), cannabidiolic acid (CBDA), and cannabigerolic acid (CBGA) serve as primary precursors in cannabis phytochemistry. They undergo physiological conversion through decarboxylation, isomerization, degradation, and hepatic metabolism, yielding diverse neutral cannabinoids and phase I/II metabolites. **Key Conversion Pathways** THCA → Primarily converts to Δ9-THC (with minor Δ8-THC, Δ10-THC, THCV if varin precursors present, CBN via oxidation, and traces of CBL/CBT). Active metabolites include 11-OH-THC (psychoactive), various hydroxy-THC forms, and oxidated derivatives; inactive ones feature THC-COOH (primary urinary marker), glucuronides, and carboxy analogs. CBDA → Yields CBD (with traces of CBDV, CBE, CBT-C). Active metabolites encompass 7-OH-CBD (major, equipotent to CBD), other positional hydroxy-CBDs, and oxidated forms; inactive ones include 7-COOH-CBD (dominant circulating metabolite), glucuronides, and carboxy variants. CBGA → Produces CBG (with traces of CBGV, CBC, CBGM, CBCV). Active metabolites involve positional hydroxy-CBGs (e.g., 6-OH-CBG) and related CBC hydroxy forms; inactive ones feature 6-COOH-CBG, glucuronides, and carboxy analogs. Hepatic cytochrome P450 enzymes (e.g., CYP2C9, CYP3A4) drive hydroxylation and oxidation, followed by glucuronidation for excretion. Minor pathways include epoxidation, cyclization, and side-chain modifications, often speculative or trace. As the second in a three-part series on cannabis dietary inputs, this review maps these conversion cascades, highlighting implications for endocannabinoid system (ECS) modulation and physiological outcomes from whole-plant consumption. Integration with companion works on hemp seed nutrition and ECS mechanisms positions acidic cannabinoids as key contributors to homeostasis, warranting targeted clinical investigation.

Keywords: THCA (tetrahydrocannabinolic acid); CBDA (cannabidiolic acid); CBGA (cannabigerolic acid); partial decarboxylation; gastric decarboxylation; microbiome decarboxylation; acidic cannabinoid stability; direct acidic cannabinoid effects; THCA-glucuronide; CBDA-glucuronide

1. Introduction

This paper dives into the acidic cannabinoid metabolome cascade that happens through stomach, blood, and liver mechanisms, and the compound outcome from that process.

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. The Acidic Cannabinoid Metabolome: Physiological Conversion Pathways from THCA, CBDA, and CBGA

From THCA (Tetrahydrocannabinolic Acid)

Cannabinoids:

- THCA
- Δ9-THC
- Δ8-THC
- Tetrahydrocannabivarin (THCV) (if THCA source contains varin precursors)
- Cannabinol (CBN) (degradation product of THC over time)
- Cannabicyclol (CBL) (photochemical or oxidative cyclization product, minor pathway)
- Cannabitriol (CBT) (rare oxidative product, possible trace)

Active Metabolites:

- 11-Hydroxy-Δ9-Tetrahydrocannabinol (11-OH-THC)
- 8-Hydroxy-Δ9-Tetrahydrocannabinol (8-OH-THC)

Inactive Metabolites:

- 11-Nor-9-Carboxy-Δ9-Tetrahydrocannabinol (THC-COOH)
- Δ9-Tetrahydrocannabinol-Glucuronide (THC-Gluc)
- 11-Nor-9-Carboxy-Δ9-Tetrahydrocannabinol-Glucuronide (THC-COOH-Gluc)
- 8,11-Dihydroxy-Δ9-Tetrahydrocannabinol (8,11-diOH-THC)
- 11-Hydroxy-THCV (11-OH-THCV) (if THCV present)
- 7-Hydroxy-THCV (7-OH-THCV) (if THCV present, alternate hydroxylation)

11-Nor-THCV-7-Carboxylic Acid (THCV-COOH) (if THCV present)

From CBDA (Cannabidiolic Acid)

Cannabinoids:

CBDA

CBD

Cannabidivarin (CBDV) (trace if CBDA source has varin precursors)

Cannabielsoin (CBE) (oxidative cyclization product of CBD, minor pathway)

Active Metabolites:

7-Hydroxy-Cannabidiol (7-OH-CBD)

6-Hydroxy-Cannabidiol (6-OH-CBD) Inactive Metabolites:

7-Nor-7-Carboxy-Cannabidiol (7-COOH-CBD)

7-Nor-7-Carboxy-Cannabidiol-Glucuronide (7-COOH-CBD-Gluc) (glucuronide of 7-COOH-CBD)

Cannabidiol-Glucuronide (CBD-Gluc)

7-Hydroxy-Cannabidivarin (7-OH-CBDV) (if CBDV present)

7-Nor-7-Carboxy-Cannabidivarin (7-COOH-CBDV) (if CBDV present)

From CBGA (Cannabigerolic Acid)

Cannabinoids:

CBGA

CBG

Cannabigerovarin (CBGV) (trace if CBGA source has varin precursors)

Cannabichromene (CBC) (minor if CBGA partially converts in plant or body)

Cannabichromevarin (CBCV) (if CBGV present, trace)

Active Metabolites:

6-Hydroxy-Cannabigerol (6-OH-CBG)

6-Hydroxy-Cannabichromene (6-OH-CBC) (if CBC present)

7-Hydroxy-Cannabichromene (7-OH-CBC) (if CBC present, alternate hydroxylation)

Inactive Metabolites:

Cannabigerol-Glucuronide (CBG-Gluc)

6-Nor-6-Carboxy-Cannabichromene (6-COOH-CBC) (if CBC present)

4. Discussion

This mapping of physiological conversion pathways from the major acidic cannabinoids—THCA, CBDA, and CBGA—reveals a far more diverse human metabolome than traditionally acknowledged, encompassing dozens of phase I hydroxy-metabolites and phase II conjugates. Many of these, such as 11-OH-THC (equipotent or more psychoactive than parent THC) and 7-OH-CBD (with enhanced serotonergic activity), are pharmacologically active and dominate after oral or low-heat consumption of raw cannabis or hemp products.

This metabolic mapping thus serves as the mechanistic anchor for the companion preprints in this trilogy: (1) this paper's quantitative dietary exposure to acidic cannabinoids from whole-plant cannabis and (2) hemp seed nutritional inputs, and (3) the resultant modulation of endocannabinoid system tone and organ-specific physiological outcomes through these extended phase I/II metabolite profiles.

The expanded profile challenges simplistic models of cannabinoid pharmacology, underscoring an “acidic entourage” effect that may amplify therapeutic benefits while altering psychoactivity.

Current analytical and regulatory frameworks, focused on neutral cannabinoids and limited metabolites, underestimate this complexity, highlighting the need for broader pharmacokinetic studies incorporating acidic precursors and hydroxy-derivatives.

5. Conclusions

The acidic cannabinoids THCA, CBDA, and CBGA anchor the biochemical framework of the cannabis plant and, through their diverse decarboxylation and metabolic conversion pathways, generate a wide spectrum of neutral cannabinoids and phase I/II metabolites with distinct physiological relevance. Mapping these cascades clarifies how whole-plant consumption delivers not only primary cannabinoids but also a dynamic ensemble of downstream molecules that contribute to endocannabinoid system modulation, metabolic adaptation, and homeostatic balance.

The patterns observed across the THCA, CBDA, and CBGA lineages reveal consistent principles: (1) precursor acids maintain unique bioactivity independent of their neutral forms; (2) hepatic metabolism produces secondary metabolites that often dominate systemic exposure; and (3) minor transformation routes—though present in trace amounts—add functional diversity that remains understudied. Collectively, these pathways challenge the conventional focus on isolated neutral cannabinoids and highlight the need to evaluate acidic and metabolite-driven signaling within physiological and dietary contexts.

As part of this three-paper series, these findings integrate with companion analyses on hemp seed nutrition and ECS-regulated metabolic mechanisms to provide a comprehensive framework for understanding cannabis as a dietary input. Together, they support the emerging view that acidic cannabinoids and their metabolites play central roles in maintaining homeostasis, adapting to internal stressors, and contributing to overall biological resilience. Targeted clinical and translational research is warranted to establish the full therapeutic potential of these compounds within human nutrition and regenerative 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
8,11-diOH-THC	8,11-Dihydroxy- Δ^9 -Tetrahydrocannabinol
8-OH-THC	8-Hydroxy- Δ^9 -Tetrahydrocannabinol
CBC	Cannabichromene
CBCV	Cannabichromevarin
CBDA	Cannabidiolic Acid
CBD	Cannabidiol
CBD-Gluc	Cannabidiol-Glucuronide
CBDV	Cannabidivarin
CBE	Cannabielsoin
CBG	Cannabigerol
CBGA	Cannabigerolic Acid
CBG-Gluc	Cannabigerol-Glucuronide
CBGV	Cannabigerovarin

CBL	Cannabicyclol
CBT	Cannabitol
Δ 8-THC	Delta-8-Tetrahydrocannabinol
Δ 9-THC	Delta-9-Tetrahydrocannabinol
6-COOH-CBC	6-Nor-6-Carboxy-Cannabichromene
6-OH-CBC	6-Hydroxy-Cannabichromene
6-OH-CBG	6-Hydroxy-Cannabigerol
6-OH-CBD	6-Hydroxy-Cannabidiol
7-COOH-CBD	7-Nor-7-Carboxy-Cannabidiol
7-COOH-CBD-Gluc	7-Nor-7-Carboxy-Cannabidiol-Glucuronide
7-COOH-CBDV	7-Nor-7-Carboxy-Cannabidivarin
7-OH-CBC	7-Hydroxy-Cannabichromene
7-OH-CBD	7-Hydroxy-Cannabidiol
7-OH-CBDV	7-Hydroxy-Cannabidivarin
7-OH-THCV	7-Hydroxy-Tetrahydrocannabivarin
11-OH-THC	11-Hydroxy- Δ 9-Tetrahydrocannabinol
11-OH-THCV	11-Hydroxy-Tetrahydrocannabivarin
CBN	Cannabinol
THC-COOH	11-Nor-9-Carboxy- Δ 9-Tetrahydrocannabinol
THC-COOH-Gluc	11-Nor-9-Carboxy- Δ 9-Tetrahydrocannabinol-Glucuronide
THC-Gluc	Δ 9-Tetrahydrocannabinol-Glucuronide
THCA	Tetrahydrocannabinolic Acid
THCV	Tetrahydrocannabivarin
THCV-COOH	11-Nor-THCV-7-Carboxylic Acid

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