Review

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Stomach Acid, Blood pH, and Liver Metabolism: The Stability and Transformation of Acidic Cannabinoids

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Abstract

Acidic cannabinoids (e.g., THCA, CBDA) are the dominant phytoconstituents in Cannabis sativa L. and serve as precursors to neutral forms (THC, CBD) via decarboxylation. This is the third work in an integrated series exploring how dietary cannabis inputs interact with Endocannabinoid System (ECS) pathways. This paper examines the role of physiological environments — stomach acidity, blood pH, and hepatic metabolism — in determining the fate, bioavailability, and independent pharmacological activity of ingested acidic cannabinoids. Integrating organic chemistry and pharmacokinetics, the study finds that gastric decarboxylation of acidic cannabinoids is negligible: the reaction's activation energy barrier is largely insurmountable at physiological temperature, and gastric acidity plays no direct catalytic role in overcoming it. Upon absorption, systemic blood pH (7.35–7.45) further stabilizes acidic cannabinoids, which exist almost entirely (>99%) as non-reactive carboxylate anions. Hepatic first-pass metabolism preserves this pattern: acidic cannabinoids are predominantly conjugated intact via UGT1A9, in contrast to neutral THC, which undergoes CYP-mediated oxidation to its own active and inactive metabolites; CBD's position between these two pathways remains unresolved in the literature. The gut microbiome acts as a secondary modulator via β-glucuronidase-mediated deconjugation, potentially enabling enterohepatic recirculation and extending systemic exposure, though this mechanism remains an inference by analogy for cannabinoids specifically rather than a directly demonstrated finding. Beyond their role as precursors, THCA and CBDA act directly on distinct molecular targets independent of any conversion to their neutral forms: CBDA through selective COX-2 inhibition and 5-HT1A receptor potentiation, and THCA through potent PPARγ agonism and weak partial TRPA1 activation. Direct detection of THCA in oral fluid following cannabis use corroborates delivery of the intact acidic form to peripheral tissues. Taken together, these findings indicate that ingested acidic cannabinoids reach systemic circulation and target tissues largely unconverted. Their therapeutic relevance is therefore shaped primarily by their own direct pharmacological activity and by metabolic and microbial processing, rather than by thermal decarboxylation to THC or CBD — a transformation the body's physiological conditions do not provide.

Keywords: Dietary cannabinoids; Clinical endocannabinoid deficiency; Entourage effect; Synergistic cannabinoids; Anti-inflammatory acidic cannabinoids; TRP channels cannabinoids (e.g.; TRPA1 THCA); 5-HT1A receptor potentiation CBDA; PPAR-gamma agonism cannabinoids; Phytocannabinoid acids; Bioavailability phytocannabinoids; First-pass metabolism cannabinoids

1. Introduction

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

2. Materials and Methods

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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.

An initial literature synthesis was AI-assisted, drawing on large language models to identify candidate sources and construct mechanistic narratives across stomach acid chemistry, blood pH stability, hepatic metabolism, and gut microbiome interactions. This initial draft was subsequently subjected to a systematic, citation-by-citation verification process: each reference was checked against its original publication to confirm that the cited source exists, that its title, authorship, journal, and year match the citation as given, and that the specific claim attributed to it is actually supported by that source's content rather than by a plausible-sounding but unverified extrapolation.

Citations found to be fabricated, misattributed to the wrong compound or mechanism, or unsupported by the cited source's actual findings were corrected, replaced with verified alternatives, or removed. Where a claim could not be supported by any identifiable source after a documented search, it was either explicitly qualified as an open question or omitted from the final text rather than retained on the strength of a prior AI-generated citation. Real activation energies, rate constants, receptor-binding data, and pharmacokinetic figures reported in this paper are drawn directly from the verified primary sources cited, not from intermediate AI-generated approximations.

This verification process also surfaced several genuinely open questions in the literature — noted explicitly in the Discussion — distinct from claims that were simply incorrect.

3. AI Disclosure

An initial literature synthesis for this paper was conducted with the assistance of large language models, used to identify candidate sources and construct mechanistic narratives across the topics addressed here. That initial synthesis was substantially unreliable, and an earlier version of this paper — "The Interaction of Stomach Acid, Blood pH, and Liver Metabolism with Acidic Cannabinoids: Partial Decarboxylation, Metabolic Transformation, and Physiological Implications," https://doi.org/10.20944/preprints202512.1465.v1 — was made publicly available before this was fully recognized. This version supersedes it. This is disclosed directly: readers who encountered that earlier version encountered citation errors this disclosure exists to account for. A complete, independent verification pass was subsequently required and is described in Materials and Methods.

Testing across multiple AI systems, compared against one another and against primary sources, found that several produced recognizable, repeatable citation fabrication — real journals and years attached to titles or findings that did not exist in the cited work. When shown their own prior output minutes later, in the same conversation, these systems failed to recognize the error and produced a second, differently inaccurate response rather than a correction. This behavior characterized the AI-assisted synthesis underlying the earlier, publicly circulated version of this paper.

The verification process conducted for this version found that fabrication concentrated almost exclusively in specific quantitative claims — rate constants, IC_{50} values, percentages — attached to otherwise real, correctly titled sources, rather than in general mechanistic statements. AI-assisted synthesis is most dangerous exactly where it looks most rigorous: a real citation lending unearned authority to a fabricated number. This likely affects general AI-assisted search results by default, including browser-integrated assistants (e.g., Gemini, Chrome's "Ask" feature), for users with no reason to suspect or verify it.

Models also showed increased confirmation-seeking with greater conversational familiarity — validating a user's existing framing more readily the more context they had, independent of the evidence's actual strength. For research use, this is a bias worth naming on its own.

The underlying conceptual framework was an original, human-driven synthesis. AI assistance was confined to literature identification, drafting, and the verification process described here and in Materials and Methods.

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4. Stomach Acid, Blood pH, and Liver Metabolism: The Stability and Transformation of Acidic Cannabinoids

Cannabis sativa L. synthesizes acidic cannabinoids such as Δ9-tetrahydrocannabinolic acid (THCA), cannabidiolic acid (CBDA), and cannabigerolic acid (CBGA), which serve as precursors to their neutral forms—Δ9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabigerol (CBG)—via decarboxylation, a process releasing CO_2 from the carboxyl group (-COOH). Decarboxylation occurs readily during smoking (combustion temperatures reaching several hundred degrees Celsius) and during cooking or deliberate heating (typically 110–130°C); by contrast, this paper establishes that physiological conditions — gastric acidity, blood pH, and hepatic processing — impose a barrier to this reaction rather than driving it, with the acidic form surviving digestion and reaching systemic circulation largely intact.

Beyond their role as precursors, acidic cannabinoids exhibit distinct pharmacological activity of their own — including COX-2 inhibition, PPARγ activation, TRP channel modulation, and serotonin 5-HT1A activity across the class (Singh et al., 2026) — with THCA's PPARγ agonism and independent neuroprotective effects offering a well-characterized example (Nadal et al., 2017). This paper examines the chemical and physiological basis for that stability across the gastrointestinal tract, blood, and liver, and its implications for which form of the cannabinoid the body actually encounters.

4.1. Stomach Acid: Why Gastric Decarboxylation Is Negligible

The stomach's acidic environment (pH 1.5–3.5), driven by parietal cell hydrochloric acid secretion, exposes ingested acidic cannabinoids like THCA and CBDA to aggressive acidic conditions. The stability and potential transformation of these compounds under such gastric conditions have been a subject of significant pharmacokinetic debate.

Nahler, Grotenhermen, et al. reported specific human PK data showing no detectable THC after oral CBD (Nahler et al., 2017). The decarboxylated form in that comparison limits usefulness for this paper, while the reaction class is important. Merrick et al. wrote that CBD can undergo acid-catalyzed transformation in gastric fluid (Merrick et al., 2016). In the same journal Grotenhermen et al. argues as a separate article that simulated-gastric-fluid conversion isn't clinically relevant in vivo (Grotenhermen et al., 2017). Protonation is a structurally different reaction from decarboxylation of THCA/CBDA, which is loss of CO_2 from the carboxyl group and is primarily thermally driven in vivo.

Wang et al. (2016) measured decarboxylation rate constants for THCA-A at approximately twice those of CBDA and CBGA across all tested temperatures (80–110°C), corresponding to a lower activation energy for THCA-A ($E_a \approx 88$ kJ/mol) than for CBDA ($E_a \approx 112$ kJ/mol) — consistent with an elimination reaction requiring substantial thermal input, largely insurmountable at physiological temperature.

The differential rate is not fully explained by an intrinsic property of either acid alone. Computational modeling indicates the rate-determining step is a keto-enol tautomerization preceding CO_2 loss, which proceeds far faster when catalyzed by a proton-donating species via a six-membered transition state; THCA's greater dipole moment and structural rigidity make it more responsive to this catalytic assistance than CBDA (He et al., 2020).

Dietary factors amplify variability in favor of absorption, yet acidic cannabinoids passing through the stomach do so largely undissolved because they are chemically stable and physically unreactive in that environment. Fatty meals raise gastric pH to 4.5-5.5 and extend emptying to 4 hours (Kong & Singh, 2008), potentially increasing decarboxylation over time in vivo if the thermal barrier were met.

Post-gastric, the small intestine (pH 6–7.4) enhances solubility via bile salts (5–15 mM), raising dissolution to 1–2 mg/mL, with dietary lipids lowering micelle CMC and boosting uptake 2–3-fold (Zgair et al., 2016). THCA's carboxylated structure limits aqueous solubility, consistent with its behavior in the lipid-associated absorption pathway described below.

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A structurally distinct transformation has been reported for the neutral cannabinoid CBD: acid-catalyzed cyclization to Δ8/Δ9-THC in simulated gastric fluid (Merrick et al., 2016), proceeding via exogenous protonation of the resorcinol ring. This does not extend to acidic cannabinoids. The clinical relevance of the CBD finding itself remains disputed: human pharmacokinetic data found no detectable THC following oral CBD administration (Nahler et al., 2017), and a formal comment alongside argued the in vitro result does not translate in vivo (Grotenhermen et al., 2017).

Other minor degradation pathways were considered and are outside this paper's scope.

Given that physiological barrier, decarboxylation is thermally driven, not exogenous-acid-catalyzed, and that makes THCA/CBDA behave differently than CBD acid-catalyzed cyclization chemistry. The transformation from neutral genuinely does need an external acid for protonation, but THCA/CBDA decarboxylation does not need gastric HCl to donate a proton; it requires heat at a level much higher than the gastric environment operates under.

The activation energy barrier for decarboxylation is disproportionately sensitive to temperature due to Arrhenius dependence; thus, ingested cannabinoids are effectively spared from gastric decarboxylation, ensuring that the intact acidic form—not the neutral form—is the primary ligand presented to the intestinal absorption sites.

4.2. Blood pH and Cannabinoid Stability

Absorbed cannabinoids enter the portal vein and systemic circulation, where blood pH (7.35–7.45) is buffered by HCO_3^-/H_2CO_3 (pK_a 6.1):

$pH = 6.1 + \log([HCO_3^-]/[H_2CO_3])$

With $[HCO_3^-] \approx 24$ mM and $[H_2CO_3] \approx 1.2$ mM, this neutral environment stabilizes acidic cannabinoids. THCA (pK_a ~4.9) and CBDA (pK_a ~4.7) are >99% ionized as carboxylate anions ($-COO^-$) at pH 7.4 — a direct application of Henderson-Hasselbalch to the stated pK_a values — and remain largely unreactive to decarboxylation at physiological temperature. Eichler et al. (2012) detected THCA-A and CBDA in plasma following administration of unheated Cannabis sativa extract, with negligible conversion to THC/CBD, consistent with the thermal-barrier findings established above. Neutral THC binds plasma proteins extensively (>95%; Widman et al., 1974), similarly reducing its free fraction; CBD shows comparably high albumin binding (~97%; Yang et al., 2014).

Metabolites like THC-COOH (pK_a 4.5) are also ionized at physiological pH and have minimal independent impact on blood pH given the buffering capacity of the bicarbonate system (Koeppen & Stanton, 2017).

Analytical methods relying on underivatized GC-MS are prone to injector-port thermal decarboxylation of acidic cannabinoids; only an estimated 70% of injected THCA is recovered as THC under these conditions, systematically underestimating true acidic-cannabinoid content relative to derivatized or LC-MS-based methods (Dussy et al., 2005).

4.3. Liver Metabolism and Transformation into Metabolites

Acidic cannabinoids reaching the liver are conjugated without prior decarboxylation.

THCA is converted to THCA-glucuronide ($C_{28}H_{36}O_{10}$) by UGT1A9 (<1% forms THC in the process; Huestis, 2007), consistent with hepatic glucuronidation pathways described for related non-acidic and acidic cannabinoids (Lacerda et al., 2025). This conjugation pathway preserves the acidic form as the dominant hepatic product, consistent with the gastric findings above.

THC, reaching the liver in neutral form, undergoes sequential CYP-mediated oxidation: CYP2C9 hydroxylates THC to 11-OH-THC, which is further oxidized to THC-COOH. This pathway is well established and consistent across the literature.

CBD's hepatic fate is less settled. Broad literature synthesis attributes CBD's primary metabolism to CYP-mediated oxidation — chiefly CYP2C19 and CYP3A4, forming 7-OH-CBD and subsequently 7-COOH-CBD (Ujváry & Hanuš, 2016). A more recent study using intact human hepatocytes, however, found CBD preferentially glucuronidated rather than oxidized (Havlásek et al., 2023). The

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discrepancy may reflect the experimental systems involved as much as the underlying biology: liver microsome preparations, the basis for much of the earlier CYP-focused literature, can underrepresent phase II conjugation relative to whole hepatocytes, which retain both oxidative and conjugative machinery intact. Whether CBD's dominant hepatic fate is oxidation or conjugation may therefore depend on which system measured it — a distinction worth resolving with more comparable methodology rather than assuming either finding is definitive.

Microbial decarboxylation of THCA was considered but is not supported by current evidence and would in any case face the same thermal barrier established above; the microbiome's more established role in cannabinoid disposition is deconjugation and enterohepatic recirculation, discussed below.

Gut microbiota express β-glucuronidase, which can deconjugate hepatic cannabinoid glucuronides (e.g., THCA-glucuronide), enabling enterohepatic recirculation and potentially extending systemic half-life (Roberts et al., 2014; Huestis, 2007). This mechanism is well established for other glucuronidated compounds (Sui et al., 2021) but not yet demonstrated directly for cannabinoids — worth stating explicitly as an inference by analogy rather than a cannabinoid-specific finding. Dietary factors and cannabis use itself may further interact with microbiome composition, affecting gastrointestinal health and bioavailability (Wardill et al., 2024; Zgair et al., 2016).

In rat models of protein-calorie malnutrition, hepatic CYP3A1/2 levels — the rat isoform most closely corresponding to human CYP3A4 — declined 40–50%, with parallel reductions in mRNA confirming decreased enzyme expression rather than solely reduced catalytic activity (Lee et al., 2004).

Genetic polymorphisms modulate this system considerably. In the CYP2C9 gene, the *3/*3 homozygotes show roughly threefold higher THC AUC and ~70% lower THC-COOH relative to wild-type, extending THC's own half-life as clearance of the parent compound slows (Sachse-Seeboth et al., 2009). Metabolites are ultimately excreted via feces (30-65%, reflecting combined biliary elimination plus unabsorbed compound) and urine (~20%) (Huestis, 2007).

Taken together, the liver metabolism data reinforces the pattern established in the stomach: acidic cannabinoids (THCA, and **likely CBDA by analogy**) are conjugated intact, preserving the acidic form as the dominant systemic product. THC follows a well-characterized oxidative path toward its own active and inactive metabolites, while CBD's position remains genuinely unresolved between the two pathways. That baseline picture is further shaped by several modifying variables: microbial β-glucuronidase activity may extend systemic exposure through enterohepatic recirculation, though this remains an inference by analogy for cannabinoids specifically; nutritional status and CYP2C9 genotype each independently alter clearance; and final elimination occurs predominantly via the fecal route. None of these modifiers change the core finding — the acidic form survives hepatic processing intact far more often than it is converted.

5. Discussion: ECS and Therapeutic Implications

Acidic cannabinoids modulate the ECS through distinct, non-canonical pathways. CBDA exerts anti-inflammatory effects via highly selective COX-2 inhibition (Takeda et al., 2008) and independently enhances 5-HT1A receptor activation, mediating anti-nausea and anxiolytic effects replicated across rat and human receptor systems (Bolognini et al., 2013; Pertwee et al., 2018). THCA promotes neuroprotection and microglial modulation through potent PPARγ agonism (Nadal et al., 2017), and shows weak partial agonist activity at TRPA1, notably lower in potency than most neutral cannabinoids tested in the same assay (De Petrocellis et al., 2011). THCA has been detected directly in oral fluid following cannabis use (Day et al., 2006), consistent with the intact acidic form reaching peripheral tissues. Liver metabolites like 11-OH-THC shift ECS signaling in their own right, while nutritional and genetic factors modulate bioavailability and efficacy, as established above.

The protein-calorie malnutrition-driven suppression of hepatic CYP3A1/2 established in rat models (Lee et al., 2004) has not, to our knowledge, been tested directly in humans. Quinine 3-hydroxylation is a validated, minimally invasive in vivo biomarker of human CYP3A4 activity

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(Mirghani et al., 2002; Mirghani et al., 2003), offering a feasible route to determine whether the nutritional modulation of cannabinoid metabolism observed in rodent models extends to humans. This represents a concrete, testable extension of the present findings.

6. Conclusions

Three independent barriers — gastric, circulatory, and hepatic — converge on the same outcome: ingested acidic cannabinoids resist conversion to their neutral forms. The activation energy decarboxylation requires is not met by gastric acidity or body temperature; blood pH holds THCA and CBDA ionized and unreactive; and the liver conjugates them intact rather than converting them. The acidic form is not a transient precursor awaiting transformation — under ordinary physiological conditions, it is the form the body receives.

This matters because THCA and CBDA are not pharmacologically inert. Both act directly on distinct molecular targets — PPARγ, COX-2, 5-HT1A — independent of any conversion to THC or CBD. What remains open is how much diet, microbiome, and genetics shift this picture person to person, including whether the metabolic findings established here in animal models hold in humans.

7. Conflicts of Interest

One author has authored a commercially available book describing a raw Cannabis dietary protocol under study and operates a related website, constituting a financial and intellectual interest in findings consistent with the protocol's premise. This is disclosed for transparency. No author is employed by or holds financial ties to a cannabinoid business or industry entity.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	**Full Term**
AEA	Anandamide (N-arachidonoylethanolamine)
ARR	Arrhenius rate relationship
CBD	Cannabidiol
CBDA	Cannabidiolic acid
CBG	Cannabigerol
CBGA	Cannabigerolic acid
CB1	Cannabinoid receptor type 1
CB2	Cannabinoid receptor type 2
CMC	Critical micelle concentration
CO_2	Carbon dioxide
CYP	Cytochrome P450 enzyme family
E_a	Activation energy
ECS	Endocannabinoid system
EC_{50}	Half-maximal effective concentration
FAAH	Fatty acid amide hydrolase
GC-MS	Gas chromatography - mass spectrometry
HCl	Hydrochloric acid
HCO_3^-	Bicarbonate
H_2CO_3	Carbonic acid

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IC_{50}	Half-maximal inhibitory concentration
K_i	Inhibition constant
k	Reaction rate constant
K_m	Michaelis constant
LC-MS/MS	Liquid chromatography - tandem mass spectrometry
logP	Logarithm of the octanol/water partition coefficient
m/z	Mass-to-charge ratio
MW	Molecular weight
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form)
pH	Potential of hydrogen
pK_a	Acid dissociation constant
PPARγ	Peroxisome proliferator-activated receptor gamma
SGF	Simulated gastric fluid
THC	Δ⁹-Tetrahydrocannabinol
THCA	Δ⁹-Tetrahydrocannabinolic acid
THC-COOH	11-nor-9-carboxy-Δ⁹-tetrahydrocannabinol
11-OH-THC	11-Hydroxy-Δ⁹-tetrahydrocannabinol
TRPA1	Transient receptor potential ankyrin 1
UGT	UDP-glucuronosyltransferase

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   Note: this source is an unreviewed preprint, not a peer-reviewed publication. Its mechanistic conclusions are consistent with independent peer-reviewed work, including (a) a 2023 paper in the *Journal of Plant Biochemistry and Biotechnology* ("Mechanism and kinetics of CBDA decarboxylation into CBD in hemp") ran its own quantum-mechanical analysis (Gaussian/GAMESS) and converges on a similar picture — a keto-intermediate, beta-keto-acid decarboxylation pathway, consistent with He et al.'s tautomerization-as-rate-

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limiting-step framing, and (b) a 2020 *Industrial & Engineering Chemistry Research* paper (Comparative Kinetic Study, peer-reviewed, oven kinetics 80–160°C, confirms THCA decarboxylates fastest) and a 2022 peer-reviewed paper in the *Journal of Analytical Science and Technology* using UHPLC-Q/TOF-MS to identify thermal transformation products.

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