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Bioactive Phytochemicals from Edible and Medicinal Plants: Trigonelline, Hydroxycitric Acid, and Cucurbitacins as Emerging Biotechnological Assets

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Abstract

Plants of the Cucurbitaceae family and related sources produce bioactive secondary metabolites with significant therapeutic potential. This Opinion highlights three phytochemicals-trigonelline, hydroxycitric acid (HCA), and cucurbitacins-whose mechanisms span NAD^+ metabolism, ATP-citrate lyase inhibition, and multi-targeted anticancer signaling. Recent breakthroughs include trigonelline as a nutritional NAD^+ precursor improving muscle function during aging, HCA-loaded exosomes for lung cancer therapy, and cucurbitacin B potentiating PD-1 immunotherapy via covalent targeting of MTCH2. We argue these molecules exemplify how plant-derived metabolites serve as versatile platforms for biotechnology-driven health applications.

Keywords: Trigonelline; Hydroxycitric acid; Cucurbitacin; NAD^+ metabolism; ATP-citrate lyase; Metabolic engineering

Abbreviations: HCA: Hydroxycitric Acid; NAPRT: Nicotinate Phosphoribosyltransferase; NR: Nicotinamide Riboside; NMN: Nicotinamide Mononucleotide; MTCH: Mitochondrial Carrier Homolog

Introduction

The interface between plant secondary metabolism and human health has yielded some of the most impactful therapeutic agents in medicine. Three compounds-trigonelline (from coffee and fenugreek), hydroxycitric acid (from Garcinia cambogia), and cucurbitacins (from Cucurbitaceae plants)-exemplify how structurally diverse phytochemicals converge on potent metabolic regulation. Despite their differences-a pyridine alkaloid, a polyhydroxylated tricarboxylic acid, and tetracyclic triterpenoids-they share a narrative where modern biotechnology is only beginning to unlock their full potential.

Trigonelline

NAD^+ Metabolism and Anti-Aging Mechanisms: Trigonelline (N-methylnicotinate), abundant in coffee beans (~1% dry weight) and fenugreek, has emerged as a bona fide NAD^+ precursor. In a landmark 2024 study in Nature Metabolism, Membrez et al. [1] demonstrated that trigonelline is demethylated to nicotinic acid and subsequently enters the Preiss-Handler pathway via nicotinate phosphoribosyltransferase (NAPRT), thereby raising intracellular NAD^+ levels in skeletal muscle. Aged mice receiving oral trigonelline showed improved muscle strength, endurance, and mitochondrial respiration, while circulating trigonelline was reduced in older adults with sarcopenia-a finding that positions trigonelline as both a potential biomarker and a nutritional intervention for age-related muscle decline.

Clinical Implications in Sarcopenia: This discovery positions trigonelline alongside other NAD^+ precursors such as nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) as a nutritional NAD^+ booster, with the advantage of natural dietary abundance [2]. A comprehensive review by Nguyen et al. [3]

further details trigonelline's multi-target pharmacological activities, including anti-inflammatory, neuroprotective, and anti-diabetic effects.

Biotechnological Production: Microbial production of trigonelline via engineered yeast or Bacillus subtilis offers a scalable, sustainable alternative to plant extraction, with potential applications in functional foods and nutraceuticals.

Hydroxycitric acid

ACLY Inhibition and Metabolic Regulation: (-)-Hydroxycitric acid (HCA) is a potent competitive inhibitor of ATP-citrate lyase (ACLY), blocking the gateway to de novo lipogenesis and cholesterol synthesis. While extensively studied for weight management-a 2024 meta-analysis confirmed HCA significantly reduces body weight and serum leptin levels [4]-its therapeutic scope is expanding.

From Weight Management to Cancer Metabolism

ACLY is a critical metabolic dependency in cancers driven by lipid biosynthesis. Phutela et al. [5] demonstrated that HCA-loaded exosomes achieved targeted delivery to lung adenocarcinoma cells, inhibiting ACLY activity and suppressing tumor growth in a murine model, thus opening a new avenue for repurposing natural ACLY inhibitors as antimetabolic anticancer agents.

Exosome-Based Delivery Systems

The exosome-based strategy overcomes HCA's historical limitation of poor bioavailability. This delivery platform provides a blueprint adaptable to other poorly soluble phytochemicals. Concurrently, optimized microbial fermentation routes using engineered fungi are being developed to reduce dependence on plant biomass for HCA production.

Cucurbitacins

Multitargeted Anticancer Mechanisms: Among over 20 cucurbitacins identified, cucurbitacin B (CuB) has been the most intensively studied for its anticancer properties. A comprehensive 2025 review by Sahu et al. [6] summarizes CuB's multifaceted mechanisms including JAK/STAT3 inhibition, actin depolymerization, apoptosis induction, and modulation of autophagy and oxidative stress.

JAK/STAT3 and HIF-1α Pathways: Song et al. [7] demonstrated that CuB inhibits HIF-1α signaling via upregulation of ZFP91, attenuating non-small cell lung cancer progression through the Akt/mTOR/p70S6K pathway. This represents the first demonstration of ZFP91-mediated HIF-1α regulation by a natural product.

MTCH2 Targeting and Immunotherapy Synergy: A major advance in 2025 was the elucidation by Xu et al. [8] of CuB's covalent binding to mitochondrial carrier homolog 2 (MTCH2), which triggers mitochondrial DNA release, activates the cGAS-STING innate immune pathway, and potentiates PD-1 immune checkpoint blockade in triple-negative breast cancer models.

Formulation and Biotechnological Challenges: Despite these promising mechanisms, cucurbitacins suffer from poor solubility, hepatotoxicity, and narrow therapeutic windows. Recent progress in nanoformulation-including liposomal encapsulation, polymeric nanoparticles, and albumin carriers-has improved pharmacokinetic profiles, while heterologous expression of cucurbitacin biosynthetic gene clusters in yeast advances toward scalable production.

Perspectives and Conclusion: These three phytochemicals illustrate a recurring principle: the gap between pharmacological potential and clinical translation is bridged by innovation in metabolic engineering, advanced delivery, and combinatorial strategies. Trigonelline redefines nutritional NAD^+ repletion; HCA challenges the boundary between supplement and anticancer agent; and cucurbitacins continue revealing mechanisms at the intersection of cancer biology and immunotherapy. As biotechnological tools mature, these molecules are poised to transition from ethnopharmacological resources to scalable, clinically validated products. We call for an integrated research agenda combining plant metabolic biology, chemical biology, and bioprocess engineering to unlock the full potential of these remarkable natural molecules.

CRediT authorship contribution statement

Qiancheng Mao: Conceptualization, Investigation, Writing - original draft preparation, Writing - review & editing, Methodology, Visualization. Suyun Li: Project administration, Writing - review & editing, Visualization. Tianhe Fang: Resources, Supervision.

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