BIOLOGICAL ROLES, CLINICAL EFFICACY, AND INDUSTRIAL APPLICATIONS OF CITRIC ACID: A COMPREHENSIVE REVIEW

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Abstract

Citric acid (2-hydroxypropane-1,2,3-tricarboxylic acid) represents a foundational organic tri-carboxylic acid vital to both endogenous aerobic metabolism and exogenous bio-industrial systems. This comprehensive review examines the multifaceted contributions of citric acid and its conjugate base, citrate, across biological domains. Endogenously, it dictates cell signaling, regulates enzymatic checkpoints, governs bone mineralization, and exhibits key antioxidant/anti-inflammatory competencies within neural and hepatic microenvironments. Exigently, citric acid is heavily utilized as a multifunctional pharmaceutical excipient, pH buffer, metal-ion chelator, and food preservative. This article coordinates findings across major clinical, biochemical, and animal trials to summarize its comprehensive physiological pathways, therapeutic benefits, and industrial landscape.

Introduction

Citric acid, primarily recognized as an intermediate in cellular respiration, exists in all aerobic living organisms. Endogenous citrate is primarily synthesized within the mitochondrial matrix via the condensation of acetyl-coenzyme A (acetyl-CoA) and oxaloacetate, an equilibrium step catalyzed by the enzyme citrate synthase during the tricarboxylic acid (TCA) or Krebs cycle (Xu et al., 2024). Beyond its textbook role in adenosine triphosphate (ATP) production, intracellular citrate levels mirror the general energetic homeostasis of the cell. Under energy surplus, citrate is retro-transported via the mitochondrial citrate carrier into the cytosol, where it modulates fatty acid biosynthesis and works as an allosteric inhibitor of phosphofructokinase-1 (PFK-1), thereby dynamically shifting glycolysis (Granchi et al., 2019).

Metabolic accumulation mechanism

Intracellular citrate serves as a crucial molecular metabolic sensor. High cytosolic concentrations directly signal energetic abundance, shutting down runaway glucose degradation while concurrently initiating lipid synthesis pathways.

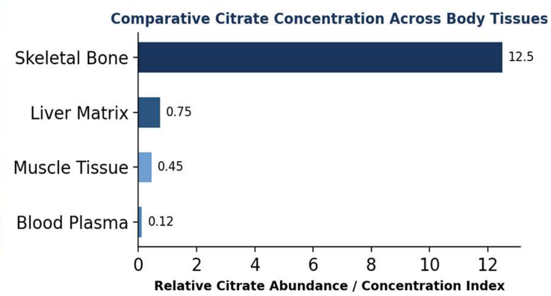

Fig.1: Relative abundance of citrate reservoirs in different physiological sections, highlighting its structural importance in the skeletal system.

Systemic Health Benefits and Therapeutic Performance

Skeletal Mineralization and Matrix Maintenance

Historically viewed as a passive component of bone tissue, recent structural analyses show that citrate constitutes up to 1-2% of the total dry weight of standard cortical bone matrix (Granchi et al., 2019). Bound tightly between nanocrystalline hydroxyapatite plates, citrate acts as an essential stabilizer preventing crystalline over-aggregation, imparting vital biomechanical plasticity, fracture resistance, and structural strength to the skeleton. Bone-forming osteoblasts actively utilize localized metabolic networks to complete extracellular matrix citration, a process found to break down during advanced osteoporotic decay (Granchi et al., 2019).

Mitigating Neural and Hepatic Oxidative Stress

In vivo animal models evaluating systemic inflammation have isolated pronounced neuroprotective and hepatoprotective actions attributed directly to exogenous citric acid supplementation. Studies executing lipopolysaccharide (LPS)-induced systemic challenges in mice demonstrated that administration of citric acid (at doses of 1-2 g/kg) significantly lowered lipid peroxidation byproducts such as malondialdehyde (MDA) and down-regulated prominent inflammatory cytokines including Tumor Necrosis Factor-alpha (TNF-α) and interleukin-1β (IL-1β) in brain tissues (Abdel-Salam et al., 2014). Within hepatic structures, citric acid protects against DNA fragmentation, prevents dangerous transaminase elevations (AST/ALT), and restricts inducible nitric oxide synthase (iNOS) expressions, proving its role as an asset against severe oxidative tissue injury (Abdel-Salam et al., 2014).

Intestinal Barrier Integrity and Immunomodulation

Recent research identifies citric acid as an efficient modulator of the gastrointestinal brush border and local immune response. Supplementation models demonstrate that citric acid significantly enhances the microvillus-to-crypt ratio in mammalian intestines, accelerating epithelial cell growth (Hu et al., 2024). At the molecular layer, it drives the expression of vital structural tight-junction proteins—namely occludin, zonula occludens-1 (ZO-1), and claudin-1. This action successfully seals the intestinal barrier against dangerous luminal pathogen translocation. Furthermore, it expands localized populations of health-promoting commensal bacteria (such as Bifidobacterium and Lactobacillus), providing an environment hostile to viral and bacterial pathogen replication (Hu et al., 2024; Islam, 2012).

Global Industrial and Pharmaceutical Applications

Due to its harmless nature, high solubility, and strong metal-chelating capacity, industrial-scale demand for citric acid has reached approximately 2.8 million tons annually, synthesized globally through industrial fermentation using Aspergillus niger or Yarrowia lipolytica strains (Książek, 2023).

- Food and Beverage Preservative: Acting as an elite acidity regulator, flavor enhancer, and antioxidant synergist, citric acid prevents bacterial spoilage and enzymatic browning across commercial foodstuffs (Książek, 2023).
- Pharmaceutical Excipient and Buffer: It is widely utilized as a buffering agent to maintain precise pH balances in liquid medications, as an effervescent agent in solid tablets, and as an active anticoagulant chelator that binds calcium ions in blood storage systems (Lambros et al., 2022).
- Biomaterial Synthesis Frameworks: In tissue engineering, citric acid acts as a core monomer for biodegradable elastomers. These citrate-based polymers possess excellent bio-compatibility and shape-memory features, used in skin wound healing, vascular grafts, and bone repair constructs (Xu et al., 2024).

Analytical Mapping of Core Academic Literature

The table below structures a targeted comparison of core research studies examined in this review, clarifying the biological model, primary evaluated mechanism, and reported outcomes:

Primary Reference	Experimental Model	Mechanistic Focus Area	Key Scientific Conclusion
Xu et al. (2024)	Biomaterial Synthesis	TCA intermediate integration	Regulates cell metabolism and drives stem cell differentiation.
Hu et al. (2024)	In Vivo Murine Model	Intestinal tight junctions	Upregulates ZO-1 & Occludin; bolsters gut mucosal immunity.
Książek (2023)	Industrial Micro-biology	A. niger fermentation	Maps industrial scalability and global chelating applications.
Lambros et al. (2022)	Pharmaceutical Trial	pH buffering & formulation	Optimizes drug delivery kinetics; identifies injection pain buffers.
Granchi et al. (2019)	Pathophysiology Review	Osteoblast hydroxyapatite	Identifies citrate as 1-2% of dry bone weight, vital for bone strength.

Conclusion and Future Horizons

Citric acid is a master regulator spanning fundamental human physiology and multi-sector industrial technology. From preserving the micro-structural integrity of skeletal bones to safeguarding neural tissues from acute oxidative surges, its biological value is immense. Simultaneously, its deployment as a functional biomaterial and pharmaceutical stabilizer positions it at the leading edge of medical engineering. Future research should prioritize optimizing clinical delivery systems to utilize its natural anti-inflammatory capabilities without disrupting delicate local acid-base balances.

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