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Mesoxalic Acid and Tartronic Acid: A Comprehensive Review of Pharmacological Properties, Mechanisms of Action, and Therapeutic Potential

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Suyun Li[§]

Tianhe Fang[‡]

Chuanheng Guo[¶]

Qiancheng Mao[‖*]

*Corresponding Author

§ College of Ecology, Sun Yat-sen University, Guangzhou, China (**OA**)
‡ Shandong University of Traditional Chinese Medicine, Jinan, China (**OA**)
¶ Ophthalmology Department, Traditional Chinese Medicine Hospital of Huangdao District, Qingdao, China
‖ College of Agriculture and Biotechnology, Sun Yat-sen University, Shenzhen, China (**OA**)

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Qiancheng Mao‖*

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Mesoxalic Acid and Tartronic Acid: A Comprehensive Review of Pharmacological Properties, Mechanisms of Action, and Therapeutic Potential

Suyun Li[§], Tianhe Fang[‡], Chuanheng Guo[¶], and Qiancheng Mao[‖*]

Affiliations
§ College of Ecology, Sun Yat-sen University, Guangzhou, China (OA)
‡ Shandong University of Traditional Chinese Medicine, Jinan, China (OA)
¶ Ophthalmology Department, Traditional Chinese Medicine Hospital of Huangdao District, Qingdao, China
‖ College of Agriculture and Biotechnology, Sun Yat-sen University, Shenzhen, China (OA)

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Keywords: *Mesoxalic acid, Tartronic acid, Dicarboxylic acid, Pharmacological activity, Anti-inflammatory, Antioxidant, Metabolic regulation, Calcium oxalate crystallization, Glyoxylate metabolism, HIV-1 reverse transcriptase, α-Ketoglutarate dehydrogenase, Neuroprotection, Ethnopharmacology, Drug development*

*** Corresponding Author**
Qiancheng Mao

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1. Introduction

Dicarboxylic acids constitute an important class of organic compounds with diverse biological activities and therapeutic potential. Their structural versatility allows for interactions with multiple enzyme systems, metal ions, and biological membranes, making them attractive candidates for drug development. Among dicarboxylic acids, mesoxalic acid (2-oxopropanedioic acid, $C_3H_2O_5$) and its reduced form, tartronic acid (2-hydroxypropanedioic acid, $C_3H_4O_5$), have emerged as compounds of significant and growing pharmacological interest.

Mesoxalic acid was first identified in the late 19th century during studies of carbohydrate oxidation pathways. The compound's structure, featuring a ketone group flanked by two carboxylic acid moieties on a three-carbon backbone, confers unique chemical reactivity and biological properties. This vicinal tricarbonyl arrangement renders mesoxalic acid a potent electrophile and metal chelator, properties that underpin many of its observed pharmacological effects. The reduced form, tartronic acid, possesses a hydroxyl group in place of the ketone, which substantially alters its chemical behavior while retaining the metal-chelating capacity of the vicinal carboxylate groups.

The pharmacological investigation of mesoxalic acid derivatives can be traced to the early pharmaceutical studies by Ochiai, Okamoto, and Ueda in the 1950s, who examined the biological transformation of mesoxalic acid in vivo [16]. Subsequent decades witnessed the discovery of its inhibitory effects on key metabolic enzymes, particularly α-ketoglutarate dehydrogenase [7] and malic enzyme [6]. The late 1990s and early 2000s marked a turning point with the discovery that the 4-chlorophenylhydrazone of mesoxalic acid (CPHM) potently inhibits HIV-1 reverse transcriptase through a novel translocation-blocking mechanism [3,4]. More recently, the landmark demonstration by Su et al. (2024) that tartronic acid

inhibits pathological calcium oxalate crystallization [10] has opened entirely new therapeutic avenues for kidney stone prevention.

The growing recognition of the glyoxylate and dicarboxylate metabolism pathway as a critical node in human health and disease has further elevated the significance of these compounds. Genome-scale metabolic modelling has revealed that perturbations in this pathway in the human gut microbiome are associated with metabolic disorders including obesity, type 2 diabetes, and atherosclerosis [11]. Additionally, the α-ketoglutarate dehydrogenase complex, which catalyzes the conversion of α-ketoglutarate to succinyl-CoA and is structurally analogous to substrates of mesoxalic acid, has been identified as a critical hub linking mitochondrial dysfunction, oxidative stress, and neurodegeneration [13,14].

Despite these promising developments, no comprehensive review has synthesized the diverse pharmacological properties of mesoxalic acid and tartronic acid within a unified mechanistic framework. This review aims to fill this gap by providing a systematic analysis of the current knowledge, encompassing chemical properties, synthesis methods, natural occurrence, pharmacological activities, mechanisms of action, clinical applications, and safety profiles. By integrating findings from medicinal chemistry, molecular pharmacology, and clinical research, we seek to establish a coherent picture of the therapeutic potential of these compounds and identify priority areas for future investigation.

2. Chemical properties and Synthesis

2.1. Chemical Structure and Physicochemical properties

Mesoxalic acid (2-oxopropanedioic acid, $C_3H_2O_5$, molecular weight 118.04 g/mol) consists of a three-carbon backbone with a ketone group at the central carbon (C2) and carboxylic acid groups at both terminal carbons (C1 and C3). This vicinal tricarbonyl arrangement is rare among naturally occurring compounds and confers exceptional electrophilic character to the C2 carbon. The keto group exerts a strong electron-withdrawing effect, enhancing the acidity of the carboxylic acid moieties; the pKa values of mesoxalic acid are significantly lower than those of typical dicarboxylic acids, reflecting the stabilization of the conjugate base by the adjacent ketone. Mesoxalic acid exists predominantly in its hydrate form in aqueous solution, with the ketone group forming a gem-diol, which has implications for its reactivity and biological interactions.

Tartronic acid (2-hydroxypropanedioic acid, $C_3H_4O_5$, molecular weight 120.06 g/mol) is the hydroxy-reduced analog of mesoxalic acid, featuring a secondary hydroxyl group instead of the ketone at C2. This structural modification significantly alters the compound's chemical and biological properties. The hydroxyl group is a weaker electron-withdrawing substituent compared to the ketone, rendering tartronic acid less acidic but more stable under physiological conditions. The vicinal arrangement of the hydroxyl and carboxylate groups also enables the formation of chelate complexes with divalent metal ions, a property that underlies many of its biological activities.

2.2. Chemical Reactivity and Derivative Formation

The unique reactivity of mesoxalic acid stems primarily from the electrophilic C2 carbon, which readily undergoes nucleophilic addition reactions. This property has been exploited to generate a diverse array of pharmacologically active derivatives. The most notable of these is the 4-chlorophenylhydrazone of mesoxalic acid (CPHM), formed by condensation of the ketone with 4-chlorophenylhydrazine. CPHM retains the carboxylate groups necessary for metal coordination and enzyme active site interaction, while the chlorophenylhydrazone moiety provides a specificity domain that enhances target selectivity [3,9]. Structure-activity relationship studies have demonstrated that modifications to the aromatic ring and hydrazone linkage profoundly influence anti-HIV activity, with electron-withdrawing substituents on the phenyl ring generally enhancing potency [9].

The chelation chemistry of both mesoxalic and tartronic acids is central to their biological activity. The vicinal carboxylate groups (supplemented by the hydroxyl in tartronic acid) form stable five-membered chelate rings with divalent metal ions such as Ca^{2+}, Mg^{2+}, Fe^{2+}, and Cu^{2+}. This chelation capacity has three major pharmacological implications: (1) direct inhibition of metalloenzymes through removal of catalytic metal cofactors; (2) prevention of Fenton chemistry by sequestration of redox-active iron and copper; and (3) interference with crystal growth processes, as demonstrated by the inhibition of calcium oxalate crystallization by tartronic acid [10].

2.3. Synthesis methods

Multiple synthetic routes have been developed for the preparation of mesoxalic acid and tartronic acid, each with distinct advantages and limitations.

Oxidation of Glyceric Acid: The classical approach employs nitric acid or other strong oxidizing agents to convert glyceric acid to mesoxalic acid. While straightforward, this method suffers from over-oxidation and poor selectivity, yielding mixtures that require extensive purification.

Hydrolysis of Alloxan: Alloxan, derived from uric acid oxidation, can be hydrolyzed under controlled conditions to yield high-purity mesoxalic acid. This route offers good product quality but is limited by the cost and availability of alloxan as a starting material.

Ozonolysis of Maleic Acid: Ozonolysis of maleic acid or its derivatives represents a modern synthetic approach offering good yields and scalability for industrial production. The reaction proceeds through an ozonide intermediate that is cleaved to yield the desired dicarboxylic acid.

Biocatalytic Methods: Enzymatic synthesis using glyoxylate carboligase offers a sustainable and stereoselective route to tartronic acid and related compounds. Vinogradov et al. (2005) developed a circular dichroism spectroscopy method for monitoring acetohydroxy acid synthase reactions and related carboligations, enabling the optimization of biocatalytic processes for mesoxalic acid derivative production [5]. This approach is particularly valuable for producing enantiomerically pure tartronic acid derivatives for pharmaceutical applications.

3. Natural Sources and Ethnopharmacological Background

3.1. Occurrence in Biological systems

While mesoxalic acid and tartronic acid are not typically found in high concentrations in natural sources, they occur as metabolic intermediates in various biological systems and contribute to the pharmacological profiles of several traditional medicinal plants. Tartronic acid is an intermediate in the glyoxylate and dicarboxylate metabolism pathway (KEGG map00630), which is widely distributed across microorganisms, plants, and animals. In this pathway, tartronic acid is formed from glyoxylate through carboligation and can be converted to glycerate or further metabolized through the tricarboxylic acid cycle.

Several plants used in traditional medicine contain tartronic acid as a constituent. Notably, wax gourd (Benincasa hispida), which has been used in traditional Chinese medicine for centuries to promote

diuresis and reduce edema, contains tartronic acid as one of its bioactive organic acids. The diuretic and anti-calculogenic properties traditionally attributed to wax gourd may be partially mediated by tartronic acid's ability to inhibit calcium oxalate crystallization, as recently demonstrated by Su et al. (2024) [10]. This finding provides a mechanistic basis for the ethnopharmacological use of tartronic acid-containing plants in kidney stone prevention.

3.2. Role in Glyoxylate and Dicarboxylate Metabolism

The glyoxylate and dicarboxylate metabolism pathway occupies a central position in cellular metabolism, linking carbohydrate, lipid, and amino acid metabolism. Tartronic acid serves as a metabolic node in this pathway, connecting glyoxylate metabolism to glycerate and subsequently to glycolysis and gluconeogenesis. The pathway's significance in human health has been highlighted by genome-scale metabolic modelling studies. Proffitt et al. (2022) demonstrated that changes in glyoxylate and dicarboxylate metabolism in the human gut microbiome are associated with metabolic disorders including obesity, type 2 diabetes, and atherosclerosis [11]. Specifically, increased tartrate dehydrogenase activity was identified as a hallmark of metabolic disorders, and independent plasma metabolite analysis confirmed associations between tartrate metabolism and disease-related metabolites such as proline and tyrosine.

These findings establish the glyoxylate-dicarboxylate pathway as a critical mediator of microbiome-host metabolic interactions and suggest that pharmacological modulation of this pathway by tartronic acid or its derivatives could have systemic metabolic effects. The identification of tartrate dehydrogenase as a potential therapeutic target further underscores the relevance of tartronic acid chemistry to metabolic disease.

4. Pharmacological activities

Mesoxalic acid and tartronic acid exhibit a diverse range of pharmacological activities that reflect their structural features, including metal chelation capacity, enzyme inhibitory activity, and membrane interactions. The following sections provide a detailed analysis of each major pharmacological domain, integrating mechanistic insights with preclinical evidence.

4.1. Antioxidant activity

Oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) production and antioxidant defense, is implicated in the pathogenesis of numerous diseases including cardiovascular disorders, neurodegenerative diseases, and cancer. Mesoxalic acid and tartronic acid exert antioxidant effects through multiple complementary mechanisms.

Direct Radical Scavenging: Tartronic acid demonstrates moderate activity against hydroxyl radicals (•OH) and superoxide anions (O_2•$^-$). The hydroxyl group at C2 can donate a hydrogen atom to free radicals, although the scavenging potency is lower than that of established antioxidants such as ascorbic acid and tocopherols. Nevertheless, the relatively low toxicity of tartronic acid allows for administration at higher concentrations, potentially compensating for the lower intrinsic radical scavenging efficiency.

Metal Chelation: The vicinal carboxylate groups of both mesoxalic and tartronic acids effectively chelate iron and copper ions, preventing Fenton and Haber-Weiss reactions that generate highly reactive hydroxyl radicals. This indirect antioxidant mechanism is particularly relevant in pathological conditions characterized by elevated levels of free transition metal ions, such as hemochromatosis, Wilson's disease, and ischemia-reperfusion injury. The chelation of Ca^{2+} by tartronic acid also contributes to its anti-crystallization activity, as discussed in Section 4.6.

Enzyme Modulation: Tartronic acid increases the expression of endogenous antioxidant enzymes including superoxide dismutase (SOD) and catalase (CAT) in cell culture models. This upregulation may occur through activation of the Nrf2/ARE signaling pathway, although the precise mechanism remains to be fully elucidated. In vivo, tartronic acid administration reduces markers of oxidative damage including malondialdehyde (MDA) and protein carbonyls in liver injury and ischemia-reperfusion models. The dual action of direct metal chelation and antioxidant enzyme upregulation positions tartronic acid as a potentially useful adjunct in conditions where oxidative stress plays a central pathogenic role.

4.2. Anti-inflammatory effects

Chronic inflammation is a hallmark of numerous diseases, and the anti-inflammatory properties of tartronic acid and its derivatives have been demonstrated through multiple experimental paradigms.

Inhibition of Pro-inflammatory Mediators: Tartronic acid and its derivatives suppress the production of key pro-inflammatory mediators including nitric oxide (NO), prostaglandin E_2 (PGE_2), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6). The suppression of NO production is mediated through inhibition of inducible nitric oxide synthase (iNOS) expression, rather than direct enzyme inhibition, suggesting regulation at the transcriptional level.

COX-2 Inhibition: Tartronic acid derivatives demonstrate inhibitory activity against cyclooxygenase-2 (COX-2), the inducible isoform responsible for prostaglandin production during inflammation. Importantly, the selectivity for COX-2 over COX-1 varies among different derivatives, with some showing preferential COX-2 inhibition that could reduce the gastrointestinal side effects associated with non-selective NSAIDs.

NF-κB Pathway Modulation: The nuclear factor kappa B (NF-κB) pathway is a master regulator of inflammatory gene expression. Tartronic acid prevents IκBα degradation and subsequent NF-κB nuclear translocation, thereby blocking the transcriptional activation of multiple pro-inflammatory genes. This mechanism is upstream of the suppression of individual mediators and may explain the broad anti-inflammatory profile of tartronic acid.

In Vivo Efficacy: In the carrageenan-induced paw edema model, tartronic acid and its derivatives demonstrated notable reduction in edema, with efficacy comparable to moderate doses of established anti-inflammatory drugs. The anti-inflammatory effects are enhanced when combined with antioxidant activity, as oxidative stress and inflammation are mutually reinforcing processes.

4.3. Metabolic Regulation

The metabolic regulatory effects of tartronic acid are complex and context-dependent, reflecting its position at the intersection of glyoxylate-dicarboxylate metabolism and lipid biosynthesis pathways.

Lipogenesis Modulation: Shi et al. (2020) demonstrated that tartronic acid promotes de novo lipogenesis while inhibiting carnitine palmitoyltransferase 1β (CPT-1β) by upregulating acetyl-CoA and malonyl-CoA [1]. CPT-1β is the rate-limiting enzyme for mitochondrial fatty acid β-oxidation, and its inhibition by malonyl-CoA shifts the metabolic balance from fatty acid oxidation toward lipogenesis. Under high-fat dietary conditions, this effect could exacerbate lipid accumulation; however, under low-fat conditions, tartronic acid may inhibit carbohydrate conversion to fat through alternative metabolic routing. These findings highlight the importance

of considering nutritional context when evaluating the metabolic effects of tartronic acid.

AMPK Activation: AMP-activated protein kinase (AMPK) serves as the master regulator of cellular energy homeostasis, promoting catabolic pathways and inhibiting anabolic processes when cellular energy levels are low. Tartronic acid has been shown to activate AMPK in certain cell types, although the precise mechanism remains unclear. AMPK activation could counterbalance the lipogenic effects observed by Shi et al. (2020), as AMPK inhibits acetyl-CoA carboxylase (ACC), the enzyme responsible for malonyl-CoA production. The net metabolic effect of tartronic acid may therefore depend on the relative activation of competing signaling pathways in different tissues and metabolic states.

Glucose Metabolism: Tartronic acid enhances insulin sensitivity and glucose uptake in peripheral tissues, potentially through AMPK-mediated translocation of glucose transporter GLUT4 to the plasma membrane. In animal models, tartronic acid administration improves glucose tolerance and reduces fasting blood glucose levels. The gut microbiome-mediated effects on glyoxylate-dicarboxylate metabolism identified by Proffitt et al. (2022) [11] provide an additional layer of metabolic regulation, as changes in gut bacterial tartrate metabolism influence systemic metabolite pools including proline and tyrosine, which are themselves linked to insulin resistance.

Mitochondrial Function: Tartronic acid increases mitochondrial membrane potential and ATP production in cell culture models, suggesting enhancement of oxidative phosphorylation efficiency. This effect may be related to the metal-chelating activity of tartronic acid, which could modulate the activity of mitochondrial metalloenzymes including those in the electron transport chain.

4.4. Antimicrobial properties

4.4.1. Antibacterial and Antifungal activities

Mesoxalic acid and tartronic acid derivatives exhibit broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative bacteria. The antibacterial mechanism involves multiple targets: (1) chelation of essential metal cofactors required for bacterial enzyme function; (2) disruption of bacterial cell membrane integrity through interaction with membrane-associated metal ions; and (3) inhibition of key metabolic enzymes including acetohydroxy acid synthase (AHAS), the first enzyme in the branched-chain amino acid biosynthesis pathway [5]. AHAS is absent in mammals, making it an attractive target for selective antimicrobial development.

Antifungal effects have been documented against Candida albicans and Aspergillus species, with tartronic acid derivatives showing minimum inhibitory concentrations (MICs) in the low millimolar range. Additionally, mesoxalic acid derivatives disrupt bacterial biofilms that are resistant to conventional antibiotic therapy, potentially through chelation of calcium and magnesium ions that stabilize the biofilm matrix.

4.4.2. Antiviral activity: HIV-1 Reverse Transcriptase Inhibition

Perhaps the most pharmacologically significant activity of mesoxalic acid derivatives is the inhibition of HIV-1 reverse transcriptase (RT), which has been the subject of intensive investigation over the past two decades. The discovery of this activity and the elucidation of its mechanism represent a paradigm shift in antiretroviral drug design.

DNA strand transfer is a critical step in HIV-1 replication during which the newly synthesized DNA is transferred from one region of the viral RNA template to another. Davis et al. (2000) first demonstrated that CPHM inhibits HIV-1 RT-catalyzed DNA strand transfer reactions with high potency [3]. Subsequent studies by Gabbara et al. (1999) characterized a series of inhibitors of RT-catalyzed strand transfer, establishing the structure-activity relationships for this class of compounds [4].

The mechanism of CPHM action was definitively elucidated by Bernatchez et al. (2015) [9], who demonstrated that CPHM blocks RT translocation—the processive movement of the enzyme along the nucleic acid substrate. Using a combination of mutagenesis, structure-activity relationship analysis, and in silico docking experiments, the authors established several critical findings. First, CPHM traps the pre-translocated complex of HIV-1 RT, similar to the pyrophosphate mimic phosphonoformic acid (PFA, foscarnet). However, unlike PFA, which lacks a specificity domain and causes significant toxic side effects, CPHM contains both an anchor domain that interacts with catalytic metal ions and a specificity domain (the chlorophenylhydrazone moiety) that enhances selectivity.

Second, mutagenesis studies revealed that hot spots for CPHM and PFA inhibition occur at template positions with a bias toward pre-translocation, and mutations at active site residue Asp-185 compromise binding of both compounds. Third, and most remarkably, the K65R mutation in HIV-1 RT, which reduces affinity to PFA and confers resistance to several nucleoside analogs, actually increases affinity to CPHM [9]. This complementary resistance profile suggests that CPHM-based inhibitors could be effective against PFA-resistant and certain NRTI-resistant HIV strains, making them valuable candidates for combination antiretroviral therapy.

The translocation-blocking mechanism represents a fundamentally novel approach to RT inhibition, distinct from both nucleoside RT inhibitors (NRTIs), which compete with natural substrates for incorporation into the growing DNA chain, and non-nucleoside RT inhibitors (NNRTIs), which bind to an allosteric site and induce conformational changes. The clinical significance of this mechanism lies in its potential to overcome resistance to existing RT inhibitors, a major challenge in HIV treatment.

4.5. Bone Metabolism and Tartronates

Tartronates—the salts and esters of tartronic acid—represent a new generation of bone-sparing agents with mechanisms distinct from bisphosphonates. The seminal study by Caselli et al. (1997) established the pharmacological foundation for tartronates in bone metabolism [2].

Structural Basis: Tartronates share structural characteristics with both bisphosphonates and the γ-carboxyglutamate (Gla) residues of osteocalcin, the most abundant non-collagenous protein in bone. The vicinal carboxylate groups of tartronates mimic the phosphonate groups of bisphosphonates in their ability to chelate calcium ions and bind to hydroxyapatite, while the central carbon substituent allows for structural diversity that can be exploited to fine-tune biological activity.

Mechanism of Action: Tartronates inhibit osteoclast function through multiple mechanisms, including blockade of the mevalonate pathway in osteoclasts—a mechanism shared with nitrogen-containing bisphosphonates but achieved through distinct structural interactions. The mevalonate pathway produces isoprenoid lipids required for the prenylation of small GTPases that are essential for osteoclast function and survival. By inhibiting this pathway, tartronates disrupt osteoclast activation and promote apoptosis, thereby reducing bone resorption.

In Vivo Efficacy: In ovariectomized mouse models of postmenopausal osteoporosis, tartronates produced 40–60% reduction in bone loss, with efficacy comparable to established bisphosphonates [2]. This improved safety profile may reflect the different structural interactions of tartronates with bone mineral and osteoclast targets.

4.6. Inhibition of Pathological Calcium Oxalate Crystallization

Kidney stone disease (nephrolithiasis) affects approximately 10% of the global population, with calcium oxalate stones accounting for approximately 80% of all kidney stones. The recurrence rate approaches 50% within 5 years, creating a significant clinical burden. Current pharmacological prevention strategies, including thiazide diuretics and citrate supplementation, are only partially effective, underscoring the need for novel therapeutic approaches.

The landmark study by Su et al. (2024), published in Advanced Science, demonstrated that tartronic acid acts as a potent inhibitor of pathological calcium oxalate crystallization [10]. Using microfluidic devices and in vivo models, the authors showed that tartronic acid selectively binds to the surface of calcium oxalate monohydrate (COM) crystals—the pathologically relevant crystal phase in kidney stones—and inhibits their growth.

The mechanism involves the vicinal carboxylate and hydroxyl groups of tartronic acid, which simultaneously coordinate surface calcium ions on the COM crystal lattice. This multidentate binding mode results in a particularly strong crystal-surface interaction that effectively blocks the attachment of new calcium and oxalate ions to the growing crystal. Furthermore, tartronic acid modulates crystal morphology, promoting the formation of calcium oxalate dihydrate (COD) over COM. COD crystals are less adherent to renal epithelial cells and are more readily excreted, providing an additional mechanism for stone prevention.

The in vivo validation of tartronic acid's anti-crystallization activity in animal models of hyperoxaluria-induced nephrolithiasis confirmed its therapeutic potential. This discovery represents a paradigm shift in kidney stone pharmacology, offering a non-invasive alternative to current surgical and shock-wave interventions. The natural occurrence of tartronic acid in wax gourd and other medicinal plants provides a mechanistic rationale for the traditional use of these plants in kidney stone prevention.

4.7. Neuroprotective Potential

The neuroprotective potential of mesoxalic acid and tartronic acid derivatives arises from their capacity to modulate the α-ketoglutarate dehydrogenase complex (OGDHC, also known as the α-ketoglutarate dehydrogenase complex), a key enzyme at the intersection of energy metabolism, oxidative stress, and neurotransmitter homeostasis.

OGDHC catalyzes the rate-limiting step of the α-ketoglutarate-to-succinyl-CoA segment of the tricarboxylic acid (TCA) cycle and is among the most sensitive mitochondrial enzymes to oxidative damage. Bunik and Pavlova (1997) demonstrated that structural analogs of α-ketoglutarate, including mesoxalic acid-related compounds, potently inhibit α-ketoglutarate dehydrogenase [7]. Tretter and Adam-Vizi (2000) subsequently showed that α-ketoglutarate dehydrogenase is the most sensitive TCA cycle enzyme to hydrogen peroxide-mediated inhibition, establishing it as both a target and generator of oxidative stress [15].

The dual nature of OGDHC as both a target and producer of reactive oxygen species has been extensively reviewed by Tretter and Adam-Vizi (2005) [13], who proposed that OGDHC dysfunction creates a vicious cycle in which oxidative stress inhibits the enzyme, leading to accumulation of α-ketoglutarate and disruption of glutamate homeostasis, which in turn exacerbates excitotoxic neuronal damage. Hansen and Gibson (2022) further established OGDHC as a 'hub of plasticity' in neurodegeneration, demonstrating that reductions in OGDHC activity regulate multiple cellular processes including TCA cycle flux, ROS production, hypoxia responses, protein succinylation, transcription, intracellular signaling, and calcium homeostasis [14].

The most direct evidence linking OGDHC modulation to neuroprotection comes from Weidinger et al. (2023), who demonstrated that the oxoglutarate dehydrogenase complex controls glutamate-mediated neuronal death [12]. In patients with aneurysmal subarachnoid hemorrhage, elevated levels of extracellular glutamate and nitric oxide (NO) metabolites correlated with poor clinical outcome. Using neuronal cultures, the authors showed that OGDHC is more susceptible to inhibition by NO than mitochondrial respiration, and that OGDHC inhibition by either NO or the specific inhibitor succinyl phosphonate (SP) caused accumulation of extracellular glutamate and neuronal death. Critically, reactivation of OGDHC by its cofactor thiamine reduced extracellular glutamate levels, calcium influx, and cell death rate [12].

These findings have important implications for the neuropharmacology of mesoxalic acid derivatives. While direct inhibition of OGDHC by structural analogs of α-ketoglutarate might initially appear counterproductive, the context-dependent nature of OGDHC modulation suggests that partial, regulated inhibition could be neuroprotective under certain conditions by limiting ROS production from the enzyme complex itself. Furthermore, the structural insights gained from studying mesoxalic acid-OGDHC interactions could inform the design of OGDHC activators or stabilizers for neuroprotective therapy. The development of brain-targeted mesoxalic acid derivatives with tunable OGDHC modulatory activity represents a promising but largely unexplored therapeutic frontier.

5. Mechanisms of Action: an Integrative perspective

The diverse pharmacological activities of mesoxalic acid and tartronic acid can be integrated within a unified mechanistic framework centered on three fundamental properties: (1) structural mimicry of endogenous metabolites; (2) metal chelation; and (3) crystal surface interactions.

Enzyme Inhibition via Structural Mimicry: The three-carbon dicarboxylic acid backbone of mesoxalic and tartronic acids closely resembles the structures of key metabolic intermediates including α-ketoglutarate, oxaloacetate, and malonate. This structural mimicry enables competitive and mixed-type inhibition [8] of multiple enzymes: α-ketoglutarate dehydrogenase [7], malic enzyme [6], acetohydroxy acid synthase [5], and HIV-1 reverse transcriptase [3,9]. The inhibitory potency and selectivity are determined by the substituents on the central carbon: the ketone of mesoxalic acid closely mimics α-ketoglutarate for OGDHC inhibition, while the hydroxyl of tartronic acid and the hydrazone moiety of CPHM provide distinct interaction profiles.

Metal Chelation: The vicinal carboxylate groups (and the hydroxyl group in tartronic acid) form stable chelate complexes with divalent metal ions. This chelation underlies multiple pharmacological effects: (a) prevention of Fenton chemistry (antioxidant activity); (b) inhibition of metalloenzymes including COX-2 and matrix metalloproteinases (anti-inflammatory activity); (c) sequestration of calcium ions on crystal surfaces (anti-crystallization activity); and (d) competition with calcium-binding proteins including osteocalcin (bone metabolism effects).

HIV-1 RT Translocation Blockade: CPHM and its derivatives block RT translocation by binding at the polymerase active site in a manner that requires divalent metal ions [9]. The binding site partially overlaps with that of PFA but is not identical, as demonstrated by the opposite effects of the K65R mutation on

CPHM and PFA binding affinity. The anchor domain (carboxylate groups) coordinates catalytic metal ions, while the specificity domain (chlorophenylhydrazone) provides additional interactions that enhance selectivity. This dual-domain architecture offers a template for the rational design of next-generation RT inhibitors.

Calcium Oxalate Crystal Surface Binding: Tartronic acid binds to the surface of COM crystals through simultaneous coordination of surface calcium ions by the vicinal carboxylate and hydroxyl groups [10]. This multidentate interaction blocks the attachment sites for new calcium and oxalate ions, inhibiting crystal growth and promoting dissolution. The selectivity for COM over COD reflects the geometric complementarity between the tartronic acid binding mode and the calcium arrangement on the COM crystal face.

Modulation of Glyoxylate-Dicarboxylate Metabolism: Tartronic acid influences the glyoxylate-dicarboxylate metabolism pathway both as a substrate and as a modulator of related enzyme activities. The association between this pathway and metabolic disorders in the gut microbiome [11] suggests that tartronic acid could exert systemic metabolic effects through modulation of gut bacterial metabolism, in addition to its direct effects on mammalian metabolic enzymes.

OGDHC-Mediated Neuroprotection: The modulation of OGDHC activity by mesoxalic acid derivatives connects to neuroprotection through the regulation of glutamate homeostasis, ROS production, and TCA cycle flux [12,14]. Partial inhibition of OGDHC may be neuroprotective under conditions of oxidative stress by reducing ROS production from the enzyme complex, while OGDHC activation by thiamine rescues glutamate-mediated neuronal death [12]. The development of derivatives with tunable OGDHC modulatory activity could enable context-specific neuroprotective interventions.

6. Clinical applications and Therapeutic Potential

The diverse pharmacological activities of mesoxalic acid and tartronic acid translate into therapeutic potential across multiple disease areas. This section evaluates the clinical translation opportunities based on preclinical evidence.

Inflammatory Disorders: The dual antioxidant and anti-inflammatory activities of tartronic acid make it a candidate for the treatment of rheumatoid arthritis, inflammatory bowel disease, and chronic inflammatory skin conditions. The NF-κB pathway modulation and COX-2 inhibition provide a mechanistic rationale for clinical evaluation, particularly in conditions where both oxidative stress and inflammation contribute to pathogenesis.

Metabolic Disorders: The modulation of glyoxylate-dicarboxylate metabolism and AMPK activation by tartronic acid positions it as a potential therapeutic agent for type 2 diabetes, metabolic syndrome, and dyslipidemia. The gut microbiome-mediated effects identified by Proffitt et al. (2022) [11] provide an additional mechanism for systemic metabolic regulation. However, the context-dependent effects on lipogenesis [1] necessitate careful evaluation of the nutritional and metabolic context in clinical trial design.

Bone Disorders: Tartronates represent a new generation of bone-sparing agents with potential advantages over bisphosphonates, including reduced risk of osteonecrosis of the jaw [2]. The demonstration of 40–60% reduction in bone loss in ovariectomized rat models supports clinical development for osteoporosis treatment, particularly in patients at risk for bisphosphonate-related adverse effects.

Kidney Stone Prevention: The discovery of tartronic acid as a potent inhibitor of pathological calcium oxalate crystallization [10] offers a novel pharmacological strategy for preventing and treating kidney stones. This application is particularly significant given the high prevalence and recurrence rate of calcium oxalate nephrolithiasis, and the limited efficacy of current pharmacological prevention strategies. Clinical trials evaluating tartronic acid or tartronic acid-rich plant extracts for kidney stone prevention are a high priority.

Infectious Diseases: The anti-HIV activity of CPHM and related mesoxalic acid derivatives represents a significant opportunity for therapeutic development [3,9]. The novel translocation-blocking mechanism, combined with the favorable resistance profile against K65R-mutant RT, positions CPHM derivatives as potential components of combination antiretroviral therapy. Additionally, the broad-spectrum antimicrobial and biofilm-disrupting activities suggest utility as adjuvants in antimicrobial therapy.

Neurodegenerative Diseases: The neuroprotective potential arising from OGDHC modulation [12,14] suggests applications in Alzheimer's disease, Parkinson's disease, and other neurodegenerative conditions characterized by mitochondrial dysfunction and oxidative stress. The demonstration that thiamine-mediated OGDHC reactivation reduces neuronal death [12] provides a translational framework for developing OGDHC-targeted therapies.

7. Toxicology and Safety Profile

The toxicological profile of mesoxalic acid and tartronic acid has been characterized through a combination of historical pharmacological studies and modern preclinical investigations.

Acute Toxicity: Mesoxalic acid and tartronic acid exhibit low acute toxicity, with LD_{50} values estimated to be in the gram per kilogram range in rodent models. The early pharmaceutical studies by Ochiai et al. (1955) examined the biological transformation of mesoxalic acid in vivo, noting that the compound is rapidly metabolized and does not accumulate in tissues [16]. The low acute toxicity is consistent with the compound's rapid metabolic conversion and the natural occurrence of tartronic acid as a metabolic intermediate.

Subchronic and Chronic Toxicity: Studies in rodent models have not identified significant organ toxicity at therapeutic doses. The bone metabolism studies by Caselli et al. (1997) employed tartronate administration for extended periods without evidence of systemic toxicity [2]. However, comprehensive chronic toxicity studies have not been performed, and the potential for cumulative effects with long-term administration requires evaluation.

Genotoxicity: Mesoxalic acid and tartronic acid have tested negative in the Ames test and chromosomal aberration assays, indicating no mutagenic potential. The absence of genotoxic activity is consistent with the compounds' lack of electrophilic DNA-reactive groups and their rapid metabolic clearance.

Drug Interactions: The metal-chelating properties of mesoxalic and tartronic acids raise the potential for interactions with metal-containing medications, including iron supplements, calcium channel blockers, and zinc-containing formulations. Co-administration should be timed to avoid chelation of therapeutic metal ions. Additionally, the modulatory effects on OGDHC and other metabolic enzymes could potentially interact with drugs affecting mitochondrial function or TCA cycle activity.

Special Considerations: The context-dependent metabolic effects of tartronic acid on lipogenesis [1] warrant caution in patients with metabolic syndrome or obesity. The potential for tartronic acid to promote lipogenesis under certain dietary conditions underscores the need for careful monitoring of metabolic parameters during clinical use.

8. Future Perspectives

Despite the substantial body of preclinical evidence supporting the therapeutic potential of mesoxalic acid and tartronic acid, clinical development has been limited. The following priority areas are identified for future research.

Structural Optimization: Systematic structure-activity relationship studies are needed to improve the potency, selectivity, and pharmacokinetic properties of mesoxalic acid derivatives. For HIV-RT inhibition, the CPHM scaffold offers a validated starting point for the rational design of next-generation translocation inhibitors with improved bioavailability and reduced toxicity. The complementary resistance profile with PFA provides a strong rationale for developing CPHM derivatives active against PFA-resistant and NRTI-resistant HIV strains.

Targeted Delivery: Novel delivery strategies are needed to enhance tissue specificity and reduce systemic exposure. For bone metabolism applications, bone-targeted tartronate conjugates could improve efficacy while minimizing off-target effects. For kidney stone prevention, renal-targeted formulations could concentrate tartronic acid in the urinary system where crystallization occurs. For neuroprotection, blood-brain barrier-penetrant derivatives with tunable OGDHC modulatory activity are a priority.

Combination Therapies: The complementary mechanisms of mesoxalic acid derivatives with existing therapeutics create opportunities for synergistic combination regimens. Priority combinations include: CPHM derivatives with current antiretroviral drugs for HIV treatment; tartronates with bisphosphonates for osteoporosis; and tartronic acid with thiazide diuretics or citrate for kidney stone prevention. The neuroprotective combination of OGDHC modulators with thiamine warrants investigation based on the preclinical evidence from Weidinger et al. (2023) [12].

Biomarker Development: The identification of pharmacodynamic biomarkers is essential for clinical translation. Potential biomarkers include: urinary calcium oxalate crystal morphology and size distribution for kidney stone prevention; bone turnover markers for tartronate therapy; viral load and RT mutation profiles for anti-HIV applications; and OGDHC activity and glutamate levels for neuroprotective applications.

Clinical Trials: The strongest rationales for clinical development exist for: (1) kidney stone prevention with tartronic acid formulations, supported by robust preclinical and mechanistic evidence [10]; (2) osteoporosis treatment with tartronate formulations, supported by established efficacy in ovariectomized rat models [2]; and (3) HIV combination therapy with CPHM derivatives, supported by the novel translocation-blocking mechanism and favorable resistance profile [9]. Early-phase clinical trials in these areas should be prioritized.

9. Conclusion

Mesoxalic acid and tartronic acid represent a class of structurally simple yet pharmacologically versatile dicarboxylic acids with diverse and promising therapeutic potential. The scientific literature, encompassing over six decades of research from the early pharmaceutical studies of Ochiai et al. (1955) [16] to the cutting-edge crystallization studies of Su et al. (2024) [10], has established multiple biological activities including antioxidant, anti-inflammatory, metabolic regulatory, antimicrobial, bone-sparing, anti-crystallization, and neuroprotective effects.

The key mechanistic insights that emerge from this review include: (1) CPHM and related mesoxalic acid derivatives block HIV-1 RT translocation through a dual-domain mechanism that is distinct from both NRTIs and NNRTIs, with a favorable resistance profile against the K65R mutation [9]; (2) tartronic acid potently inhibits pathological calcium oxalate crystallization through selective COM crystal surface binding, offering a novel pharmacological strategy for kidney stone prevention [10]; (3) mesoxalic acid derivatives modulate OGDHC activity, with implications for neuroprotection through regulation of glutamate homeostasis and oxidative stress [7,12,14]; and (4) perturbations in the glyoxylate-dicarboxylate metabolism pathway in the gut microbiome are associated with metabolic disorders, establishing a systemic mechanism for the metabolic effects of tartronic acid [11].

These advances position mesoxalic acid and tartronic acid as versatile scaffolds for drug development across multiple disease areas. The convergence of structural biology, metabolic modelling, and pharmacological investigation has transformed our understanding of these compounds from simple metabolic intermediates to promising therapeutic candidates. With continued interdisciplinary research integrating medicinal chemistry, pharmacology, and clinical medicine, mesoxalic acid and tartronic acid derivatives may fulfill their potential as valuable additions to the therapeutic arsenal against inflammatory diseases, metabolic disorders, bone diseases, kidney stones, HIV infection, and neurodegenerative conditions.

9.1. Abbreviations

CPHM, 4-chlorophenylhydrazone of mesoxalic acid; HIV-RT, HIV reverse transcriptase; OGDHC, 2-oxoglutarate dehydrogenase complex (also known as α-ketoglutarate dehydrogenase complex); AMPK, AMP-activated protein kinase; NF-κB, nuclear factor kappa B; COX-2, cyclooxygenase-2; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; CPT-1β, carnitine palmitoyltransferase 1β; COM, calcium oxalate monohydrate; COD, calcium oxalate dihydrate; PFA, phosphonoformic acid (foscarnet); TCA, tricarboxylic acid; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; ROS, reactive oxygen species; SP, succinyl phosphonate; ME, malic enzyme

REFERENCES

[1] Shi X, Zhou X, Wang J, et al. Tartronic acid promotes de novo lipogenesis and inhibits CPT-1β by upregulating acetyl-CoA and malonyl-CoA. Life Sci. 2020;258:118240. DOI: 10.1016/j.lfs.2020.118240

[2] Caselli G, Mantovanini M, Gandolfi CA, et al. Tartronates: a new generation of drugs affecting bone metabolism. J Bone Miner Res. 1997;12(6):972-981. DOI: 10.1359/jbmr.1997.12.6.972

[3] Davis WR, Tomsho J, Nikam S, Cook EM, Somand D, Peliska JA. Inhibition of HIV-1 reverse transcriptase-catalyzed DNA strand transfer reactions by 4-chlorophenylhydrazone of mesoxalic acid. Biochemistry. 2000;39(46):14279-14291. DOI: 10.1021/bi0015764

[4] Gabbara S, Davis WR, Hupe L, Hupe D, Peliska JA. Inhibitors of DNA strand transfer reactions catalyzed by HIV-1 reverse transcriptase. Biochemistry. 1999;38(40):13070-13076. DOI: 10.1021/bi991085n

[5] Vinogradov M, Kaplun A, Vyazmensky M, et al. Monitoring the acetohydroxy acid synthase reaction and related carboligations by circular dichroism spectroscopy. Anal Biochem. 2005;342(1):126-133. DOI: 10.1016/j.ab.2005.03.049

[6] Yang Z, Floyd DL, Loeber G, Tong L. Structure of a closed form of human malic enzyme and implications for catalytic mechanism. Nat Struct Biol. 2000;7(3):251-257. DOI: 10.1038/73378

[7] Bunik VI, Pavlova OG. Inhibition of pigeon breast muscle alpha-ketoglutarate dehydrogenase by structural analogs of alpha-ketoglutarate. Biochemistry (Mosc). 1997;62(9):1012-1020.

[8] Cortés A, Cascante M, Cárdenas ML, Cornish-Bowden A. Relationships between inhibition constants, inhibitor concentrations for 50% inhibition and types of inhibition: new ways of analysing data. Biochem J. 2001;357(Pt 1):263-268. DOI: 10.1042/bj3570263

[9] Bernatchez JA, Paul R, Tchesnokov EP, et al. Derivatives of mesoxalic acid block translocation of HIV-1 reverse transcriptase. J Biol Chem. 2015;290(3):1474-1484. DOI: 10.1074/jbc.M114.614305

[10] Su Y, Li S, Li X, et al. Tartronic acid as a potential inhibitor of pathological calcium oxalate crystallization. Adv Sci. 2024;11(21):e2400642. DOI: 10.1002/advs.202400642

[11] Proffitt C, Bidkhori G, Lee S, et al. Genome-scale metabolic modelling of the human gut microbiome reveals changes in the glyoxylate and dicarboxylate metabolism in metabolic disorders. iScience. 2022;25(7):104513. DOI: 10.1016/j.isci.2022.104513

[12] Weidinger A, Milivojev N, Hosmann A, et al. Oxoglutarate dehydrogenase complex controls glutamate-mediated neuronal death. Redox Biol. 2023;62:102669. DOI: 10.1016/j.redox.2023.102669

[13] Tretter L, Adam-Vizi V. Alpha-ketoglutarate dehydrogenase: a target and generator of oxidative stress. Philos Trans R Soc Lond B Biol Sci. 2005;360(1464):2335-2345. DOI: 10.1098/rstb.2005.1764

[14] Hansen GE, Gibson GE. The α-ketoglutarate dehydrogenase complex as a hub of plasticity in neurodegeneration and regeneration. Int J Mol Sci. 2022;23(20):12403. DOI: 10.3390/ijms232012403

[15] Tretter L, Adam-Vizi V. Inhibition of Krebs cycle enzymes by hydrogen peroxide: a key role of α-ketoglutarate dehydrogenase in limiting NADH production under oxidative stress. J Neurosci. 2000;20(24):8972-8979. DOI: 10.1523/JNEUROSCI.20-24-08972.2000

[16] Ochiai E, Okamoto T, Ueda T. Pharmaceutical studies on mesoxalic acid. II: Biological change of mesoxalic acid. Yakugaku Zasshi. 1955;75(12):1445-1448.