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The ergothioneine enigma: Navigating the chasm between anti-aging hype and clinical validation

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Ergothioneine (EGT) has garnered widespread attention due to its purported antioxidant and anti-aging effects, even sparking considerable debate. However, its clinical translation remains hindered by insufficient and fragmented evidence. This article focuses on EGT's newly identified molecular targets—MPST and CSE—and the indirect regulatory mechanisms mediated by hydrogen sulfide (H_2S), thereby exploring key challenges in its clinical application. We highlight major issues in pharmacokinetics, formulation development, and long-term safety, and advocate for interdisciplinary efforts and target-driven clinical evaluation strategies to advance EGT from a cosmetic additive and dietary supplement to a mechanism-based therapeutic agent with a solid scientific foundation.

Discovered in 1909 yet largely overlooked for nearly a century, ergothioneine (EGT) has recently garnered attention due to its potent antioxidant, healthspan-extending, and cytoprotective properties—attributes extensively validated in in vitro and animal models. Advances in synthetic biology have enabled scalable production, accelerating its transition from bench to industry. This progress, alongside rising consumer interest in healthspan extension and substantial investment, has expanded EGT's use in cosmetics and functional foods; its market is growing rapidly and attracting significant investor attention.[1,2] EGT has achieved broad regulatory approval in cosmetics across China, the US, and the EU. However, food applications are uneven: only certain developed countries (e.g., US, Japan, Australia, and New Zealand) permit EGT as a dietary supplement or additive, whereas the EU and China maintain cautious policies. Medicinal research is progressing, with multiple clinical trials registered, though most remain in early phases.[3] The absence of large-scale confirmatory studies has resulted in incomplete safety and efficacy profiles. Currently, evidence is insufficient to support pharmaceutical use; validation through large-scale randomized controlled trials is still needed.[4-6]

Driven by market potential and industrial expansion, some companies have engaged in aggressive marketing—including overstated efficacy and obfuscation of application scope—prompting scientific skepticism. This phenomenon has become particularly pronounced following the debunking of so-called "anti-aging stars" such as NMN, whose inflated efficacy claims have now been demonstrated to yield negligible therapeutic effects.[7,8] The ongoing debate between academia and consumer markets regarding EGT's actual efficacy not only reflects a rational shift among modern consumers—from blind worship of "miracle ingredients" to reliance on scientific validation—but also highlights the long-standing lack of regulatory norms in the health products industry concerning efficacy claims.[6,9]

From a pharmacological perspective, we argue that evaluating EGT's potential must rest on two pillars: critical appraisal of existing evidence and prospective prediction of translational viability. A systematic understanding of its mechanistic network, combined with classical drug development approaches, can help chart a path toward clinical translation and build a multidimensional framework integrating mechanisms, development routes, and risk assessment (Figure 1).

MECHANITIC NETWORKS OF EGT

EGT is a white, highly water-soluble (0.9 mol/L at room temperature) crystalline compound that remains stable at physiological pH, existing as a tautomeric mixture of thiol and thione forms.[2] It is not synthesized by mammals and must be obtained through the diet, mainly from mushrooms and animal products. Biosynthesis is limited to bacteria and fungi, and mammalian cellular uptake depends on the OCTN1 transporter (SLC22A4).[1,6,9] Compared to glutathione (-0.24 V) and certain antioxidant vitamins, EGT exhibits a higher redox potential (-0.06 V), enhancing its free radical scavenging capacity. Additionally, EGT demonstrates high stability under physiological conditions, resisting autoxidation (unlike vitamin C, which is rapidly oxidized) and maintaining its integrity upon exposure to light or heat.[1] Recent studies have expanded its role beyond antioxidation, revealing precise molecular targets:

Allosteric activation of MPST

Sprenger et al. first revealed via thermal proteome profiling that EGT directly binds to mitochondrial 3-mercaptopyruvate sulfurtransferase (MPST) with a dissociation constant of 3.2 μM, allosterically activating its enzymatic activity. This interaction promotes the decomposition of 3-mercaptopyruvate (3-MP) into hydrogen sulfide (H_2S) and pyruvate, enhancing mitochondrial respiratory chain function and ATP production. In mice, EGT improved exercise endurance by 19–28%, linked to increased mitochondrial biogenesis and oxidative phosphorylation. Unlike typical substrates, EGT stabilizes MPST's active conformation, doubling catalytic efficiency. Structural analyses reveal EGT binds an allosteric site near the active pocket, stabilized via hydrogen bonding (Tyr377 to EGT's imidazole nitrogen), establishing an "EGT-MPST functional axis" that redefines EGT as an enzymatic modulator.[4]

Substrate-specific regulation of CSE

Petrovic et al. confirmed that EGT acts as a specific substrate for cystathionine γ-lyase (CSE), generating H_2S through a pyridoxal phosphate (PLP)-dependent desulfurization reaction. Nuclear magnetic resonance spectroscopy shows that the sulfur atom of EGT forms a covalent enzyme-substrate intermediate with Cys248 of CSE, accompanied by the generation of hercynine rather than complete degradation. Unlike natural substrates like cysteine, EGT's reaction with CSE exhibits substrate selectivity—the trimethylammonium group of EGT forms specific electrostatic interactions with the negatively charged region of the CSE active pocket, reducing H_2S production efficiency by 40% compared to cysteine while significantly inhibiting by-product thiosulfate formation. In aging *Caenorhabditis elegans*, 5 mM EGT treatment extends median lifespan by 20%, improves motility, and reduces age-related lipofuscin accumulation. In aged rats, EGT elevates muscle NAD^+ levels, promotes angiogenesis, and doubles treadmill endurance, effects completely abolished in CSE knockout models. Mechanistically, CSE-mediated H_2S production triggers a persulfidation cascade, activating cytosolic glycerol-3-phosphate dehydrogenase (cGPDH) and linking EGT to metabolic rejuvenation. This "incomplete desulfurization" allows EGT to regulate H_2S signaling while avoiding sulfur metabolic disorders.[5]

Indirect regulated signaling pathways

Pharmacological understanding of EGT has evolved through cumulative evidence, revealing its pleiotropic effects across multiple signaling pathways. Much like the parable of "blind men and the elephant," these findings capture fragmented yet valuable perspectives on its mechanisms. We propose, however, that many of EGT's observed pleiotropic effects can be traced to two core actions: direct targeting of MPST/CSE and the indirect multimodal regulation triggered by subsequent H_2S elevation.

EGT - MPST axis orchestrates mitochondrial and redox signaling. Through activating MPST and augmenting H_2S production, this functional axis triggers downstream signaling events critical for cellular homeostasis. The generated H_2S modifies mitochondrial proteins via persulfidation, opti-

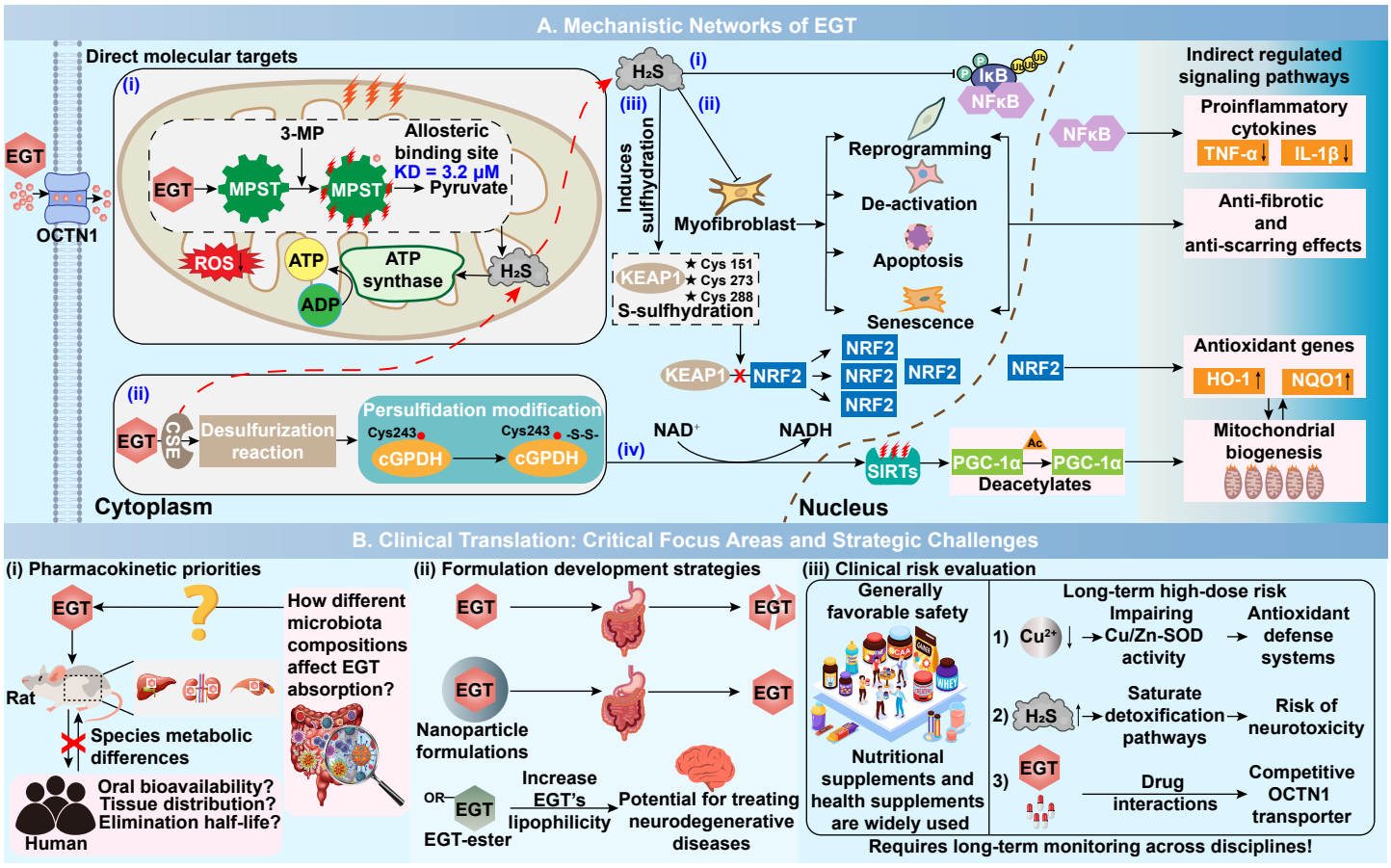

Figure 1. Mechanisms and translational challenges of ergothioneine (A) Mechanistic Networks: (i) MPST activation enhances H_2S/pyruvate production and energy metabolism; (ii) CSE desulfurization generates H_2S and reduces byproducts; H_2S mediates anti-inflammatory, antioxidant, and metabolic effects via NF-κB inhibition, NRF2 activation, NAD^+ elevation, and sirtuin signaling. (B) Clinical Challenges: (i) Pharmacokinetics: Human data are limited; gut microbiota metabolism is unelucidated; (ii) Formulation: Nanoparticles improve GI stability; prodrugs enhance CNS delivery; (iii) Risks: Long-term use may disrupt copper homeostasis; H_2S overproduction may cause toxicity; OCTN1-mediated interactions require monitoring.

mizing the function of the oxidative phosphorylation system. Concurrently, H_2S plays a pivotal role in modulating the KEAP1 - NRF2 - ARE pathway. H_2S modifies cysteine residues in KEAP1, leading to the release of NRF2. NRF2 then translocates to the nucleus, where it upregulates antioxidant genes such as SOD and HO − 1.[1] Thus, the EGT-MPST axis links its mitochondrial effects to the orchestration of systemic redox homeostasis. This dual regulatory role is exemplified by the MPST-dependent enhancement of exercise performance observed in mice following EGT supplementation.[4]

CSE - mediated H_2S signaling fuels metabolic rejuvenation. Beyond its substrate-selective engagement with CSE, EGT-derived H_2S initiates specific downstream signaling crucial for counteracting aging. Wen et al. (2025) delineate the molecular sequelae: the generated H_2S activates cGPDH, thereby enhancing glycolytic flux and mitochondrial coupling efficiency. Further downstream, EGT-induced H_2S elevates muscle NAD^+ levels in aged rats, which in turn activates sirtuin pathways, including SIRT1 and SIRT6. Collectively, this signaling cascade - encompassing H_2S, cGPDH activation, NAD^+ elevation, and sirtuin stimulation - underpins the profound metabolic rejuvenation effects observed with EGT supplementation, such as markedly improved endurance and angiogenesis. This intricate mechanism elucidates how the "incomplete desulfurization" of EGT by CSE precisely channels H_2S signaling towards systemic metabolic revitalization.[6]

Crosstalk between MPST and CSE pathways

MPST and CSE collaboratively regulate H_2S homeostasis, with EGT serving as a common modulator to fine-tune sulfur metabolism. The resulting H_2S integrates into metabolic networks, promoting significant bioenergetic adaptations. Chen et al. highlight its ability to inhibit mitochondrial complex IV under high oxidative stress, shifting cellular energy production towards glycolysis.[1] This metabolic shift is accompanied by broad anti-inflammatory and antifibrotic effects. H_2S suppresses NF-κB activation, thereby lowering pro-inflammatory cytokine expression (e.g., pro-IL-1β, TNF-α). Furthermore, EGT-mediated H_2S, acting via both pathways, inhibits myofibroblast differentiation, preventing tissue scarring in fibrotic models.[6]

Thus, EGT's orchestration of the MPST and CSE pathways establishes its role as a key regulator of metabolism and redox signaling. This understanding holds profound implications for aging, metabolism, and disease prevention. To fully realize EGT's therapeutic potential, future research must systematically integrate existing mechanistic studies—progressively reconstructing the connections between its indirect regulatory actions and direct molecular targets.

CLINICAL TRANSLATION: CRITICAL FOCUS AREAS AND STRATEGIC CHALLENGES

Clinical translation of EGT must be target-driven to maximize therapeutic efficacy. We propose EGT's most promising therapeutic applications include mitochondrial dysfunction disorders via MPST activation, age-related diseases through CSE-cGPDH-mediated NAD^+ elevation, and metabolic diseases like type 2 diabetes. Developing EGT into a regulated therapeutic agent faces key challenges in the following domains.

Pharmacokinetic priorities

In rats, EGT rapidly accumulates in the liver, kidneys, and muscle, yet human data remain limited. Critical research priorities include establishing human oral bioavailability, tissue distribution, and elimination half-life. Given that gut microbiota—such as *E. coli* and *Lactobacillus*—degrade EGT via ergothionease,[6,9] further studies must evaluate how compositional variations affect absorption.[10] This could enable microbiome-tailored EGT supplementation.

Formulation development strategies

Formulation development is essential to enhance EGT's stability and bioavailability. Although EGT is thermostable in aqueous solutions, it is vulnerable to gastric acid and enzymatic degradation in the gastrointestinal tract. Encapsulation technologies can protect EGT from these harsh conditions. Nanoparticle formulations, such as liposomes or polymeric micelles, offer the potential to improve cellular uptake, especially in tissues with low expression of the OCTN1, which is responsible for EGT uptake. Additionally, prodrug design, like the creation of ester conjugates, can increase EGT's lipophilicity. This modification may enhance its penetration across the blood - brain barrier, making it more effective for treating neurodegenerative diseases.

Clinical risk evaluation

EGT has a strong safety record as a food ingredient, but pharmaceutical use requires rigorous evaluation. Long-term chronic intake of EGT may disrupt copper ion homeostasis due to its high binding affinity, potentially impairing Cu/Zn-SOD activity and compromising antioxidant defense systems. Sustained elevation of H_2S resulting from EGT metabolism could saturate detoxification pathways such as SUOX, thereby increasing the risk of neurotoxicity. Furthermore, EGT's competition with cationic drugs (e.g., cimetidine, verapamil) for OCTN1-mediated transport necessitates thorough investigation of potential drug–drug interactions that could alter pharmacokinetics and therapeutic efficacy. Additional concerns include possible impacts on thyroid function arising from interference with selenium metabolism and effects on hematopoietic dynamics, which warrant comprehensive longitudinal assessment. The prolonged treatment durations and high interindividual variability inherent to aging-related and metabolic diseases further underscore the need for interdisciplinary trial designs to standardize efficacy and safety endpoints.

CONCLUSIONS

To critically evaluate the scientific controversies surrounding EGT, a calm and pragmatic approach across multiple dimensions is imperative. Achieving EGT's clinical translation hinges on the balanced integration of mechanistic research and translational validation, necessitating concerted efforts among capital stakeholders, pharmacologists, and clinicians through systematic collaboration. While this process demands substantial time, financial investment, and multidisciplinary resources, it remains indispensable for advancing EGT from a "conceptual anti-aging ingredient" to an evidence-based therapeutic agent.

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AUTHOR CONTRIBUTIONS

Q.T. and Y. Z. conceptualized and supervised this work. Q.T. wrote the manuscript; Z.Z. created figures. R.Z. contributed to discussions on the writing framework. All authors read and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

Not applicable.