Ergothioneine

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summary

Ergothioneine is a naturally occurring amino acid, chemically classified as L-(+)-ergothioneine, notable for its unique antioxidant and anti-inflammatory properties. With the molecular formula C9H15N3O2S, it is primarily produced by certain Actinomycetales bacteria and fungi, making it particularly abundant in various mushrooms such as shiitake and reishi.[1][2][3] Ergothioneine has gained attention for its potential health benefits, particularly in the context of aging, cardiovascular health, and neurodegenerative diseases, prompting researchers to explore its role as a conditionally essential nutrient.[4][5][6]

The compound's significance is underscored by its function as a potent antioxidant that can scavenge reactive oxygen species (ROS) and protect cells from oxidative stress. Studies have demonstrated its protective effects on endothelial cells and its ability to inhibit lipid peroxidation, suggesting a promising role in mitigating conditions linked to oxidative damage, such as cardiovascular disease and diabetes.[6][7][8] Furthermore, ergothioneine has been linked to immune modulation and may activate key cellular defenses, adding to its therapeutic potential.[6]

Despite the promising properties of ergothioneine, notable controversies surround the current state of research, particularly concerning its efficacy in humans. While animal studies and preliminary clinical trials indicate safety and potential health benefits, there remains a lack of comprehensive human clinical trials to substantiate these claims. The existing studies often focus on dosage and metabolic pathways rather than direct health outcomes, highlighting a critical need for further research to clarify its role as a nutritional supplement and therapeutic agent.[9][10][6]

In addition to its biological functions, ergothioneine can be ingested through dietary sources and supplements, offering a convenient means for individuals to potentially harness its health benefits. While mushrooms represent the primary source, the compound is also found in grains and certain koji-based products.[3][11] As interest in ergothioneine continues to grow, its unique properties and potential implications for health and longevity are subjects of ongoing research and discussion in the scientific community.[6][7][3]

Chemical Structure

Ergothioneine, chemically known as L-(+)-Ergothioneine, has the molecular formula C9H15N3O2S and a unique structure that comprises oxygen-, nitrogen-, and sulfur-containing functional groups[1][2]. It is classified as a low-molecular-weight thiol due to the presence of a sulfhydryl (-SH) group, which contributes to its antioxidant properties and biological functions[4][5].

Structural Characteristics

The structural elucidation of ergothioneine is often supported by advanced spectroscopic techniques such as Nuclear Magnetic Resonance (NMR) Spectroscopy, Mass Spectrometry, and UV-Vis Spectroscopy[12][4]. These techniques provide detailed

insights into its molecular arrangement and the behavior of its constituent atoms, particularly the hydrogen atoms in the sulfhydryl group[12][13].

Biosynthesis

Ergothioneine is primarily biosynthesized by certain Actinomycetales bacteria and fungi. The biosynthetic pathway involves a series of enzymatic reactions, notably catalyzed by the Egt family of enzymes (EgtA, EgtB, EgtC, EgtD, and EgtE), which sequentially facilitate the conversion of histidine and hercynine into ergothioneine[8-][14]. The pathway also involves the shikimate pathway and the histidine biosynthetic pathway, illustrating the interconnected nature of metabolic processes in these organisms[14][15].

Ergothioneine's distinctive chemical structure and biosynthetic origin highlight its significance in both health-related research and its nutritional presence in various dietary sources such as mushrooms, grains, and certain koji-based products[13][5].

Biological Functions

Ergothioneine, a naturally occurring thiol compound, exhibits a range of biological functions that contribute to its potential health benefits.

Antioxidant Properties

One of the primary biological roles of ergothioneine is its function as an antioxidant. It has been shown to scavenge reactive oxygen species (ROS), thereby mitigating oxidative stress, which is implicated in various diseases, including cardiovascular disease (CVD) and neurodegenerative disorders[6][8]. Studies indicate that ergothioneine protects endothelial cells from hyperglycemia-induced oxidative damage by maintaining nitric oxide activity and reducing superoxide anions, thus preserving vascular integrity[7][8]. Furthermore, ergothioneine has been found to inhibit lipid peroxidation and promote the overexpression of heat shock protein 70 in liver injury models, enhancing tissue tolerance to oxidative stress[6][8].

Immunomodulatory Effects

Ergothioneine also plays a role in immune system modulation. The transcription of the SLC22A4 gene, which encodes the ergothioneine transporter, is regulated by inflammatory cytokines such as IL-1²and TNF-±suggesting a link between ergothioneine accumulation and cellular immune defense[6]. Additionally, ergothioneine has been shown to activate the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2), which initiates the cellular antioxidant defense system[6]. This activation is thought to contribute to ergothioneine's cytoprotective effects beyond mere redox activity.

Potential Role in Healthy Ageing and Cardiometabolic Health

Recent research has proposed that ergothioneine may act as a conditionally essential nutrient, particularly in the context of healthy aging and the prevention of cardiometabolic diseases[6][7]. Clinical data are emerging suggesting that ergothioneine supplementation could yield therapeutic benefits for conditions associated with oxidative stress, such as obesity and cardiovascular disease[6]. However, there is currently a lack of comprehensive human clinical trials investigating ergothioneine's efficacy, underscoring the need for further research in this area[6].

Neuroprotective Effects

In neurodegenerative contexts, ergothioneine's protective mechanisms appear to be multifaceted. It has been found to inhibit the accumulation of amyloid-beta (A²)in the hippocampus and reduce lipid peroxidation in neuronal cells, which may alleviate neurotoxicity[8]. Additionally, ergothioneine supports other antioxidants by maintaining the GSH/GSSG ratio and enhancing superoxide dismutase activity, contributing to its neuroprotective properties[8]. These actions may help mitigate neurodegeneration related to diabetes and other conditions characterized by increased oxidative stress.

Sources

Dietary Sources of Ergothioneine

Ergothioneine is a unique antioxidant compound predominantly found in fungi, particularly in various mushroom species. It is not synthesized by plants or animals, making mushrooms the primary dietary source of this amino acid.[3][16]. Certain soil bacteria also contribute to the production of ergothioneine, but the highest concentrations are typically found in mushrooms such as Shiitake, Oyster, and Reishi mushrooms.[3][11]. While plants can absorb ergothioneine from the soil, their levels are significantly lower compared to those found in mushrooms.[3].

Supplementation

In addition to obtaining ergothioneine through dietary sources, individuals can also increase their intake through supplements. These supplements may be made from dried fruiting bodies or mycelium-based products derived from ergothioneine-rich fungal species. This approach provides a convenient option for those seeking to enhance their ergothioneine consumption and potentially benefit from its health-promoting properties.[11].

Metabolism

Ergothioneine is a naturally occurring compound that plays significant roles in human health and development. This compound can accumulate at high levels in the body through dietary sources, primarily from mushrooms, grains, and koji-based products[7][15]. The transport of ergothioneine into cells is facilitated by the organic cation transporter OCTN1 (SLC22A4), which is crucial for its biological activity and potential therapeutic effects[15].

Biological Roles

Ergothioneine exhibits unique properties, including antioxidant activity, which allows it to combat oxidative stress. It is thought to play a role in protecting cells from damage caused by free radicals and other oxidative agents. The dynamic regulation of its metabolism in mitochondria highlights its importance in cellular functions and overall metabolic health[17][15]. Additionally, ergothioneine's ability to chelate metal ions further contributes to its protective mechanisms within the body.

Accumulation and Excretion

The pharmacokinetics of ergothioneine indicate that it undergoes saturation kinetics during absorption, which means the extent of its uptake can plateau at certain doses-[9]. This phenomenon complicates the prediction of optimal ergothioneine dosages for health benefits, especially in clinical settings such as metabolic syndrome, where the compound is being researched for its potential effects on oxidative stress and inflammation[9].

Clinical Implications

Despite the promising roles of ergothioneine, evidence regarding its efficacy and metabolic functions in humans remains limited. Most studies have focused on animal models and in vitro experiments, necessitating further clinical research to ascertain its potential as a conditionally essential nutrient[6]. Understanding ergothioneine's transport dynamics, retention mechanisms, and metabolic pathways is critical for evaluating its therapeutic benefits and establishing guidelines for supplementation[-6][15].

Research and Clinical Studies

Overview of Ergothioneine Research

Ergothioneine (ERGO) is a naturally occurring amino acid with potent antioxidant and anti-inflammatory properties, which has garnered interest in the context of aging and chronic diseases. It is considered highly bioavailable from dietary sources and has been labeled by some as a "longevity vitamin" due to its potential in mitigating chronic age-related diseases[10]. Despite its promising profile, there is a notable scarcity of published intervention trials that specifically examine its efficacy in humans[9].

Clinical Studies

Safety and Dosage

A short-term human clinical study indicated that ergothioneine is safe for consumption, even at high doses of 25 mg per day[10]. The ErgMS study has been designed as a randomized, double-blind, placebo-controlled pilot trial to investigate the effects of ergothioneine supplementation specifically in individuals with metabolic syndrome. Participants in this study will receive either a placebo or doses of 5 mg or 30 mg per day of ergothioneine for 12 weeks[9].

Study Design and Objectives

The ErgMS study aims to assess various metabolic syndrome risk factors and measure serum markers associated with oxidative stress, inflammation, and liver function. Key parameters include malondialdehyde (MDA) levels as a marker of oxidative stress, alongside other inflammatory markers such as tumor necrosis factor-alpha (TNF-±) and c-reactive protein (CRP)[9]. The trial will also utilize advanced statistical analyses, including linear regression and two-way ANOVA, to evaluate the data collected[9].

Recruitment and Compliance

Participants will be recruited from previous studies and through broad advertising, including outreach to relevant health organizations. The study anticipates a recruitment period of approximately two years, considering potential challenges such as unforeseen events or low recruitment rates[9]. Compliance with the supplementation protocol will be monitored through capsule counting and plasma ergothioneine levels measured at baseline, 6 weeks, and 12 weeks[9].

Adverse Events Monitoring

In terms of safety monitoring, any adverse events reported by participants will be documented and assessed for causality. Although the study population is considered low risk, an independent data monitoring committee is not established due to the short duration of the trial and the minimal risks associated with ergothioneine supplementation[9].

Implications for Neurodegenerative Diseases

Research has increasingly highlighted the link between oxidative stress and neurodegenerative diseases, suggesting that ergothioneine's antioxidant properties may have implications in this domain. For instance, oxidative stress is believed to play a critical role in the pathogenesis of diseases such as Alzheimer’s and Parkinson’s-[13]. The growing understanding of the role of oxidative stress in these conditions underscores the importance of further studies on ergothioneine and its potential therapeutic applications.

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