

White Paper

L-Ergothioneine

A Unique Healthy Aging Ingredient



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What is L-ergothioneine?

L-ergothioneine (Ergo) is a naturally occurring amino acid and is a thiol/thione derivative of histidine [1]. Ergo is found in highest concentrations in mushrooms and bacteria, but other foods known to have lower levels of Ergo include king crab, beef, pork, lamb, and chicken. Despite the presence of Ergo in foods humans consume, its biosynthesis has only been observed in certain bacteria and fungi [2]. Humans produce a highly specific transport protein called OCTN1 for Ergo that makes it highly bioavailable and avidly retained, leading many to speculate about its potential importance to human health, because such specific transporters are rarely present for non-nutrient bioactive compounds [3].

Longevity Vitamins and Healthy Aging

The Triage Theory by renowned scientist Bruce Ames, PhD states that when the body runs low on a certain vitamin or just one mineral, it's forced to make a decision about how to use its meager supply: Should it be used to fix immediate issues, or should it be used to keep everything else running smoothly [4]?

A recent study by Ames showed that that the body prioritized the use of scarce micronutrients in favor of short-term survival at the expense of long-term health [5]. However, Ames postulated that if the body is always well-supplied, it should never have to make that choice, resulting in healthy aging.

In 2018 Ames proposed classifying the existing vitamins and minerals as "survival vitamins and minerals," but adding two new classifications. First, a group he called "conditional vitamins," and finally compounds that are required for the function of longevity proteins as "longevity vitamins." Impairment of the function of longevity proteins results in an acceleration of the risk of diseases associated with aging. Longevity vitamins are not synthesized in the body (similar to other vitamins), and are also those for which the triage hypothesis is most applicable, compounds for which asymptomatic deficiencies lead to short-term maintenance at the cost of long-term health. Included in the small list of proposed longevity vitamins is Ergo [6].

Unfortunately, nutrient deficiencies are highly prevalent in the United States (and elsewhere). Preliminary evidence indicates that Ergo levels in the American food supply might be compromised because of reduced fungal populations in agricultural soils caused by some cultivation practices [3].

Ames postulated that appropriate supplementation and/or an improved diet including longevity vitamins such as Ergo may reduce much of the consequent risk of chronic disease and premature aging [6].

Antioxidant Ability

The Mitochondrial Theory of Aging, first proposed in 1972 by Denham Harman, PhD suggests that it's free radical damage to our cells' power source that leads to a loss of cellular energy and function over time. It's a little like charging your cell phone over time; every time you charge it the capacity gets reduced.

Elevations in biomarkers of oxidative damage and low-grade inflammation have long been known to be a hallmark of aging and risk of age-related diseases [7,8]. One of the putative basic mechanisms of aging is age-dependent mitochondrial deterioration, closely associated with damage mediated by reactive oxygen species (ROS). Given the central role that mitochondria and mitochondrial dysfunction play not only in aging but also in apoptosis, cancer, neurodegeneration and other age-related diseases there is great interest in approaches to protect mitochondria from ROS-mediated damage.

Ergo has been shown to scavenge oxygen radicals and other ROS [1,9-10]. This suggests that the compound may act as an antioxidant and anti-inflammatory agent in vivo [11-14]. It is possible that the elevation in oxidative damage with aging and age-related pathology may in part be attributed to declining levels of blood Ergo.

In a 2018 unpublished report on a naturally fermented Ergo powder, antioxidant potential using oxygen radical absorbance capacity (ORAC) was tested on a 98% material and a 5% Ergo raw material. The radical scavenging activity (EC50, µg/ml) of Ergothioneine 5% and Ergothioneine 98% were 40.50 µg/ml and 4.11 µg/ml respectively. Briefly, the lower the EC50 number is of higher radical scavenging activity [15].

Ergo is one of the only antioxidants concentrated in mitochondria, suggesting a specific role in protecting mitochondrial components such as DNA from oxidative damage associated with mitochondrial generation of superoxide. In combating cytotoxic effects of pyrogallol, a known superoxide generator, Ergo is as potent as glutathione. Because of its dietary origin and the toxicity associated with its depletion, Ergo may represent a new vitamin whose physiologic roles include antioxidant cytoprotection. [16] Cells lacking Ergo are also more susceptible to oxidative stress, resulting in increased mitochondrial DNA damage, protein oxidation and lipid peroxidation [7].

Prostate Health

A 2019 study looked at a total of 36,499 participants between the ages of 40 and 79 and asked them to complete a questionnaire about lifestyle choices such as diet (including mushroom consumption), physical activity, smoking and drinking habits. After following one group of men for 24.5 years and another for 13.25 years, the researchers found that the men who consumed mushrooms once or twice a week had an 8 percent lower risk of developing prostate compared to those who ate mushrooms less than once per week. Eating mushrooms more often appeared to bring even bigger benefits, with those who consumed mushrooms three or more times per week showing a 17 percent lower risk than those who ate mushrooms less than once a week.

The researchers indicated mushrooms may have this positive effect on prostate health partly because they are rich in Ergo. They believed Ergo to be useful to the body for combating oxidative stress, a cellular imbalance that results from a poor diet and unhealthy lifestyle as well as exposure to environmental toxins. This can lead to chronic inflammation that can ultimately result in cancer. [17].

Cognitive Decline

Aging is a major risk factor for many diseases including neurodegenerative disorders such as Alzheimer's, Parkinson's, and other areas affecting dementia or cognitive decline. One study showed that participants who consumed several portions of mushrooms each week had reduced odds of having mild cognitive impairment (MCI). The cross-sectional data supports the potential of mushrooms and their bioactive compounds such as Ergo in delaying neurodegeneration and have neuroprotective properties [18] (Figure 1).

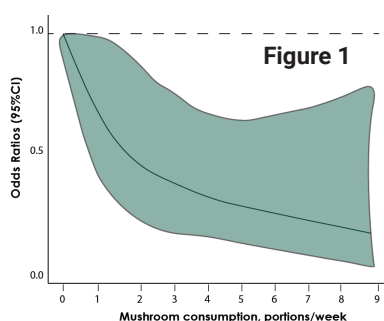


Figure 1: Functional dependence of mild cognitive impairment on mushroom consumption (treated as a continuous variable): the solid curve is estimated via the smoothing spline approach. Adjusted for age, gender, education, cigarette smoking, alcohol consumption, hypertension, diabetes, heart diseases, stroke, physical activities, social activities.

A second study on an elderly population group showed that Ergo levels specifically declined beyond 60 years of age, and are further significantly decreased (relative to age-matched subjects) with onset of MCI [19] (Figure 2 and 3). This decline suggests that deficiency in Ergo

may be a risk factor of predisposing individuals to neurodegenerative diseases.

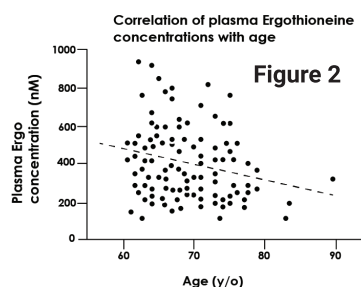
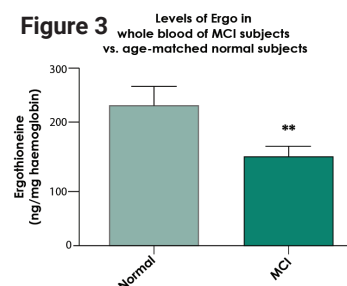


Figure 2: Decreasing trend in Ergo levels with age: significant decreasing trend is seen in whole blood ($P < 0.01$, $r = -0.2159$) with increasing age, which is expected since plasma and whole blood Ergothioneine concentrations are highly correlated.

Figure 3: Comparison of whole blood Ergo levels between MCI subjects and cognitively-normal age-matched individuals. Subjects with MCI had significantly lower average blood Ergo relative to age-matched normal counterparts. $**P < 0.01$; Mann-Whitney test.



Safety and Absorption

A double blind, placebo controlled clinical study on 25 healthy male volunteers was conducted where each group was given either 5 mg of Ergo (equivalent to one serving of mushrooms), 25 mg of Ergo, or a placebo over the course 7 days. Whole blood, plasma and urine levels were then tracked for several weeks. The results showed that after oral administration, Ergo is avidly absorbed and retained by the body with significant elevations in plasma and whole blood concentrations, and relatively low urinary excretion (<4% of administered Ergo).

This uptake suggests an important physiological function. Similar to safety results from animal studies, there were no reported adverse effects from the administration of pure Ergo in humans. In addition, no changes were observed in liver function tests and lipid profiles (measured at commencement and conclusion of the study) from administration of Ergo [20].

In the United States, the naturally fermented (not synthetic) form of L-ergothioneine received GRAS status in May 2018. The Panel on Dietetic Products for the European Food Safety Authority found that safe daily limits of 2.82 mg/kg of body weight for infants, 3.39 mg/kg for small children, and 1.31 mg/kg for adults, including pregnant and breastfeeding women. The target population is children above 3 years of age and the general adult population [21].

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