

ErgoActive[®] L-Ergothioneine

Understanding its impact on cognition, frailty, and telomere length

Written by: Priscilla Samuel, PhD





Table of Contents

Introduction	2
What is L-Ergothioneine?	2
Bioavailability	2
Decreasing Levels of L-ET as We Age	3
L-ET Impact on Cognition	4
Frailty and Mobility	6
L-ET Impact on Telomeres and Aging	7
Safety	8
Sources of L-ET in the Human Diet	9
Conclusion	9
References	10

Introduction

The median age of populations around the world is increasing as life expectancy is on the rise. According to the World Health Organization,¹ over one billion people worldwide are aged 60 years or older, and by the year 2050, this number is expected to exceed two billion. The surge in the number of older adults will

The years 2021 – 2030 are the United Nations Decade of Healthy Aging with a goal to collaboratively improve the lives of older people, their families, and communities around the world.²

also increase the prevalence of disease and disability, including cognitive impairment that may range from mild deficits that are not clinically detectable to dementia.³ Cognitive impairment leads to reduced quality of life, loss of autonomy, and increased risk of dementia.³

The aging process is highly complex and results in a progression of molecular and cellular damage over time that eventually leads to a decrease in physical and mental capacity that varies from one individual to another. While some aging adults enjoy good health and physical mobility, others are frail and require assistance from others. Frailty, a consequence of cumulative age-related decline in multiple physiological systems, is characterized by increased falls, delirium, and institutionalization.^{4,5}

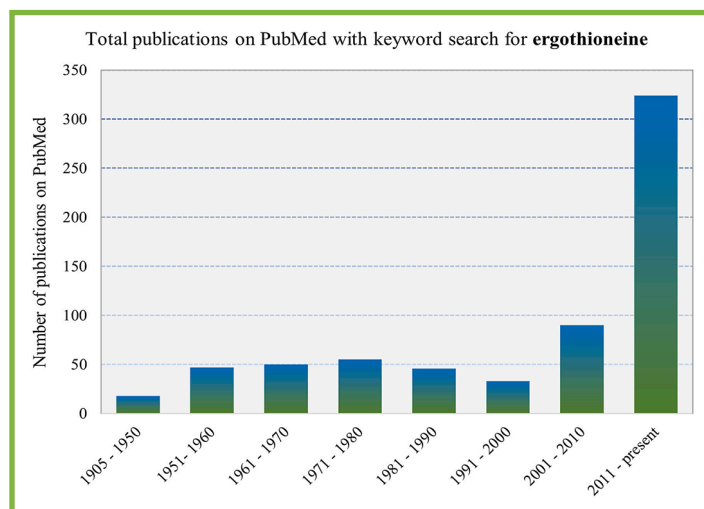
Oxidative stress is postulated to be one of the hallmarks of aging and thought to actively contribute to the development of chronic diseases, including neurodegeneration.^{6,7} Normal physiological reactions in the body, as well as exogenous sources such as air and water pollution, tobacco, heavy metals, industrial solvents, cooking methods and radiation produce reactive oxygen species (ROS) and reactive nitrogen species (RNS).⁶ The oxidative stress theory of aging suggests that age-associated tissue and organ functional losses are due to the accumulation of ROS and RNS related damages resulting from increased production of reactive species and/or decreased antioxidant defenses.^{6,7} Therefore, there has been considerable interest in antioxidants that help defend against this damage, and L-ergothioneine (L-ET) has had some additional focus in the news due to some recent promising results.

This white paper defines what L-ergothioneine is and what makes it unique from other antioxidants, followed by a discussion on its bioavailability. The remaining sections discuss L-ET's positive impact on cognition, frailty and mobility, and its influence on telomere length and longevity. The conclusion reviews the safety and various sources of L-ET and the advantages of Blue California's ErgoActive®.

What is L-Ergothioneine?

L-ergothioneine is a naturally occurring amino acid, a derivative of histidine,⁸ known to be synthesized only by non-yeast fungi and certain bacteria.⁹ L-ET is found in trace amounts in a wide variety of foods, but the highest concentrations are found in certain species of mushrooms.⁸ Although L-ET was discovered about a century ago, there has been a surge of recent interest as seen by a dramatic increase in scientific publications. This surge, as shown in Figure 1, is in part due to the discovery of the ET-transporter.¹⁰ It has been proposed that L-ET may have an age-delaying or "longevity" function in addition to a "survival" function.¹¹

Figure 1: The Last 10 Years Has Seen a Dramatic Increase in Scientific Publications on L-ET



Reproduced from Cheah IK, et al.¹⁰

Bioavailability

All mammals, including humans, synthesize a cell membrane transport protein that is highly specific for L-ET, called the ET transporter (ETT) that is encoded by the *slc22a4* gene.¹² Through the aid of the ETT, dietary L-ET is readily absorbed from the intestine and distributed into most or all tissues.^{8, 10, 12} Using knockout animal models, it has been demonstrated that without the ETT, L-ET is absent in cells and tissues.^{13, 14}

In a study of 47 healthy young male volunteers, Cheah et al.¹⁵ were the first to show that the oral consumption of pure L-ET is quickly absorbed and retained in the body with significant elevations in plasma and whole blood concentrations, with less than 4% being excreted in urine. During the 8 days of consumption, plasma levels dose-dependently increased following the intake of two doses of L-ET (5 mg/d and 25 mg/d), followed by a gradual decline over the 4-week follow-up period. Subjects that consumed the 25 mg/d dose had plasma levels that remained significantly higher than the basal level at the start of the study and the control substance without L-ET.

The increased levels of L-ET in plasma and whole blood, as well as minimal excretion in urine, indicate a high level of L-ET retention by the body. L-ET levels in whole blood were found

The increased levels of L-ET in plasma and whole blood, as well as minimal excretion in urine, indicate a high level of L-ET retention by the body.

to be highly correlated to the levels of hercynine and S-methyl-ergothioneine, which are thought to be metabolites. An overview schematic of the metabolism of L-ET is shown in Figure 2. Human studies of mushroom intake, a source of L-ET, similarly show an increase in L-ET concentrations in red blood cells or serum.^{16, 17}

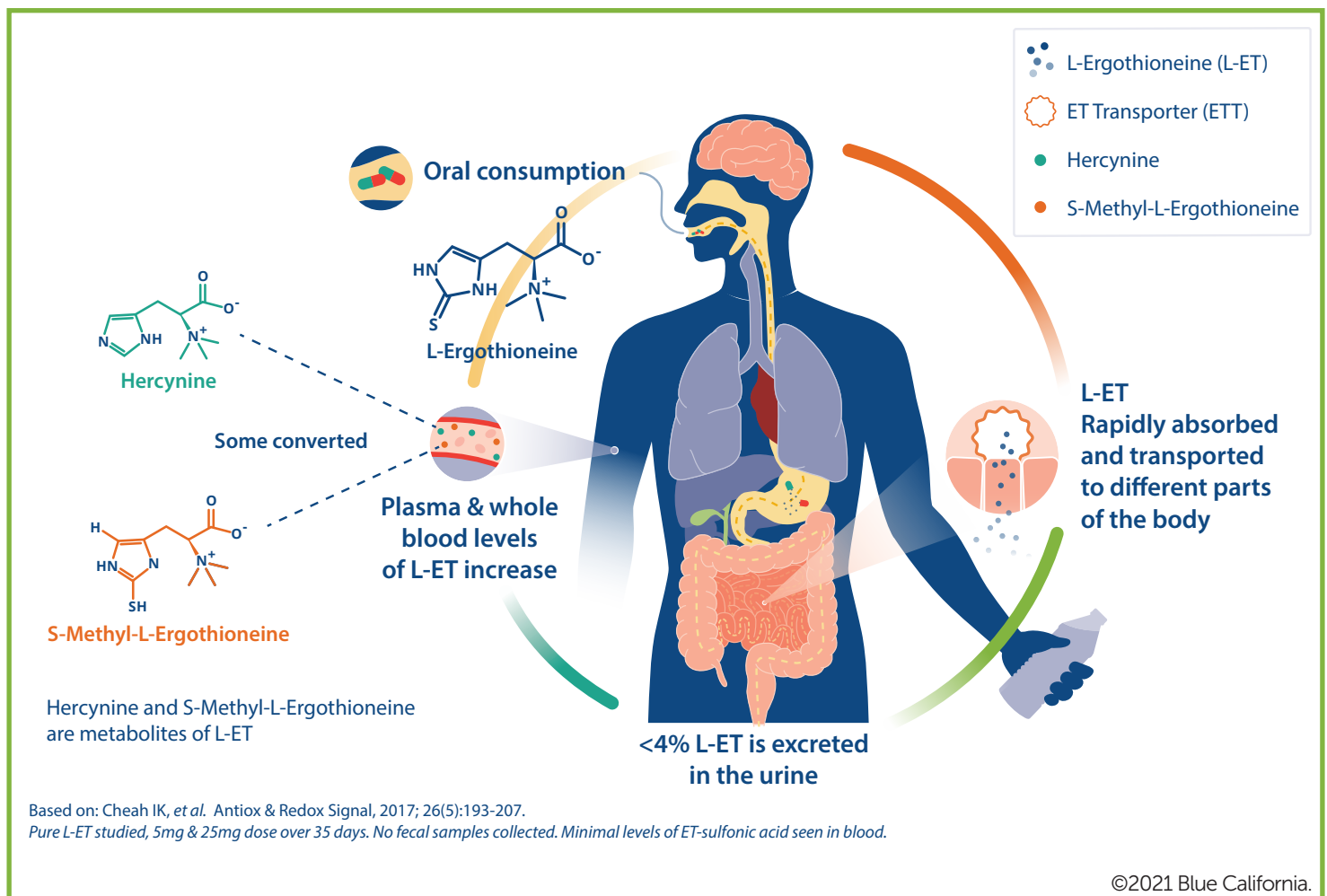
Decreasing Levels of L-ET as We Age

The distribution of L-ET in red blood cells of healthy Saudi men

showed that levels are highest during the ages 11-18 years (3.6 -3.7 mg/100 ml), a period of rapid physiological changes. Levels of L-ET gradually decline with advancing age with 3.0-2.3 mg/100 ml found in the 19-50 year age range, and 2.8 mg/100 ml observed in those 51 years or older.¹⁸ A study of 439 middle-aged and older Australian adults 55-85 years of age indicated decreasing L-ET levels with increasing age.¹⁹ These findings are consistent with another cross-sectional study of elderly individuals in Singapore that showed, despite a wide variation in plasma and whole blood L-ET levels due to different diets, polymorphisms for ETT, and other factors, there was a significant inverse correlation of L-ET with increasing age.²⁰ Whole blood L-ET levels declined significantly beyond 60 years of age²⁰ as shown in Figure 3.

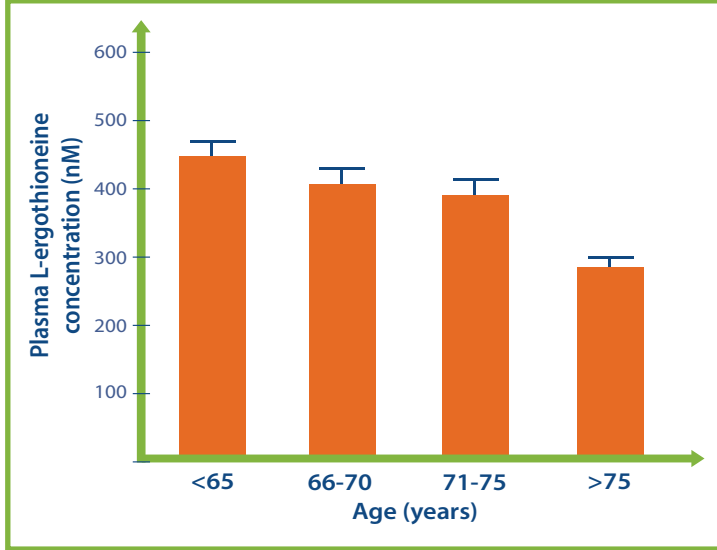
Given the specificity of the L-ET transporter (ETT) and the presence of L-ET in cells and organs that are prone to oxidative stress and inflammation, experts have suggested a cytoprotection (i.e., cytoprotective compounds protect cells from harmful chemicals, compounds or agents) role for L-ET.¹⁵ Together, these studies suggest that declining blood levels of L-ET are inversely

Figure 2: L-Ergothioneine Absorption and Metabolism in Humans



associated with age and could be due to multiple factors, such as increased turnover, slc22a4 gene expression, or altered transport due to impairment of the ETT.

Figure 3: Average Plasma L-Ergothioneine Levels Between Age Groups



Adapted from: Cheah IK, et al.²⁰

While it is not clear to date if it is a cause or a consequence of a disorder or disease, blood levels of L-ET have been inversely associated with the incidence of several conditions. The risk of frailty, mild cognitive impairment (MCI), Parkinson's, and Crohn's disease have been associated with low L-ET blood levels. In contrast, higher blood levels have been associated with reduced risk of peripheral neuropathy, cardiometabolic disorders, and mortality.¹⁰ *In vitro* research has also suggested a potential role in longevity via the preservation of telomere length.²¹

The following sections go over some of the potential benefits associated with L-ET.

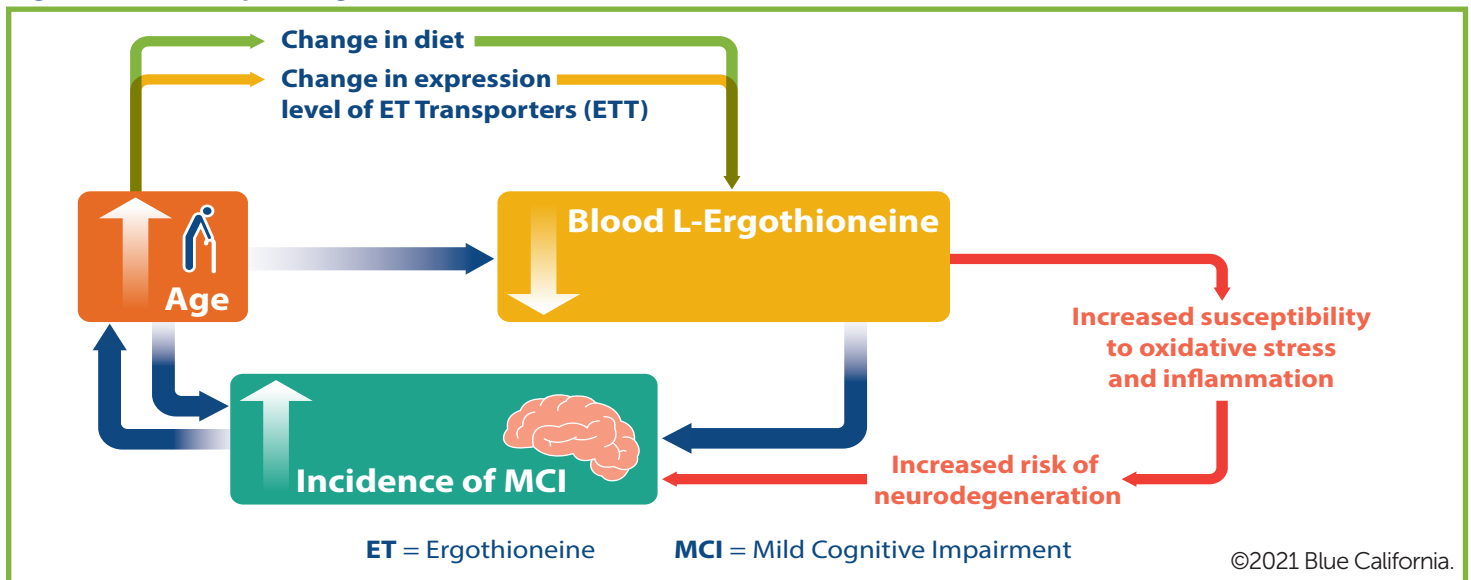
L-ET Impact on Cognition

As we age, the brain's cognitive abilities slow down, i.e., the ability to learn, focus, process information, remember and solve problems. Most people start to notice changes in their 50s or 60s. Certain regions of the brain, such as the hippocampus and frontal lobes, undergo anatomical and neurochemical changes over time that affect how the brain processes information. Evidence to date suggests that L-ET crosses the blood-brain barrier and accumulates in the brain, suggesting it may protect against oxidative damage and neuro-inflammation, toxic accumulation of β -amyloid, and possibly the underlying potentiators of neurodegeneration such as mitochondrial dysfunction.^{10, 20}

It has been suggested that the age-associated decline in blood L-ET levels may be a risk factor for neurodegeneration in the elderly. Plasma L-ET concentrations were significantly lower in elderly subjects with MCI (150.9 ng/mg Hb) compared with age-matched, healthy elderly subjects (232.5 ng/mg Hb)²⁰ (see Figure 4).

Similarly, mushrooms, a dietary source of L-ET, have been associated with better cognitive performance. Feng et al.²² found that participants who consumed more than 2 portions/week had lower odds of having MCI versus those who consumed less than 1 serving/week. They proposed that L-ET from mushrooms may promote cognitive health. Another study of cognitively impaired elderly also observed that levels of L-ET were significantly decreased compared to elderly who were not cognitively impaired.²³ While observational studies cannot indicate causal inference, animal studies provide mechanistic and plausible support that L-ET is an important antioxidant in the brain until more clinical evidence is available.

Figure 4: The Impact Age and Diet Have on L-ET and Incidence of MCI



Adapted from: Cheah IK, et al.²⁰

Table 1. Human, Animal and *In Vitro* Studies Evaluating the Potential Benefits of Ergothioneine Supplementation for Cognitive Health

Population/ Sample Size	Study Design	Duration (days)	Main Findings	Reference
Cognition				
Elderly (China) (70y) N=135 N=25, subsample with MCI	Observational Cross- Sectional	N/A	Favorable: <ul style="list-style-type: none"> Significant inverse correlation between plasma or whole blood L-ET levels and increasing age. Whole blood L-ET levels significantly lower in mildly cognitively impaired subjects compared to healthy age-matched subjects. 	Cheah <i>et al.</i> ²⁰
Frail & Non-Frail Elderly, some impaired cognition (Japan) (84y) N=19	Observational Cross- Sectional	N/A	Favorable: <ul style="list-style-type: none"> Comparison of cognitively impaired subjects with normal subjects detected L-ET levels were significantly decreased. 	Kameda <i>et al.</i> ²³
C57BL/6 Mice Injected with D-galactose, an oxidative stress inducing agent	Oral L-ET Intervention	88	Favorable: <ul style="list-style-type: none"> L-ET significantly improved learning and memory deficits in mice injected with D-galactose compared to similar mice not given L-ET. 	Song <i>et al.</i> ²⁴
Normal ICR Mice	Oral L-ET Intervention	14	Favorable: <ul style="list-style-type: none"> L-ET fed mice had enhanced object recognition memory compared to mice not fed L-ET. In mice fed L-ET there was evidence of neuronal maturation in the hippocampus 	Nakamichi <i>et al.</i> ²⁷
CBA Mice administered cisplatin, an oxidative stress inducing agent	Oral L-ET Intervention	58	Favorable: <ul style="list-style-type: none"> L-ET significantly protected against neuronal injury and diminished cognitive function in cisplatin treated mice compare to similar mice not given L-ET. This was likely achieved by the inhibition of oxidative stress and restoration of acetylcholinesterase (AChE) activity by L-ET in neuronal brain cells. 	Song <i>et al.</i> ²⁵
C67BL/6 Mice given intra-cerebroventricular injection of β -amyloid ($A\beta$ 1-40)	Oral L-ET Intervention	39	Favorable: <ul style="list-style-type: none"> L-ET significantly reduced β-amyloid ($A\beta$) plaque in the hippocampus and cortex and protected against $A\beta$-induced memory and learning deficits in $A\beta$ treated mice versus similar mice not given L-ET. In the brain tissue of L-ET treated mice, L-ET also significantly reduced brain lipid peroxidation, restored AChE activity, maintained glutathione/glutathione disulfide ratio and superoxide dismutase activity. 	Yang <i>et al.</i> ²⁶
Rat pheochromocytoma (PC12) cells incubated with β -amyloid peptide, an inducer of oxidative stress	<i>In Vitro</i>	N/A	Favorable: <ul style="list-style-type: none"> L-ET pretreatment attenuated $A\beta$-induced apoptosis or cell death by eliminating peroxynitrite 	Jang <i>et al.</i> ²⁸

L-ET: L-ergothioneine; Age: mean age; MCI: mild cognitive impairment

Administration of D-galactose has been used in animal models to induce memory and learning impairment as an excess amount of D-galactose increases ROS and advanced glycation end products, causing oxidative damage that leads to impairment. Several weeks of oral supplementation of L-ET in mice with learning and memory deficits and oxidative brain damage using D-galactose injection resulted in significant improvements in information storage and cognitive flexibility (i.e., learning and memory activity) compared to the control.²⁴ A dose of L-ET of 0.5 mg/kg body weight/day, which is equivalent to a human consumption level of 2.5 mg/day, was used in this study to demonstrate L-ET's potential neuroprotective effects from the damage caused by D-galactose. L-ET counteracted D-galactose's impact by increasing the reduced glutathione/ glutathione disulfide ratio, known for protecting cells from oxidative damage, and by significantly limiting increased lipid peroxidation of brain tissues that has been shown to change the structure and function of the membranes.

Further, β -amyloid is a sticky protein fragment that accumulates to form amyloid plaques in the brain and is known to disrupt communication between brain cells and affect immune cells, causing inflammation. It is also toxic, eventually killing brain cells. As expected, in this same study, D-galactose significantly increased the deposition of β -amyloid plaque in the hippocampus, known to generate oxidative stress in the brain. Supplementation with L-ET prevented the accumulation of β -amyloid protein. L-ET also prevented the D-galactose-induced increase in acetylcholinesterase (AChE) brain activity, suggesting that L-ET may play a role in maintaining acetylcholine synaptic levels.²⁴

Other studies of L-ET supplementation in mice treated with ROS producing compounds (e.g., cisplatin) or an intra-cerebroventricular injection of β -amyloid protein in the hippocampus showed that L-ET restored the neurotoxic

effects of these compounds on brain tissue lipid peroxidation, glutathione/glutathione disulfide ratio, and AChE activity.^{25,26} In another study, the administration of L-ET for 14 days in normal mice showed a dose-dependent increase of L-ET in the hippocampus and an increase in neuronal spines in the dentate gyrus, along with enhanced object recognition memory – reflective of memory and learning. These effects appeared to occur in part via the promotion of neuronal maturation, likely through the increased expression of the synapse formation marker synapsin and neurotrophin-3 and-5.²⁷ L-ET doses used in the mice studies were equivalent to easily achievable levels of human consumption.

The neuroprotective effects of L-ET are also supported by *in vitro* studies. Primary cortical neuron cells incubated with cisplatin inhibited the outgrowth of axon and dendrites. Whereas, when the same cells were pretreated with L-ET, damage to the neuronal cells was prevented.²⁵ L-ET pretreatment of pheochromocytoma cells incubated with β -amyloid peptide attenuated cell death by directly scavenging peroxynitrite formation.²⁸ Although the molecular mechanisms underlying β -amyloid toxicity are not completely elucidated, there is increasing evidence supporting the involvement of oxidative and nitrosative stress caused by reactive nitrogen species such as peroxynitrite, implicated in brain ischemia, inflammation, and neurodegeneration.²⁸

Overall, the data suggest that L-ET accumulates in the brain and helps shield the brain against neuronal injury and cognitive deficits, possibly by inhibiting oxidative and nitrosative stress and by the preservation and activity of cholinergic neurons. The evidence for L-ET's potential benefit and the mechanisms by which it may be beneficial for cognition are provocative and promising. Additional clinical studies will hopefully confirm and expand upon the positive effects observed to date in human observational studies, animal and *in vitro* studies.

Frailty and Mobility

Frailty is a geriatric syndrome of significant public health importance and manifests itself in various ways with adverse outcomes such as mobility issues and falls, delirium, institutionalization, disability and mortality, along with corresponding high healthcare costs. By 2050 approximately 21.3% of the global population or over two billion people will be over 60 years of age, up from 9.3% in 1990.¹ According to a recent analysis of pooled data from 46 studies from 28 countries, 1 in 6 community-dwelling older people may have frailty, with a higher incidence of frailty and pre-frailty in women than men.⁴

In order to understand the metabolic basis of frail elderly, an observational study using metabolomics evaluated 131 metabolites and identified 22 markers of frailty, cognition, and hypomobility. L-ET was identified as one of the frailty markers in whole blood, which was significantly decreased in frail elderly compared to non-frail elderly in Japan.²³ These researchers concluded that “the antioxidant L-ET, which decreases in frailty, is neuroprotective.”



Table 2. Human, Animal and In Vitro Studies Evaluating the Potential Benefits of Ergothioneine Supplementation for Frailty and Mobility, and Telomeres and Aging

Population/ Sample Size	Study Design	Dose & Duration	Main Findings	Reference
Frailty & Mobility				
Frail & Non-Frail Elderly (84y) N=19	Observational Cross- Sectional	N/A	Favorable: <ul style="list-style-type: none"> L-ET was one of the 15 frailty markers identified in whole blood. There was a significant decrease in L-ET in frail elderly compared to non-frail elderly. 	Kameda <i>et al.</i> ²³
Adults (84y) N>1,298 subsample N=282	Observational Cross- Sectional	N/A	Favorable: <ul style="list-style-type: none"> L-ET was one of the 35 serum metabolites associated with gait speed. Subsample: L-ET levels were associated with preservation or improvement in gait speed. 	Nierenberg <i>et al.</i> ²⁹
Adults with mild-moderate complaints of chronic pain affecting range of motion (ROM) (52 Y) N=12	Open Label/ Intervention study	Oral 500 µg L-ET*/ 6 weeks *in combination with acai, cat's claw, white willow bark	Favorable: <ul style="list-style-type: none"> ROM and pain in primary and secondary areas were significantly improved compared to baseline, starting at 1 wk. 	Benson <i>et al.</i> ²⁴
Mouse diaphragm fiber bundles	<i>In vitro</i>	10 mM / 60 min	Null: <ul style="list-style-type: none"> Muscle force-frequency and rate of contraction was not affected by L-ET treatment. 	Ferreira <i>et al.</i> ³⁰
Telomeres & Aging				
Human fibroblasts treated under standard and oxidative (H2O2) conditions	<i>In vitro</i>	0.04-1.0 mg/mL / 8 weeks	Favorable: <ul style="list-style-type: none"> L-ET treatment decreased the rate of telomere shortening and preserved telomere length under oxidative stress conditions. 	Samuel <i>et al.</i> ²¹

These researchers concluded that *"the antioxidant L-ET, which decreases in frailty, is neuroprotective."*²³

In a US study, the association between serum metabolites and physical performance was assessed in the large cohort participating in the Bogalusa Heart Study.²⁹ Thirty-five metabolites were associated with gait (i.e., manner of walking) speed, of which L-ET was one. In a subsample of participants that were followed for 2.9 years, L-ET was one of three metabolites positively associated with preservation or improvement in gait speed.²⁹ On the other hand, an *in vitro* study indicated that L-ET exposed to mouse diaphragm fiber bundles did not delay skeletal muscle fatigue.³⁰ However, a small pilot intervention study of a nutraceutical blend containing 500 µg L-ET and

other compounds for joint, cartilage and inflammatory support improved range of motion and pain in adults with mild to moderate complaints of chronic pain affecting range of motion.³¹

Since oxidative damage has been proposed as one of the underlying pathways of age-related skeletal muscle decline, it has been suggested that antioxidant supplementation may contribute to reducing oxidative stress and diminished physical function linked to aging.³² L-ET supplementation may be one of the antioxidants to reduce oxidative stress.

L-ET Effect on Telomeres and Aging

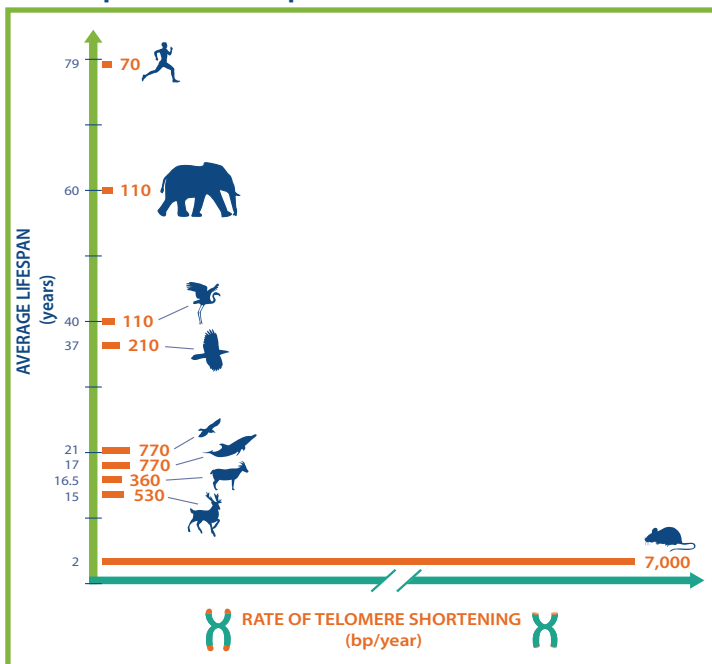
The word "telomere" is based on two Greek words – "telos" which means "end" and "meros" which means "part." Telomeres are protective caps at the end of our DNA strands that shield our chromosomes from degradation and are therefore vital to our health, similar to how the plastic tips at the end of shoelaces keep them from fraying. These caps or telomeres are non-

coding genetic material with repetitive nucleotide sequences found at the end of chromosomes in all human cells.³³ As we age, telomeres shorten with every cell division and after several divisions, reach a critical length or get too short to do their job, causing cells to age and stop functioning properly known as “cellular senescence”.³³ Telomere length has come to be known as a marker of “biological age” as opposed to chronological age and studies have shown a strong relationship between short telomeres and cellular aging.

Telomeres can also be shortened by stress, smoking, lack of exercise and poor diet. Various health conditions have been associated with telomere shortening such as infections, obesity, cardiovascular disease, diabetes, osteoporosis, as well as neurological disorders such as Alzheimer’s Disease and depression.^{21, 33} Oxidative stress and inflammation are known to accelerate telomere shortening. Diets rich in antioxidants or anti-inflammatory compounds such as carotenoids, vitamin C, vitamin E, and omega-3 fatty acids are associated with longer telomere length.²¹

While many researchers have focused on telomere length, the shortening rate is also becoming of importance. This was illustrated in a recent study across a wide variety of animal species of different sizes and life spans (e.g., a goat, elephant, mouse, flamingo, etc.) that concluded that the telomere shortening rate was a powerful predictor of species life span.³⁴ These researchers further noted that the cellular effects induced by short telomeres, such as cellular senescence, may be a critical factor that determines species longevity (see Figure 5).

Figure 5: The Rate of Telomere Shortening and the Impact on Lifespan



Animals featured: human, elephant, flamingo, Griffon vulture, Audouin’s gull, bottlenose dolphin, goat, reindeer, mouse. Adapted from: Whittemore K, et al.³⁴

Antioxidant supplementation may protect or reduce telomere erosion. This premise was tested using Blue California’s ErgoActive® L-ET in an *in vitro* study of cultured primary human fibroblasts under normal and oxidative stress conditions.²¹ Under oxidative stress conditions, the results showed longer median telomere length, a lower percentage of short telomeres, and a reduction in telomere shortening rate by 27 – 52% by week 4 of the 8 weeks that were studied, demonstrating that L-ET helped preserve telomere length under oxidative stress, in part by slowing the rate of shortening (see Figures 6 and 7).²¹

Concentrations of L-ET used were within physiological ranges observed in human tissues and blood. While these *in vitro* findings warrant additional research in animals and or humans, the evidence to date suggests this unique amino acid L-ET, through its antioxidant properties at the cellular level, may help support healthy aging. L-ET’s potential benefits for aging are also why the well-known Bruce Ames¹¹ included L-ET on his list of “longevity vitamins” – i.e., substances not required for survival but help reduce the accumulation of long-term oxidative damage.

Safety

ErgoActive® L-ET produced via fermentation technology has Generally Recognized As Safe (GRAS) status with a No-Objection letter from the US FDA to Blue California’s GRAS notification (GRN No. 734).³⁵ The safety of L-ET has also been evaluated by the European Food Safety Authority (EFSA), and a synthetic form has novel food status in Europe.³⁶ To date, no tolerance issues, adverse clinical side effects or toxicological issues have been

Figure 6: Effect of L-ET on Median Telomere Length at Week 4 and 8, Under Oxidative Stress

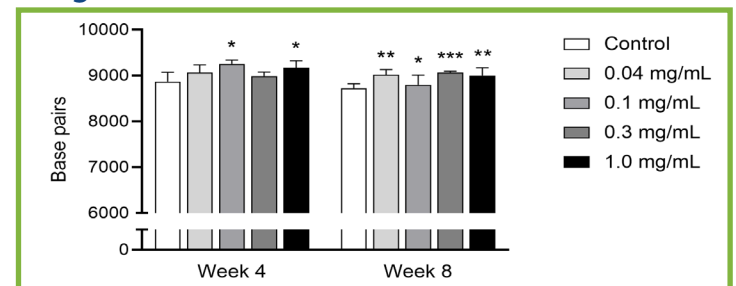
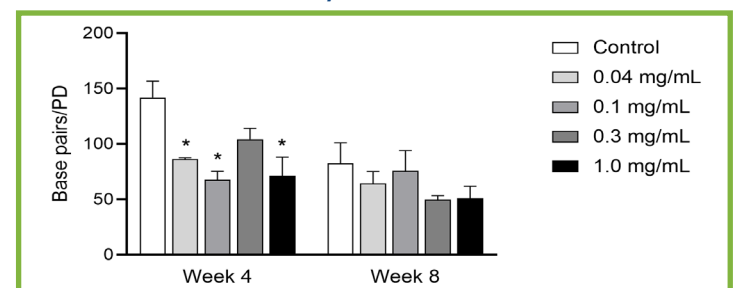


Figure 7: Effect of L-ET on Telomere Shortening Rate at Week 4 and 8, Under Oxidative Stress



Figures 6 and 7 from: Samuel P, et al.²¹

observed in human and animal studies.^{15, 35}

Sources of L-ET in the Diet

L-ET is a naturally occurring amino acid with potent antioxidant properties. It is synthesized exclusively by fungi, cyanobacteria, and mycobacteria.⁹ L-ET can be found in trace amounts in a wide variety of foods, though higher levels can be found in certain species of mushrooms, black and red beans, organ meats, and oat bran.³⁷ Specific varieties of mushrooms have the highest concentrations and thus are one of the best sources of L-ET in the traditional diet. However, for those who do not or cannot consume mushrooms due to food allergies for instance, supplementation of L-ET is a good way to increase ergothioneine as part of a healthy diet and lifestyle.

Conclusion*

There is considerable and growing interest in L-ET for its potential health benefits. L-ET is naturally present in the diet, but for those who do not or cannot eat mushrooms, which are the highest contributor to the diet, ErgoActive® L-ET is safe and can be used to develop supplements and/or fortify foods and beverages. While additional research is needed, evidence to date suggests that L-ET accumulates in the brain, and the mechanisms by which it may be beneficial for cognition are provocative and promising. Emerging data also suggests that L-ET may help preserve telomere length and longevity.

ErgoActive® L-Ergothioneine from Blue California

- Produced using a proprietary fermentation manufacturing process
- US FDA no objection to Notification of Self-Affirmed GRAS
- Kosher certified
- Water soluble
- Neutral in taste, color and odor

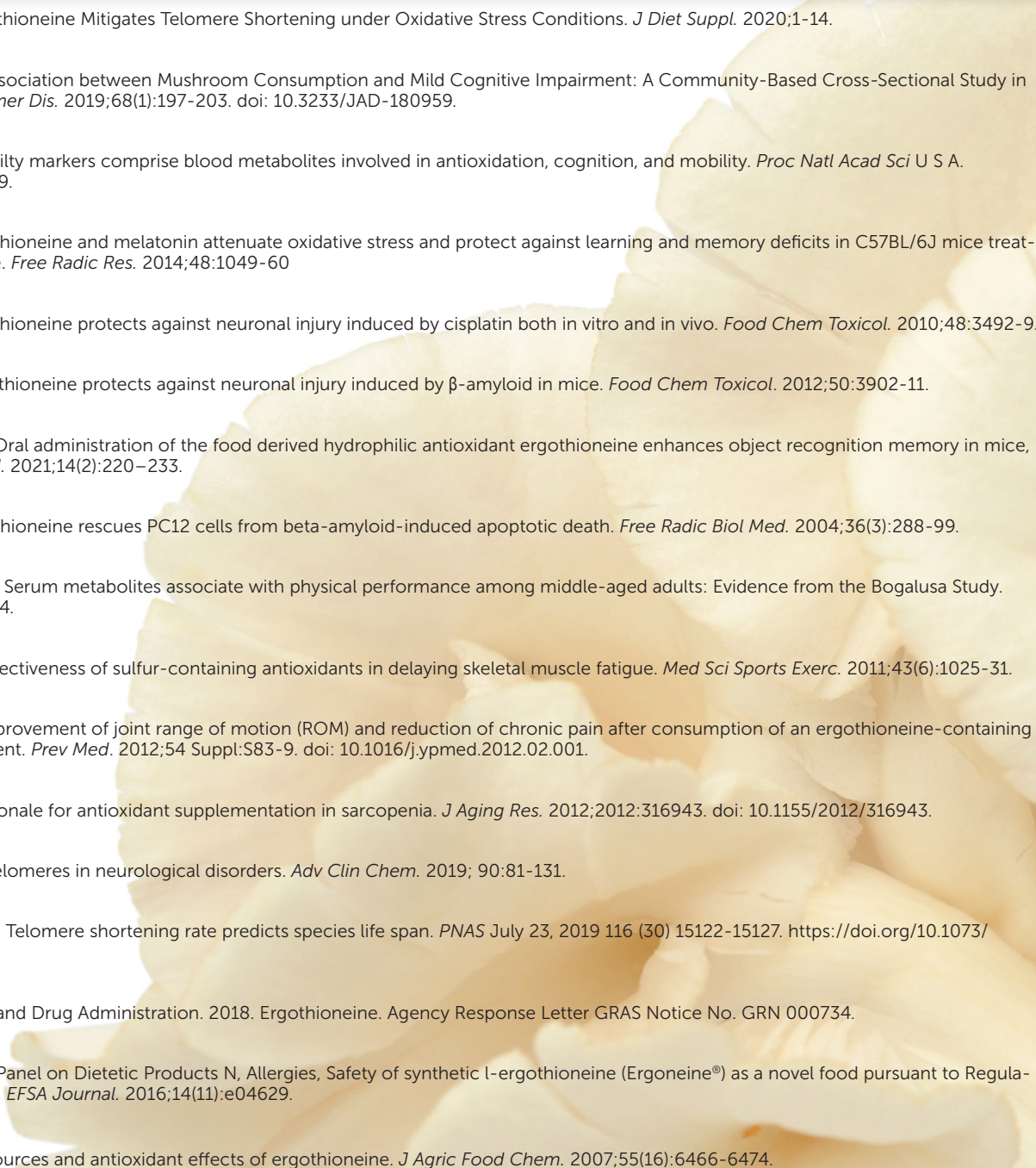
ErgoActive® L-ET is safe and can be used to develop supplements and/or fortify foods and beverages.



*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to treat, diagnose or cure a disease.
©2021 Blue California. ErgoActive is a Registered Trademark in the USA. All Rights Reserved. Ver: 1.0

References

1. World Health Organization 2018. Ageing and health. Factsheet. <https://www.who.int/news-room/fact-sheets/detail/ageing-and-health>.
2. World Health Organization 2021. United Nations Decade of Healthy Ageing. <https://www.who.int/initiatives/decade-of-healthy-ageing>. Accessed March 30, 2021.
3. Pais R, et al. Global Cognitive Impairment Prevalence and Incidence in Community Dwelling Older Adults-A Systematic Review. *Geriatrics* (Basel). 2020;5(4):84.
4. Ofori-Asenso R, et al. Global Incidence of Frailty and Prefrailty Among Community-Dwelling Older Adults: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2019; 2:e198398.
5. Clegg A, et al. Frailty in elderly people. *Lancet* 2013; 381:752-762. doi:10.1016/S0140-6736(12)62167-9.
6. Liguori I, et al. Oxidative stress, aging, and diseases. *Clin Interv Aging*. 2018;13:757-772.
7. Hajjar L, et al. Oxidative stress predicts cognitive decline with aging in healthy adults: an observational study. *J Neuroinflammation*. 2018;15:17. doi:10.1186/s12974-017-1026-z.
8. Halliwell B, et al. Ergothioneine - a diet-derived antioxidant with therapeutic potential. *FEBS Lett*. 2018;592:3357-3366.
9. Cheah IK, Halliwell B. Ergothioneine; antioxidant potential, physiological function and role in disease. *Biochim Biophys Acta*. 2012;1822:784-93.
10. Cheah IK, et al. Ergothioneine, recent developments. *Redox Biol* (January 26, 2021), Online <https://doi.org/10.1016/j.redox.2021.101868>.
11. Ames BN. Prolonging healthy aging: Longevity vitamins and proteins. *Proc Natl Acad Sci U S A*. 2018;115:10836-10844.
12. Beelman RM, et al. Is ergothioneine a "longevity vitamin" limited in the American diet? *J Nutritional Sci*. 2020; 9:e62. doi:10.1017/jns.2020.44
13. Kato Y, et al. Gene knockout and metabolome analysis of carnitine/organic cation transporter OCTN1. *Pharm. Res.* (N. Y.), 27 (5) (2010), pp. 832-840.
14. Pfeiffer C, et al. Knockout of the ergothioneine transporter ETT in zebrafish results in increased 8-oxoguanine levels. *Free Radic. Biol. Med.* 83 (2015), pp. 178-185.
15. Cheah IK, et al. Administration of pure ergothioneine to healthy human subjects: uptake, metabolism, and effects on biomarkers of oxidative damage and inflammation. *Antioxid Redox Signal*. 2017; 26:193-206.
16. Weigand-Heller AJ, et al. The bioavailability of ergothioneine from mushrooms (*Agaricus bisporus*) and the acute effects on antioxidant capacity and biomarkers of inflammation. *Prev Med*. 2012; 54:S75-S78.
17. Calvo MS, et al. A Retrospective Study in Adults with Metabolic Syndrome: Diabetic Risk Factor Response to Daily Consumption of *Agaricus bisporus* (White Button Mushrooms). *Plant Foods Hum Nutr*. 2016 ;71:245-51.
18. Kumosani TA. L-ergothioneine level in red blood cells of healthy human males in the Western province of Saudi Arabia. *Exp Mol Med*. 2001;33:20-2.
19. Sotgia S, et al. Clinical and biochemical correlates of serum L-ergothioneine concentrations in community-dwelling middle-aged and older adults. *PLoS One*. 2014;9:e84918.
20. Cheah IK, et al. Ergothioneine levels in an elderly population decrease with age and incidence of cognitive decline: a risk factor for neurodegeneration? [dx.doi.org/10.1016/j.bbrc.2016.07.074](https://doi.org/10.1016/j.bbrc.2016.07.074)

- 
21. Samuel P, *et al* Ergothioneine Mitigates Telomere Shortening under Oxidative Stress Conditions. *J Diet Suppl*. 2020;1-14.
 22. Feng L, *et al*. The Association between Mushroom Consumption and Mild Cognitive Impairment: A Community-Based Cross-Sectional Study in Singapore. *J Alzheimer Dis*. 2019;68(1):197-203. doi: 10.3233/JAD-180959.
 23. Kameda M, *et al*. Frailty markers comprise blood metabolites involved in antioxidation, cognition, and mobility. *Proc Natl Acad Sci U S A*. 2020;117:9483-9489.
 24. Song TY, *et al*. Ergothioneine and melatonin attenuate oxidative stress and protect against learning and memory deficits in C57BL/6J mice treated with D-galactose. *Free Radic Res*. 2014;48:1049-60
 25. Song TY, *et al*. Ergothioneine protects against neuronal injury induced by cisplatin both in vitro and in vivo. *Food Chem Toxicol*. 2010;48:3492-9.
 26. Yang NC, *et al*. Ergothioneine protects against neuronal injury induced by β -amyloid in mice. *Food Chem Toxicol*. 2012;50:3902-11.
 27. Nakamichi N, *et al*. Oral administration of the food derived hydrophilic antioxidant ergothioneine enhances object recognition memory in mice. *Curr Mol Pharmacol*. 2021;14(2):220–233.
 28. Jang JH, *et al*. Ergothioneine rescues PC12 cells from beta-amyloid-induced apoptotic death. *Free Radic Biol Med*. 2004;36(3):288-99.
 29. Nierenberg JL, *et al*. Serum metabolites associate with physical performance among middle-aged adults: Evidence from the Bogalusa Study. *Aging* 2020; 12:11914.
 30. Ferreira LF, *et al*. Effectiveness of sulfur-containing antioxidants in delaying skeletal muscle fatigue. *Med Sci Sports Exerc*. 2011;43(6):1025-31.
 31. Benson KF, *et al*. Improvement of joint range of motion (ROM) and reduction of chronic pain after consumption of an ergothioneine-containing nutritional supplement. *Prev Med*. 2012;54 Suppl:S83-9. doi: 10.1016/j.ypmed.2012.02.001.
 32. Cerullo F, *et al*. Rationale for antioxidant supplementation in sarcopenia. *J Aging Res*. 2012;2012:316943. doi: 10.1155/2012/316943.
 33. Ayyappan A, *et al*. Telomeres in neurological disorders. *Adv Clin Chem*. 2019; 90:81-131.
 34. Whittemore K, *et al*. Telomere shortening rate predicts species life span. *PNAS* July 23, 2019 116 (30) 15122-15127. <https://doi.org/10.1073/pnas.1902452116>.
 35. United States Food and Drug Administration. 2018. Ergothioneine. Agency Response Letter GRAS Notice No. GRN 000734.
 36. Turck D, *et al*. EFSA Panel on Dietetic Products N, Allergies, Safety of synthetic l-ergothioneine (Ergoneine®) as a novel food pursuant to Regulation (EC) No 258/97. *EFSA Journal*. 2016;14(11):e04629.
 37. Ey J, *et al*. Dietary sources and antioxidant effects of ergothioneine. *J Agric Food Chem*. 2007;55(16):6466-6474.



About Blue California

Blue California is an entrepreneurial, science-based solutions provider and manufacturer of clean, natural, and sustainable ingredients used in food, beverage, flavor, fragrance, dietary supplements, personal care and cosmetic products. For more than 25 years, Blue California has built a strong reputation for creating value in these diverse natural product and nature-inspired industries. We are one of the few vertically integrated companies in our focus industries.

Blue California Headquarters

30111 Tomas

Rancho Santa Margarita, CA 92688

+1-949-635-1991

email: info@bluecal-ingredients.com

www.bluecal-ingredients.com/portfolio/specialty-ingredients/

Follow us on Social Media at



https://twitter.com/BlueCal_Ing



<https://www.linkedin.com/company/bluecalifornia>

