



Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Ergothioneine

Evidence Summary

Low levels are associated with poor health outcomes. Supplementation protects against oxidative stress in preclinical studies, but human data is limited. It may improve sleep and has a strong safety profile.

Neuroprotective Benefit: Serum ergothioneine levels are lower in those with cognitive impairment. Supplementation may improve sleep quality, though its effect on cognition has not yet been tested in humans. It may protect neurons from oxidative stress.

Aging and related health concerns: Few clinical studies, which were not well-powered or well-designed, have been performed. Observational studies suggest a link between higher intake levels and healthy aging, likely by mitigating oxidative stress damage.

Safety: Ergothioneine is safe with no reported toxicity at doses exceeding those obtained through food or supplements. It may interact with gabapentin.

<p>Availability: OTC and in diet (mushrooms).</p>	<p>Dose: 5-20 mg daily based on supplement companies, but no dose recommendations currently available based on lack of clinical data</p>	<p>Chemical formula: C₉H₁₅N₃O₂S MW: 229.298 g/mol</p>
<p>Half-life: (Based on rat studies) Whole-body half-life 1 month. It is stored in cells/tissues. The tissue concentration is dependent on transporter expression.</p>	<p>BBB: Not membrane permeable. Enters cells through OCTN1 transporter. Cells in brain (including neurons) express OCTN1 and take up l-ergothioneine.</p>	 <p>Source: PubChem</p>
<p>Clinical trials: One trial in healthy volunteers for safety (n=45), one RCT in healthy volunteers on sleep (n=92). Several small studies using proprietary combination formulations with largely unreported results for diabetic anemia, joint pain, and kidney disease.</p>	<p>Observational studies: Serum ergothioneine levels are lower with age and dementia. Mushroom intake is associated with lower mortality and better age-related cognition.</p>	

What is it?

L-ergothioneine is a sulfur containing metabolite of histidine and diet derived amino acid. It is synthesized in *Actinomycetales* bacteria and non-yeast fungi. The highest concentrations of l-ergothioneine are found in mushrooms, particularly *Boletus edulis* (porcini mushroom, 528.14 mg/kg) and *Pleurotus ostreatus* (oyster mushroom, 118.91 mg/kg) [1]. The l-ergothioneine derived from mushrooms has been shown to be bioavailable (taken up by red blood cells) within one hour of consumption. It is also found in relatively high concentration in liver (chicken, 10.78 mg/kg), black turtle beans (13.49 mg/kg), red kidney beans (4.52 mg/kg), and oat bran (4.41 mg/kg).

L-ergothioneine is rapidly cleared from circulation and retained in cells/tissues [2]. It is minimally metabolized, possibly by an oxidative degradation mechanism into hercynine and free sulfate before being excreted [3]. L-ergothioneine is taken up by cells that express the organic cation / carnitine transporter 1 (OCTN1), expressed by the *SLC22A4* gene [4]. It is membrane impermeable to cells that lack the transporter, consequently, ergothioneine tissue levels correspond well with OCTN1 expression levels. The highest expression is in erythrocytes, monocytes, lung, intestine, trachea, kidney, and the brain [4; 5; 6]. Since the tissue expression pattern of OCTN1 is species specific, some animal studies may not be translatable to humans. While OCTN1 preferentially transports l-ergothioneine, it does not



exclusively transport l-ergothioneine. Therefore, the phenotypes from OCTN1 knockout studies cannot be conclusively attributed to the loss of l-ergothioneine uptake.

L-ergothioneine is currently available as an OTC supplement. It is also in several skincare and haircare products to prevent skin aging and promote hair growth, respectively. It is currently being developed for use in edibles (cakes, cookies, pastries, coffee, tea, fruit drinks, soft drinks, candy at 5 mg/serving) by Tetrahedron (France), and Blue California (USA).

Neuroprotective Benefit: Serum ergothioneine levels are lower in those with cognitive impairment. Supplementation may improve sleep quality, though its effect on cognition has not yet been tested in humans. It may protect neurons from oxidative stress.

Types of evidence:

- 1 clinical trial assessing sleep in healthy volunteers
- 5 observational studies (l-ergothioneine levels)
- 1 observational study on mushroom intake and cognition
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

There have not yet been any clinical trials examining the role of l-ergothioneine on cognition. A clinical trial designed to test l-ergothioneine (10 or 25 mg/d) as a dietary supplement supplied by the Blue California Company on cognition, mood, and sleep in healthy adult men and women was terminated due to recruitment challenges stemming from the Covid-19 pandemic ([NCT04556032](#)). Observational studies regarding the cognitive trajectories of individuals taking l-ergothioneine supplements have also not been conducted, likely because these products have only become available relatively recently. Instead, l-ergothioneine has primarily been obtained from the diet through the consumption of mushrooms, thus mushroom consumption can be considered a crude correlate for l-ergothioneine exposure [7]. Other biomarker-based studies have examined the association between l-ergothioneine levels and cognitive trajectories. Overall, these studies indicate that lower levels of l-ergothioneine are associated with cognitive decline. They suggest that high levels of l-ergothioneine are neuroprotective.

However, the biological mechanism underlying the decline in l-ergothioneine levels needs to be identified to determine the most effective way to boost them. Possible explanations include reduced dietary intake, reduced uptake of dietary sources in the gastrointestinal tract, elevated retention in



gastrointestinal tract or other tissues, or altered metabolism. Lower circulating levels could be indicative of higher levels within tissues, including the brain, due to elevated levels of oxidative stress, however, this has not yet been investigated. If this is the case, then supplementation would be expected to be beneficial.

Sleep: POTENTIAL BENEFIT FOR SLEEP QUALITY

A placebo-controlled RCT assessed the impact of daily l-ergothioneine (20 mg Ergoneine® , manufactured by Tetrahedron) supplementation for four weeks in Japanese volunteers (age 40 to 75 years old) (n=92) with subjective anxiety and sleep complaints [8]. Overall sleep quality, as measured by the total Pittsburgh Sleep Quality Index (PSQI) score improved from baseline in both groups. In an assessment of PSQI sleep sub-scores, the ergothioneine-treated group showed a significant improvement relative to placebo in reducing sleeping difficulty, but the differences between the groups for the other sub-scores were not statistically significant. Based on EEG sleep monitoring, those in the ergothioneine-treated group showed a better ratio of N1 to N2 sleep, higher levels of REM sleep, a shorter latency into slow wave sleep, and fewer wakings after sleep onset, consistent with a higher sleep quality. Serum metabolome analysis indicated that ten metabolites were significantly altered with treatment, particularly those associated with D-glutamine and D-glutamate metabolism. Lipid metabolism was also altered, including a reduction in levels of deoxycorticosterone, which is the precursor to the stress hormone corticosterone. The reductions in glutamic acid and stress hormones may facilitate sleep, though the sleep-related effects of l-ergothioneine likely involve multiple mechanisms. This study suggests that l-ergothioneine supplementation may benefit cognition by improving sleep quality. Preclinical studies also support a role for l-ergothioneine in the regulation of sleep quality [9].

Cognitive Aging: ERGOTHIONEINE LEVELS ARE ASSOCIATED WITH COGNITIVE PERFORMANCE

The National Health and Nutrition Examination Survey (NHANES) from 2011 to 2014 examined the relationship between mushroom consumption based on 24-hour dietary recalls and cognition in adults ≥60 years old (n=2,840 participants) [10]. The prevalence of mushroom consumption in this study was relatively low at 4.2% (95% Confidence Interval [CI] 2.9 to 5.5%). Relative to those with the lowest mushroom intake, those with the highest mushroom intake, 13.4 g/4184 KJ (1000 kcal)/d, showed better cognitive performance on the Digit Symbol Substitution Test (DSST) and Consortium to Establish a Registry for Alzheimer's Disease Delayed Word Learnings (CERAD-WL) tests. Although this does not provide direct evidence for an effect by l-ergothioneine, baseline plasma l-ergothioneine levels were positively associated with cognitive performance on executive, visuospatial, visuomotor speed, and



memory domains, in a subgroup of elderly individuals without dementia from a memory clinic cohort (n=470) [11].

Mild Cognitive Impairment (MCI): ERGOTHIONEINE LEVELS ARE REDUCED

Individuals with MCI (n=25) were compared to age-matched individuals without signs of cognitive impairment (n=25) [12]. Individuals with MCI had lower whole blood levels of l-ergothioneine. This difference was not related to differences in mushroom consumption or differences in OCTN1 transporter expression. Decreased/altered OCTN1 transporter activity in the MCI cohort was offered as a possible explanation.

Dementia: ERGOTHIONEINE LEVELS ARE REDUCED

In a cohort of elderly individuals attending memory clinics in Singapore (n=470), baseline plasma l-ergothioneine levels were significantly lower in dementia patients [11]. Levels were lower in ApoE4 carriers, and those with hypertension, diabetes, or cardiovascular disease. Relative to individuals with the highest plasma levels of l-ergothioneine, those with the lowest levels had the worst performance on measures of global cognition. Additionally, those with lower scores at baseline has faster rates of cognitive decline, as measured by the CDR-SoB. The individuals with low l-ergothioneine levels and impaired cognition also had reduced brain volume and a greater burden of white matter hyperintensities. A whole-blood metabolomics study (n=24) aimed at determining a signature of metabolites that are altered in dementia, identified six metabolites which could differentiate dementia patients from controls [13]. Ergothioneine was found to be reduced in dementia patients and was one of the six discriminating metabolites. Plasma l-ergothioneine levels were assessed in a cohort of 496 individuals, with or without dementia [14]. Lower levels of l-ergothioneine were associated with dementia, white matter hyperintensities, and brain atrophy.

Parkinson's Disease (PD): ERGOTHIONEINE LEVELS ARE REDUCED

Patients with idiopathic PD without dementia (n=35, 49% female) were compared to age-matched healthy controls (n=15). PD patients had lower serum levels of l-ergothioneine [15]. Notably, other altered metabolites included tryptophan, caffeine, bilirubin, and biliverdin, suggestive of a disruption in the balance of redox regulators, which could contribute to an increased susceptibility to oxidative damage. In a study assessing the axillary (underarm) microbiome in PD patients with and without cognitive impairment (n=103), there were changes in the composition of the microbiome along the progression from cognitively healthy to impaired [16]. The changes in taxa were associated with changes in the biosynthesis of microbe-derived metabolites, including ergothioneine.



Human research to suggest benefits to patients with dementia:

Currently, there is no evidence to suggest that l-ergothioneine treatment benefits patients with dementia. A clinical trial was registered in 2018 aimed at testing ergothioneine in patients with MCI, however the current status of this study is unknown ([NCT03641404](#)) [17].

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Ergothioneine is an antioxidant, however, it does not act like a conventional reactive oxygen species (ROS) scavenger or alkylthiol, and the molecular mechanism(s) by which it exerts its antioxidant activity is not fully understood.

Protection against oxidative stress: *In vitro* assays using physiologically relevant concentrations of ergothioneine (based on tissue concentration of 1-2 mM) indicate that ergothioneine can inhibit the formation of free radicals (oxidative damage) following the interaction of transition metal ions (copper and iron) with peroxide [18]. Ergothioneine was shown to exhibit dose-dependent protection against DNA and protein oxidation by stabilizing copper in the Cu(I) state and forming a redox inactive ergothioneine-Cu(I) complex [19]. The strongest protection occurred in relation to heme protein associated oxidative damage, which is consistent with its high expression in erythrocytes [18].

Rat PC12 cells were protected against A β ₂₅₋₃₅ induced apoptosis by treatment with l-ergothioneine (0.5 or 1mM ET for 36 hours) [20]. The protective effect was attributed to the suppression of peroxynitrite formation and nitration of tyrosine residues. It is expected to be most effective when used in combination with other types of antioxidants (i.e. conventional ROS scavengers).

In a *C. elegans* AD model, transgenic worms (CL2006) which overexpress A β 3-42 in their body wall cells have shortened lifespans [21]. Supplemental feeding with l-ergothioneine throughout their life, increased their lifespans from 6 to 11%, dose-dependently. The effect on lifespan may stem from the dose-dependent reductions in paraquat-induced oxidative stress and A β oligomerization seen in these worms with l-ergothioneine treatment.

The promoter for the ergothioneine transporter, OCTN1, was shown to be driven by the inflammatory mediators IL-1 β , TNF α , and NF- κ B in luciferase and gel shift assays [22]. OCTN1 expression is also independently regulated by the transcription factor RUNX1, which is involved in hematopoietic stem cell differentiation [22]. Both OCTN1 expression and ergothioneine tissue levels increased in a guinea pig model of liver disease in response to rising cholesterol and iron levels/tissue damage [23]. Knockdown



(RNAi) of OCTN1 in HeLa cell reduced ergothioneine uptake, increased H₂O₂ mediated toxicity, protein carbonylation, and lipid peroxidation [24]. Pretreatment of control cells with ergothioneine (1mM for 24 hours) rescued H₂O₂ induced toxicity. Ergothioneine preferentially protected water-soluble proteins from oxidative damage. Additionally, OCTN1 knockout mice showed lower tolerance to oxidative stress, as indicated by decreased survival in an intestinal ischemic injury model [6]. This work suggests that OCTN1 is induced in response to inflammation/cellular damage to increase transport of a cytoprotective agent(s), which is likely ergothioneine.

Neuroprotection: The uptake of ergothioneine by mouse neural progenitor cells (NPCs) decreased mitochondrial activity (less ROS generation) and neurosphere area (decreased proliferation) [25]. It also promoted neuronal differentiation in an OCTN1 dependent manner. Mice on diets supplemented with mushroom extract (containing 1.2% ET) had increased doublecortin+ cells in the brain, indicating a possible effect on neuronal differentiation [26]. The authors hypothesize that ergothioneine could be neuroprotective by promoting the differentiation of NPCs in the context of neuronal damage.

In a rat NMDA induced model of retina degeneration, i.p. injection (0.2 ml 70 mg/ml) of l-ergothioneine at the time of injury decreased retinal ganglion cell loss from 81% to 44% [27]. However, their sample size (n=3) is insufficient to account for the variability in this model and the neuroprotective effect may be overestimated.

The MJFF funded a preclinical study in 2014 examining the ability of ErgoD2 (4000 IV Vitamin D + 3mg ergothioneine per serving) to reduced indicators of PD activity [28]. The stated preliminary findings indicate improved grip strength of PD mice and reduced levels of alpha-synuclein in the midbrain, however, the results do not appear to have been published, despite a [press release](#) indicating a manuscript had been submitted for peer review.

Old mice (21.5 months old) treated with standardized extracts of *H. erinaceus* (Lion's mane mushrooms) containing 10 to 350 µg/mL l-ergothioneine for two months showed a partial recovery of age-related motor declines [29]. The improvement of locomotor function was accompanied by changes in the cerebellum. Related to untreated age-matched mice, the l-ergothioneine-treated mice had larger cerebellar volumes, with a higher percentage of neurons with normal morphology.

Treatment with l-ergothioneine reduced infarct sizes in rodent models of focal transient cerebral ischemia [30]. Rats that received an intracerebroventricular (i.c.v.) infusion of 200 ng l-ergothioneine



during the post-ischemic period had significantly lower infarct volumes. Similarly, mice treated with 70 to 150 mg/kg l-ergothioneine i.p. starting three hours after ischemia for up to seven days also had significantly reduced infarct volumes. These studies suggest that l-ergothioneine can help protect neurons against ischemia-related cell death when administered centrally or peripherally.

Cognitive function: Ergothioneine pre and post treatment (daily oral ET at 0.5 mg/kg) was found to be protective in mice $A\beta_{1-40}$ [31] or D-galactose [32] mediated neurotoxicity. Ergothioneine treatment decreased latency (improved performance) on avoidance and water maze tests, prevented $A\beta$ accumulation, prevented brain lipid peroxidation, restored acetylcholine esterase activity, and maintained the glutathione ratio and superoxide dismutase (SOD) activity in the brain. In the D-galactose model, ergothioneine was also combined with melatonin (10 mg/kg) and found to have a synergistic effect [32]. This combinatorial effect is hypothesized to result from increased antioxidant activity, since ergothioneine and melatonin are different types of antioxidants.

In the 5XFAD mouse model, treatment with an oral solution of l-ergothioneine (25-50 mg/kg) three times per week for eight weeks starting prior to the onset of pathology (eight weeks old) mitigated AD-related pathology, including amyloid plaque loads, numbers of pro-inflammatory glial cells, oxidative stress, and glucose levels [33]. Treatment also partially mitigated cognitive deficits on a fear conditioning task, though deficits were generally mild, even in untreated animals, at this age. Male mice supplemented with l-ergothioneine (20-50 mg/kg) for two weeks showed better performance on the novel object recognition test, as well as more mushroom type dendritic spines, which are associated with learning and memory [34].

In a social defeat model of depression, the microbiota of depressed rats increased the uptake of l-ergothioneine locally in the gastrointestinal tract, though plasma levels did not increase, suggesting it was retained locally [9]. This is hypothesized to be a protective response. Treatment of the rats with oral l-ergothioneine (0.25 mg/ml) starting one week prior to the initiation of the social defeat protocol mitigated several depression-like behaviors, particularly sleep abnormalities. The increased l-ergothioneine uptake may influence metabolite production from the microbiome, which may account for the effect on sleep. In mice, levels of l-ergothioneine are higher in the plasma and in the brain during periods of wakefulness relative to periods of sleep [35].

APOE4 interactions:

The impact of ApoE status on l-ergothioneine supplementation has not been established.



Aging and related health concerns: Few clinical studies, which were not well-powered or well-designed, have been performed. Observational studies suggest a link between higher intake levels and healthy aging, likely by mitigating oxidative stress damage.

Types of evidence:

- 3 clinical trials testing l-ergothioneine supplementation
- 1 clinical trial for mushroom extract supplementation
- 4 observational studies examining l-ergothioneine blood levels
- 2 metabolomics studies assessing frailty-related metabolites
- 1 metabolomics study assessing cardiovascular disease-related metabolites
- 1 observational study on mushroom intake and mortality
- Numerous laboratory studies

Lifespan: EXTENDS LIFESPAN IN FLIES

The association between mushroom intake, a surrogate for l-ergothioneine intake, and mortality was assessed in 30,378 participants from the NHANES study (2003 to 2014) [36]. The study found a non-significant association between mushroom consumption and all-cause mortality (adjusted Hazard ratio [HR]: 0.84, 95% Confidence Interval [CI] 0.67 to 1.06). However, mushroom consumption was significantly associated with a lower risk for all-cause mortality in a meta-analysis of four prospective cohort studies including 601,893 participants (pooled risk ratio: 0.94, 95% CI 0.91 to 0.98) [36].

Ergothioneine (100 μ M) was shown to extend the lifespan of *Drosophila melanogaster* by 10 to 15%, with a stronger effect in males relative to females [37]. Ergothioneine-treated flies maintained their ATP levels throughout their lifespans, and showed higher tolerance to heat, starvation, and oxidative stress. Treated flies showed improved climbing activity during old age, but not when young, suggesting l-ergothioneine is impacting a mechanism of aging. Notably, the uptake of l-ergothioneine was microbiome-dependent. Additionally, treatment with l-ergothioneine transiently increased telomerase activity, and mitigated telomere shortening under oxidative conditions in human primary fibroblasts [38].

A *C. elegans* study showed that worms with mutant OCT-1 had decreased (mean and max) lifespan and decreased survival in response to an oxidative stress challenge [39]. However, these mutant worms were still able to uptake ergothioneine, suggesting OCT-1 is not the correct transporter homolog or the effects are due to another function of the transporter. Wildtype (N2) *C. elegans* worms did not show lifespan extension with an l-ergothioneine supplemented diet [21].



Aging: ERGOTHIONEINE LEVELS DECREASE WITH AGING

In a cohort of community-dwelling adults aged 55-85 (n=439, 48% female) in Newcastle, Australia, participants were classified as healthy and unhealthy based on the presence of a chronic medical condition [40]. Serum ergothioneine levels were inversely correlated with age. Levels were slightly, but not significantly, higher in male, and not significantly affected by health status, body mass index (BMI), L-cysteine-L-glycine levels, which is involved in thiol redox homeostasis, or tau levels. An inverse relation between serum ergothioneine levels and age also found in a cohort of adults in Singapore [12].

OCTN1 activity may influence disease susceptibility. Polymorphisms in the OCTN1 gene (SLC22A4) (rs273909 (T→C)) have been associated with susceptibility to ischemic stroke and chronic kidney disease progression in a Japanese cohort [41]. The L503F variant shows altered substrate specificity [42] and is associated with Crohn's disease in Caucasians [43]. Crohn's disease patients in a Japanese cohort have been shown to have decreased blood levels of ergothioneine [6]. Progression of chronic kidney disease (CKD) has also been correlated with decreasing blood levels of ergothioneine, with levels being restored following kidney transplant in a Japanese cohort [44].

Frailty: ERGOTHIONEINE LEVELS ARE INVERSELY ASSOCIATED WITH FRAILITY

Cross-sectional associations between metrics associated with frailty, namely gait speed (n=1,227) and grip strength (n=1,164), and serum metabolites were assessed in middle-aged participants from the Bogalusa Heart Study [45]. Three metabolites were found to be associated with the preservation of gait speed over the 2.9-year follow-up, including ergothioneine. Similarly, a metabolomics study of whole blood from 10 frail and nine non-frail elderly (mean age 84.2 ± 6.9) participants identified ergothioneine as a frailty marker [46]. Low levels of ergothioneine were associated with both physical and cognitive frailty.

In wildtype (C57bl6/J) male mice, treatment with *H. erinaceus* (Lion's mane) primordium extract, which is enriched in l-ergothioneine (1.30 ± 0.57 mg/g), for eight months starting at 15 months of age, improved locomotor performance, relative to untreated aged mice [47]. The cerebellar tissue from the treated mice showed lower levels of oxidative stress. Ergothioneine appears to be enriched within the cerebellum, relative to other brain regions, due to higher expression of its transporter [48]. Although it is generally more resistant to most neurodegenerative diseases, there is increasing evidence that degeneration in the cerebellum plays a critical role in age-related frailty and cognitive aging [49]. The associations between higher levels of ergothioneine with resiliency and cerebellar volumes in human



and animal studies, supports the hypothesis that the maintenance of ergothioneine levels helps protect the cerebellum against damage.

Cardiovascular disease: LOW ERGOTHIONEINE LEVELS ARE ASSOCIATED WITH POOR OUTCOMES

As part of the Malmö Diet and Cancer study, 112 plasma metabolites were assessed in 3,236 participants without cardiovascular disease and diabetes at baseline [50]. A proportion of the participants developed cardiovascular disease, diabetes, and or died during the follow-up period (median of 21.4 years). Four dietary biomarkers were associated with a health-conscious food pattern at baseline and were associated with at least one of the outcomes. Ergothioneine was the metabolite that best associated with the healthy food pattern. Higher ergothioneine levels were also associated with a lower risk of coronary disease (HR per one standard deviation increment of ergothioneine: 0.85, $p=0.01$), cardiovascular mortality (HR: 0.79, $p=0.002$) and overall mortality (HR: 0.86, $p=4e^{-5}$).

Endothelial cells are exposed to high levels of oxidized cholesterol, such as 7-ketocholesterol, in patients with cardiovascular disease and diabetes. In a line of cultured brain endothelial cells (hCMEC/D3), exposure to 7-ketocholesterol reduces cell viability, and alters the localization of tight junction proteins, critical for the maintenance of the blood-brain-barrier [51]. Treatment with l-ergothioneine protected against 7-ketocholesterol induced cell loss and inflammation. This suggests that l-ergothioneine may have a protective effect on the vascular endothelium.

Exercise: POTENTIAL BENEFIT TOWARD REDUCING EXERCISE-INDUCED OXIDATIVE STRESS

Healthy men in Poland ($n=14$) consumed a diet supplemented with Shitake mushroom extract (700 mg 2x/day, estimated l-ergothioneine intake 2.77 mg) for 10 days [52]. Following exercise designed to induce skeletal muscle damage, l-ergothioneine supplementation increased thiol redox status and nitric oxide concentration but had no other measurable effects on inflammation or antioxidant activity.

Five-month-old female mice (C57Bl6/J) treated with 70 mg/kg l-ergothioneine per day for one week showed a longer time to exhaustion (71.55 ± 14 min vs 50.4 ± 8.41 min; +41.22%) on a treadmill running test [53]. The treated animals showed higher activation of protein synthesis in leg (gastrocnemius and soleus) muscle tissue, as well as lower levels of lipid and protein peroxidation, indicative of reduced oxidative stress, lower levels of inflammatory cytokines, and a greater induction of the endogenous Nrf2 antioxidant system following exercise. Notably, ergothioneine treatment appeared to reduce the metabolic stress of exercise without impairing mitochondrial recovery in the mice.



Diabetes: POTENTIAL BENEFIT (Preclinical)

In a clinical study sponsored by Entia Biosciences (manufacturer of ErgoD2), ErgoD2 Hemo (Vitamin D + l-ergothioneine) was tested for its ability to alleviate diabetes associated anemia. The company claims that ErgoD2 stimulated iron export from cells and increased red blood cell production, but the results have not been published.

In a preclinical model of hyperglycemic cytotoxicity in PC12 cells, treatment with ergothioneine, hispidin (PKC inhibitor), or the combination prevented hyperglycemia induced cytotoxicity, and increased AGE, RAGE and NF- κ B [54]. There was a synergistic effect on antiglycation activity/inhibiting AGE formation, but not on antioxidant activity (ROS, protein carbonyl levels), due to possible inhibitory effect of ergothioneine on hispidin activity *in vitro*.

Ergothioneine pretreatment (0.01-1 mM for 12 hours) protected endothelial cells from high glucose-induced cytotoxicity and cell senescence, and reduced ROS production. The cytoprotective effect was mediated through the upregulation of SIRT1 and SIRT6 and downregulation of p66Shc and NF- κ B [55]. In a rat model of type 2 diabetes (streptozotocin plus a high fructose diet), treatment with l-ergothioneine (35 mg/kg) starting after the induction of diabetes, reduced markers of liver injury, hypertrophy, oxidative stress, and inflammation, alone or in combination with metformin [56]. The protection against oxidative stress damage was associated with the upregulation of SIRT1 and Nrf2, and the downregulation of NF- κ B signaling.

Joint pain: UNCLEAR BENEFIT

In a clinical study sponsored by OXIS International, the manufacturer of ErgoFlex (glucosamine, hyaluronic acid, glucosaminoglycans, collagen, acai, cat's claw, white willow bark, and 500 ug ergothioneine), individuals with range of motion limiting joint pain (n=12, 50% female) received 2 capsules ErgoFlex/day for 6 weeks [57]. Supplementation showed slightly significant improvements in joint range of motion during the 6-12 week period, and decreased perceived pain in primary and secondary areas at use within 1 week and sustained for 12 weeks. All changes were relative to baseline and could potentially represent a placebo effect. Additionally, the effects cannot be clearly attributed to ergothioneine.

Kidney disease: POTENTIAL BENEFIT

In a clinical study sponsored by Entia Biosciences (manufacturer of Ergo4Health), patients with chronic kidney disease (n=60) were treated with 500mg capsules of Ergo4Health /Kidney (0.75mg l-ergothioneine +1250 IU Vitamin D2/capsule) 2x daily [58]. The reported results for 3 and 6 months



(Bonaire site only) indicate moderate improvement in the estimated Glomerular Filtration Rate (eGFR), decreased creatine and blood urea nitrogen levels at 3 months (not significant at 6 months), and improved quality of life (survey).

Ergothioneine (70 mg/kg 7 days pretreatment) protected against lipid peroxidation of some fatty acids (22:6, 20:3 n6, 20:4, 18:2, 18:1) in kidney and liver, significantly reduced levels of conjugated dienes and conserved the concentrations of α -tocopherol and glutathione in the kidney and liver in rats with ferric-nitritotriacetate induced oxidative damage [59].

In a mouse model of CKD, the intestinal uptake of ergothioneine by OCTN1 was impaired, leading to lower blood levels. OCTN1 KO mice with CKD had worse kidney fibrosis and increased oxidative stress damage [44].

Skin/UV damage: POTENTIAL BENEFIT (Preclinical)

OCTN1 was shown to be expressed in skin cells and capable of ergothioneine uptake. Ergothioneine pretreatment (10, 50, or 100 μ M for 24 hours) protected cells against UV induced apoptosis, DNA fragmentation, ROS generation, lipid peroxidation. This study has been used as the basis for the use of l-ergothioneine in skincare products.

Intestinal ischemic injury: POTENTIAL BENEFIT (Preclinical)

In a rat model of ischemia and reperfusion, serum TNF α , IL-1 β , MDA, MPO (inflammatory and oxidative stress markers) were reduced and Hsp70 levels increased by ergothioneine pretreatment (10mg/kg orally for 15 days prior to injury)[60]. There was also less histological evidence of tissue damage at four hours reperfusion suggesting possible cytoprotection for ischemic injury. The results are consistent with a connection between OCTN1 polymorphisms and ischemic stroke susceptibility.

Safety: Ergothioneine is safe with no reported toxicity at doses exceeding those obtained through food or supplements. It may interact with gabapentin.

Types of evidence:

- 1 clinical study
- Numerous laboratory studies



Mutagenesis: Bacterial mutagenesis assays [61] and cell culture genotoxicity assays [62] have indicated no mutagenic activity.

Toxicity: Mice treated with doses of l-ergothioneine up to 1500 mg/kg (HED= 122 mg/kg) showed no treatment-associated mortality, but did exhibit decreased activity at the highest dose (1500 mg/kg) [62]. No clinical signs of toxicity were demonstrated at lower doses (375, and 750 mg/kg).

Rats treated with oral l-ergothioneine daily for 90 days (400, 800, 1600 mg/kg) showed no associated mortality, changes in food consumption or body weight, or macroscopic changes at necropsy [63]. At high doses there was some intermittent alopecia and minor hematological changes considered non-adverse. Hematological changes were generally dose and gender specific. The NOAEL of 800 mg/kg/day (HED= 129 mg/kg) used in safety assessments by the FDA and EFSA came from this study.

No reproductive toxicity was demonstrated in a rat study (diet contained with up to 0.9% l-ergothioneine). No effects were observed on mating, reproduction performance, lactation, duration of gestation, fertility, size of pups, litter size, cannibalization of pups, or litter sex-ratio [64].

One human safety study has been conducted. Forty-five healthy men of Chinese ethnicity (aged 21-35) were treated with oral placebo, 5 mg or 25 mg l-ergothioneine daily for 7 days [65]. Plasma ergothioneine levels varied widely, possibly due to polymorphisms in OCTN1. No adverse effects were reported.

FDA and EFSA guidelines:

L-ergothioneine from OXIS International was granted Generally Recognized as Safe (GRAS) status by the FDA in 2011 [66]. L-ergothioneine from Blue California (fermentation based product) was granted GRAS status by the FDA in 2018 for use in foods at 5 mg/serving [67]. Consumption of products based on company recommendations expected to produce total daily exposure to l-ergothioneine of 0.633 mg/kg/day for adults.

L-ergothioneine (Ergoneine®) from Tetrahedron was determined to be safe by the European Commission EFSA panel in 2016 for use in food at 5 mg/serving and as supplements at 30 mg/day for adults and 20 mg/day for children [68]. Total daily exposure based on company recommendations is not expected to exceed 1.7 mg/kg/day. It is also considered safe for infants, toddlers, and pregnant women.

Ergothioneine is classified as likely safe by WebMD.



Drug interactions

The L-ergothioneine transporter, OCTN1, is also capable of transporting other drugs (tetraethylammonium (TEA), gabapentin, pregabalin,) and endogenous biological molecules (carnitine, hercynine, proline betaine, selenoneine), albeit at lower affinity [69] [48]. However, there are conflicting reports on several of the compounds that OCTN1 has been reported to transport [48]. Due to the discrepancies in these *in vitro* assays, it is unclear whether the transport of most of these agents would be significantly impacted *in vivo*. High levels of L-ergothioneine could potentially affect the ability of the transporter to transport other drugs.

Biguanides: Polymorphisms in OCTN1 and/or OCTN1 cellular expression levels may also affect the transport of these molecules. The OCTN1 L503F variant (prevalent in Caucasians) increased the transport of biguanides, such as metformin, while the I306T variant reduced transport of gabapentin in cell assays [69]. The effect on gabapentin transport has been validated, but the potential impact to biguanide transport remains tenuous [48].

Consumption of a high Shitake mushroom (250 g 3x/day) diet at a level that elevated blood L-ergothioneine levels (425 ng/ml vs 172 ng/ml in controls) impacted renal clearance of gabapentin but did not affect other gabapentin pharmacokinetics [70].

Chemotherapeutic agents: OCTN1 may be capable of transporting nucleoside analogs, such as cytarabine (chemotherapy agent), though the assay data is mixed. Low expression of the OCTN1 gene (SLC22A4) is associated with worse survival in acute myeloid leukemia (AML) following chemotherapy, and is a predictor of treatment response [71]. OCTN1 may also transport the chemotherapeutic agent oxaliplatin into neurons, which can lead to peripheral neuropathy in some patients. In a rat study, supplementation with ergothioneine (15 mg/kg) reduced oxaliplatin associated neuropathy [72]. It is unclear whether ergothioneine supplementation could potentially impact responsiveness to some chemotherapy agents.

Anti-tuberculosis (or anti-fungal) drugs: L-ergothioneine plays a critical role in maintaining redox balance in *Mycobacterium tuberculosis* [73]. Strains that can't utilize L-ergothioneine have decreased virulence and are more susceptible to anti-tuberculosis drugs. L-ergothioneine is also required by some opportunistic fungal pathogens [74]. Therefore, supplementation with ergothioneine could impact (weaken) the efficacy of anti-tuberculosis or anti-fungal drugs.



Sources and dosing:

L-ergothioneine is currently available on the market in the US and Europe. [Blue California](#) (US) is developing its fermentation-based l-ergothioneine (ErgoActive®) and [Tetrahedron](#) (France) is developing its product Ergoneine® for use in food and beverage products. The few clinical intervention studies performed have primarily involved l-ergothioneine in combination.

ErgoActive® is the formulation of l-ergothioneine developed by Blue California. It is the active ingredient in the l-ergothioneine supplements sold by [Life Extension](#) and [Sundita](#).

Ergoneine® is the formulation of l-ergothioneine developed by Tetrahedron, which has been approved for use as a food product in the European Union. It has undergone regulatory mutagenicity, toxicology and reprotoxicology studies. This is the formulation that was used in the clinical study assessing the effect of l-ergothioneine on sleep in healthy adults.

L-ergothioneine is also available in a variety of skincare products. Entia Biosciences has a line of products ([Groh](#)) that use the ErgoD2 formulation.

The doses used in the clinical studies vary based on the formulation, as several were combination supplements. The only human study to date which provides evidence that the l-ergothioneine intervention, not in combination, had a measurable effect and appreciably increased plasma levels, was the study in healthy adults using 20 mg/day of Ergoneine®. In this study, plasma l-ergothioneine levels were increased 3.2-fold, from 2.97 to 9.51 µM over the course of the four-week study [8].

Supplements containing ErgoActive® recommend dosages of 5 mg/day (Life Extension) or 20 mg/day (Sundita).

A study assessing serum l-ergothioneine levels in middle-aged and older adults (age 55–85 years) found that the median concentration was 1.01 µmol/L (interquartile range 0.78 to 1.33 µmol/L) [40]. A separate study found the average erythrocyte levels of l-ergothioneine vary by age, and that for men ≥51 years, the average level was 122.11 µM [75].

Timing:

The OCTN1 transporter (*SLC22A4*) is regulated in a circadian manner. *Slc22a4* is a PPARα-regulated gene and in mice its intestinal expression exhibited circadian oscillations in a bile acid-dependent manner (protein levels peak before start of active/feeding phase) [76]. Consequently, there were dose timing dependent changes in OCTN1 substrate (gabapentin) intestinal uptake, with higher uptake at times with

higher OCTN1 expression. This suggests that the time the l-ergothioneine is taken could affect its uptake/efficacy.

This work also calls into question the reliability of studies looking at levels of serum l-ergothioneine in different populations if the samples were collected at different times of day in different patients/groups.

Research underway:

There is one clinical trial planned (anticipated completion by 2021, not yet recruiting) entitled 'Investigating the Efficacy of Ergothioneine to Delay Cognitive Decline' ([NCT03641404](#)) [17]. As of 2022, the status of this study is unknown.

Ergothioneine, provided by Blue California, is being tested in combination with the polyphenol taxifolin, on immune biomarkers in healthy volunteers ([NCT05190432](#)).

Ergothioneine (25 mg/day), sponsored by Natural Immune Systems Inc, will be tested in healthy adults for its antioxidant and immune effects ([NCT05042674](#)).

A study will compare the metabolic profiles of those consuming mushrooms varieties low (white button) or high (yellow oyster) in ergothioneine ([NCT04257201](#)).

Search terms:

Pubmed, Google: L-ergothioneine

+ aging, + dementia, + Alzheimer's, +safety, +tissue distribution, +lifespan, +oxidative stress, + clinical trials, + diabetes, +kidney, +human, +mushrooms, +transporter, +cancer, +diet, +supplements, +inflammation, +mechanism

Websites visited for l-ergothioneine:

- [Clinicaltrials.gov](#)
- [WebMD.com](#)
- [PubChem](#)

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