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Short review

Ergothioneine and exercise: A match made in (cognitive) heaven?

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ABSTRACT

Cognitive decline is one of the key challenges with aging, with significant implications for independence, quality of life, and healthcare burden. As pharmacological treatments remain limited in efficacy and often carry adverse effects, there is growing interest in safe, accessible, non-pharmacological strategies to preserve cognitive function. This *Short Review* explores the potential of combining two approaches that, individually, have shown beneficial effects on cognitive function: ergothioneine, a naturally occurring amino acid with antioxidant and anti-inflammatory properties, and physical exercise. Ergothioneine accumulates in the brain and other high-stress organs, where it modulates the redox balance, dampens chronic inflammation and supports mitochondrial function. Meanwhile, physical exercise has well-documented benefits for neuroplasticity, cerebral perfusion, and cognitive performance. Preclinical studies suggest ergothioneine supports exercise performance and muscle recovery without attenuating adaptive responses. Despite their distinct and complementary mechanisms, currently there are no available studies exploring the combined effects of ergothioneine and exercise on cognition. We propose a future research agenda that includes mechanistic animal studies, dose-response trials, and clinical interventions in at-risk populations. Together, the combination of ergothioneine and exercise may offer a low-risk, multifaceted approach to enhancing cognitive resilience in aging.

1. Introduction

Aging causes progressive physical and cognitive decline (Gianfredi et al., 2025), with cognitive decline having the greater impact on independence and quality of life (Harada et al., 2013; Song et al., 2023). Preserving memory, language, executive function, and processing speed is centric to healthy aging (Prince et al., 2024) and aligns with World Health Organization's intrinsic capacity framework, which defines cognition as a core determinant of resilience and adaptability (Beard et al., 2016; Cohen et al., 2025). Shifting from disease-focused care to maintaining function through lifestyle and nutritional interventions aligns with healthcare goals of prevention, healthy ageing, and sustaining quality of life (Hanushek et al., 2025). Reducing cognitive impairment is a public health priority, as affected individuals incur higher healthcare costs, largely from emergency visits and hospitalisation (Chay et al., 2024).

Age-related cognitive decline is shaped by physiological factors, including neuroinflammation, mitochondrial dysfunction, beta-amyloid and phosphorylated tau accumulation, and cerebrovascular dysfunction (Gonzales et al., 2022), often manifesting decades before symptoms, complicating early detection and timely intervention. Pharmacological treatments have yielded limited success or result in severe side effects (Reish et al., 2023; Sims et al., 2023; van Dyck et al., 2023; Withington and Turner, 2022; Xu et al., 2024; Zhang et al., 2022). Consequently,

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non-pharmacological interventions that target the underlying biology of cognitive decline, without the burden of side effects, are being increasingly studied (Yao et al., 2020).

Here, we review two distinct non-pharmacological strategies to attenuate cognitive aging: ergothioneine, a low-cost, naturally occurring amino acid with cytoprotective properties, and physical exercise (Fig. 1). While both have individually demonstrated benefits on cognitive function, their combined effects remain unexplored. This review examines current evidence on ergothioneine and exercise in relation to cognitive function and suggests areas for future research to investigate their combined effect in maintaining cognitive function during aging.

2. Literature review

References were identified via PubMed/MEDLINE (using terms for ergothioneine, exercise, and cognition) with no date limits, prioritising interventional trials and recent reviews while supplementing with mechanistic/animal-model studies. Reference-list snowballing was also employed to identify the relevant literature.

3. Ergothioneine and cognition

Ergothioneine is a naturally occurring sulfur-containing derivative of histidine that humans cannot synthesise and must obtain through their diet, primarily from mushrooms, fermented foods, and red meat (Cheah and Halliwell, 2012; Cheah et al., 2017; Ishimoto and Kato, 2022). First discovered over a century ago, ergothioneine remained poorly understood until the identification of a specific transporter, OCTN1 (SLC22A4), revealed its active uptake and selective retention in human tissues (Grundemann et al., 2005; Paul and Snyder, 2010). Accumulation of ergothioneine is highest in organs exposed to oxidative stress, such as the brain, eyes, liver, kidneys, and bone marrow (Cheah and Halliwell, 2021; Tang et al., 2018). Ergothioneine's unique chemistry enables it to exist predominantly in the thione form at physiological pH, rendering it highly resistant to autooxidation and allowing it to scavenge a broad range of reactive oxygen and nitrogen species (Fu and Shen, 2022; Halliwell, 2024). Its cellular functions span antioxidant protection, anti-inflammatory signalling, mitochondrial preservation, and immunomodulation (Borodina et al., 2020; Halliwell et al., 2018; Paul, 2022). Ergothioneine has been associated with systemic protection against metabolic and cardiovascular diseases. A metabolomics study found higher plasma ergothioneine levels were associated with lower incidence of coronary disease, cardiovascular mortality and overall mortality in a population free from cardiovascular disease and diabetes mellitus, and an average age of 57.4 years, at baseline (Smith et al., 2020). Given its role in safeguarding vulnerable tissues and long half-life in human systems, ergothioneine has been proposed to be reclassified as a vitamin or 'longevity nutrient' (Halliwell and Cheah, 2022; Tian et al., 2023). Accordingly, future trials should measure circulating ergothioneine levels to verify exposure and guide dose optimisation, ideally considering OCTN1 status as a potential modifier.

In human cellular models, ergothioneine protected stem cell-derived dopaminergic neurons against mitochondrial stress, oxidative damage, and cell death (Leow et al., 2024), and preserved mitochondrial integrity in brain endothelial cells exposed to 7-ketocholesterol, a cytotoxic compound (Leow et al., 2023). RNA interference studies have shown that knockdown of the OCTN1 transporter abrogates these protective effects, supporting the need for transporter-mediated ergothioneine uptake for cellular defence (Paul and Snyder, 2010). Findings from preclinical studies support a compelling role for ergothioneine in cognitive health. In mice, 1 mg/day (mirroring the typical human oral intake of 1 g/day) of ergothioneine supplementation improved memory performance and decreased markers of inflammation and oxidative stress (Roda et al., 2023). Life-long administration of 4 $\sim$ 5 mg/kg/day ergothioneine also extended lifespan and attenuated cerebral decline in aging male mice (Katsube et al., 2024). Further studies using rodent

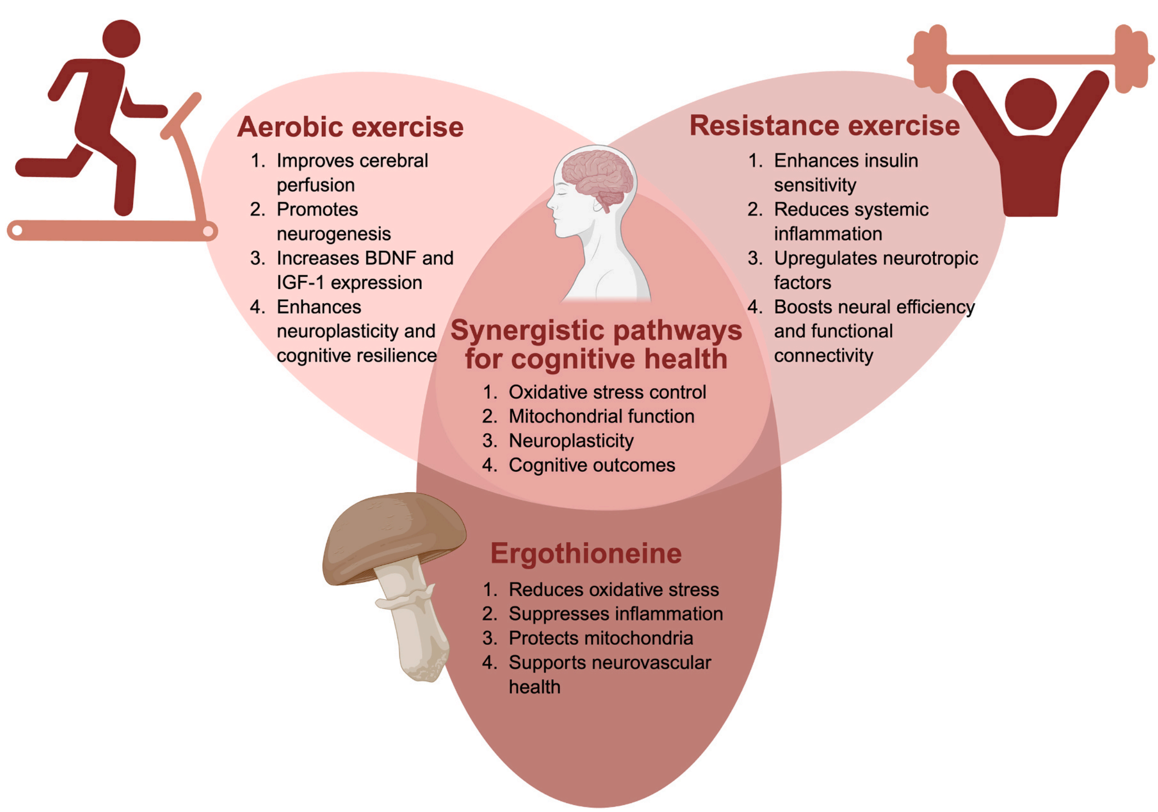

Fig. 1. Conceptual model illustrating how aerobic exercise, resistance training, and ergothioneine supplements may each benefit cognitive function through independent biological pathways.

models of ischemic stroke have demonstrated a dose-dependent neuroprotective role for ergothioneine, where ergothioneine administration reduced brain infarct volumes, protected against neuronal injury, and improved behavioural outcomes (Ong et al., 2023).

In humans, observational studies consistently report that low plasma ergothioneine is associated with cognitive impairment and brain atrophy. The Singapore-based Diet and Healthy Aging (DaHA) study found that ergothioneine levels were lower at higher age and in individuals over the age of 55 years with mild cognitive impairment and dementia (Cheah et al., 2016). In another population study in Singapore, lower plasma ergothioneine levels were also associated with increased white matter hyperintensity and a brain atrophy marker (Wu et al., 2021; Wu et al., 2021). Furthermore, individuals with lower plasma ergothioneine concentrations demonstrate poorer performance across all tested cognitive domains, including executive attention, language, visuospatial function, visuomotor speed, and memory (Wu et al., 2022).

Population-level associations between mushroom consumption (which are high in ergothioneine) and cognitive outcomes further support the role of diet in modulating ergothioneine levels. A cross-sectional study in Singapore found that older adults who consumed more than two portions of mushrooms per week had 57 % lower odds of mild cognitive impairment compared with participants who consumed mushrooms less than once per week (Feng et al., 2019). This prompted the design of a clinical trial now underway to test whether mushroom consumption can delay cognitive decline in middle-aged to young-old adults (Shan et al., 2025).

In a pilot study involving 19 participants with mild cognitive impairment, prolonged ergothioneine supplementation (25 mg taken 3 times per week for a year) showed no signs of toxicity and improved verbal learning and memory (as measured by the Rey Auditory Verbal Learning Test) compared to the placebo (Yau et al., 2024). In a larger, 16-week randomized, placebo-controlled trial involving 147 adults aged 55–79 years with subjective memory complaints using ergothioneine daily doses of 10 or 25 mg for 16 weeks, the larger dose improved subjective prospective memory and sleep initiation, with potential benefits in composite memory and cognitive flexibility (Zajac et al., 2025). While the cognitive benefits were modest and variable among subgroups, the results support further investigation in populations with lower baseline ergothioneine or greater cognitive risk.

Conceptually, ergothioneine's ability to modulate redox balance, dampen chronic inflammation, and protect mitochondria from damage supports its potential against aging-associated neurological diseases (Halliwell and Cheah, 2024; Nakamichi et al., 2022). Several reviews have underscored that ergothioneine is retained specifically in tissues experiencing inflammatory stress, and suggest it plays a homeostatic role in immune cell activation and cytokine regulation (Halliwell et al., 2023; Paul, 2022). In conclusion, the available literature indicates that ergothioneine is a chemically stable, diet-derived compound with targeted transport and broad protective effects relevant to cognitive health and systemic aging. Its accumulation in the brain, alongside observational and experimental data, positions it as a promising candidate for nutritional or therapeutic strategies aimed at mitigating age-related cognitive decline. Given that current human studies are small and exploratory, future larger-scale trials should verify plasma ergothioneine exposure, and use objective, domain-specific cognitive endpoints alongside imaging biomarkers to test mechanistic effects.

4. Exercise and cognition

Engaging in regular physical activity is regarded as a non-pharmacological preventative strategy to counteract cognitive decline during aging (Blondell et al., 2014). In older adults, regular physical activity not only preserves physical function but also supports cognitive health by influencing both the structure and function of the central nervous system (Yaffe et al., 2001). Numerous epidemiological studies suggest that higher levels of physical activity are associated with a reduced risk of cognitive decline and dementia (Best et al., 2017; Erickson et al., 2010; Iso-Markku et al., 2022). Another indicator closely related with physical activity levels, aerobic fitness, is also positively correlated with brain volume and white matter integrity, particularly in the prefrontal cortex and hippocampus; regions most susceptible to aging-related atrophy (Best et al., 2017; Erickson et al., 2010; Iso-Markku et al., 2022). Further studies provide support for the benefits of physical exercise on cognition, demonstrating that exercise participation can enhance executive function, memory, and processing speed in both cognitively healthy older adults and those with mild cognitive impairment (Casaletto et al., 2022; Dorsman et al., 2020; Sexton et al., 2016). These benefits are corroborated by neuroimaging findings that show increased hippocampal volume, functional connectivity, and cerebral blood flow following exercise interventions (Falck et al., 2019; Ludyga et al., 2020; Northey et al., 2018; Sanders et al., 2019). The cumulative body of evidence positions physical activity as a modifiable and accessible lifestyle factor capable of mitigating age-related cognitive decline (Boa Sorte Silva et al., 2024).

Among the various modalities, aerobic exercise has been the most consistently studied and associated with cognitive improvement across diverse age groups and health states (Han et al., 2025). Mechanistically, aerobic activity enhances brain function by improving cerebral perfusion, promoting neurogenesis, and increasing the expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and Insulin-like Growth Factor 1 (IGF-1), all of which contribute to neuroplasticity and cognitive resilience (Hillman et al., 2008; Valenzuela et al., 2020). Randomised controlled trials have provided direct support for these mechanisms. For example, a 12-week aerobic intervention in sedentary adults resulted in increased hippocampal cerebral blood flow, which was associated with improvements in both immediate and delayed memory performance (Chapman et al., 2013). Systematic reviews reinforce these findings, indicating that moderate-intensity aerobic activity improves cognitive domains such as working memory, reaction time, and response accuracy in healthy adults (Fernandes et al., 2018). Moreover, dose-response data of moderate-intensity aerobic training highlight that even 75 min per week may improve cognitive control, with further benefits obtained using larger training volumes (i.e., 150 and 225 min per week) (Vidoni et al., 2015). This trial further demonstrated that gains in aerobic fitness are associated with improvements in executive function and task performance (Vidoni et al., 2015).

Resistance training is another exercise modality that has been shown to induce cognitive enhancement, particularly in older adults and clinical populations. Randomised controlled trials indicate that resistance exercise can improve executive function, including attention, planning, and cognitive flexibility (Han et al., 2025). In individuals with Parkinson's disease, resistance training interventions have led to improvements in these cognitive domains, underscoring their relevance in neurorehabilitation contexts (Murray et al., 2014). In adults over the age of 50 years, a meta-analysis reported an inverted U-shaped dose–response between resistance training and global cognition (Gallardo-Gómez et al., 2022). The minimum effective dose identified in this analysis was ~80–135 mins/week for predicted clinically significant cognitive improvements while the optimal dose was ~100–170 mins/week, with the exact dose being intensity-dependent (Gallardo-Gómez et al., 2022).

The mechanisms behind these effects may involve enhanced insulin sensitivity, reduced systemic inflammation, and the upregulation of neurotrophic factors, pathways closely associated with cognitive aging (Valenzuela et al., 2020). Additionally, resistance training improves neural efficiency and functional brain connectivity, contributing to cognitive gains. Notably, studies report cognitive improvements even in the absence of significant changes in physical fitness, suggesting that the effects of resistance training may occur through neuromodulatory pathways distinct from those engaged by aerobic exercise (Ludyga et al., 2020). Importantly, the cognitive benefits of resistance training appear across multiple domains, including executive function, working memory, and general cognitive ability, although outcomes can vary depending on the specific design and duration of the intervention (Boa Sorte Silva et al., 2024; Liu-Ambrose and Donaldson, 2009). Despite this variability, findings are generally consistent in showing moderate cognitive improvements.

While concurrent aerobic–resistance training improves overall cognition, with the greatest benefits in adults aged above 65 years, whether its effects are superior to single-modality exercise remains unclear (Zhang et al., 2025). In adults aged 65–84 years with mild cognitive impairment, a randomised trial found that incorporating computerised cognitive training to aerobic–resistance exercise resulted in greater cognitive benefits than exercise alone (Montero-Odasso et al., 2023). Furthermore, across the different modalities, cognitive benefits appear domain-specific. For example, resistance training demonstrated the greatest improvement in global cognitive function, and mind-body exercises (requiring both physical movement and mental focus) are most effective for executive function, especially task-switching ability and working memory (Han et al., 2025). Thus, personalised exercise programmes, emphasising resistance training for global cognition, mind-body exercise for executive function, and aerobic exercise for memory, should be considered when designing clinical trials to improve cognition.

5. Ergothioneine and exercise performance

While we hypothesise that ergothioneine and exercise may produce additive effects on cognitive function, given their distinct mechanisms of action, ergothioneine may also enhance exercise performance and support muscle recovery, providing an additional rationale why this combination of interventions may offer unique benefits. However, it is important to note that the evidence on this topic comes from preclinical studies, underscoring the need for further clinical research. Short-term supplementation with ergothioneine extended the time to exhaustion in mice running on a treadmill (at 70 % of their maximal aerobic speed) by over 40 %, suggesting improved aerobic performance (Fovet et al., 2022). This enhancement occurred without impairing early muscle recovery pathways, which are often attenuated by conventional antioxidant supplements. These effects appear to be mediated by modulation of redox balance and inflammation. Ergothioneine supplementation led to decreased expression of metabolic stress markers (e.g., AMPKα phosphorylation) and pro-inflammatory cytokines (e.g., IL-1β and TNF-α mRNA), even after prolonged exertion (Fovet et al., 2022). Unlike some antioxidants (e.g., vitamins C and E (Merry and Ristow, 2016)) that suppress beneficial exercise-induced adaptations, ergothioneine did not impair mitochondrial biogenesis markers such as PGC1α or inhibit muscle protein synthesis. Notably, muscle protein synthesis markers were elevated post-exercise, and satellite cell markers (e.g., MyoD, Myogenin) were upregulated, indicating enhanced regenerative capacity (Fovet et al., 2022). Mechanistically, another study demonstrated that ergothioneine directly activates the enzyme MPST (3-mercaptopyruvate sulfurtransferase), thereby enhancing mitochondrial function and oxidative phosphorylation in muscle tissue. This activation contributes to improved energy metabolism and exercise performance, establishing MPST as a potential molecular target for ergothioneine's effects (Sprenger et al., 2025). Together, these findings highlight ergothioneine's dual role in enhancing endurance and promoting muscle adaptation after exercise, distinguishing it from primary antioxidants that may compromise training benefits. These preliminary data support further investigation into ergothioneine as a nutritional intervention to enhance physical performance. Additionally, it remains unclear if improved exercise performance via ergothioneine supplementation would contribute to cognitive benefits, or whether they arise from the combined effects of ergothioneine and exercise, independent of any performance enhancement.

6. Suggestions for future research

Despite growing evidence for the individual cognitive benefits of ergothioneine and exercise, their combined effects remain unexamined. To address this gap, we propose the following studies:

1. Evaluate the combined effects of ergothioneine with both aerobic and resistance training on hippocampal neurogenesis, synaptic plasticity, neuroinflammation, and behaviour in aging rodent models.
2. Determine the optimal ergothioneine dose for cognitive benefit, using cognitive performance as the primary endpoint. The only available studies in humans used ergothioneine doses of 10 and/or 25 mg; therefore, it remains unclear whether further cognitive benefits may be attained using higher doses. Future trials should also evaluate whether dietary intake of mushrooms high in ergothionine or the supplement form of ergothionine is more effective in raising ergothioneine levels and sustaining cognitive outcomes.
3. Investigate the short-term and long-term effects of combined ergothioneine and exercise on cognitive function and aging biomarkers (e.g., BDNF, proinflammatory cytokines, mitochondrial biogenesis) in healthy middle-aged and older adults.
4. Test combined ergothioneine and exercise interventions in individuals with mild cognitive impairment, vascular dementia, or early-stage Alzheimer's disease, using cognitive outcomes and neuroimaging biomarkers such as brain magnetic imaging (MRI) and Positron Emission Tomography (PET).
5. Explore how ergothioneine and exercise may act synergistically, for example through: (a) shared regulation of redox signalling and mitochondrial biogenesis via PGC-1α and MPST pathways; (b) overlapping effects on BDNF, IGF-1, and cerebral perfusion; and (c) mutually reinforcing anti-inflammatory and immunomodulatory responses.

7. Conclusion

The increasing burden of cognitive decline with age calls for synergistic, non-pharmacological strategies that address the multifactorial drivers of neurodegeneration. We propose that ergothioneine and exercise present a promising combination as they target complementary biological pathways. Ergothioneine modulates oxidative stress, inflammation, and mitochondrial function, while exercise promotes neuroplasticity, vascular perfusion, and the expression of trophic factors. Together, they could provide an additive approach to enhance brain resilience during aging, although there is a current lack of high-quality randomised controlled trials in humans to confirm these effects, thus highlighting that this area is ripe for further scientific exploration.

Ethics declarations

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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