Potential health benefits of the nutrient ergothioneine

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Abstract:

The low-molecular weight thione, ergothioneine, can accumulate at high levels in cells and tissues in humans and other animals from dietary sources, especially mushrooms. The existence of a selective transporter for ergothioneine (OCTN1) responsible for its uptake, and the avid accumulation and retention by the body suggest that ergothioneine may be important for the human body. Indeed, numerous studies have shown that low blood ergothioneine levels (compared to healthy age-matched individuals) are associated with a wide range of disorders including mild cognitive impairment, dementia, Parkinson’s disease, chronic kidney disease, frailty, and cardiometabolic disorders. This suggests that a deficiency in this compound may predispose an individual to increased risk of these age-related disorders and that supplementation may be beneficial as a prophylactic or therapeutic agent against disease. Numerous studies have demonstrated the antioxidant and other cytoprotective properties of ergothioneine. Here we summarise some of the latest findings and potential therapeutic applications of this compound.

Keywords; ergothioneine, thione, antioxidant, mushrooms, longevity nutrient
Introduction – What is ergothioneine?

- Ergothioneine is naturally occurring thiol/thione (Fig. 1) derivative of histidine

![Thione – thiol tautomerism of ergothioneine](image)

- Only produced by a few bacteria (e.g. *actinobacteria, cyanobacteria*) and most fungi
- Animals and humans take up ergothioneine from dietary sources (Fig. 2) through a specific transporter, OCTN1 (organic cation transporter novel type-1)
- Ergothioneine can accumulate in cells and tissues following oral administration and is *not* rapidly metabolised or excreted
Introduction – Dietary sources of ergothioneine

- Ergothioneine is present in low levels in a range of foods (Fig. 2)
- Most abundant in mushrooms where it can be synthesized

**Figure 2:** Levels of ergothioneine in certain foods. Assessed using LC-MS/MS (n = 3) in foods obtained locally.
Findings – Ergothioneine uptake in mice and humans

- When orally administered to mice at 35 mg/kg and 70 mg/kg for 1 to 28 days, levels in a wide range of tissues, including the brain, are significantly elevated (Fig. 3)

- Blood ergothioneine also increased in healthy human volunteers when supplemented

**Figure 3:** Uptake of ergothioneine in whole blood, liver and brain following oral administration.

**Figure 4:** Increasing in whole blood ergothioneine (subtracting baseline) following oral supplementation in healthy human subjects for 7 days (5 or 25 mg/day) and monitored for a further 28 days.

\( P < 0.0001 \) control vs. high dose: one way ANOVA
Findings – What does ergothioneine do?

- The avid uptake and retention suggests an important physiological function
- A range of *in vitro* and *in vivo* studies indicate that ergothioneine is cytoprotective
- Amongst other things it has been shown to (Fig. 5):
  - Scavenge free radicals such as *OH, HOCl and ONOO⁻*
  - Chelate divalent metal ions e.g. Cu²⁺ & Fe²⁺ forming redox-inactive complexes
  - Modulate inflammation
  - Upregulation of endogenous defences e.g. Nrf2 & HSP70

*Figure 5: Possible physiological roles of ergothioneine.*
Findings – Blood ergothioneine levels with age and disease

- Blood ergothioneine levels were found to decline with advancing age (>60 y/o)
- We also observed significant lower blood levels of ergothioneine in subjects with mild cognitive impairment (Fig. 6) and Parkinson’s disease (not shown)

![Average plasma ergothioneine levels between age groups](image)

**Figure 6:** Mean plasma levels decline with age beyond 60 y/o (left; **P < 0.01 vs < 65 y/o). Blood ergothioneine levels in MCI subjects are significantly lower than age-matched healthy individuals (right; **P < 0.01 vs normal).

- Other studies have shown declining blood ergothioneine levels were significantly correlated to risk of cardiometabolic diseases, chronic kidney disease and frailty
Findings – Therapeutic potential of ergothioneine

- A potential side effect of the common chemotherapeutic drug, doxorubicin, is cardiotoxicity, potentially leading to heart failure
- Ergothioneine protected cardiac function (systolic/diastolic function) in a mouse model of doxorubicin-induced cardiotoxicity/cardiomyopathy (Fig. 7)

Figure 7: Ergothioneine protects cardiac ejection fraction (systolic function; left) and myocardial performance index (diastolic function; right) against doxorubicin cardiomyopathy. Ergothioneine administered orally at 70 mg/kg for 7 days prior to doxorubicin.
Findings – Therapeutic potential of ergothioneine

- Ergothioneine has been shown to be protective in transgenic *Drosophila* models of Parkinson’s disease (preserved climbing function and dopaminergic neurons; Fig. 8)

**Figure 8:** Ergothioneine (1mM; administered in food and media) preserved climbing function (left) and dopaminergic neuron counts (right) in Parkin null flies.
Conclusions:
Ergothioneine can accumulate in the body at high levels and may play important physiological roles in human health. Blood levels of ergothioneine are seen to decline with age and onset of age-related diseases. As such, ergothioneine has been suggested to be longevity nutrient, whereby supplementation may reduce the risk of, or prove to be therapeutic against age-related disorders. Controlled clinical studies are needed to further evaluate the therapeutic potential of ergothioneine.

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