

## Press release

**+++ UNDER EMBARGO UNTIL 20/01/2025, 5PM (CET) +++**

### Molecular mechanism of Ergothioneine decoded

## Prolonged Health with a Compound Found in Mushrooms?

Dortmund/ Belgrade/ Cambridge, January 20, 2025. Many people wish not only to live as long as possible, but above all to do so without any health restrictions. However, with increasing age, the risk of age-related diseases such as Alzheimer's or sarcopenia (loss of muscle mass and muscle strength with age) also increases. Research into ageing is therefore increasingly focussing on the time during a person's lifetime when they are healthy. Under the leadership of the Leibniz-Institut für Analytische Wissenschaften (ISAS), a team of researchers from the University of Belgrade (Serbia), the University of Cambridge (UK) and Heidelberg University has now shown that the natural substance ergothioneine improves the health span of ageing animals. Other collaborators are researchers in Berlin, Munich, France, Italy and Spain. The international team describes their results and the underlying molecular mechanism in the scientific journal *Cell Metabolism*.

Ergothioneine is a natural compound found in certain fungi such as oyster or shiitake mushrooms as well as fermented foods. The amino acid is often marketed as a dietary supplement or as an ingredient in cosmetics with 'anti-ageing' effects. Even though there are indications of the health-promoting and cell-protective properties of ergothioneine, the underlying mechanism of action was previously unknown. "Our analyses now finally provide clarity about the mechanism and also show that ergothioneine has promising therapeutic potential for the prevention of age-related diseases", reports Dr habil. Miloš Filipović, corresponding author and head of the ERC Sulfaging research group at ISAS.

### Positive effects on mobility, stress resistance and endurance

For the publication, the researchers studied several animals, including the model organism *Caenorhabditis elegans* (a nematode). The group at ISAS observed that treatment with ergothioneine from young adulthood not only extended the lifespan of the worms, but also increased their mobility as well as their resistance to stress and reduced age-related biomarkers. "As the animals got older, the contrast with the control group became more significant. In addition, we did not observe any undesirable side effects – nor did other studies," says Dr Dunja Petrovic, whose doctoral project at ISAS led to the publication.

The project partners at the University of Belgrade were also able to observe these positive effects in mammals. For three weeks, they treated six nine-month-old rats with a daily

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dose of about 10 milligrams of ergothioneine – roughly the same amount contained in 4.5 grams of dried oyster mushrooms. Compared to the control group, the rats' endurance did not only improve, but muscle mass, vascularisation (formation of new small blood vessels) of the muscle tissue and the number of muscle stem cells also increased. All of which could make the substance interesting in connection with the prevention of sarcopenia, for example.



Petrovic et al. show that the naturally occurring compound ergothioneine extends lifespan and healthspan of aged animals by boosting  $\text{NAD}^+$  via persulfidation of cytosolic glycerol-3-phosphate dehydrogenase. The illustration, inspired by Asterix comics, illustrates a “magic” potion made from ergothioneine-rich mushrooms. Yellow fumes hint at hydrogen sulfide, produced from ergothioneine by cystathionine gamma-lyase, driving protein persulfidation and metabolic remodeling to rejuvenate muscles and enhance performance. Illustration: Maud Vignane.

### **Ergothioneine provides more protective hydrogen sulfide**

The researchers investigated the molecular mechanisms behind their observations using mass spectrometry analyses. Based on human and mouse cell cultures, they were able to show that ergothioneine acts as an alternative substrate for the enzyme cystathionine- $\gamma$ -lyase (CSE). This enzyme plays a central role in the production of the gaseous signalling molecule hydrogen sulfide ( $\text{H}_2\text{S}$ ), which protects cells from oxidative stress through the process of persulfidation. Reduced persulfidation is associated with aging, cardiovascular diseases and neurodegenerative diseases. Previously in 2019, a team led by Filipović already showed that persulfidation decreases with age, but can be positively influenced by reducing food intake, for example ([see Zivanovic et al., 2019](#)).

The new research results complement the previous findings: Ergothioneine stimulates persulfidation, especially that of a specific enzyme, glycerol-3-phosphate dehydrogenase (GPDH). This increased activity of GPDH in turn boosts the formation of  $\text{NAD}^+$  – a known coenzyme that has a positive effect on the lifespan. “The human body is not able to produce ergothioneine itself. However, such a specific utilisation mechanism suggests that it is very important for us,” summarises Petrovic. Researchers in Heidelberg, Cambridge and at ISAS were able to independently confirm the CSE-dependent mechanism of ergothioneine action.

### **Performance-enhancing effects: Study with humans planned**

Due to the promising results, the researchers also tested the effects of a five-day treatment with ergothioneine on a group of young rats. A daily dose of about 10 milligrams of the substance led to a significant increase in endurance, as well as a significantly increased  $\text{NAD}^+$  level in the blood serum. “This indicates that ergothioneine influences the metabolism in a similar way to performance-enhancing agents,” says Filipović. He is planning to do a study with healthy human subjects to investigate this very potential.

## Original publication

<https://doi.org/10.1016/j.cmet.2024.12.008> (The link will be activated on January 20, 5PM (CET) once the Embargo is lifted. A copy of the article can be requested in advance under observance of the embargo period via [presse@isas.de](mailto:presse@isas.de))



Left: Dr habil. Miloš Filipović heads the research group ERC-Sulfaging at ISAS. Picture: ISAS.

Right: Dr Dunja Petrovic was a PhD student at ISAS from 2020 to 2024. The research work was carried out in the context of her doctorate. Picture: ISAS / Hannes Woidich

## About ERC-Sulfaging

The research group ERC-Sulfaging investigates the connection between ageing processes and so-called gasotransmitter signalling. The researchers focus on the signal transmission in cells via hydrogen sulfide. The researchers want to decode the exact mechanisms of hydrogen sulfide actions, for example with the help of worms. Their work on metabolic biochemistry provides important insights, for example for a better diagnosis and treatment of age-related diseases in the future. For this purpose, the European Research Council (ERC) has awarded Dr habil. Miloš Filipović the Consolidator Grant.



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