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Research Article

A Mushroom-Derived Compound That Could Change Your Life: Ergothioneine

Mike Amaranthus*

Associate Adjunct Professor Oregon State University and President of Myco Analytics LLC in Grants Pass, Oregon

***Corresponding author**: Mike Amaranthus, Associate Adjunct Professor Oregon State University and President of Myco Analytics LLC in Grants Pass, Oregon

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Humans through time have been captivated and, at times, intimidated by the enigmatic and mysterious lifeforms of mushrooms. This sense of awe extends to the equally peculiar and mysterious chemical components that mushrooms harbor. Within mushrooms, a plethora of compounds exist, including beta-glucans, melanin, vitamins, minerals, polyphenols, triterpenoids, glutathione, and ergothioneine. Many of these compounds boast documented health benefits, and their concentrations can be scarce in other foods. Do you require an organic chemistry degree to unravel the science behind these compounds and understand their benefits? Certainly not. However, one compound that occurs in wild and culinary mushrooms should demand your complete attention.

Its name is ergothioneine.

Why? Because ergothioneine may just be a compound that will help you live a longer and better life. Ergothioneine is not produced by humans or plants and is only made by fungi. It has recently gained attention as a potent antioxidant and anti-inflammatory, and as such, it has been labeled as a potential “longevity vitamin” and “powerhouse nutrient” [1]. In this paper I will present to you our current understanding of the potential health benefits of this amazing compound.

Figure 1: Boletus edulis (king bolete) is an exceptional source of ergothioneine.

Ergothioneine is abundantly concentrated in specific wild and cultivated mushroom species and their fungal mycelium. Which fungi possess this compound? What are the specific benefits associated with it? How well-documented is the research on ergothioneine? How does the cultivation of food and the presence of mycorrhizal fungi in soil affect ergothioneine levels? This paper aims to provide essential information to address these questions.

What is Ergothioneine?

Ergothioneine might be one of the most crucial, yet lesser-known compounds linked to human health. ergothioneine an antioxidant and anti-inflammatory present throughout the body, is obtainable solely through food, with mushrooms being the most concentrated source by far. Despite its minimal presence in other foods like grains, vegetables, and meat, its biosynthesis has only been observed in specific fungi [2].

The discovery of ergothioneine dates back over a century, but its role in human health has gained significant recognition only in the last two decades. Initially discovered in 1909 in the Ergot fungus (Claviceps purpurea), ergothioneine has proven to be an effective antioxidant, attributed in part to the stability of its "thione" form of sulfur, making it resistant to the oxidative process. As an antioxidant, ergothioneine scavenges oxygen radicals present in the cells of your body [3-5]. Notably, it is one of the few antioxidants concentrated in mitochondria. Cells lacking ergothioneine have shown increased susceptibility to oxidative stress, leading to heightened mitochondrial DNA damage (Lu et al., 2016). Considering the role of mitochondrial deterioration in age-related illnesses and neurodegeneration, the content of ergothioneine may be crucial for the body to resist oxidative stress resulting from aging, poor diets, and lifestyles.

Biologically, humans produce a specific transport protein for ergothioneine (OCTN1), rendering it highly bioavailable and readily retained. This unique presence of transport proteins for this compound underscores the potential importance of ergothioneine in human health [6].

Brain Health

Numerous studies suggest a connection between ergothioneine levels and cognition. However, can supplementing ergothioneine in your diet slow mental decline or age-related diseases such as dementia or Alzheimer's? Let's delve into recent research.

Blood level of ergothioneine may serve as an indicator of brain health. Studies have demonstrated low blood levels of ergothioneine in patients with mild cognitive impairment and dementia [7-9]. Dementia patients with the lowest ergothioneine levels exhibited faster rates of brain volume loss and cognitive decline. While this might not establish an ergothioneine cause-and-effect relationship (e.g., lower ergothioneine levels could be a consequence of brain cell loss), it underscores the potential significance of this compound.

Here's another reason to enjoy a healthy assortment of wild and cultivated edible mushrooms - mushroom consumption is considered an approximate surrogate for ergothioneine intake [10]. In a study of 2840 individuals aged 60 or older, those with the highest mushroom consumption in the U.S. demonstrated improved cognitive performance compared to those with lower intake rates [11]. A more specific study tied to blood levels of ergothioneine evaluated 470 individuals over the age of 50 for cognitive performance, revealing improved memory and executive function in individuals with higher plasma blood levels of ergothioneine [12].

Additionally, a double-blind, parallel-group, placebo-controlled trial (considered the "gold standard" in clinical research) was conducted on 50- to 80-year-old Japanese individuals diagnosed with mild cognitive impairment to examine the efficacy of oral administration (3 gms/day mycelial powder) of Lion's Mane (*Hericium erinaceus*) [13] The Lion's Mane group showed significantly increased scores on the cognitive function scale compared with the placebo group at weeks 8, 12, and 16 of the trial. Although ergothioneine plasma levels were not specifically measured in the study, Lion's Mane mycelium contains high levels of ergothioneine at 370 mg/kg dry weight [14]. Similarly, a cross-sectional study in Singapore by [14] found an association between lower levels of mushroom consumption and mild cognitive impairment.

Figure 2: Paul Stamets with Lion's Mane (left) the author with Hen of the Woods, *Griffola frondusa* (right). Both mushrooms contain significant levels of ergothioneine and have documented health benefits.

In a noteworthy study published in 2017, researchers found that the consumption of mushrooms significantly decreased the incidence of dementia among elderly Japanese individuals [15]. The study involved 13,230 participants aged 65 years or older, residing in Ohsaki city in northeastern Japan. Over a span of 5.7 years, the incidence of dementia in the non-mushroom eating population was 8.7%. However, for those consuming mushrooms 1-2 times a week, the dementia incidence dropped to 0.95%, reflecting a nearly 10-fold reduction. Participants who consumed mushrooms 3 or more times a week exhibited an even lower incidence of dementia at 0.81%. While the data doesn't establish a direct cause-and-effect relationship, it strongly suggests that regular mushroom consumption is correlated with a reduced incidence of dementia, even when adjusted for potential confounding factors.

While these studies are promising, more large-scale clinical trials are needed to assess the potential of increasing ergothioneine intake to improve cognitive health and address brain diseases. Clinical trials conducted in diverse countries and considering different dietary patterns are imperative to ascertain whether elevating ergothioneine levels can effectively slow or prevent cognitive decline. Mushrooms containing ergothioneine are recognized for harboring a variety of other beneficial bioactive compounds aside from ergothioneine, which could also contribute to improved cognitive performance.

Figure 3: Enokitake mushrooms (*Flamulina filiformis*) contain high levels of ergothioneine.

Protection from cardiovascular disease and reduced mortality

Ergothioneine may serve as a protective factor for the heart. Recent research conducted by [16] suggests a significant association between higher ergothioneine levels and reduced mortality, as well as a lower risk of cardiovascular disease. In this study, 3236 individuals without pre-existing cardiovascular disease were examined, with measurements taken for 112 plasma metabolites (small molecules resulting from metabolism). Over a median follow-up time of 21.4 years, 603 participants developed cardiovascular disease, 362 developed diabetes, and 843 participants passed away. Notably, ergothioneine emerged as the plasma metabolite most strongly linked to a decreased risk of coronary disease ($p=0.01$), cardiovascular mortality ($p=0.002$), and overall mortality ($p=0.0004$). The researchers identified higher ergothioneine as an independent marker associated with lower cardiovascular disease and mortality. While further research is essential to determine if a specific dietary intake of ergothioneine-containing foods can effectively protect the heart, the preliminary results from this large-scale study are encouraging, suggesting that foods rich in ergothioneine could be a valuable tool for promoting heart health.

Figure 4. Should certain mushrooms like these king boletes (right, *Boletus edulis*) be included with foods considered to be heart healthy?

Reduced risk of cancer

The relationship between higher mushroom intake, elevated ergothioneine levels, and a reduced risk of cancer is a topic undergoing rapid evolution in our understanding. A recent comprehensive systematic review and meta-analysis conducted by Ba et al. in 2021 [17], focusing on epidemiological studies, revealed that increased mushroom consumption was associated with a lower incidence of cancer in Asian cultures. However, this correlation might not extend to Western cultures where the predominant consumption of the common button mushroom (*Agaricus bisporus*) is lower in ergothioneine. In Asian cultures, where mushrooms such as Enokitake, Shiitake (*Lentinula edodes*), Hen of the Woods, and Oyster Mushrooms (*Pluerotus ostreatus*), rich in ergothioneine, are more commonly consumed, the observed association may be more pronounced.

Specifically, regarding breast cancer, epidemiological studies, including those by [18-21] have suggested that higher mushroom intake may be linked to a reduced risk of breast cancer. For example, [20] studied 362 Korean women and found indications of a lowered risk of breast cancer associated with a diet high in mushrooms. However, these findings require further validation through large-scale studies encompassing diverse diets and countries.

Moreover, a study published in the International Journal of Cancer by [22] in 2019 associated regular mushroom consumption with a lower risk of prostate cancer. Involving over 36,000 men aged 40-79, the study revealed a significant reduction in prostate cancer incidence with regular mushroom consumption, irrespective of other dietary factors. Although the data does not establish a cause-and-effect relationship, the authors suggest that the high levels of ergothioneine in mushrooms could contribute to the antioxidant and cancer-preventive properties of the compound.

Studies conducted in Korea and Japan have also indicated that increased mushroom intake may reduce the incidence of gastric cancers [23-24]. While ergothioneine levels were not specifically measured in these studies, the correlation between ergothioneine levels and mushroom consumption has been established. It is crucial again to note that Asian cultures often incorporate mushrooms with higher ergothioneine content, such as Shiitake, Enokitake, Hen of the Woods, and Oyster Mushrooms, into their diets. The need for large-scale replication of these studies in Western cultures is evident to further validate these associations.

Figure 5: Shiitake (left),) and Oyster Mushrooms (right) are important sources of ergothioneine.

A recent study [25] highlights the potential of ergothioneine to mitigate the side effects associated with cisplatin chemotherapy treatment. Cisplatin, a potent antitumor agent widely employed in the chemotherapy of various solid malignancies, is notorious for severe side effects such as nausea, vomiting, cognition loss, neurotoxicity, and neuropathy. In a rat-based investigation, ergothioneine demonstrated a protective effect against cisplatin-induced neuropathy and improved cognition, potentially by inhibiting oxidative stress and restoring nervous system activity.

Safety

Is the ingestion of ergothioneine supplements considered safe? A study conducted by the Panel on Dietetic Products for the European Food Safety Authority in 2017 concluded that ergothioneine is safe for children above 3 years of age and the general adult population, including pregnant and breastfeeding women. The panel assessed doses of 3.39 mg/kg for small children and 1.31 mg/kg for adults. Most ergothioneine supplement brands recommend daily intake levels of 5-10 mg. Both animal and human studies have shown no toxicity or adverse effects even at high ergothioneine doses. The U.S. Food and Drug Administration has also generally recognized ergothioneine as safe. Consequently, the augmentation of low ergothioneine levels through supplementation appears to have no apparent safety concerns.

Dietary Sources

How much ergothioneine is present in foods? Although ergothioneine was discovered in 1909, comprehensive information on its levels in foods emerged almost a century later. Utilizing advanced methodologies [26-27], it was observed that most mushrooms contained significantly higher levels of ergothioneine compared to grains, vegetables, and meat. An exception was the common commercial button mushroom in Western diets, *Agaricus bisporus*, which exhibited lower ergothioneine levels compared to other tested mushrooms (Table 1)

Source	Ergothioneine Content
Mushroom Fruiting Body (ergothioneine= mg/kg wet wt.) [26,28]	
Grifola frondusa (Hen of the Woods)	30.00
Lentinula edodes (Shiitake)	284.00
Boletus edulis (King Bolete)	528.14
Pleurotus ostreatus (Oyster Mushroom)	118.91
Flammulina velutipes (Enokitake)	298.00
Agaricus bisporus[1] (white cultivated button mushroom)	0.46
Mushroom Mycelia (ergothioneine= mg/kg dry wt.) [27]	
Armillaria mellea (Honey mushroom)	219.60
Coprinus comatus (Shaggy mane)	399.00
Cordyceps sinensis (Caterpillar fungus)	142.00
Hericium erinaceus (Lion's Mane)	376.20
Coriolis versicolor (Turkey Tail)	13.00
Ganoderma lucidum (Reishi)	16.50
Meat and Seafood (ergothioneine= mg/kg wet wt.) [26]	
Pork (loin fillet)	1.68
Beef (loin steak)	1.33
Lamb (loin fillet)	1.20
Chicken (breast)	1.15
Salami (from pork)	0.51
Trout	0.07
Grains and Vegetables (ergothioneine= mg/kg wet wt.) [26]	
Whole grain wheat bread	0.53
Whole grain rye bread	0.47
Brown rice	0.04
Garlic	3.11
Broccoli	0.24

Onion	0.23
Spinach	0.11
Celery	0.08
Beverage (ergothioneine= mg/l.) [26]	
Beer	0.02

Table 1. Ergothioneine content in various mushrooms, meats, grains, vegetables, and beverages**.**

Figure 6: The common cultivated button mushroom is low in ergothioneine compared to many other wild and cultivated mushrooms.

There may be variations in ergothioneine content in specific foods based on factors such as variety and cultivation methods. However, the three studies used to compile Table 1 underscore significant differences between mushrooms and grains, vegetables, and meat, as well as variations among mushroom species. Key insights from these studies include:

* Fruiting bodies of gourmet wild and cultivated mushrooms, such as Hen of the Woods, Shiitake, King Boletes, Enokitake, and Oyster Mushroom species, exhibited ergothioneine levels 500x to 1000x higher than those found in grains and vegetables.

* In comparison to meat, the ergothioneine content in the fruiting bodies of gourmet wild and cultivated mushrooms was 100x to 300x greater.

* Fruiting bodies of gourmet wild and cultivated mushrooms, including Hen of the Woods, Shiitake, King Boletes, Enokitake, and Oyster Mushroom species, contained ergothioneine levels 50x to 1000x higher than the common cultivated button mushrooms.

* Ergothioneine intake can be substantial from mushroom mycelium, particularly in species such as Lion's Mane, Reishi, and Turkey Tail, commonly available in dry form in tea and capsules.

* Conversely, beer is identified as a very poor source of ergothioneine.

Heathy soil = healthy people: the ergothioneine bridge

While not everyone includes mushrooms in their diet, humans naturally acquire some ergothioneine in their systems through other sources. As shown in Table 1, grains and vegetables contain only small to modest amounts of ergothioneine. Fungi, particularly mycorrhizal fungi, play a pivotal role as the primary contributors to ergothioneine entering the food chain [26]. It seems that mycorrhizal fungi, along with other soil fungi, transfer or produce ergothioneine in plants through their symbiotic or close relationships with the roots of grain and vegetable plants [10,29]. This process underscores the interconnected nature of ecosystems, where fungi act as conduits for essential compounds, enriching the nutritional profile of plants and subsequently contributing to the overall dietary intake of ergothioneine in humans.

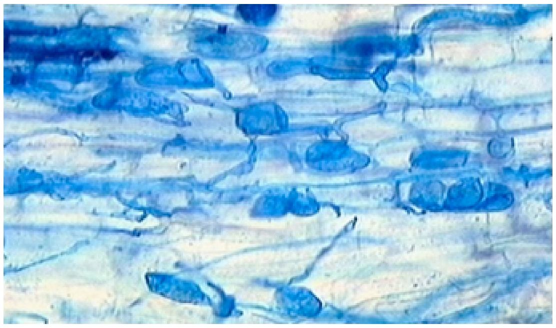

Figure 7: Arbuscular mycorrhiza. The blue colored tissues are mycorrhizal fungal structures in the root.

Mycorrhizal fungi are essential for a healthy soil. These unique fungi engage in a mutualistic relationship with the vast majority of plant root systems. In this symbiotic association, the portions of the roots that accommodate the fungi are referred to as mycorrhizae, a term derived from "fungus roots." Arbuscular mycorrhizal fungi, previously known as endomycorrhizal fungi, establish a mutually beneficial mycorrhizal relationship with a wide range of essential crop species [30]. Within this partnership, the host crops generate photosynthates—products of photosynthesis—to support the activities of the arbuscular fungi that colonize their roots. In reciprocation, these fungi extend outward from the roots, extracting nutrients and water from the soil and making them available for use by the host crops. This collaborative interaction enhances the nutrient and water uptake efficiency of the plants, contributing to the overall health and vitality of both the fungi and the associated plant species.

The vast mycorrhizal networks associated with plants, play a crucial role in enhancing plant health and may contribute significantly to the presence of ergothioneine in the human diet. It transports essential nutrients and water elements back to the root. Recent research by [29] indicates that mycorrhizal inoculation and higher level of mycorrhizal colonization significantly increased the level of ergothioneine in asparagus, black beans, oats, and wheat. The colonization of mycorrhizal fungi increased the ergothioneine levels in these crops several fold in most cases. This strongly suggests that agricultural practices that promote healthy populations of mycorrhizal fungi can improve the nutritional quality of plants.

The profound impact of mycorrhizal relationships on plant health is well-documented [31]. It's conceivable that this close symbiotic alliance between fungi and plants is also a key mechanism for the incorporation of ergothioneine into the plant system. The intricate web of interactions between fungi and plants not only benefits plant health but also represents a crucial pathway for the introduction of ergothioneine into the human diet, highlighting the interconnectedness of ecosystems and their impact on human health.

Suppressing the symbiosis

Regrettably, many conventional agricultural methods have detrimental effects on mycorrhizal fungal activity in the soil and roots [10,32]. Practices such as the use of certain pesticides, chemical fertilizers, tillage, compaction, organic matter loss, and erosion can all negatively impact beneficial mycorrhizal fungi. Extensive laboratory and field testing has demonstrated that most intensively managed agricultural lands often lack sufficient populations of mycorrhizal fungi [33,34] The absence of the binding power of mycorrhizal filaments not only leads to the deterioration of soil structure but also compromises a substantial amount of soil fungi protected within soil aggregates. These fungi may not only contribute to increasing the ergothioneine content of food but also play a critical role in the health and function of the entire soil ecosystem [35].

Certain conventional agricultural practices, such as soil tillage, have been identified as particularly disruptive to beneficial mycorrhizal fungal populations [36-38]. On the contrary, no-till farming practices have shown promise in increasing mycorrhizal fungal populations compared to conventional tillage methods [39]. Additionally, no-till practices have been found to boost the populations of other soil fungi compared to conventional tillage [40]. These findings underscore the potential benefits of adopting more sustainable agricultural practices that support mycorrhizal fungi, not only for the enhancement of food quality but also for the overall health and resilience of soil ecosystems.

Figure 8: Tractor tills agricultural soil before planting and adversely impacts mycorrhizal soil fungi.

Recent research in 2021, conducted by Beelman and colleagues, reveals a significant correlation between no-till farming practices and increased ergothioneine content in three prominent food crops—corn, soybeans, and oats. Comparing the results to soil tillage with a plow, the study found that ergothioneine levels in these crops increased by a substantial 25-30% when utilizing no-till methods [10]. This underscores the positive impact of adopting no-till practices on the ergothioneine content of key food crops.

The common agricultural practice of ploughing before planting, often executed with a plow, is known for its efficacy in eliminating existing vegetation like sod and weeds by inverting the soil. However, this practice comes with drawbacks, as it is highly detrimental to mycorrhizal fungi and disrupts soil aggregates that harbor fungal populations [35]. Additionally, ploughing can expose soils to issues such as loss of soil organic matter, compaction, and erosion. The research findings highlight the potential dual benefits of no-till farming—enhancing ergothioneine levels in crops while mitigating the adverse effects on mycorrhizal fungi and soil structure and erosion associated with traditional ploughing methods [41].

Figure 9: No till farming practices, like this soybean field, minimize soil disturbance and encourages mycorrhizal soil fungi.

No-till or minimum till methods have become increasingly available for many agricultural crops. These practices, along with others such as incorporating cover crops and organic matter inputs that foster mycorrhizal populations, hold promise as tools to boost ergothioneine levels throughout the food chain. Regenerative soil practices, characterized by maximizing organic matter inputs, maintaining plant cover, and minimizing soil disturbance and chemical inputs, could play a crucial role in fostering healthy and abundant populations of soil fungi, ultimately influencing ergothioneine levels [42].

Increasing Ergothioneine Intake

The amount of ergothioneine we ingest, and its variation based on our diet is still an area of ongoing research. Ramirez-[43] studied ergothioneine uptake in six countries (four European countries, Japan, and the USA), and [6] converted these data to average daily values. For the average person, the daily uptake was lowest in the USA at 1.1 mg/day, followed by Finland (1.3 mg/day), France (2.2 mg/day), Ireland (3.6 mg/day), Italy (4.6 mg/day), and Japan (6.6 mg/day).

Data from this study revealed that lower rates of ergothioneine uptake were associated with higher rates of Parkinson's and Alzheimer's diseases, as well as lower life expectancies. Utilizing World Health Organization data from 2010, [44] found a positive correlation between ergothioneine consumption and longevity, as well as a negative correlation with mortality from neurological diseases. These findings underscore the potential impact of ergothioneine intake on health outcomes and suggest that agricultural practices influencing ergothioneine levels may have broader implications for public health.

Japan's high ergothioneine consumption is likely linked to the popularity of Shiitake and Enokitake mushrooms in Japanese society. Shiitake and Enokitake mushrooms boast ergothioneine levels that are hundreds of times higher than those found in button mushrooms, grains, vegetables, or meat. Life expectancy in Japan is notably high, reaching 85 years, second only to Hong Kong globally, and is believed to be influenced by the quality of the Japanese diet [45]. Moreover, Japan reports a low death rate associated with Parkinson's and Alzheimer's diseases.

The Japanese diet, characterized by a higher mushroom consumption, particularly Shiitake and Enokitake varieties, stands out. Japanese mushroom consumption, at 15 grams per day, is three times higher than that of American diets, which average 5 grams per day [45]. It's worth noting that a significant portion of American mushroom consumption is attributed to the button mushroom, which contains comparatively lower amounts of ergothioneine compared to Shiitake and Enokitake mushrooms. These dietary distinctions may contribute to the variations in ergothioneine intake between the two populations and potentially influence health outcomes, providing valuable insights into the potential health benefits associated with mushroom consumption.

Mushrooms are rich in various bioactive compounds, including beta-glucans, triterpenes, glutathione, minerals, and vitamin D. Among these, ergothioneine stands out as a compound that has been demonstrated to correlate with a reduction in chronic diseases associated with aging and an increase in life expectancy. Several strategies can be employed to boost ergothioneine intake.

1. Agricultural Practices: Ergothioneine levels are typically minimal to modest in grains, vegetables, and meats. However, adopting practices such as no-till, regenerative agriculture and mycorrhizal inoculation has shown promise in increasing ergothioneine levels in the existing food supply.

2. Mushroom Consumption: Consuming gourmet wild and cultivated mushrooms, such as Hen of the Woods, Shiitake, King Boletes, Enokitake, and Oyster Mushroom species, is an effective way to significantly enhance ergothioneine intake.

3. Supplements: Another approach is to increase ergothioneine intake through capsules or powder made from dried fruiting bodies or mycelium-based products from ergothioneine-rich fungal species. This provides a convenient option for individuals to supplement their diet with this beneficial compound.

By incorporating these strategies, individuals can actively work towards increasing their ergothioneine intake, potentially reaping the health benefits associated with this unique compound.

Figure 10: Baked stuffed Shiitake caps a rich source of ergothioneine.

Ergothioneine levels are typically low in the commonly consumed commercial button mushroom species prevalent in Western diets, such as *Agaricus bisporus*. However, an increasing variety of mushrooms, including King Boletes, Shiitake, Enokitake, Oyster Mushrooms, Hen of the Woods, and Lion's Mane, are becoming more readily available in grocery stores and farmers' markets. Alternatively, you can explore nature by taking a walk in the woods and foraging for your own wild, edible gourmet mushrooms. Delicious meals and ergothioneine rich!

Final thoughts

Consuming mushrooms with elevated levels of ergothioneine should not be viewed as a panacea for addressing all health concerns. While numerous studies have demonstrated a noteworthy correlation between mushroom consumption or ergothioneine levels and health and longevity, it's crucial to recognize that correlation does not establish causation. Additional research is imperative, particularly in understanding the mechanisms of efficacy. Moreover, investigations involving diverse human and mushroom populations from Western cultures and diets are also essential to draw more conclusive insights.

Figure 11: Hiking and collecting wild mushrooms like these ergothioneine rich boletes are a healthy pursuit.

Achieving health and longevity encompasses more than adopting a singular approach. Regular exercise, maintaining a healthy body weight, undergoing medical screening, and engaging in mental, social, and spiritual activities are all integral components of a long and healthy life. Taking an integrated and holistic approach may also involve incorporating the consumption of unique and enigmatic mushroom lifeforms containing ergothioneine.

For those not particularly inclined towards eating mushrooms, an alternative is to consume foods produced through regenerative farming methods that support robust populations of soil fungi, thereby increasing ergothioneine intake. Ongoing studies worldwide are exploring the correlation between agricultural practices, ergothioneine levels and human health.

Embarking on a "walk in the woods" to discover your own wild, edible, and delightful mushrooms not only contributes to exercise but also addresses aspects of body weight, mental well-being, social engagement, and spiritual fulfillment. The ergothioneine and other compounds present in these edible mushrooms may indeed play a role in promoting health and longevity, potentially making a significant difference in overall well-being.

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