

Micronutrients and Bioactive Compounds in Mushrooms

A Recipe for Healthy Aging?

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Mushrooms have been used both as food and as medicine in many cultures, and their popularity as both is growing in the United States. We have shown that they are inherently, or can easily be made to be, excellent dietary sources of 4 important bioactive compounds that are all known to decrease in humans as they age. These are the micronutrients selenium and vitamin D₂ and antioxidants glutathione and ergothioneine (Ergo). All of these except for Ergo can be found in significant amounts in other foods; hence, it will be the primary focus of this review. Because Ergo is made in nature primarily by nonyeast fungi, mushrooms are by far the best human dietary source. Humans produce a highly specific transport protein for Ergo that makes it highly bioavailable and avidly retained, leading many to speculate about its potential importance to human health because such specific transporters are rarely present for nonnutrient bioactive compounds. Ergo is found in small amounts throughout the food chain presumably owing to fungi in the soil passing it on to plants and then animals that eat them. We have preliminary evidence that Ergo levels in the American food supply might be compromised because of

reduced fungal populations in agricultural soils caused by some cultivation practices. Relationships observed between estimated Ergo consumption and average longevity and reductions in chronic neurodegenerative diseases across different countries supports additional interest in Ergo as a dietary chemopreventive agent for aging-related diseases. *Nutr Today*. 2019;54(1):16–22

Mushrooms have been consumed as food and sometimes used as medicine for millennia. The production of cultivated, edible mushrooms worldwide has increased more than 30-fold since 1978, whereas the population has only increased by about 1.7-fold during the same period.¹ Worldwide per capita consumption has increased 4.7-fold since 1978. Most of these increases have occurred in China, but mushroom consumption in the United States is growing as well. Figure 1 presents recent data on world production by genera. The common button mushroom (*Agaricus bisporus*) ranks fourth behind shiitake, oyster, and wood ear but is the primary mushroom produced and consumed in the United States (Figure 2).² However, brown buttons are gaining in popularity, either as criminis (harvested with caps closed, as seen in Figure 2) or portabellas (harvested as large open caps, Figure 2). All of the nonbutton mushrooms consumed in the United States are considered “specialty mushrooms” and comprise only about 3% of the production. Some noncultivated (wild) mushrooms, such as morels and porcinis, are also consumed in small amounts.

Healthy aging is a primary goal of many people today. There is a growing awareness both among gerontologists and lay consumers that diet plays an important role in healthy aging. Consuming more fruits and vegetables is a primary emphasis of a healthy diet. Although mushrooms are normally considered to be a vegetable, they actually are neither a plant nor animal but belong to the fungal kingdom. Mushrooms are consumed by most Americans for their culinary properties and by some as a healthy food because they are low in fat, calories, and sodium and do not contain cholesterol, sugars, or gluten. Recently, it has been recognized that mushrooms are a valuable source of

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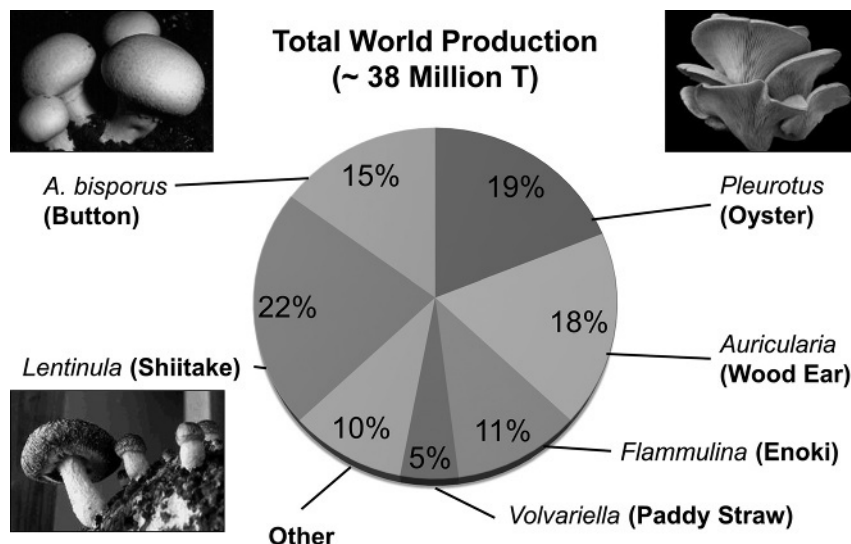


FIGURE 1. World production statistics for the top mushroom species. Adapted from Roysse et al (2017).¹

protein, fiber, B vitamins, phenolic compounds, potassium, and beta-glucans. Feeney et al (2014)³ recently reviewed the unique nutritional properties of mushrooms.

Research conducted in our laboratories at The Pennsylvania State University has demonstrated that mushrooms can be a rich source of 4 critical bioactive compounds important to human health: selenium,^{4,5} vitamin D,^{6,7} l-ergothioneine (Ergo),^{8,9} and glutathione (GSH).¹⁰ Vitamin D is an essential nutrient, and selenium, GSH, and Ergo are important antioxidants thought to mitigate oxidative stress/damage, a key contributor to aging and its related diseases. Indeed, most chronic degenerative diseases that occur during aging have oxidative damage. Such damage may be a causal factor for development and/or progression. Hence, the potential to mitigate these diseases of aging by increasing these antioxidant compounds in the diet through mushroom consumption is intriguing. All of these bioactive

compounds, except for Ergo, can be found in significant amounts in foods other than mushrooms. Hence, Ergo will be the focus of this article.

Different types of mushrooms vary considerably in Ergo and GSH content. Dubost et al (2006)¹¹ demonstrated that button mushrooms were lowest, with about 0.30 to 0.6 mg/g, dry weight (dw) of Ergo and the specialty mushrooms like shiitake, oyster, and maitake contained about 3 to 4 times as much (Figure 3). Oyster mushrooms were shown to contain about 10 times more Ergo than chicken livers and black beans and 30 times more than oat bran, which are the best dietary sources other than mushrooms.¹² In a later study,¹⁰ we demonstrated that mushrooms were high in Ergo but also contained quite high levels of GSH (Figure 4), making them the best single dietary source of both antioxidants.

Ergo is an amino acid antioxidant that was originally discovered in 1909 in Ergot fungus but hardly studied until

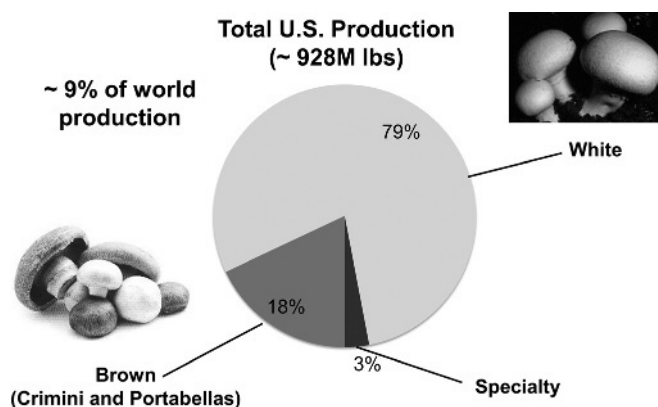


FIGURE 2. US mushroom production statistics. Adapted from USDA (2017).²

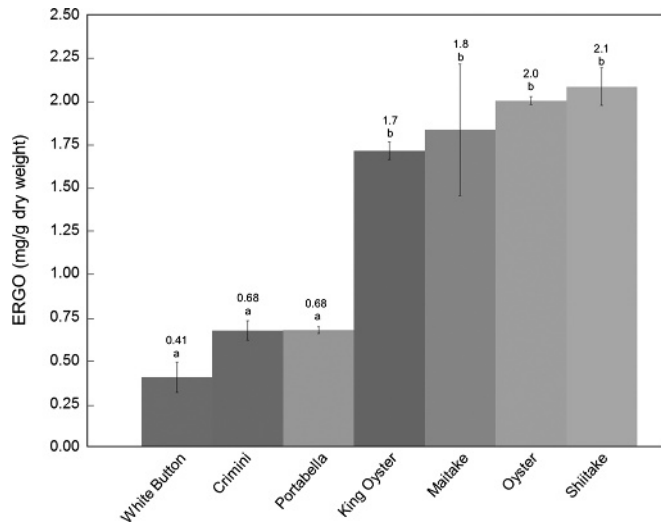


FIGURE 3. Concentration of ergothioneine in various mushrooms. Data are expressed as means. Bars on the columns represent standard deviation. Graphics with different letters differ significantly ($P = .05$). Adapted from Dubost et al (2006).¹¹

recently (the structures of Ergo and GSH are provided in Figure 4 insert). Ergo cannot be made by higher plants and animals, but is produced primarily by nonyeast fungi, Cyanobacteria, and some Mycobacteria. Because mushrooms are actually the fruiting bodies of fungi, it was not surprising that research demonstrated that cultivated mushrooms are the leading dietary source of Ergo.¹¹ Humans cannot synthesize Ergo, so it must be obtained from the diet. Interestingly, humans, like all mammals, produce a highly specific transporter protein that mediates the adsorption, distribution, and retention of Ergo, which implies that it might provide a beneficial physiological role.¹³

Paul and Snyder (2009)¹⁴ suggested that Ergo is a valuable physiological cytoprotectant and should be desig-

nated as a new vitamin. Bruce Ames has suggested that Ergo is a “longevity vitamin” as defined by his Triage Theory,¹⁵ which hypothesizes that bioactive compounds like Ergo have multiple functions in the body. He suggests that functions related to short-term survival and reproduction have priority over long-term functions protecting against chronic degenerative diseases of aging. Hence, if Ergo levels in an individual are low, then chances are increased that protection against diseases of aging would be compromised. Recently, Halliwell et al (2016)¹⁶ hypothesized that Ergo is an adaptive antioxidant for the protection of injured tissues. This concept was demonstrated in a model study with guinea pigs subjected to a diet causing nonalcoholic fatty liver disease.¹⁷ In this study, the Ergo

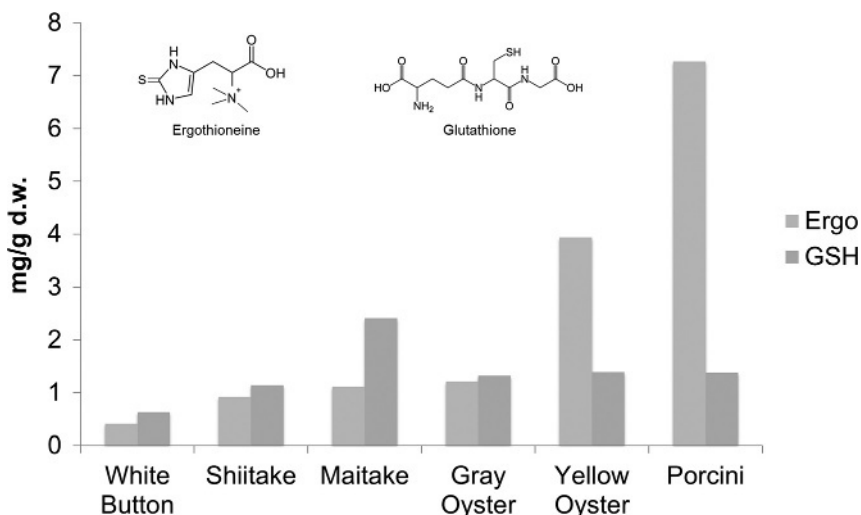


FIGURE 4. Ergothioneine and glutathione content of mushrooms (mg/g dw). Adapted from Kalaras et al (2017).¹⁰

transporter in the liver was upregulated and high levels of Ergo accumulated in response to tissue damage. According to the Triage Theory, this situation would represent the use of Ergo for short-term survival, which would then predispose those animals to diseases of aging, especially if Ergo levels were already low due to dietary limitations. However, data are not available on whether the animals were more susceptible to age-related diseases and more research is needed on this point. Halliwell et al (2018)¹⁸ recently reviewed the potential therapeutic uses for Ergo for treatment of various diseases and speculated that supplementation of humans with additional Ergo might be beneficial to mitigation of diseases. Overall, although the data on the beneficial effects of Ergo are accumulating, supporting its role as a protective bioactive, it should be noted that Ergo does not currently fit the definition of a vitamin because no clear set of symptoms or disease has been identified to result from Ergo deficiency which can be cured by its replenishment.

Ergo is widespread in the human food chain, albeit in very small amounts except for mushrooms. We assume that soil-borne fungi produce Ergo, which is then passed on to plants, as demonstrated by Park et al (2010),¹⁹ and then on to animals, which consume the plants. Therefore, Ergo in the food chain depends on a healthy fungal population in agricultural soils. However, we have speculated that some modern agricultural cultivation practices have depleted the soil fungal populations, which may reduce the Ergo content of food crops for human and animals. We are currently pursuing research in collaboration with the Rodale Institute to determine if organic agricultural practices may mitigate this possibility. Preliminary results have indicated that soil tilling seems to reduce the Ergo content of oats compared with using a no-till practice.

Weigand-Heller et al (2012)²⁰ demonstrated that Ergo in mushrooms was bioavailable to humans when served as portabella powder combined with a meal. Ergo levels increased in the red blood cells within 1 hour after consumption. In a later human clinical trial, adults with metabolic syndrome were served 100 g of button mushrooms per day in a prepared entree for 16 weeks.²¹ Blood samples were taken before they started consuming the mushrooms, after 16 weeks of consumption and 4 weeks after stopping. Average Ergo levels doubled from baseline, and significant increases in the anti-inflammatory hormone adiponectin and decreases in serum oxidative stress inducing factors carboxymethyllysine and methylglyoxal were detected. Four weeks after cessation of mushroom feeding, levels of plasma Ergo and relevant biomarkers reversed toward original levels. The authors concluded that the mushrooms contained a variety of components, including Ergo, with potential anti-inflammatory and antioxidant health benefits.

Glutathione in mushrooms would presumably be bioavailable to humans as it was recently demonstrated that

oral consumption of GSH supplements was effective in increasing body compartment stores of GSH.²² To our knowledge, only 1 double-blind placebo-controlled clinical trial with mushrooms has been conducted focusing on the mitigation of cognitive impairment, and the roles of Ergo and GSH were not considered.²³

Limited data are available regarding how much Ergo is consumed in the human diet. However, a recent study²⁴ estimated Ergo consumption in the United States and 4 European countries. Using data for the entire population of each country (both mushroom eaters and nonvoters) from that study, estimates were made for the daily Ergo consumption of an average 150lb person from each country. Results are presented in Figure 5. The lowest estimated daily Ergo consumption was for the United States (1.1 mg/d) and the highest was for Italy (4.6 mg/d). The high consumption of Ergo-rich Porcini mushrooms in Italy was considered to be a factor in this outcome. Figure 6 presents a graph of estimated Ergo consumption versus life expectancy by country.²⁵ The positive association between Ergo consumption and life expectancy is intriguing but, of course, it does implicate a causal relationship. However, this association does contribute to the formation of hypotheses regarding the potential role of Ergo (or mushroom consumption) in fostering healthy aging as represented by increased life expectancy.

Recently, it was demonstrated that Ergo levels in an elderly population in Singapore decreased with age and with the incidence of cognitive decline.²⁶ The authors suggested that a deficiency in Ergo may predispose people to mild cognitive impairment and possibly other neurodegenerative diseases. In another study,²⁷ it was observed that people with Parkinson's disease (PD) had significantly lower blood Ergo levels than did age-matched individuals without PD, suggesting that a deficiency in Ergo level may predispose people to PD. The data in Figure 7 demonstrate an apparent negative association between estimated Ergo consumption in the United States and 4 European countries and the mortality rates caused by Alzheimer's dementia (AD) and PD.²⁵ Again, this association cannot be interpreted as causal in nature, but may be used to help develop hypotheses relating that low Ergo consumption with increased risk of AD and PD. Also, a recent epidemiological study with a cohort exceeding 13 000 elderly Japanese revealed a significant inverse dose-response association between mushroom consumption and incident dementia, supporting this hypothesis.²⁸

Cognitive impairment during aging is a growing problem, and there is a near-exponential increase in people with dementia in the United States. According to the Alzheimer's Association, there are currently more than 5 million Americans who have been diagnosed with AD. The healthcare cost for treating AD in 2017 was around \$259 billion. Despite extensive efforts to develop medications

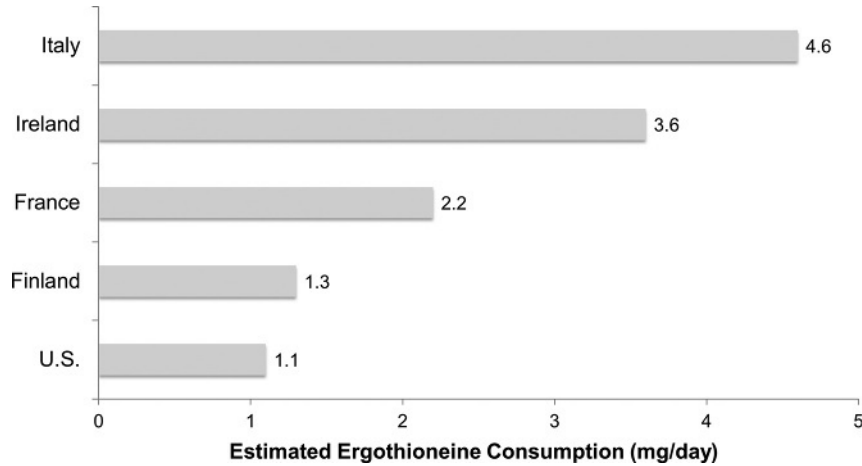


FIGURE 5. Estimated average ergothioneine consumption (mg/d). Calculated based on an average human weighing 150 lb or 68 kg. Adapted from Ramirez-Martinez et al (2016).²⁴

for cognitive impairment and AD, the management of these diseases has been largely ineffective. Thus, some have suggested that it would be prudent to explore nutritional-based solutions to control these diseases. Mori et al (2009)²³ conducted a small human clinical trial showing that oral administration of Lion’s Mane mushroom powder was effective in improving mild cognitive impairment in elderly Japanese subjects. A recent review paper²⁹ has described mushrooms as an emerging “brain food” for the mitigation of neurodegenerative diseases because they contain numerous chemicals in addition to Ergo that exhibit positive effects on brain cells. However, much more research is needed.

Mushrooms are such a rich dietary source of Ergo and the master antioxidant GSH, which suggests that they might be a possible candidate to be a nutritional solution to help prevent diseases like mild cognitive impairment, AD, and

PD. Nakamichi and Kato (2017)³⁰ have suggested that uptake of Ergo in the brain via the Ergo transporter may contribute to reducing oxidative stress, thereby possibly reducing signs or symptoms of neurological diseases. Ishimoto et al (2017)³¹ have suggested that Ergo may suppress chronic overactivation of microglia in the brain that is involved in the development of various neurodegenerative disease like AD and PD.

These findings have led us to the following hypothesis: The American diet may be lacking in sufficient Ergo to adequately protect against the chronic degenerative diseases of aging, especially neurodegenerative diseases like cognitive impairment, Alzheimer’s dementia, and Parkinson’s disease. Hence, the main goal of our current research is to determine the ways to increase the consumption of Ergo in the American diet by about 3 mg/d and then to assess how

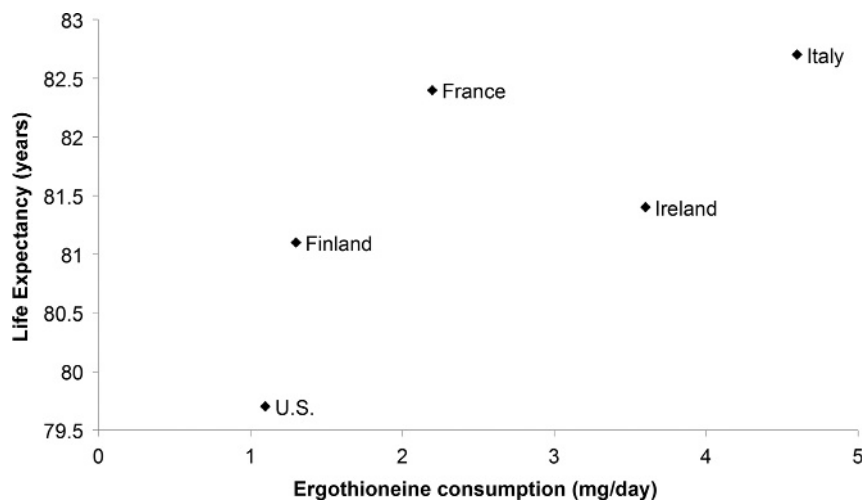


FIGURE 6. Life expectancy in selected countries versus estimated ergothioneine consumption (World Health Rankings, 2017).²⁵

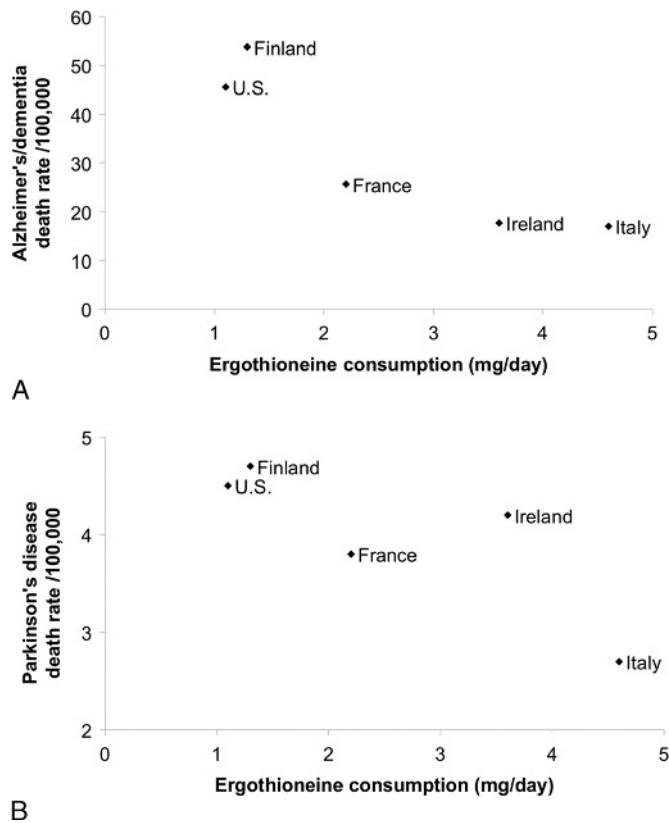


FIGURE 7. Death rate/100,000 in selected countries from (a) Alzheimer's disease and (b) Parkinson's disease versus estimated ergothioneine consumption (World Health Rankings, 2017).²⁵

this change might mitigate the diseases of aging related to cognitive impairment and chronic neurodegenerative diseases (like AD and PD) through human clinical trials. An increase of 3 mg/d can be accomplished by consumption of about 100 g of fresh button mushrooms per day or around 25 g of fresh specialty mushrooms such as shiitake, oyster, or maitake mushrooms. One potential way to add fresh button mushrooms to the diet would be to embrace the meat-blend approach in which about 30% to 40% ground, fresh button mushrooms are blended with 60% to 70% ground beef to replace pure ground beef in burgers or other common commonly consumed dishes.^{32,33} Another approach could be to use small amounts of dried powders of Ergo-rich specialty mushrooms as a new food ingredient into current or new food products. In many cases, such products would not affect the sensory properties of food. One such product we developed in the past was a whole wheat bread.³⁴ Recently, we made similar bread with sufficient dry specialty mushroom powder added to the flour that the resultant bread could contain up to 1 mg of Ergo per slice without any detectable effect on the sensory properties. Hopefully, such food products could someday be used in human clinical trials to study the potential of Ergo and GSH-rich mushrooms to mitigate

neurodegenerative diseases of aging such as cognitive impairment, AD and PD.

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