NAGASE

L-Ergothioneine

A Stable, Safe, and Powerful Natural Antioxidant

NAGASE & CO. is working on fermentative production of the natural antioxidant ergothioneine (Figure 1), which is stable, safe, and can be transported to the brain as well.

What is Ergothioneine?

Ergothioneine (EGT), a rare amino acid, is a natural compound with excellent antioxidant properties. Certain mushrooms (in the class basidiomycetes), fungi such as *Aspergillus oryzae*, *Streptomyces* species, and cyanobacteria are the only organisms capable of producing EGT. Humans cannot synthesize EGT in the body, therefore must eat mushrooms or foods fermented by *A. oryzae* to obtain it.

EGT was discovered in 1909[1], so it has been known for some time, but in recent years it has been found to have interesting properties, and there is evidence that it is promising against diseases involving the brain, the nervous system, and aging.

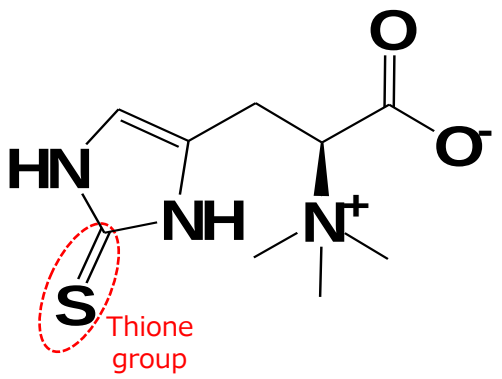


Fig. 1. L-Ergothioneine (EGT)

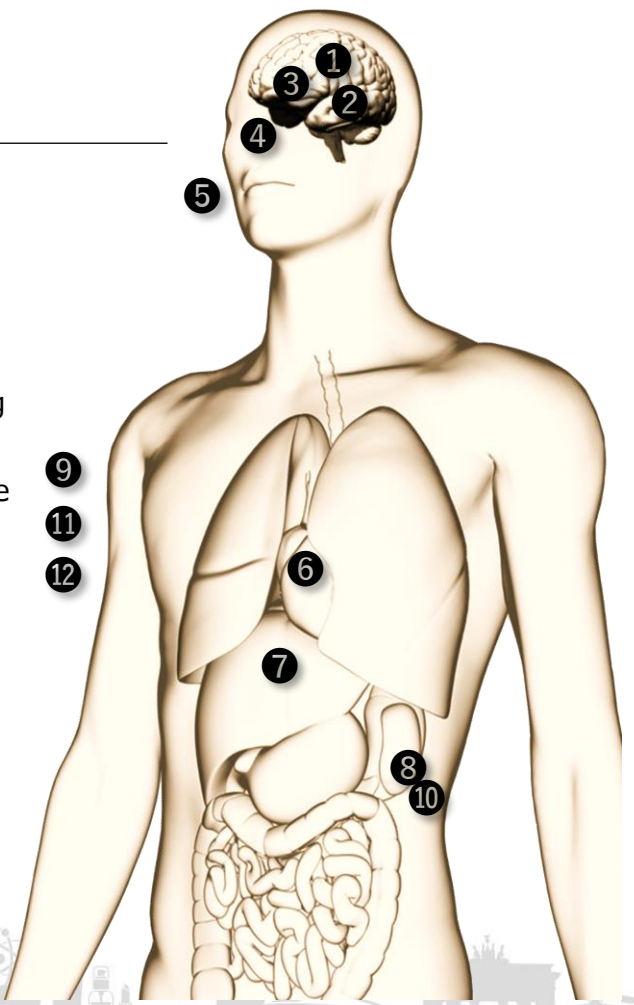
Longevity Vitamin

Dr. Bruce Ames (of the famous Ames test) is the leading researcher in aging and proposed “longevity vitamins” as a new group of vitamins which though are not required for survival, but are vital compounds to maintain health in the long term. Ames also noted how EGT may contribute to maintaining mitochondrial activity, and suggested it as a potential longevity vitamin[2]. With the longer lifespans of the modern era, healthy longevity has become a major concern, and longevity vitamins are likely to become progressively more important.

Clinical research has suggested that EGT is vital to healthy longevity. The decline in mental and physical capability due to aging is known as frailty. In a comparison of EGT levels between people with high frailty and low frailty, those who were frailer had lower EGT levels[3]. This indicates that EGT can help to battle aging. It has also been reported in a comparison between countries that the countries which consume the most EGT may have the longest lifespans[4].

Potential Targets of L-Ergothioneine

① Parkinson’s Disease
② Cognitive impairment
② Depression
④ Cataract, Retinopathy
⑤ UV-induced skin aging (Wrinkle, Blotches)
⑥ Cardiovascular disease
⑦ Liver disease (Fatty liver, Fibrosis)
⑧ Kidney disease
⑨ Complications of diabetes
⑩ Pre-eclampsia
⑪ Cancer
⑫ Frailty



1. Excellent Antioxidant Properties

EGT is an excellent antioxidant, with a capacity for neutralizing reactive oxygen species (ROS) 3 to 30 times higher (depending on the type of ROS) than glutathione, the most common antioxidant in the body[5]. These powerful antioxidant properties are due to a unique part of the structure of EGT, the thione group (Figure 1). Since oxygen molecules are a type of radical, many antioxidants become unstable when oxygen is present. Since EGT has a thione radical, it reacts quickly to strong ROS such as hydroxyl radicals and singlet oxygen, but has very low reactivity with oxygen, and avoids breaking down even over long periods in the presence of oxygen. It is also very stable when exposed to heat or acid[6]and is highlysafe[7].

2. Discovery of the Ergothioneine Transporter

The primary reason that EGT has received attention in recent years is due to the discovery in 2005 of the ergothioneine transporter (ETT) for the uptake of EGT into cells in humans[8]. As mentioned above, only some microorganisms can produce EGT, but it is now known that EGT is used via ETT in various lifeforms including plants, fish, and mammals. ETT has been found in various tissues in humans, and it has been reported that maintaining a high concentration (approximately 2 mM) of EGT in a cell will protect the cell from oxidative stress[6].

i. Mitochondria are an important organelle that consume oxygen to produce energy (ATP), but as a result they are destined to be susceptible to oxidative stress. A decline in mitochondria function is closely related to various diseases and aging. Studies have shown large amounts of ETT in the membrane of this vital organelle[9].

ii. One of the cell types where the most ETT occurs is in red blood cells, the transporters of oxygen, and red blood cells have been found to have high concentrations of EGT[10]. Approximately 100-500 μM of EGT is found in human blood, but in some people this can exceed 1000 μM (unpublished data).

iii. ETT is also found in skin tissue, and it has been reported that there is a particularly large amount of ETT in epidermal cells, so they tend to accumulate EGT more easily[11]. It is believed that the reason epidermal cells are able to accumulate EGT easily is to resist oxidative stress due to ultraviolet rays.

iv. Despite EGT being highly water soluble, it can pass through the blood-brain barrier and is known to accumulate in the central nervous system as well. Oxidative stress and the onset of neurodegenerative diseases are closely related, and there have been multiple studies showing the effectiveness of EGT in preventing neurodegenerative diseases[12, 13].

As described above, it is interesting physiologically that there is a high occurrence of ETT in cells and organelles which are susceptible to oxidative stress, allowing for EGT, a powerful antioxidant, to accumulate easily. ETT is also known to occur more frequently in inflamed areas (making it easier to absorb EGT to fight inflammation).

3. Inducing Differentiation in Stem Cells

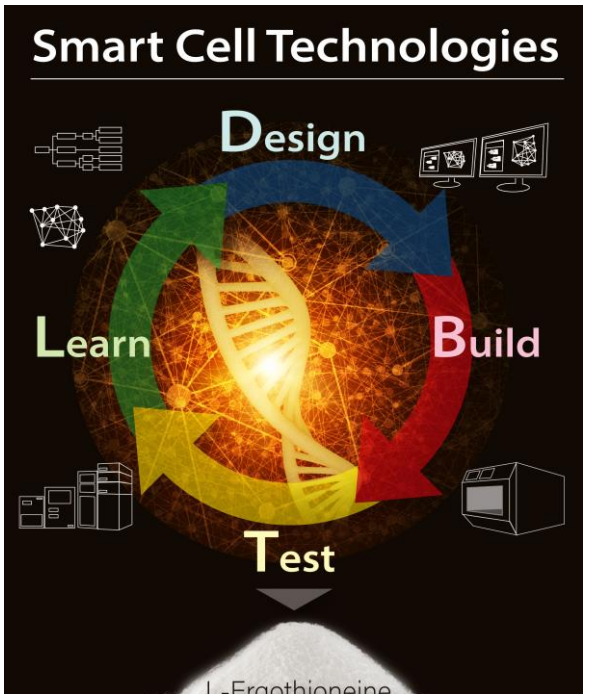
Recent research has shown that EGT can promote the differentiation of stem cells. For example, providing EGT to neural stem cells can encourage them to differentiate into neurons. Studies have indicated the possibility of promoting nerve reconstruction by ingesting EGT if nerve damage occurs[13, 14].

Potential Effects of Ergothioneine

EGT is a promising agent in preventing neurodegenerative diseases (Alzheimer's, Parkinson's), depression, skin aging due to ultraviolet rays (wrinkles and discoloration), cataracts, and glycative stress. However, EGT levels in cells decline with age[12]. Therefore, it may be possible to prevent various diseases caused by aging by actively increasing EGT intake.

NAGASE & CO., LTD's Ergothioneine Production Technology

As explained above, EGT is a very appealing substance, but with existing methods such as extracting it from mushrooms, it is difficult to mass produce it in stable quantities at a low cost. By utilizing the Streptomyces (N-STePP®) smart cell technology which NAGASE has established through years of research, NAGASE aims to develop a revolutionary fermentative production process to make ergothioneine from inexpensive sugar[15].



The NAGASE BIO-INNOVATION CENTER is committed to developing processes for efficiently producing a wide range of compounds with proprietary fermentation technologies.

Contact Our BIO-INNOVATION CENTER ▷

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