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Usefulness of Ergothioneine

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Introduction

Ergothioneine (EGT) is a hydrophilic sulfur-containing amino acid discovered by Tanret in 1909 in the ergot fungus [1]. In addition to *Pseudomonas aeruginosa*, other mushrooms such as shiitake, eringi, and tamogi mushrooms [2-4], yeasts such as *Pichia pastori* and *Rhodotorula toruloides* [5,6], and bacteria such as *Mycobacterium smegmatis* and *Mycobacterium tuberculosis* [7,8] are also reported to be able to synthesize EGT based on cysteine and histidine [9]. On the other hand, the human body cannot biosynthesize EGT, therefore the concentration of EGT in the body is maintained at a constant level through dietary intake of EGT [10]. EGT exists as thionic and thiol tautomers, with the thionic form predominating at physiological pH [11]. No rapid reaction with superoxide or hydrogen peroxide, which are reactive oxygen species (ROS), and stable under oxidative stress [12]. EGT works independently of oxidative defense systems in the body, such as superoxide dismutases and glutathione peroxidase, and because it is a thione body, it exhibits strong antioxidant activity that can remove hydroxyl radicals and singlet oxygen, which existing defense systems in the body cannot handle. Its potent removal of reactive oxygen species is 3~30 times higher than that of glutathione, an antioxidant present in the body, making EGT a functional ingredient that strongly inhibits oxidative damage to cells [13].

Cellular uptake of EGT requires the specific transporter Solute carrier family 22, member 4 (SLC22A4) [14], and through SLC22A4, EGT has a tendency to accumulate in organs susceptible to oxidative stress, such as liver, kidney and spleen [11]. Furthermore, SLC22A4 uptake is directional, promoting intracellular accumulation of EGT but not extracellular efflux, allowing EGT to be retained in the body for long periods of time [10]. EGT taken into cells by SLC22A4 is further transferred to mitochondria, where it binds to and activates 3-mercaptopyruvate sulfurtransferase (MPST), enhancing mitochondrial function and increasing intracellular antioxidant capacity [15]. On the other hand, the mechanism of EGT efflux from the cells has not been clarified.

In recent years, diverse physiological effects of EGT have been reported, affecting various parts of the body. The following is a summary of reports on the effects of EGT reported to date. In the skin, EGT has potent antioxidant and cytoprotective effects; it suppresses ultraviolet (UV)-B-derived oxidative stress and inflammatory cytokines (IL-6, TNF-α, etc.), thereby reducing the melanin index and preventing UV-induced spots [16,17]. EGT can also directly remove free radicals and protect skin cells from ROS [18].

In the musculoskeletal system, EGT has been reported to improve age-related sarcopenia and muscle performance by directly binding to MPST in mitochondria, thereby enhancing mitochondrial respiratory capacity (the ability to break down organic matter with oxygen and synthesize ATP) [15,19]. EGT also inhibits the progression of osteoarthritis by markedly reducing the expression of the inflammatory factor IL-1β [20]. In the respiratory and cardiovascular systems, EGT has been shown to protect lung epithelial cells from oxidative stress, which may contribute to the prevention of chronic obstructive pulmonary disease by suppressing the expression of inflammatory factors such as TNF-α and IL-8 [21,22]. Furthermore, it has been suggested

that EGT may reduce the risk of cardiovascular diseases such as atherosclerosis by preventing the destruction of nitric oxide by superoxide anion radicals (O2-), thereby maintaining nitric oxide-dependent endothelial function and preventing vascular endothelial dysfunction [23-25]. In the nervous system, it has been reported that inhibition of amyloid-β accumulation may inhibit the onset of Alzheimer's disease [26].

However, it has been reported to be involved in an increased risk of Alzheimer's disease [27], so further reports are awaited. In Parkinson's disease, reducing oxidative stress inhibits alpha-synuclein aggregation and contributes to the prevention of disease onset [28]. EGT has also been suggested to serve as a potential therapeutic strategy in the study of brain aging because it restores aging cells by improving mitochondrial function [29]. In addition, in relation to psychiatric disorders, since reduced blood EGT levels have been reported in patients with mental distress [30], EGT may act as a neurotransmission stimulator, stimulating neurogenesis [31] and alleviating psychiatric symptoms. In the gastrointestinal and endocrine systems, EGT has been shown to suppress inflammatory responses and maintain the gastrointestinal environment in patients with radiation gastroenteritis [32]. In ulcerative colitis, it also suppresses CD4-positive T cells and macrophages, thereby restoring the intestinal mucosa and promoting the resolution of inflammation [33]. In the liver, anti-inflammatory and antioxidant effects have been reported, as well as reduction of iron overload-induced hepatocellular injury due to chelation of iron by EGT [34-42]. It has also been reported to have antithyroid effects and to inhibit diabetic encephalopathy caused by hyperglycemia [43,44].

In the urinary system, EGT has been reported to protect cells and reduce renal dysfunction by suppressing oxidative stress and inflammatory cytokines such as NF-κB, TNF-α and IL-1β in the kidney [45,46]. It has also been suggested that SLC22A4 expression contributes to the suppression of stromal fibrosis under oxidative stress in diabetic kidney disease [47]. In the reproductive system, EGT administration is known to protect sperm from ROS, improve sperm motility, and increase fertilization rate by improving egg quality [48-50]. In addition, its involvement in obstetric and gynecological disorders such as endometriosis and preeclampsia has been reported, suggesting that EGT may be effective as a therapeutic agent [51,52]. In the immune system, EGT acts on both innate and acquired immunity and acts as an immune modifier by regulating macrophage M1/M2 polarity to maintain an appropriate immune response while suppressing excessive inflammatory responses [53,54]. Thus, EGT has potent antioxidant and anti-inflammatory properties and is being investigated as a potential therapeutic agent for a variety of diseases. In the developmental and reproductive systems, the effects of EGT in fertilized eggs and chorionic villi have been reported [55,56], but the significance of EGT in the endometrium is unknown.

We were the first in the world to show that SLC22A4 is up-regulated in decidualization, which is essential differentiation for embryo implantation, in endometrial stromal cells, and that EGT promotes placentation by enhancing IGFBP1 secretion from endometrial stromal cells [57]. Finally, blood EGT levels derive not only from dietary intake but also from synthesis by fungi and gut microbiota [10,58]. On the other hand, it has also been suggested that *Helicobacter pylori*. and intestinal bacteria in the stomach may metabolize dietary EGT and contribute to the production of trimethylamine N-oxide, a metabolite linked to disease [59]. This suggests that EGT produced by gut bacteria may also influence health. In mentally stressed rats, levels of *Lactobacillus reuteri*, a gut bacterium, are elevated, and this is associated with increased EGT production [60]. Oral administration of EGT to such rats reduces stress. This suggests that microbiota-derived EGT may have a role not only in stress reduction but also in preventing miscarriage, a condition closely linked to stress—particularly that caused by disturbances in the autonomic nervous system.

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