Adah et al. MKH (2023).36-52
DOI: 10.20473/mkh.v34i1.2023.36-52

The Potentials of Ergothioneine in The Management of Diseases in animals

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ABSTRACT

The amino acid histidine is the source of the special nutraceutical ergothioneine (ET), which is a potent antioxidant. Higher plants and animals obtain it from the soil and their food, respectively, and do not synthesize it; instead, they obtain it through specific microorganisms, such as actinobacteria and also from mushrooms. The solute carrier family 22, member 4 (SLC22A4), sometimes referred to as organic cation transporter novel type-1(OCTN-1) is an incredibly selective transporter for ergothioneine and is only present in animals. Organic cation transporter novel type-1OCTN 1 is expressed in tissues differently and is expressed more in tissues that are highly susceptible to oxidative stress, such as erythrocytes. The concentrations of ergothioneine decline in several chronic inflammatory diseases, and it appears to have potent cytoprotective actions. It has been certified to be relatively safe by regulatory authorities compared to many other antioxidants.

Keywords: anti-inflammatory; antioxidant; diseases; ergothioneine

INTRODUCTION

Higher organisms may accumulate ergothioneine (ET), a thiourea derivative of histidine synthesized by non-yeast fungi, mycobacteria, and cyanobacteria, at levels up to millimolar via an organic cation transporter (OCTN1) (Sotgia*et al.*, 2013; Li *et al.*, 2014; Forster *et al.*, 2015; Frigeni*et al.*, 2016). Ergothioneine antioxidant has been shown to possess cytoprotective properties in several in vitro studies against a variety of cellular stressors,

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Available at https://e-journal.unair.ac.id/MKH/index

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although its antioxidant role in vivo has not been fully explored. However, the scavenging, tissue distribution, and accumulating qualities all point to ergothioneine's ability to serve as a physiological antioxidant (Cheah and Halliwell, 2012; Cheah *et al*., 2016). Due to the sulphur in ergothioneine's thione form, which transforms into the sulfhydryl form to scavenge oxygen radicals, it possesses a potent and unique antioxidant effect (Kei *et al*., 2005; Nakamachi*et al*., 2016).

Ergothioneine is present in a variety of foods in small proportions, with the largest concentrations being found in specific mushroom species including *Lentinus edodes, Pleurotusostreatus*, and *Pleurotuseryngii*, while moderate concentrations are also present in various meat products like kidney (Ey*et al*., 2007; Schauss*et al*., 2010; Fu and Shen, 2022). Despite being exclusively synthesised in fungi, cyanobacteria, and mycobacteria, no evidence, for now, exists for the direct biosynthesis of ergothioneine in animals and higher plants. Ergothioneine is largely present in most cells and tissues of plants and animals (Halliwell *et al*., 2018; Song *et al*., 2014).

The specific transporter organic cation transporter novel type 1 (OCTN1) is responsible for distributing ET throughout the body. ET is degraded and eliminated slowly in urine (Gründemann*et al*., 2005; Forster *et al*., 2015; Cheah *et al*., 2017). Because ET mostly resides in the thione tautomer at physiological pH, it is more stable than other thiols like glutathione and has a longer half-life and the potential to accumulate in the body (Cheah *et al*., 2016).

Ergothioneine also known to be a special low molecular weight dietary thiol/thione, has recently attracted a lot of attention. This substance may accumulate in large concentrations in the body due to diet and may have significant physiological effects on animal development and health as well as the potential to prevent and manage diseases. Ergothioneine levels in the blood decrease with aging and the start of certain disorders (Cheah and Halliwell, 2021). This review aims to highlight from the literature the potential of ergothioneine in the management of diseases in animals.

ORIGIN OF ERGOTHIONEINE

In 1909, ergot (*Claviceps purpurea*), a fungus that infects rye grain, was first used to isolate ergothioneine. Since then, millimolar quantities of ergothioneine have been discovered in people, animals, fungi, plants, and microorganisms (Kei *et al*., 2005, Encarnacion *et al*., 2010). Only a few fungi and the *Actinomycetales* bacteria have been reported as capable of synthesising ergothioneine thus far (Kei *et al*., 2005; Muramatsu*et al*., 2013). The fungus *Lyophyllumconnatum* has been shown to contain the ergothioneine

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derivative -hydroxyergothioneine (Smith *et al*., 2020). It is thought that organisms that do not produce ergothioneine through biosynthesis receive it from their environments (Nakamichi*et al*., 2016). Ergothioneine is believed to be obtained by plants from the soil (Cheah and Halliwell, 2021). It has been reported that the nature of an animal's diet can alter its ergothioneine content thus it is believed that animals receive ergothioneine through their diets (Cheah and Halliwell, 2012).

DISTRIBUTION OF ERGOTHIONINE IN THE BODY

Ergothioneine levels vary depending on the species and type of tissue, but they are mostly present in tissues that are vulnerable to oxidative stress, such as the kidneys, liver, eye lens, kidneys, and erythrocytes (Vickers and Fairlamb, 2004; Sotgia*et al*., 2013, Sotgia*et al*., 2015). It was discovered that erythrocytes absorb ergothioneine at levels two to nine times higher than those of blood plasma. Earlier research (Zhang *et al*., 1996; Day, 2008; Wang *et al*., 2013) suggested that ergothioneine was integrated into erythrocytes during cell formation. However, work by Feng *et al*. (2006) demonstrates that ergothioneine is slowly taken up by the erythrocyte and maintained against a concentration gradient. Ergothioneine transporter has been identified in human kidney cells, and cells expressing the transporter were shown to accumulate ergothioneine in high concentrations and retain it. This suggests that ergothioneine uptake is transporter-dependent. Ergothioneine was discovered to be absent from cells lacking this transporter because ergothioneine cannot cross the plasma membrane (Grundemann*et al*., 2005). The ergothioneine transporter protein is securely anchored in cellular membranes by a scaffold made up of 12 hydrophobic transmembrane helices. The human variant of the amino acid chain, which has 551 AA, has both ends most likely located in the cytosol. The precise 3D structure is yet unclear, though. There are no obvious signs of multimers, hence the transporter most likely functions as a monomer. The ergothioneine transporter, which has a PDZ-binding motif at the C-terminus, might influence membrane trafficking if PDZK1 or other proteins with a PDZ domain are present (Futatsugi*et al*., 2016). The plasma membrane, or cell envelope, and the surface of the organelle mitochondria are where the transporter is mostly found (Shinozaki *et al*., 2017).

TRANSPORTATION OF ERGOTHIONINE IN THE BODY

Ergothioneine is water soluble, therefore it is transported in the body dissolved in water by its high-affinity transporter, the organic cation

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transporter 1 (OCTN1), ET accumulates in several animal tissues up to millimolar concentration (Servillo *et al*., 2017). Even though ET is found in many cells, plasma membranes appear to be impermeable to it, therefore a special mechanism for absorption and accumulation in cells is required (Nakamura *et al*., 2007). The cell's absorption of ET reveals a considerable Na+-dependence.

The organic cation transporter (OCTN1), which is produced by the gene solute carrier 22 family member 4 (SLC22A4), is a crucial transport protein that is in charge of moving ET across the membrane in a pH-dependent manner (Grundemann*et al*., 2005). In cell lines, turning off the OCTN1 gene limits the absorption of ET (Lamhonwah*et al*., 2006). Similar to this, a structural study of the OCTN1 knockout mice showed that nearly all of their tissues were devoid of ET, indicating the lack of an alternate channel for its uptake (Grigat*et al*., 2007).

The high levels of ET found in erythrocytes are likely caused by the high expression of OCTN1 in the bone marrow, which was discovered through analysis of many body tissues. Similar to this, the levels of ET in intestinal tissue and peripheral blood cells are not influenced by diet but are closely linked to the expression of OCTN1 mRNA (Zhu *et al*., 2011).

According to research utilizing natively expressed OCTN1 in HeLa cells, ergothioneine is preferentially transported via OCTN-1 when compared to other alternative substrates. Except for the general transport inhibitors quinidine, verapamil, and pyrilamine, no other potential substrate significantly impeded the transfer of ergothioneine, with carnitine showing just a minor inhibition. The high selectivity of OCTN1 is indicated by the fact that not even substances with structures comparable to ergothioneine were able to prevent ergothioneine absorption. HeLa cells were observed to readily absorb ergothioneine even at low concentrations (300 nM) (Tucker *et al*., 2019).

ANTIOXIDANT PROPERTIES OF ERGOTHIONINE

Because it does not autooxidise at the normal physiological pH of the body, ergothioneine is a special and extremely stable antioxidant (Hartman, 1990). Additionally, it inhibits the production of hydroxyl radicals from hydrogen peroxide and iron ions (Fenton reaction). This is due to the predominating thione moiety rather than thiol. According to Kalaras*et al*. (2017), ergothioneine protects the liver from radical-induced hepatocytotoxicity, but its derivative-hydroxy ergothioneine is more effective

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than ergothioneine at shielding hepatocytes l from the harmful effects of carbon tetrachloride. Under experimental conditions, the extra hydroxyl group of -hydroxyergothioneine appears to have a positive impact. Ergothioneine's capacity to create stable complexes with the ions of copper, zinc, and iron may be what causes it to have antioxidant properties (Li *et al*., 2014; Pluskal*et al*., 2014). Additionally, ergothioneine interacts with ROS, perhaps by quenching singlet oxygen (Sotgia*et al*., 2015; Ramirez-Martinez *et al*., 2016). Additionally, the substance combines with hydroxyl radicals and scavenges peroxyl radicals, hypochlorous acid, and peroxynitrite (Akanmu*et al*., 1991; Aruoma*et al*., 1999; Cumming *et al*., 2018).

Ergothioneine has been studied for its antioxidant qualities, but different groups have reported varying results. This is partly because the settings of the experiments were different and the quantities employed were frequently not physiological, which has further complicated the role of ET (Cheah and Halliwell, 2012; Sao-Emani *et al*., 2013).

Finally, even though numerous tests demonstrate that ergothioneine has special reactive properties, such as the capacity to scavenge hydroxyl (Paul and Snyder, 2009) or to allow oxidized ergothioneine to be restored by glutathione, it is prudent to recognize that these conditions may differ from those in vivo and thus may not be applicable as reported by Cheah and Halliwell (2012) and Khonde and Jardine (2015). Ergothioneine has beneficial physiologic characteristics such as rapid clearance from the circulation into retained tissues with little metabolism and high stability (Halliwell and Gutteridge, 2007), a long half-life of about 30 days (Cheah and Halliwell, 2012), and a decreased propensity to auto-oxidize or produce free radicals from peroxide and iron at physiological pH(Halliwell and Lee, 2010;Seet*et al*., 2011; Song *et al*., 2015; Marone*et al*., 2016;Clerkin*et al*., 2017).

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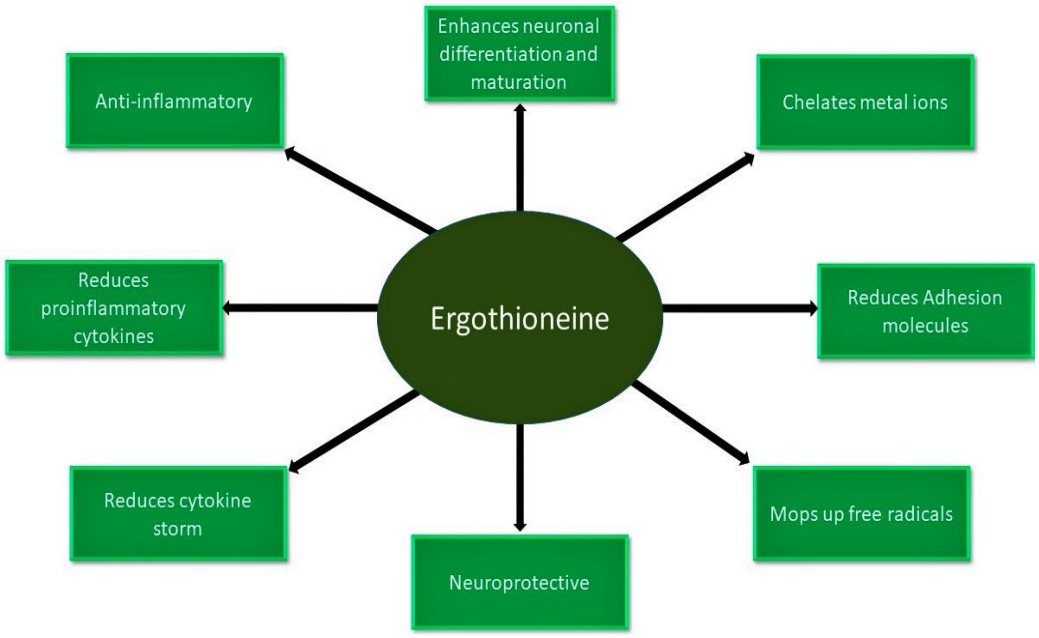

Figure 1. A schematic diagram of the properties of ergothionine.

ERGOTHIONINE AND INFLAMMATION

It is not yet understood what part ET plays in inflammation. On one hand, Crohn's disease and rheumatoid arthritis (Asahi *et al*., 2015) have both been linked to mutations in the ergothioneine transporter (OCTN1) gene, SLC22A4 (Peltekova*et al*., 2004). The levels of ET in erythrocytic and monocytic tissues were shown to be considerably greater in patients with mildly active rheumatoid arthritis, and these levels were strongly linked with the expression of OCTN1 mRNA in CD14+ cells (Taubert*et al*., 2006; Pochini*et al*., 2015). Additionally, OCTN1 is substantially expressed in the hematopoietic and immune systems of inflamed joints in mice with collagen-induced arthritis (Kobayashi *et al*., 2004). It may be advantageous for ET's immunomodulatory activities to prevent the atherogenic production of pro-inflammatory cytokines and adhesion molecules. According to research done on human aortic endothelial cells, ET reduces the expression of the adhesion molecules VCAM-1, ICAM-1, and E-selectin and prevents monocytes from adhering to

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the endothelium which occurs during inflammation (Martin, 2010).

However, it is still unclear exactly how reactive oxygen species are involved in the etiology and inflammation process of atherosclerosis and other cardiovascular inflammatory disorders (Libby *et al*., 2011). Studies of ischaemia, a condition involving oxidative stress, provide evidence for the preventive function of ET against cardiovascular disease as reported by Nauta*et al*. (1990) and Ramirez-Martinez *et al*. (2016). Ergothioneine has been demonstrated to protect the liver and heart tissue from inflammation during ischaemia in vivo (Bedirli*et al*., 2004). Although at lower levels than those seen in the liver, kidneys, and gut, OCTN1 expression has been observed in the brains of mice and rats (Yang *et al*., 2018). This is corroborated by several studies of ET concentrations in the brains of mice, rats, guinea pigs, rabbits, cats, sheep, and oxen ranging from 0.3 to 1 mg per 100 g of brain tissue, demonstrating the potential of ET to cross the blood-brain barrier to protect against inflammation (Kaneko *et al*., 1980).

It has been also been documented that ET protects neuronal cells from a variety of oxidative stresses and inflammatory disorders (Pike *et al*., 1991;Cheah and Halliwell, 2012). Pre-treatment with ET reduced inflammation, and reversed the cell death, ROS production, DNA damage, and apoptosis of keratinocytes caused by ultraviolet radiation (UVA), according to experimental data from the work of Hseu*et al*. (2015). When exposed to UVA, the mitochondria, which are essential for cell survival, lost their antioxidant capacity and membrane potential. With ET therapy, on the other hand, there was improvement of mitochondrial membrane potential and subsequently causing a rise in levels of intracellular glutathione before UVA exposure.

Additionally, ergothioneine prevents inflammatory response by enhancing nuclear factor-k (NFk) activation and restricting the transcriptional activation of the IL-8 gene, a chemotaxin that may be responsible for neutrophil recruitment into the lungs of ARDS patients (Repine and Elkins, 2012).

Gao *et al*. (2022) also recently reported that ergothioneine protects against dextran sulfate sodium-induced colitis in mice.

EFFECT OF ERGOTHIONINE ON THE NERVOUS SYSTEM

Cell culture and animal studies provide evidence that ET prevents neurodegeneration because it overcomes the key barrier of accumulation in the brain and translocation across the blood-brain barrier (Paul and Snyder, 2009).

According to reports, ET is essential for the differentiation and maturation of neurons, which may be important in

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brain regeneration after damage (Moncaster*et al*., 2002; Song *et al*., 2014; Bull and Plummer, 2014) Studies by Zhu *et al*. (2011) have shown that ET supplementation in mice improved learning and memory (object recognition test) and increased the number of mature spines in the hippocampus. The report also showed that exposure of cultured hippocampal neurons to ET elevated the expression of the synapse formation marker synapsin-1 and neurotrophin-3 and neurotrophin -5 (Zhu *et al*., 2011).

Another critical component is that oral ingestion of ET could lead it to cross the blood-brain barrier and accumulate in the brain, which is frequently a significant obstacle and the reason why many neuroprotective medication agents, including antioxidants, fail (Paul and Snyder, 2009). Numerous studies have shown that OCTN1 is present in the neurons of the mouse brain's hippocampus, hypothalamus, cerebellum, and motor cortex (Lamhonwah*et al*., 2008). As previously indicated, unlike certain other medications and dietary supplements, ET has a high bioavailability to the brain, as shown by research in animals (Tang *et al*., 2013) and postmortem human samples (Graham *et al*., 2016).

There is a good chance that ET may have a protective function, especially when the pathology involves oxidative damage and inflammation. However, the pathology behind neurological symptoms in many disorders is still not entirely understood. Undoubtedly, further research is required and necessary to determine if ET may protect against chronic neurological disorders through these and other pathways (Cheah *et al*., 2016).

HOW SAFE IS ERGOTHIONINE ?

Except for mushrooms, which it is present in high quantities, ET is a naturally occurring substance that is found in many foods in low amounts (Kalaras*et al*., 2017). Even though there are several research on ET in the literature, none of them even at high concentrations have yet documented any toxicity associated with its administration (EFSA, 2017). High doses of ET were given to pregnant female rats, yet neither the mother nor the offspring displayed any sign of toxicity (Forster *et al*., 2015).

In the chromosomal aberration experiment using the classic Hodgkin lymphoma cell line, ergothioneine doses up to 5000 µg/mL, with and without metabolic activation, were investigated, and it was discovered that none caused structural chromosome abnormalities. Ergothioneine was given orally to male mice at levels up to 1500 mg/kg for possible genotoxic activities in the in vivo mammalian erythrocyte micronucleus test. There was no rise in the number of micronucleated polychromatic erythrocytes.

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Ergothioneine was often shown to be non-genotoxic in these trials, adding more experimental proof to its usage as a viable dietary supplement (Schauss*et al.*, 2011)

Additionally, the European Dietary Safety Authority has approved the use of ET as a food supplement even in babies, toddlers, pregnant women, and nursing mothers earning the classification of "generally recognized as safe" (GRAS) from the United States Food and Drug Administration. Ergothioneine has been approved as a nutraceutical in the European Union countries by the European Food Safety Authority (EFSA, 2017) and also in the United States by the Food and Drug Administration (Kalaras *et al*., 2017).

CONCLUSION

Although most of the publications reviewed in this paper involved human and rat subjects, there is potential that ergothioneine supplementation in other animals may be beneficial in the management of diseases in other species of animals especially domestic animals such as horses, dogs, cats, cattle and small ruminants as ergothioneine has been established to be a potential antioxidant and antinflammatory agent. It possesses potential in the management of chronic diseases and disorders such as neurological disorders, respiratory diseases, gastrointestinal disorders such as colic in horses, laminitis and bowel inflammatory diseases.

REFERENCES

Akanmu, D., Cecchini, R., Aruoma, O.I. and Halliwell, B. 1991. The antioxidant action of ergothioneine. Archives of Biochemistry and Biophysics; 288: 10–16.

Aruoma, O. I., Spencer, J. P., and Mahmood, N. 1999. Protection against oxidative damage and cell death by the natural antioxidant ergothioneine. Food and Chemical Toxicology; 37(11), 1043–1053.

Asahi, T., Wu, X., Shimoda, H., Hisaka,S., Harada, E., Kanno, T., Nakamura, Y., Kato, Y. and Osawa, T. 2016.A mushroom-derived amino acid, ergothioneine, is a potent inhibitor of inflammation-related DNA halogenation. Journal of Bioscience, Biotechnology, and Biochemistry; 80(2): 313-317.

Bedirli, A., Sakrak, O., Muhtaroglu, S., Soyuer, I., Guler, I., Riza, A. and Erdogan, E. M. 2004. Ergothioneine pre-treatment protects the liver from ischaemia–reperfusion injury caused by increasing hepatic heat-shock-protein 70. Journal of Surgical Research; 122: 96–102.

Bull, M.J. and N.T. Plummer. 2014. Part 1: The Human Gut Microbiome in Health and Disease. Integrative Medicine (Encinitas);13(6): 17-22.

Cheah, I. K. and Halliwell, B. 2012. Ergothioneine; antioxidant

Received:06-09-2022, Accepted: 02-11-2022, Published online: 08-01-2023
Available at https://e-journal.unair.ac.id/MKH/index

Adah et al. MKH (2023).36-52
DOI: 10.20473/mkh.v34i1.2023.36-52

potential, physiological function and role in disease. Biochimica et Biophysica Acta; 1822: 784–793.

Cheah, I. K., and Halliwell, B. 2021. Ergothioneine, recent developments. Redox Biology, 42, 101868. https://doi.org/10.1016/j.redox.2021.101868

Cheah, I. K., Tang, R., Ye, P., Yew, T. S. Z., Lim, K. H. S. and Halliwell, B. 2016. Liver ergothioneine accumulation in a guinea pig model of non-alcoholic fatty liver disease. A possible mechanism of defence. Free Radical Research; 50(1): 14-25.

Cheah, I.K., Tang, R. M.Y., Yew, T.S.Z. Lim, H.H.C and Halliwell, B. 2017. Administration of pure ergothioneine to healthy human subjects: uptake, metabolism, and effects on biomarkers of oxidative damage and inflammation. Antioxidants and Redox Signaling; 26(5): 193-206.

Clerkin, C. G., Matzinger, M. Selo, M.A., Talbot, B.N. Walsh, J.J. and Ehrhardt, C. 2017. Aromatic Substitution Reaction of Ergothioneine - a Novel Mechanism of Xenobiotic Deactivation. The FASEB Journal; 31(S1): 821.1-821.1.

Cumming, B.M., Chinta, K.C. Reddy, V.P. and Steyn A.J.C. 2018. Role of Ergothioneine in Microbial Physiology and Pathogenesis. Antioxidants and Redox Signalling; 28(6): 431- 444.

Day, B.J. 2008. Antioxidants as potential therapeutics for lung fibrosis. Antioxidants and Redox Signaling; 10: 355–370.

European Food Safety Authority. 2017. Panel on Dietetic Products, Nutrition, and Allergies (NDA); Turck, D.; Bresson, J.-L.; Burlingame, B.; Dean, T.; Fairweather-Tait, S.; Heinonen, M.; Hirsch-Ernst, K.I.; Mangelsdorf, I.; McArdle, H.J.; et al. Statement on the safety of synthetic l-ergothioneine as a novel food—Supplementary dietary exposure and safety assessment for infants and young children, pregnant and breastfeeding women. EFSA Journal; 2017, 15 .

Encarnacion, A.B., F. Fagutao, I. Hirono, H. Ushio, and T. Ohshima, 2010. Effects of ergothioneine from mushrooms (*Flammulinavelutipes*) on melanosis and lipid oxidation of kuruma shrimp (*Marsupenaeus japonicus*). Journal of Agriculture and Food Chemistry; 58(4): 2577-85.

Ey, J., Schomig, E. and Taubert, D. 2007. Dietary sources and antioxidant effects of ergothioneine. Journal of Agriculture and Food Chemistry; 55: 6466–6474.

Futatsugi, A., Masuo, Y., Kawabata, S., Nakamichi, N., & Kato, Y. 2016. L503F variant of carnitine/organic cation transporter 1 efficiently transports metformin and other biguanides. The Journal of Pharmacy and Pharmacology; 68(9):

Received:06-09-2022, Accepted: 02-11-2022, Published online: 08-01-2023
Available at https://e-journal.unair.ac.id/MKH/index

Adah et al. MKH (2023).36-52
DOI: 10.20473/mkh.v34i1.2023.36-52

1160–1169. https://doi.org/10.1111/jphp.12574.

Feng, F.; Zhang, J.; Wang, Z.; Wu, Q.; Zhou, X. 2019. Efficacy and safety of N-acetylcysteine therapy for idiopathic pulmonary fibrosis: An updated systematic review and meta-analysis. Experimental and Therapeutical Medicine; 18: 802–816.

Feng, J., Che, Y.S., Milse, J., Yin, Y.J., Liu. L., Ruckert, C., Shen, X.H., Qi, S.W., Kalinowski, J. and Liu, S.J. 2006. The gene ncgl2918 encodes a novel maleylpyruvate isomerase that needs mycothiol as a cofactor and links mycothiol biosynthesis and gentisate assimilation in Corynebacterium glutamicum. Journal of Biological Chemistry; 281: 10778-10785.

Forster, R., Spezia, F., Papineau, D., Sabadie, C., Erdelmeier, I., Moutet, M. and Yadan, J. C. 2015. Reproductive safety evaluation of L-Ergothioneine. Food and Chemical Toxicology; 80: 85-91.

Franzoni, F., Colognato, R, Galetta, F, Laurenza, I., Barsotti,, D.,. Stefano, R,., Bocchetti, R., Regol, F., Carpi, A. and Balbarini, H. 2006. An in vitro study on the free radical scavenging capacity of ergothioneine: comparison with reduced glutathione, uric acid and trolox . Biomedicine Pharmacotherapy; 60: 453-457.

Fu T-T and Shen L .2022. Ergothioneine as a Natural Antioxidant Against Oxidative Stress Related Diseases. Frontiers in Pharmacology; 13:850813. doi: 10.3389/fphar.2022.850813.

Gao, Y., Zhou, B., Zhang, H., Chen, L., Wang, X., Chen, H., & Zhou, L. 2022. l-Ergothioneine Exhibits Protective Effects against Dextran Sulfate Sodium-Induced Colitis in Mice. ACS Omega; 7(25), 21554–21565. https://doi.org/10.1021/acsomega.2c01350

Graham, S.F.; Chevallier, O.P.; Kumar, P.; Türkoglu, O.; Bahado-Singh, R. 2016. Metabolomic profiling of brain ˇ from infants who died from sudden infant death syndrome reveals novel predictive biomarkers. Journal of Perinatology; 37, 91–97.

Grigat, S. Harlfinger, S. Pal, S. Striebinger, R. Golz, S Geerts, A. Lazar, A Schomig, E Grundemann, D. 2007. Probing the substrate specificity of the ergothioneine transporter with methimazole, hercynine, and organic cations. Biochemical Pharmacology; 74:309–316.

Grundemann, D Harlfinger, S. Golz, S Geerts, A. Lazar, A Berkels, R. Jung, N. Rubbert, A. Schomig, E. 2005. Discovery of the ergothioneine transporter. Proceedings of the National Academy of Science of the USA; 102: 5256–5261.

Received:06-09-2022, Accepted: 02-11-2022, Published online: 08-01-2023
Available at https://e-journal.unair.ac.id/MKH/index

Adah et al. MKH (2023).36-52
DOI: 10.20473/mkh.v34i1.2023.36-52

Halliwell, B. and Gutteridge, J.M. 2007. Free Radicals in Biology and Medicine, Fourth Ed.Clarendon Press. Oxford. UK.

Halliwell, B. and Lee, C.Y. 2010. Using isoprostanes as biomarkers of oxidative stress: some rarely considered issues. Antioxidant and Redox Signalling; 13: 145–156.

Halliwell, B.; Cheah, I.K.; Tang, R.M.Y. 2018. Ergothioneine—A diet-derived antioxidant with therapeutic potential. FEBS Letters; 592: 3357–3366.

Hartman, P. E. 1990. Ergothioneine as antioxidant, Methods in Enzymology; 186: 310–318.

Hseu, Y. C., Lo, H. W., Korivi, M., Tsai, Y. C., Tang, M. J. and Yang, H. L. 2015. Dermato-protective properties of ergothioneine through induction of Nrf2/ARE-mediated antioxidant genes in UVA-irradiated Human keratinocytes. Free Radical Biology and Medicine; 86: 102-107.

Kalaras, M.D.; Richie, J.P. Calcagnotto, A.; Beelman, R.B. 2017. Mushrooms: A rich source of the antioxidants ergothioneine and glutathione. Food Chemistry; 233: 429–433.

Kaneko, I., Takeuchi, Y., Yamaoka, Y., Tanaka, Y., Fukuda, T., Fukumori, Y., Mayumi, T. and Hama, T. 1980. Quantitative determination of ergothioneine in plasma and tissues by TLC-densitometry. Chemical and Pharmaceutical Bulletin (Tokyo); 28: 3093–3097.

Kei, O., Kouji, K., Yuri, O, Hitoshi, M. and Daniel, B.Y. 2005. L-Ergothioneine scavenges superoxide and singlet oxygen and suppresses TNF- and IVIIVIP expression in UV-irradiated human dermal fibroblasts. Journal of Cosmetics Science; 56: 17-27.

Khonde, P.L. and Jardine, A. 2015. Improved synthesis of the super antioxidant, ergothioneine, and its biosynthetic pathway intermediates. Organic and Biomolecular Chemistry; 13: 1415-1419.

Kobayashi, D., Aizawa, S., Maeda, T., Tsuboi, I., Yabuuchi, H., Nezu, J., Tsuji, A., and Tamai, I. 2004. Expression of organic cation transporter OCTN1 in hematopoietic cells during erythroid differentiation. Experimental Haematology; 32(12), 1156–1162.

Lamhonwah, A.M. Tein, I . 2006. Novel localization of OCTN1, an organic cation/carnitine transporter, to mammalian mitochondria. Biochemical and Biophysical Research Communications; 345: 1315–1325.

Lamhonwah, A.M., Hawkins, C.E., Tam, C., Wong, J., Mai, L., Tein, I. 2008. Expression patterns of the organic cation/carnitine transporter family in adult murine brain. Brain Development, 30: 31–42

Li, R. W. S., Yang, C., Sit, A.S.M., Kwan, Y.W., Lee, S. M. Y., Hoi, M. P. M.,

Received:06-09-2022, Accepted: 02-11-2022, Published online: 08-01-2023
Available at https://e-journal.unair.ac.id/MKH/index

Adah et al. MKH (2023).36-52
DOI: 10.20473/mkh.v34i1.2023.36-52

Chan, S. W., Hausman, M., Vanhoutte, P. M. and Leung, G. P. H. 2014. Uptake and protective effects of ergothioneine in human endothelial cells. The Journal of Pharmacology and Experimental Therapeutics; 350: 691–700.

Libby, P., Ridker, P. M. and Hansson, G. K. 2011. Progress and challenges in translating the biology of atherosclerosis. Nature; 473: 317–325.

Marone, P.A., Trampota, J. and Weisman, S. 2016. A safety evaluation of a nature-identical L-ergothioneine in Sprague-Dawley rats. International Journal of Toxicology; 35(5): 568-583.

Martin, K.R. 2010. The bioactive agent ergothioneine, a key component of dietary mushrooms, inhibits monocyte binding to endothelial cells characteristic of early cardiovascular disease. Journal of Medicine and Food; 13: 1340–1346.

Mitsuyama, H. and May, J.M. 1999.Uptake and antioxidant effects of ergothioneine in human erythrocytes. Clinical Science; 97(4): 407-411.

Moncaster, J.; Walsh, D.T.; Gentleman, S.M.; Jen, L.S., Aruoma, O.I. 2002. Ergothioneine treatment protects neurons against N-methyl-D-aspartate excitotoxicity in an in vivo rat retinal model. Neuroscience Letters; 328: 55–59.

Muramatsu, H., Matsuo, H., Okada, N., Ueda, M., Yamamoto, H. and Kato, S. I. 2013. Characterization of ergothionase from Burkholderia specie HME13 and its application to enzymatic quantification of ergothioneine. Applied Microbiology and Biotechnology; 97: 5389–5400.

Nakamichi, N. Nakayama, K., Ishimoto, T., Masuo, Y., Wakayama, T., Sekiguchi, H., Satoh, K., Usumi, K., Iseki, S. and Kat, Y. 2016. Food-derived hydrophilic antioxidant ergothioneine is distributed to the brain and exerts antidepressant effect in mice. Brain and Behaviour; 6(6): 477-484.

Nakamura, T Sugiura,S Kobayashi, D Yoshida, K Yabuuchi, H. Aizawa, S Maeda, T Tamai. 2007. Decreased proliferation and erythroid differentiation of K562 cells by siRNA-induced depression of OCTN1 (SLC22A4) transporter gene. Pharmaceutical Research; 24:1628–1635.

Nauta, R. J., Tsimoyiannis, E., Uribe, M., Walsh, D. and Miller, A. 1990. Butterfield, oxygen-derived free radicals in hepatic ischemia and reperfusion injury in the rat. Surgery Gynecology and Obstetrics; 171: 120–125.

Paul, B.D. and Snyder, S.H. 2009. The unusual amino acid L-ergothioneine is a physiologic cytoprotectant. Cell Death and Differentiation; 17: 1-7.

Peltekova, V. D., Wintle, R. F., Rubin, L. A., Amos, C. I., Huang, Q., Gu, X., Newman, B., Van, B., Oene, M.,

Received:06-09-2022, Accepted: 02-11-2022, Published online: 08-01-2023
Available at https://e-journal.unair.ac.id/MKH/index

Adah et al. MKH (2023).36-52
DOI: 10.20473/mkh.v34i1.2023.36-52

Cescon, D., Greenberg, G., Griffiths, A. M. and St George-Hyslop, P. H. 2004. Functional variants of OCTN cation transporter genes are associated with Crohn disease. Nature Genetics; 36(5): 471-5

Pike, C.J., Walencewicz, A.J., Glabe, C. G. and Cotman, C.W. 1991. In vitro aeging of beta amyloid protein causes peptide aggregation and neurotoxicity. Brain Research; 563: 311–314.

Pluskal, T, Ueno, M. and Yanagida, M. 2014. Genetic and metabolic dissection of the ergothioneine and selenoneine biosynthetic pathway in the fission yeast, *Sacromycetespombe* and construction of an over production system. PLoS ONE, 9:e97774. doi:10.1371/journal.pone.0179360.

Pochini, L., Scalise, M., and Indiveri, C. 2015. Immuno-detection of OCTN1 (SLC22A4) in HeLa cells and characterization of transport function. International immunopharmacology; 29(1), 21–26. https://doi.org/10.1016/j.intimp.2015.04.040.

Ramirez-Martinez, A., Wesolek, N., Yadan, J.C., Moutet, M. and Roudot, A. C. 2016. Intake assessment of L-ergothioneine in some European countries and in the United States. Journal of Human and Ecological Risk Assessment; 22(3): 12-18.

Repine, J. E., and Elkins, N. D. 2012. Effect of ergothioneine on acute lung injury and inflammation in cytokine insufflated rats. Preventive Medicine; 54 Suppl(Suppl), S79–S82. https://doi.org/10.1016/j.ypmed.2011.12.006

SaoEmani, C., Williams, M.J., Wiid, I.J., Hiten, N.F., Viljoen, A.J. and Pietersen, R.D.D. 2013. Ergothioneine is a secreted antioxidant in *Mycobacterium semegmatis*. Antimicrobial Agents and Chemotherapy; 57: 3202–3207.

Schauss, A.G., Béres, E., Vértesi, A., Frank, Z.,Pasics, I., Endres, J., Aruoma, O.I., Hirka, G. 2011. The Effect of Ergothioneine on Clastogenic Potential and Mutagenic Activity. International Journal of Toxicology; 30, 405–409

Schauss, A.G., Béres, E.,Vértesi, A.,Frank, Z.,Pasics, I.,Endres, J.,Aruoma, O.I., Hirka, G. 2011. The Effect of Ergothioneine on Clastogenic Potential and Mutagenic Activity. International Journal of Toxicology; 30: 405–409.

Schauss, A.G.; Vértesi, A.; Endres, J.R.; Hirka, G.; Clewell, A.E.; Qureshi, I.; Pasics, I. 2010. Evaluation of the safety of the dietary antioxidant ergothioneine using the bacterial reverse mutation assay; Toxicology, 278: 39–45.

Seet, R.C., Lee, C.Y., Loke, W.M., Huang, S.H., Huang, H., Looi, W.F., Chew, E.S., Quek, A.M., Lim, E.C. and Halliwell, B. 2011. Biomarkers

Received:06-09-2022, Accepted: 02-11-2022, Published online: 08-01-2023
Available at https://e-journal.unair.ac.id/MKH/index

Adah et al. MKH (2023).36-52
DOI: 10.20473/mkh.v34i1.2023.36-52

of oxidative damage in cigarette smokers: which biomarkers might reflect acute versus chronic oxidative stress. Free Radical Biology and Medicine; 50: 1787–1793.

Servillo, L., D'Onofrio, N., and Balestrieri, M. L. 2017. Ergothioneine Antioxidant Function: From Chemistry to Cardiovascular Therapeutic Potential. Journal of Cardiovascular Pharmacology; 69(4), 183–191. https://doi.org/10.1097/FJC.0000000000000464.

Sheridan, K. J., Lechner, B. E., Keeffe, G. O., Keller, M. A., Werner, E. R., Lindner, H., Jones, G. W., Haas, H., and Doyle, S. 2016. Ergothioneine Biosynthesis and Functionality in the Opportunistic Fungal Pathogen, *Aspergillus fumigatus*. Scientific Reports; 6: 35306. https://doi.org/10.1038/srep35306

Shinozaki, Y., Furuichi, K., Toyama, T., Kitajima, S., Hara, A., Iwata, Y., Sakai, N., Shimizu, M., Kaneko, S., Isozumi, N., Nagamori, S., Kanai, Y., Sugiura, T., Kato, Y., and Wada, T. 2017. Impairment of the carnitine/organic cation transporter 1-ergothioneine axis is mediated by intestinal transporter dysfunction in chronic kidney disease. Kidney International; 92(6), 1356–1369. https://doi.org/10.1016/j.kint.2017.04.032

Smith, E., Ottosson, F., Hellstrand, S., Ericson, U., Orho-Melander, M., Fernandez, C., and Melander, O. 2020. Ergothioneine is associated with reduced mortality and decreased risk of cardiovascular disease. Heart (British Cardiac Society); 106(9), 691–697. https://doi.org/10.1136/heartjnl-2019-315485.

Song, H, Hu, W., Naowarojna, N., Her, A. S., Wang, S., Desai, R., Qin, L., Chen, X. and Liu, P. 2015).Mechanistic studies of a novel C-S lyase in ergothioneine biosynthesis: the involvement of a sulpenic acid intermediate. Scientific Reports; 5: 118-126.

Song, T. Y., Lin, H. C., Chen, C. L., Wu, J. H., Liao, J. W., and Hu, M. L. 2014. Ergothioneine and melatonin attenuate oxidative stress and protect against learning and memory deficits in C57BL/6J mice treated with D-galactose. Free Radical Research; 48(9), 1049–1060. https://doi.org/10.3109/10715762.2014.920954].

Sotgia, S., Pisanu, E, Pintus, G., Erre, G. L. and Pinna, G. A. 2013. Plasma l-ergothioneine measurement by high-performance liquid chromatography and capillary electrophoresis after pre-column derivatization with 5-iodoacetamidofluorescein (5-iaf) and fluorescence detection. PLoS ONE; 8(7): e70374. doi:10.1371/journal.pone.01693623

Sotgia, S., Zinellu, A., Arru, D., Nieddu, S., Strina, A., Ariu, F., Pintus, G.,

Received:06-09-2022, Accepted: 02-11-2022, Published online: 08-01-2023
Available at https://e-journal.unair.ac.id/MKH/index

Adah et al. MKH (2023).36-52
DOI: 10.20473/mkh.v34i1.2023.36-52

Carru, C., Bogliolo, L. and Ledda, S. 2015. Amniotic fluid l-ergothioneine concentrations in pregnant sheep after natural mating and transfer of vitrified/thawed in vitro produced embryos. Research in Veterinary Science; 102: 238-241.

Tamai, H. Yabuuchi, J. Nezu, Y. Sai, A. Oku, M. Shimane, A. Tsuji, O. 1997. Cloning and characterization of a novel human pH-dependent organic cation transporter, OCTN 1. FEBS Letters; 419: 107–111.

Tang, R.M., Cheah, I.K., Yew, T.S. and Halliwell, B. 2018. Distribution and accumulation of dietary ergothioneine and its metabolites in mouse tissues. Scientific Reports; 8: 1601-1615.

Tang, R.M.Y.; Cheah, I.K.-M.; Yew, T.S.K.; Halliwell, B. 2018. Distribution and accumulation of dietary ergothioneine and its metabolites in mouse tissues. Scientific Reports; 8: 1601.

Taubert, D., Lazar, A., Grimberg, G., Jung, N., Rubbert, A., Delank, K. S., Perniok, A., Erdmann, E. and Schomig, E. 2006. Association of rheumatoid arthritis with ergothioneine levels in red blood cells: a case control study. Journal of Rheumatology; 33: 2139–2145.

Tucker, R., Cheah, I. K., & Halliwell, B. 2019. Specificity of the ergothioneine transporter natively expressed in HeLa cells. Biochemical and Biophysical Research Communications; 513(1), 22–27. https://doi.org/10.1016/j.bbrc.2019.02.122.

Turck, D., Bresson, J.L.,Burlingame, B.,Dean, T.,Fairweather-Tait, S.,Heinonen, M., Hirsch-Ernst, K.I., Mangelsdorf, I., McArdle, H.J., Naska, A., et al. 2016. Safety of synthetic l-ergothioneine (Ergoneine®) as a novel food pursuant to Regulation (EC) No 258/97. EFSA Journal; 14: e04629.

Vickers, T.J. and Fairlamb, A.H. 2004. Trypanothione S-transferase activity in a trypanosomatid ribosomal elongation factor 1B. Journal of Biological Chemistry; 279: 27246–27256.

Wang, L.Z., Thuya, W.L., Toh, D.S., Lie, M.G., Lau, J.Y., Kong, L.R., Wan, S.C., Chua, K. N, Lee, E.J, Goh, B.C. 2013. Quantification of L-ergothioneine in human plasma and erythrocytes by liquid chromatography-tandem mass spectrometry. Journal of Mass Spectrometry; 48(3) 406-412. doi:10.1002/jms.3150. PMID: 23494799.

Yang, N. C., Lin, H. C., Wu, J. H., Ou, H. C., Chai, Y. C., Tseng, C. Y., Liao, J. W. and Song, T. Y. 2012. Ergothioneine protects against neuronal injury induced by β-amyloid in mice. Food and Chemical Toxicology; 50(11): 3902-3911.

Yoshida, S, Shime, H., Funami, K., Takaki, H., Matsumoto, M. and

Received:06-09-2022, Accepted: 02-11-2022, Published online: 08-01-2023
Available at https://e-journal.unair.ac.id/MKH/index

Adah et al. MKH (2023).36-52
DOI: 10.20473/mkh.v34i1.2023.36-52

Kasahara, M. 2017. The Antioxidant ergothioneine augments the immunomodulatory function of TLR agonists by direct action on macrophages. PLoS ONE; 12(1): e0169360, doi:10.1371/journal.pone.0169360.

Zhang, Y., Bond, C. S., Bailey, S., Cunningham, M. L., Fairlamb, A. H. and Hunter, W. N. 1996. The crystal structure of trypanothione reductase from the human pathogen *Trypanosomacruzi* at 2.3 A resolution. Protein Science; 5(1): 52-61.

Zhu, B. Z., Mao, L., Fan, R. M., Zhu, J. G., Zhang, Y. N., Wang, J., Kalyanaraman, B., and Frei, B. 2011. Ergothioneine prevents copper-induced oxidative damage to DNA and protein by forming a redox-inactive ergothioneine-copper complex. Chemical Research in Toxicology; 24(1), 30–34. https://doi.org/10.1021/tx100214t

Received:06-09-2022, Accepted: 02-11-2022, Published online: 08-01-2023
Available at https://e-journal.unair.ac.id/MKH/index