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Review on Anticancer Activity of Mushroom Derived Ergothioneine

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ABSTRACT: Mushrooms are rich in bioactive compounds including polysaccharides, lectins, and L-ergothioneine (EGT), which contribute to their therapeutic potential, particularly in cancer prevention and treatment. Ergothioneine (EGT), a potent antioxidant amino acid found in high concentrations in mushrooms, plays a unique role in protecting cells from oxidative stress, especially when primary antioxidants like glutathione are depleted. It has shown promise in reducing the risk of cancers such as prostate, colorectal, and ovarian, and in mitigating the adverse effects of chemotherapeutic agents like cisplatin. EGT a influences key cellular signalling pathways, particularly those involving sirtuins (SIRT1–SIRT7), which are integral to redox regulation and epigenetic control in cancer biology. Studies highlight EGT's ability to induce necroptosis in colorectal cancer cells via the SIRT3–MLKL pathway, suggesting a mechanistic link between its antioxidant function and cell death induction. EGT's dual role in redox balance and sirtuin modulation positions it as a potential candidate for future cancer therapies.

Keywords: Sirtuin, Ergothioneine, Anticancer activity, Colectoral cancer, Ovarian cancer, Mushrooms, Redox signalling.

INTRODUCTION

Mushrooms are known for their abundance in fiber, vitamins, and minerals like potassium, phosphorus, and vitamin B. Bioactive substances, such as anticancer polysaccharides, are also present in them. Numerous mushroom species have been reported to possess anticarcinogenic properties primarily due to their ability to modulate the immune system and stimulate the body's defense against cancer. Phase I or II clinical trials have examined a number of mushrooms, primarily for the treatment of breast cancer (18.6%), colorectal cancer (14%), and prostate cancer (11.6%). Different metabolites derived from mushrooms present a potential pathway for cancer treatment and prevention by harnessing their capacity to regulate the immune system, suppress tumor development, trigger apoptosis, and impact cancer cell metabolism.

For example, lectins recovered from mushroom might activate macrophages and prevent the growth of implanted cancer cells in mice, whereas phytochemicals included in white button mushroom extracts have been reported to inhibit aromatase activity and proliferation in breast cancer cell lines. These phytochemicals also have an impact on oxidative stress inhibition and free radical scavenging activities. Suppression of DNA synthesis, changes to membrane shape, and competition for estrogen receptors are other possible pathways (Lee *et al*., 2013).

MUSHROOM METABOLITES

Mushrooms are rich in nutrients, minerals, vitamins, proteins, and bioactive substances such polysaccharides, steroids, phenolic compounds, and terpenes (Sarita *et al*., 2023). The most well-known components extracted from mushrooms are polysaccharides. One of the most prevalent types of polysaccharides is β-glucan, a glucose polymer that comes from a variety of sources. Fungal β-glucans, a class of high molecular weight polysaccharides, such as lentinan, grifolan, and GL-1, are among the bioactive ingredients in mushrooms. Other active substances include lectins, triterpenes, ganoderans, protein-bound polysaccharides, lignins, purines, and polyphenols, particularly flavonoids; proteoglycans (maitake D-fraction) and polysaccharide peptides (e.g., PSP, PSK); and glycans. Further, activity-guided isolation led to the discovery of aromatic compounds and sphingolipids from the coculture broth of *T. versicolor* SY630 and *V. robiniophila* SY341 (Ji *et al*., 2024).

The role of lectins is to attach to carbohydrates in membranes. Its general mechanism is to attach itself to the mutant cell's membrane or its receptors, which triggers apoptosis and, as a result, aids in the tumor's reduction (Chang and Miles 1989). *In vitro*, animal, and clinical trials have demonstrated anticancer properties of lectin as a therapeutic agent. Certain lectins from *G. frondosa* and *A. bisporus* have anticancer as well as antiproliferative properties. The

reduction of growth of breast cancer cells have been reported by maitake D fraction from *G. frondosa* by exerting proapoptotic effects and reducing tumor cell viability (Manzi *et al.*,1999).

Terpenoids extracted from fungal species have exhibited anti-inflammatory effects by reducing nitric oxide (NO) and pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. Additionally, they demonstrate anti-microbial effects against pathogens like *Escherichia coli*, *Staphylococcus aureus*, and *Bacillus cereus* (Zhang *et al.*, 2021; Bunbamrung *et al*., 2017; Duan *et al*., 2018). With their medicinal effects, terpenes and their derivatives hold promise for the treatment of various malignancies, prompting further research to enhance understanding and practical applications in anticancer therapy. Some Triterpenoids from *Ganoderma lucidum* have already reported to possess anticancer properties (Dasgupta and Acharya 2021).

L-ERGOTHIONEINE (EGT)

Furthermore, mushrooms contain l-ergothioneine, an uncommon amino acid with antioxidant qualities that can shield cells from oxidative stress by blocking free radicals. It has recognized as one of the strongest dietary antioxidants. It is present in common foods like grains, chicken liver, and oat bran, but preliminary research has shown that mushrooms have the highest concentration of EGT of any food (Kalaras *et al*., 2017). It might play a beneficial effect for long-term human health by acting as a last line of defense against oxidation in cells where glutathione may have been depleted. Additionally, because of its special function in shielding mitochondria from oxidation, ergothioneine has been proposed as a longevity vitamin based on triage theory.

Because of their many therapeutic uses, edible mushrooms are utilized all over the world and contain bioactive chemicals that promote health. L-ergothioneine (LE), a water-soluble antioxidant amino acid that contains thiols, is one of the special bioactive substances present in mushrooms. High pH and temperatures do not cause it to break down because it is a stable antioxidant molecule. Neither plants nor animals, including humans, can manufacture L-ergothioneine (EGT). Thus, LE is acquired by nutrition, primarily from edible mushrooms including *Grifola frondosa, Agaricus bisporus, Lentinula edodes, and Pleurotus ostreatus.* There have been reports of a high EGT content in some types of mushrooms. LE is known as the longevity vitamin and is thought to be a chemical for longevity (Pachaimuthu *et al*., 2019). It has been observed that decreased blood and/or plasma levels of ergothioneine in some diseases, suggesting its deficiency could be relevant to the disease onset or progression (Halliwell *et al*., 2018).

ANTIOXIDANT ACTIVITY OF L ERGOTHIONEINE

Ergothioneine is a powerful scavenger of hydroxyl radicals (‘OH) and an inhibitor of iron or copper ion-dependent generation of ‘OH from hydrogen peroxide (H,O,). Similar to ascorbic acid, the naturally occurring amino acid ergothioneine (EGT) has a strong capacity to scavenge free radicals. EGT is reported to have hydrogen peroxide scavenging, hydroxyl radicals, and superoxide anions activity with IC_{50} values of 11.65 ± 0.31, 70.31 ± 1.59, and 160.44 ± 0.32 µg/ml. (Liu *et al.*, 2020). Although the EGT content varied considerably ($p < 0.05$) among the diverse species of mushrooms, it had no significant relationship with the mushrooms' capacity to scavenge reactive oxygen species ($p > 0.05$) (Liu *et al.*, 2020).

Ergothioneine may not principally react to ROS the same way as primary antioxidants do. It becomes important only when primary antioxidants, such as GSH, are exhausted during oxidative stress (Paul, 2022; Halliwell *et al.*, 2023). Ergothioneine has been suggested to act as an antioxidant *in vivo* and has been reported to be present in human and other mammalian tissues at concentrations up to l-2 mM (Akanmu *et al*., 1991). Liu *et al*. (2020) investigated EGT's stability and discovered that it possesses outstanding acid-base, light, and thermal stability. Cu^{2+}, on the other hand, reduced the EGT concentration. The EGT isolated from *Pleurotus citrinopileatus* (PEGT) has poorer thermal stability and its concentration decreased with prolonged high-temperature heating (Liu *et al*., 2020).

ANTICANCER ACTIVITY OF L ERGOTHIONEINE

Several studies have reported decreased risk of prostate cancer with regular consumption of mushrooms (Zhang *et al*., 2020). The research indicated a negative correlation between mushroom intake and the occurrence of prostate cancer among middle-aged and older Japanese men, implying that regular consumption of mushrooms may aid in preventing prostate cancer. Regardless of other dietary considerations, the study, which involved nearly 36,000 men between the ages of 40 and 79, found that regular mushroom consumption significantly reduced the incidence of prostate cancer. The scientists hypothesize that the high concentration of ergothioneine in mushrooms may be a contributing factor to the compound's antioxidant and cancer-preventive qualities, even though the data does not prove a cause-and-effect relationship. Ba *et al.* (2021) also reported increased mushroom consumption and decreased risk of stomach malignancies, according to studies done in Korea and Japan (Ba *et al*., 2021).

Ergothioneine has the potential to reduce the negative effects of cisplatin chemotherapy treatment, according to a recent study. A powerful anticancer drug that is frequently used in the chemotherapy of many solid cancers, cisplatin is infamous for having serious adverse effects include nausea, vomiting, loss of cognition, neurotoxicity, and neuropathy. Ergothioneine, possibly through reducing oxidative stress and reviving nervous system activity, had a protective effect against cisplatin-induced neuropathy and enhanced cognition in a rat-based study (Amaranthus, 2023). Studies have reported the active compounds of mushrooms with antineoplastic properties and mechanisms of action (Kirdeeva *et al*.,

2022).

ROLE IN INHIBITION OF COLORECTAL CANCER (CRC)

A study reported by D'Onofrio *et al.* (2022). examined EGT's anti-cancer effects on colorectal cancer cells (CRC). EGT treatment increased the histone deacetylase SIRT3, caused reactive oxygen species to accumulate, decreased mitochondrial membrane potential, and exhibited cytotoxicity in a dose-dependent manner. According to immunoblotting research, the RIP1/RIP3/MLKL pathway was activated, causing necroptosis and cell death. An immunoprecipitation test revealed that during the EGT therapy, there was an increase in the interaction between SIRT3 and the terminal effector in necroptotic signaling, MLKL (Mixed Lineage Kinase Like Psuedokinase).

Silencing the SIRT3 gene prevented MLKL from being upregulated and eliminated EGT's capacity to cause necroptosis. The necroptotic effects of EGT in CRC may be mediated by the SIRT3–MLKL interaction, indicating the potential of this dietary aminothione in CRC prevention (D'Onofrio *et al.*, 2022). Further, higher Ergothioneine concentrations tended to be associated with lower prevalence of total and sensory peripheral neuropathy in colorectal cancer (CRC) patients (Winkels *et al.*, 2020).

ROLE IN PREVENTION OF OVARIAN CANCER

A study reported by Lee *et al.* (2013) says mushroom intake at high levels was associated with a reduced risk of epithelial ovarian cancer among southern Chinese women, particularly for the common *Agaricus bisporus* mushroom Lee *et al*. (2013). Similar inverse associations have been reported for gastric and breast cancers. But the molecular and biochemical mechanisms have not been elucidated yet. Ergothioneine exerted protective effects on intracellular ROS production and mitochondrial morphology. These results provide evidence to support the protective effects of EGT on chondrocytes as well as cells damaged by oxidative stress (Sakata *et al*., 2024).

ROLE IN RENAL CANCER

In rats treated with cisplatin, ergothioneine enhances kidney function. Ergothioneine inhibits the up-regulation of p53 and NF-κB (Nuclear factor kappa B) by cisplatin. In rats treated with cisplatin, ergothioneine stimulates Nrf2 (Nuclear factor erythroid 2-related factor 2) signaling and reduces gamma glutamyl transferase (GGT) activity. In renal tissues, ergothioneine inhibits oxidative damage brought on by cisplatin. But the effect on renal cancer has not been elucidated yet (Salama *et al*., 2021). Furthermore, EGT treatment has reported to elevate the expression of major antioxidant transcription factors, cytoprotective genes and decreased the expression of inflammatory genes in the kidney (Dare *et al*., 2021). Ergothioneine reported to possess antioxidant and anti-inflammatory properties that confer cryoprotection. EGT can cross the blood–brain barrier and has also reported to have beneficial effects in the brain (Paul, 2022). It has reported that supplementation with L-ergothioneine not only protects the organs against the lipid peroxidation but conserves the consumption of endogenous glutathione and alpha-tocopherol (Deiana *et al*., 2004).

ERGOTHIONEINE AND SIRTUIN SIGNALING PATHWAY IN CANCER

Sirtuins (SIRTs 1–7) comprise a group of nicotinamide adenine dinucleotide (NAD)-dependent histone deacetylases that can deacetylate both histone and nonhistone substrates. Recent research indicates that sirtuins influence the regulation of various cellular processes linked to ARS (Antioxidant and Redox Signalling). In mammals, the Sirtuin family of seven enzymes has been linked to both epigenetic functions and metabolic regulation (Brunet *et al*., 2004; Chen *et al*., 2005). Among these, SIRT1, SIRT3, and SIRT5 safeguard the cell against ROS, while SIRT2, SIRT6, and SIRT7 regulate important oxidative stress genes and processes. Notably, SIRT4 has been demonstrated to promote ROS production and also plays antioxidative roles.

Sirtuin's deacetylase utilizes NAD+, a crucial molecule for redox signaling, suggesting that Ergothioneine could influence Sirtuins' function by altering NAD+ levels. The ratio of [NAD+]/[NADH] serves as an important redox indicator for assessing the metabolic and physiological condition of the cell. (Imai and Guarente 2014), The depletion of NAD+ due to oxidative stress negatively impacts the proper operation of Sirtuins. Acting as an antioxidant, Ergothioneine may help regulate the balance between prooxidants and antioxidants while preserving the metabolic co-factor pool of NAD+, which directly influences the function of Sirtuins.

In addition, as summarized by Kalous *et al*. (2021), one of the mechanisms that decrease the activity of Sirtuins could be the oxidative post-translational modification by ROS and RNS. In stressed cells, such as those found in cancer, there is an increase in reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to a decrease in Sirtuin activity (Salminen *et al*., 2013). Ergothioneine, known for its role in scavenging ROS and RNS, may also boost Sirtuin activity by protecting Sirtuin enzymes from oxidative modifications.

A study showed that Ergothioneine induces necroptosis in colorectal cancer cells by upregulating SIRT6. Studies revealed that Ergothioneine exerts anti-ageing and anti-cancer properties via Sirtuin signaling, suggesting that Ergothioneine has a dynamic regulatory role in signaling pathways in CRC. SIRT3 also serves as a therapeutic target exhibiting both oncogenic and tumor suppressive functions.

Ergothioneine activates SIRT3 both *in vitro and in vivo*. This activation is associated with anti-cancer benefits, such as decreased cancer cell viability and progression. Ultimately, although the exact method by which Egt induces cell death remains unclear, its pr

o-oxidant and anticancer effects are associated with the upregulation of the SIRT3 protein (D'Onofrio *et al.*, 2022).

While SIRT3 has been noted to have a protective effect against cell death, recent findings reveal that its overexpression leads to metabolic reprogramming and induces cell death in colorectal cancer, as well as activating necroptosis in small-cell lung cancer by regulating the ubiquitination of mutant p53 (Tang *et al.*, 2020). However, additional research on CRC cells that overexpress SIRT3 is needed to conclusively determine if SIRT3 is a key mediator of EGT-induced necroptosis. Further research will be essential in enhancing the understanding of the molecular mechanisms and in supplying in vivo evidence regarding the anti-cancer effects of EGT in CRC (D'Onofrio *et al.*, 2022).

CONCLUSIONS

This review focused on the bioactivity of mushroom derived ergothioneine on different cancers. Ergothioneine being a diet derived amino acid with significant reported antioxidant activities on several aspects with major activities being reported with respect to neuroprotection and antiinflammation. Thus, the need to review its bioactivity with respect to different cancers where oxidative stress plays a major role is the need of the hour. On an intensive literature survey, it came to the conclusion that mushroom derived ergothioneine could inhibit the progression of colorectal cancer possibly by specific inhibition of MLKL pathway.

FUTURE SCOPE

The mechanism of action of ergothioneine in other potential gastric cancers including ovarian, hepatic, pancreatic etc. has not been reported yet which opens up way for further scientific investigations.

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REFERENCES

Amaranthus, M. (2023). A Mushroom-derived Compound that Could Change your Life: Ergothioneine. *Food Nutr J.*, *8*, 282.

Akanmu, D., Cecchini, R., Aruoma, O. I. and Halliwell, B. (1991). The antioxidant action of ergothioneine. *Archives of biochemistry and biophysics*, *288*(1), 10-16.

Ba, D. M., Ssentongo, P., Beelman, R. B., Muscat, J., Gao, X. and Richie Jr, J. P. (2021). Higher mushroom consumption is associated with lower risk of cancer: a systematic review and meta-analysis of observational studies. *Advances in Nutrition*, *12*(5), 1691-1704.

Bunbamrung, N., Intaraudom, C., Dramae, A., Boonyuen, N., Veeranondha, S., Rachtawee, P. and Pittayakhajonwut, P. (2017). Antimicrobial activity of illudalane and alliacane sesquiterpenes from the mushroom *Gloeostereum incarnatum* BCC41461. *Phytochemistry Letters*, *20*, 274-281.

Chang, S. T. and Miles, P. G. (1989). *Edible mushrooms and their cultivation* (pp. 345-pp).

Dare, A., Channa, M. L. and Nadar, A. (2021). L-ergothioneine and its combination with metformin attenuates renal dysfunction in type-2 diabetic rat model by activating Nrf2 antioxidant pathway. *Biomedicine & Pharmacotherapy*, *141*, 111921.

Dasgupta, A. and Acharya, K. (2021). Bioactive terpenoids from mushrooms. In *New and Future Developments in Microbial Biotechnology and Bioengineering* (pp. 145-154). Elsevier.

Deiana, M., Rosa, A., Casu, V., Piga, R., Dessì, M. A. and Aruoma, O. I. (2004). L-ergothioneine modulates oxidative damage in the kidney and liver of rats in vivo: studies upon the profile of polyunsaturated fatty acids. *Clinical Nutrition*, *23*(2), 183-193.

D'Onofrio, N., Martino, E., Balestrieri, A., Mele, L., Cautela, D., Castaldo, D. and Balestrieri, M. L. (2022). Diet-derived ergothioneine induces necroptosis in colorectal cancer cells by activating the SIRT3/MLKL pathway. *FEBS letters*, *596*(10), 1313-1329.

Duan, Y. C., Feng, J., Bai, N., Li, G. H., Zhang, K. Q. and Zhao, P. J. (2018). Four novel antibacterial sesquiterpene-α-amino acid quaternary ammonium hybrids from the mycelium of mushroom *Stereum hirsutum*. *Fitoterapia*, *128*, 213-217.

Halliwell, B., Cheah, I. K. and Tang, R. M. (2018). Ergothioneine–a diet-derived antioxidant with therapeutic potential. *FEBS letters*, *592*(20), 3357-3366.

Halliwell, B., Tang, R. M. and Cheah, I. K. (2023). Diet-derived antioxidants: the special case of ergothioneine. *Annual Review of Food Science and Technology*, *14*(1), 323-345.

Ji, L., Tan, L., Shang, Z., Li, W., Mo, X., Yang, S. and Yu, G. (2024). Discovery of new antimicrobial metabolites in the coculture of medicinal mushrooms. *Journal of Agricultural and Food Chemistry*, *72*(10), 5247-5257.

Kalaras, M. D., Richie, J. P., Calcagnotto, A. and Beelman, R. B. (2017). Mushrooms: A rich source of the antioxidants ergothioneine and glutathione. *Food chemistry*, *233*, 429-433.

Kalous, K. S., Wynia-Smith, S. L. and Smith, B. C. (2021). Sirtuin oxidative post-translational modifications. *Frontiers in Physiology*, *12*, 763417. Imai S, Guarente L. NAD+ and sirtuins in aging and disease. *Trends Cell Biol.*, *24*, 464–471.

Kirdeeva, Y., Fedorova, O., Daks, A., Barlev, N. and Shuvalov, O. (2022). How should the worldwide knowledge of traditional cancer healing be integrated with herbs and mushrooms into modern molecular pharmacology?. *Pharmaceuticals*, *15*(7), 868.

Lee, A. H., Pasalich, M., Su, D., Tang, L., Tran, V. D. and Binns, C. W. (2013). Mushroom intake and risk of epithelial ovarian cancer in southern Chinese women. *International Journal of Gynecological Cancer*, *23*(8), 1400-1405.

Liu, X., Huang, Y., Wang, J., Zhou, S., Wang, Y., Cai, M. and Yu, L. (2020). A study on the antioxidant properties and stability of ergothioneine from culinary-medicinal mushrooms. *International Journal of Medicinal Mushrooms*, *22*(3).

Manzi, P., Gambelli, L., Marconi, S., Vivanti, V. and Pizzoferrato, L. (1999). Nutrients in edible mushrooms: an inter-species comparative study. *Food chemistry*, *65*(4), 477-482.

Paul, B. D. (2022). Ergothioneine: a stress vitamin with antiaging, vascular, and neuroprotective roles?. *Antioxidants & Redox Signaling*, *36*(16-18), 1306-1317.

Sakata, S., Kunimatsu, R. and Tanimoto, K. (2024). Protective Effect of Ergothioneine against Oxidative Stress-Induced Chondrocyte Death. *Antioxidants*, *13*(7), 800.

Salama, S. A., Abd-Allah, G. M., Mohamadin, A. M., Elshafey, M. M. and Gad, H. S. (2021). Ergothioneine mitigates cisplatin-evoked nephrotoxicity via targeting Nrf2, NF-κB, and apoptotic signaling and inhibiting γ-glutamyl transpeptidase. *Life Sciences*, *278*, 119572.

Salminen, A., Kaarniranta, K., & Kauppinen, A. (2013). Crosstalk between oxidative stress and SIRT1: impact on the aging process. *International journal of molecular sciences*, *14*(2), 3834-3859.

Sarita, Roop, S. I., Kalpna, Y., Karan, S., Priyanka and Gagandeep S. (2023). Cultivation of Oyster Mushroom: A Review. *Biological Forum-An International Journal*, *15*(8), 412-418.

Tang, X., Li, Y., Liu, L., Guo, R., Zhang, P., Zhang, Y. and Liu, Y. (2020). Sirtuin 3 induces apoptosis and necroptosis by regulating mutant p53 expression in small-cell lung cancer. *Oncology reports*, *43*(2), 591-600.

Winkels, R. M., Van Brakel, L., Van Baar, H., Beelman, R. B., Van Duijnhoven, F. J., Geijsen, A. and Kok, D. E. (2020). Are ergothioneine levels in blood associated with chronic peripheral neuropathy in colorectal cancer patients who underwent chemotherapy?. *Nutrition and cancer*, *72*(3), 451-459.

Zhang, L., Yin, M., Feng, X., Ibrahim, S. A., Liu, Y. and Huang, W. (2021). Anti-inflammatory activity of four triterpenoids isolated from poriae cutis. *Foods*, *10*(12), 3155.

Zhang, S., Sugawara, Y., Chen, S., Beelman, R. B., Tsuduki, T., Tomata, Y. and Tsuji, I. (2020). Mushroom consumption and incident risk of prostate cancer in Japan: A pooled analysis of the Miyagi Cohort Study and the Ohsaki Cohort Study. *International Journal of Cancer*, *146*(10), 2712-2720.

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