bioclinic naturals
natural solutions + clinical results
bioclinicnaturals.com

Glutathione LipoMicel®

INTRODUCTION

Oxidative stress has long been suspected to play a causal role in the aging process by irreparably damaging DNA, proteins, and other cellular structures that promote the cellular senescence associated with impaired cellular function and "inflammaging." It is the accumulation of damage and dysfunction over time that leads to a decrease in cellular health and, ultimately, a decline in organ and system function.[1] Given that many metabolic processes produce reactive oxygen species (ROS), particularly mitochondrial energy production, exposure to oxidative stress is unavoidable. However, the degree of damage caused by ROS is only partially dependent on ROS exposure; a more significant factor may be the capacity of a cell's antioxidant defences. Multiple models of aging support this hypothesis. For example, mice strains with longer lifespans have higher expression of antioxidant enzymes and reduced oxidative stress.[2] In addition to aging, excessive oxidative damage appears to be a significant driving factor for many chronic conditions related to aging, such as cardiovascular disease.[3]

WHAT IS GLUTATHIONE?

Glutathione, a tripeptide comprised of glycine, cysteine, and glutamic acid, is the most abundant intracellular antioxidant and is found in all cells. It is synthesized intracellularly via the ATP-dependent enzymes glutamate-cysteine ligase (GCL, aka γ-glutamylcysteine ligase) and glutathione synthetase. It is regenerated by six enzyme-catalyzed reactions, known as the γ-glutamyl cycle, and exists primarily in its reduced form (GSH) with less than 1–2% as an oxidized form (GSSG).[4] The GSH/GSSG ratio may exceed 100 in resting cells, dropping to as low as 1–10 in cells exposed to oxidative stress. This allows for GSH/GSSG to be used as a predictor of the cellular redox state.[5] The rate-limiting factors for glutathione synthesis are GCL activity and cysteine availability, with the former upregulated by the transcription factor nuclear factor-erythroid 2-related factor 2 (Nrf2), the master regulator of cellular antioxidant protection.[6]

In addition to glutathione's role as an antioxidant, it also has numerous other roles related to maintaining cellular homeostasis. Many of its functions are mediated by maintaining the sulfhydryl groups of cellular proteins (post-translational modification), thereby influencing cellular signalling pathways by activating/inactivating thiol-containing enzymes.[7] Glutathione is also recognized as a storage form for cysteine, which would otherwise be degraded rapidly within the cell and become a source of oxidative damage itself.[8] By binding to sulfhydryl groups, glutathione is a critical component of a cell's detoxification ability, as many endogenous and exogenous compounds are bound and eliminated by conjugation with glutathione. In addition, glutathione is involved in the detoxification of many compounds, including estrogen, leukotrienes, acetaminophen, persistent organic pollutants, mercury, arsenic, cadmium, and lead.[9] Glutathione is also a regulator of gene expression and mitochondrial integrity, and plays a role in DNA and protein synthesis and repair.[10]

MECHANISM OF ACTION

As an example of oxidant neutralization by glutathione, hydrogen peroxide (formed from the superoxide molecule) is a strong oxidative agent converted into water by glutathione. The reaction consumes two molecules of glutathione (GSH) per hydrogen peroxide molecule, producing water and GSSG, and is catalyzed by glutathione peroxidase.[11] Glutathione can also react with many compounds spontaneously (without requiring an enzyme), though it is a cofactor or coenzyme for many cellular enzymes. For example, the enzymes known as glutathione S-transferases (GSTs) catalyze glutathione conjugation to many toxins and endogenous compounds.[4]

It's important to note that because glutathione is needed for such a diverse range of functions and detoxification reactions, it can be depleted by oxidative stress as well as exposure to environmental toxins (xenobiotics).[12] Both hyperglycemia and hyperinsulinemia have been shown to inhibit GCL activity, and are also associated with an increase in ROS that further consumes GSH.[13,14] Multiple chronic conditions have been associated with reduced cellular levels of GSH, including many cardiovascular, metabolic, and neurological conditions.[10,15] Furthermore, aging itself has been associated with a reduced capacity to synthesize glutathione, with a lower concentration of GSH in older adults compared to young adults, leading to an increase in blood markers of oxidative damage.[16] Decreased levels of GSH have been proposed as an indicator of multi-system dysfunction, as they have been linked to a greater disease burden (multimorbidity) in adults.[17]

Human clinical trials have shown that glutathione (GSH) levels, measured in plasma, erythrocytes, lymphocytes, and buccal cells, are increased with glutathione supplementation.[18] More optimal delivery forms of glutathione that are resistant to intestinal degradation and have greater bioavailability have also been developed, including liposomal glutathione and polymeric micelles.[19] Polymeric micelles disperse their ingredients into tiny microdroplets to enhance the delivery of poorly bioavailable substances.[20] Providing intact glutathione may also avoid potential limitations related to the poor activity of GCL or glutathione synthetase.

ASSESSMENT

No specific contraindications exist for glutathione supplementation, though reduced levels of GSH have been documented in a wide range of conditions.[15] However, glutathione supplementation may theoretically reduce the effectiveness of chemotherapeutic medications and should only be used concomitantly under physician guidance.[8]

GENERAL RECOMMENDATIONS AND DOSING

Take 2 easy-to-swallow softgels per day or as directed by a health care practitioner.

Head office Assured Natural Distribution Inc., 104 – 3686 Bonneville Place, Burnaby, BC, Canada V3N 4T6 | **U.S. Distribution office** 14224 167th Avenue SE, Monroe, WA, USA 98272
Customer Service 1·888·826·9625 · **Fax** 1·877·433·9862 · **Email** customerservice@bioclinicnaturals.com · **bioclinicnaturals.com**

SUMMARY

Glutathione is the backbone of intracellular antioxidant defence and has a major role in the maintenance of cellular health and function. Its vital roles in mitochondrial function, cellular signalling, protein (thiol) modification, and detoxification of numerous endogenous and exogenous molecules highlight its importance to optimal cellular health and longevity. It is also critical for mitigating the oxidative stress and damage that accompany both the aging process and increased cellular metabolic and detoxification demands.[21]

REFERENCES

1. Liang, Y., & Wang, Z. (2018). Which is the most reasonable anti-aging strategy: Meta-analysis. *Adv Exp Med Biol, 1086,* 267-82.
2. Maldonado, E., Morales-Pison, S., Urbina, F., et al. (2023). Aging hallmarks and the role of oxidative stress. *Antioxidants, 12*(3), 651.
3. Steven, S., Frenis, K., Oelze, M., et al. (2019). Vascular inflammation and oxidative stress: Major triggers for cardiovascular disease. *Oxid Med Cell Longev, 2019,* 7092151.
4. Ballatori, N., Krance, S.M., Notenboom, S., et al. (2009). Glutathione dysregulation and the etiology and progression of human diseases. *Biol Chem, 390*(3), 191-214.
5. Pastore, A., Federici, G., Bertini, E., et al. (2003). Analysis of glutathione: Implication in redox and detoxification. I*nt Journal Clin Chem, 333*(1), 19-39.
6. Lewczuk, A., Zablocka, B., & Beresewicz-Haller, M. (2023). Is Nrf2 behind endogenous neuroprotection of the hippocampal CA2-4,DG region? *Mol Neurobiol, 60*(3), 1645-58.
7. Bindoli, A., Fukuto, J.M., & Forman, H.J. (2008). Thiol chemistry in peroxidase catalysis and redox signaling. *Antioxid Redox Signal, 10*(9), 1549-64.
8. Traverso, N., Ricciarelli, R., Nitti, M., et al. (2013). Role of glutathione in cancer progression and chemoresistance. *Oxid Med Cell Longev, 2013,* 972913.
9. Franco, R., Schoneveld, O.J., Pappa, A., et al. (2007). The central role of glutathione in the pathophysiology of human diseases. *Arch Physiol Biochem, 113*(4-5), 234-58.
10. Matuz-Mares, D., Riveros-Rosas, H., Vilchis-Landeros, M.M., et al. (2021). Glutathione participation in the prevention of cardiovascular diseases. *Antioxidants, 10*(8), 1220.
11. Sekhar, R.V. (2021). GlyNAC supplementation improves glutathione deficiency, oxidative stress, mitochondrial dysfunction, inflammation, aging hallmarks, metabolic defects, muscle strength, cognitive decline, and body composition: Implications for healthy aging. *J Nutr, 151*(12), 3606-16.
12. Biswas, S.K., & Rahman, I. (2009). Environmental toxicity, redox signaling and lung inflammation: The role of glutathione. *Mol Aspects Med, 30*(1-2), 60-76.
13. Urata, Y., Yamamoto, H., Goto, S., et al. (1996). Long exposure to high glucose concentration impairs the responsive expression of gamma-glutamylcysteine synthetase by interleukin-1beta and tumor necrosis factor-alpha in mouse endothelial cells. *J Biol Chem, 271*(25), 15146-52.
14. Lagman, M., Ly, J., Saing, T., et al. (2015). Investigating the causes for decreased levels of glutathione in individuals with type II diabetes. *PLoS One, 10*(3), e0118436.
15. Minich, D.M., & Brown, B.I. (2019). A review of dietary (phyto)nutrients for glutathione support. *Nutrients, 11*(9), 2073.
16. Sekhar, R.V., Patel, S.G., Guthikonda, A.P., et al. (2011). Deficient synthesis of glutathione underlies oxidative stress in aging and can be corrected by dietary cysteine and glycine supplementation. *Am J Clin Nutr, 94*(3), 847-53.
17. Pérez, L.M., Hooshmand, B., Mangialasche, F., et al. (2020). Glutathione serum levels and rate of multimorbidity development in older adults. *J Gerontol, 75*(6), 1089-94.
18. Richie, J.P., Jr, Nichenametla, S., Neidig, W., et al. (2015). Randomized controlled trial of oral glutathione supplementation on body stores of glutathione. *Eur J Nutr, 54*(2), 251-63.
19. Zeevalk, G.D., Bernard, L.P., & Guilford, F.T. (2010). Liposomal-glutathione provides maintenance of intracellular glutathione and neuroprotection in mesencephalic neuronal cells. *Neurochem Res, 35*(10), 1575-87.
20. Solnier, J., Chang, C, Roh, K., et al. (2021). Quercetin lipoMicel—A novel delivery system to enhance bioavailability of quercetin. *J Nat Health Prod Res, 3*(2), 1-8.
21. Vázquez-Meza, H., Vilchis-Landeros, M.M., Vázquez-Carrada, M., et al. (2023). Cellular compartmentalization, glutathione transport and its relevance in some pathologies. *Antioxidants, 12*(4), 834.

Head office Assured Natural Distribution Inc., 104 – 3686 Bonneville Place, Burnaby, BC, Canada V3N 4T6 | **U.S. Distribution office** 14224 167th Avenue SE, Monroe, WA, USA 98272
Customer Service 1·888·826·9625 · **Fax** 1·877·433·9862 · **Email** customerservice@bioclinicnaturals.com · **bioclinicnaturals.com**