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Glutathione Levels after Glutathione Supplementation: A Systematic Review and Meta-analysis

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Abstract

Glutathione is a crucial antioxidant and plays a vital role in many biochemical processes within living organisms. Abnormal levels or reductions in glutathione are linked to various health conditions and diseases. While glutathione supplementation might offer health benefits, there are ongoing concerns about its low bioavailability. This research aimed to examine the effects of glutathione supplementation on body glutathione levels through a systematic review and meta-analysis of primary studies. Randomized controlled trials (RCTs) were selected from online databases, including PubMed, Scopus, Google Scholar, and Cochrane Library. The studies compared participants who received glutathione supplementation with those in placebo or control groups by evaluating their glutathione levels. The results showed that five primary studies met the inclusion criteria. The quality assessment revealed that most studies had a low risk of bias or some concerns in various areas. However, there was a high risk of bias related to the selection of reported results, primarily due to multiple measurements or analytical methods. Three articles were included in the meta-analysis, which found no statistically significant difference in glutathione levels in erythrocytes [Standardized Mean Difference: 0.74, 95% CI (-0.44, 1.91); P = 0.22] or plasma [Standardized Mean Difference: 0.44, 95% CI (-0.21, 1.09); P = 0.19] between the intervention and placebo groups. This study concluded that glutathione supplementation does not significantly increase glutathione levels in erythrocytes or plasma. However, higher doses and longer durations of supplementation may potentially lead to increased glutathione levels in the body.

Keywords**:** *glutathione; glutathione levels; glutathione supplementation*

1. Introduction

Glutathione is a tripeptide composed of three amino acids: glutamic acid, cysteine, and glycine. It plays many crucial roles in living organisms. As an important antioxidant, it protects cells from oxidative stress, maintains cellular homeostasis, eliminates toxins and foreign substances (detoxification), and regulates the function of proteins and other compounds. Additionally, glutathione is an essential component in various biochemical reactions (Forman et al., 2009; Lu, 2013; Lushchak, 2012). Alterations or deficiencies in glutathione functions are associated with the pathology of both acute and chronic diseases in humans (Ballatori et al., 2009; Vázquez-Meza et al., 2023). This has led to the use of glutathione in treating or supporting health in various conditions, including hyperpigmentation (Arjinpathana, & Asawanonda, 2012; Weschawalit et al., 2017), neurological diseases such as Parkinson's disease (Wang et al., 2021), and non-alcoholic fatty liver disease (NAFLD) (Honda et al., 2017; Irie et al., 2016).

Oral glutathione is sold as a dietary supplement and is approved as safe (Generally Recognized As Safe, GRAS) by the United States Food and Drug Administration (USFDA) (United States Food and Drug Administration, 2024). After ingestion, most of the glutathione is broken down by hydrolysis via γ-glutamyl transpeptidase or γ-glutamyl transferase (GGT) in the intestines, resulting in amino acids that serve as its precursors, which are then absorbed by the body. Partially unbroken glutathione can undergo oxidation with various substances during digestion (Baudouin-Cornu et al., 2012; Orlowski, & Meister, 1970; Witschi et al., 1992; Zhang et al., 2005).

Although various cells in the body, particularly hepatocytes, can synthesize glutathione from these amino acid precursors, the bioavailability of oral glutathione remains low. Numerous studies have established a link between glutathione supplementation and alterations in biochemical substances that impact health and treatment outcomes, particularly in conditions like non-alcoholic fatty liver disease, (NAFLD) (Honda et al., 2017; Irie et al., 2016), cystic fibrosis (Visca et al., 2015), and type 2 diabetes (Kalamkar et al., 2022). However, there is no definitive conclusion about the increase in glutathione levels in the body following oral administration, nor is there strong evidence supporting the effectiveness of glutathione supplements in raising these levels. Therefore, conducting a systematic review and meta-analysis is essential to draw reliable conclusions. The findings can serve as a valuable reference for the use of glutathione supplements in promoting health

2. Objectives

The objective of this study is to investigate the effects of glutathione supplementation on glutathione levels in the body.

3. Materials and Methods

The methodology of this research is a systematic review and meta-analysis, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). This protocol was registered in the PROSPERO (PROSPERO registration number: CRD42024576334).

3.1 Search Strategy

The search for relevant studies was conducted independently by two reviewers across multiple online databases: PubMed, Scopus, Google Scholar, and Cochrane Library. The search, which was performed in April 2024, did not have date restrictions and utilized keywords and MeSH (Medical Subject Headings) terms combined with Boolean operators. The search strategy included terms such as “oral glutathione” OR “oral GSH” AND “GSH” OR “glutathione levels”.

3.2 Eligible Criteria and Study Selection

The research included only randomized controlled trials (RCTs) published in English following these eligible criteria:

1. Population/participant: adult population aged 18 years or older, with or without comorbidities
2. Intervention: glutathione supplementation with any dose and duration
3. Comparison: placebo group or standard care
4. Outcome: glutathione levels in the body

Relevant studies were initially evaluated by reviewing their abstracts. If the abstracts met the eligibility criteria, the full-text versions were then accessed and reviewed. Additionally, we searched for other relevant studies by examining the reference lists of selected studies and checking related citations and articles suggested by the databases.

3.3 Data Extraction

Data extraction from the included studies includes general information, key characteristics or comorbidities of the population, glutathione dosage and duration, comparison groups, methods for measuring glutathione levels, results, and reported side effects.

3.4 Quality Assessment

Quality assessment of included studies was conducted by Cochrane Handbook for systematic reviews of interventions (Higgins et al., 2024), using the Cochrane risk-of-bias tool for randomized trials (RoB 2) (Sterne et al., 2019) to assess risk of 5 bias domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result. Each study was assessed for bias, with ratings categorized as low risk, some concerns, or high risk of bias.

3.5 Data Analysis

We began by combining outcomes from studies that provided multiple results due to their experimental design, specifically within the group receiving the same intervention, oral glutathione intake. This was done by calculating combined continuous data: mean and standard deviation (SD).

We then performed a meta-analysis of the included studies to determine the pooled effect size by calculating the standardized mean difference (SMD) of glutathione levels between the intervention and placebo groups. This analysis was conducted using a random effects model with the DerSimonian and Laird method in The Cochrane Collaboration's Review Manager (REVMAN) Software Version 5.4.1. Statistical significance was defined as a p-value < 0.05. The results were presented in a forest plot, and statistical heterogeneity was assessed using the Cochrane Chi-squared test, with significant heterogeneity indicated by a p-value < 0.1. The inconsistency index (I^2) was reported and categorized as low (I^2 ≤25%), moderate (I^2 ~50%), or high (I^2 ≥75%). Publication bias was evaluated using a funnel plot.

4. Results

The search identified 41 studies from PubMed, 504 from Scopus, 455 from Google Scholar, and 413 from the Cochrane Library, totaling 1,413 studies. After removing 225 duplicate records, we reviewed the titles and abstracts of 1,188 studies. Subsequently, 1,170 studies were excluded due to non-English publications (12 studies) and irrelevance (1,158 studies). We then obtained the full-text versions of 18 studies. Of these, 7 were not randomized controlled trials (RCTs) and 6 did not assess glutathione levels. In total, 5 studies met the eligibility criteria and were included in the analysis. (Figure 1)

All included studies were conducted between 2011 and 2022. Participants ranged in age from 21 to 72 years and had various characteristics, including normal health, cirrhosis, and type II diabetes. The intervention group received oral glutathione doses ranging from 250 to 1,000 mg per day, administered once or twice daily for a duration of 4 to 24 weeks. Most measurements of glutathione levels were derived from erythrocytes. The studies generally reported only mild adverse side effects. (Table 1).

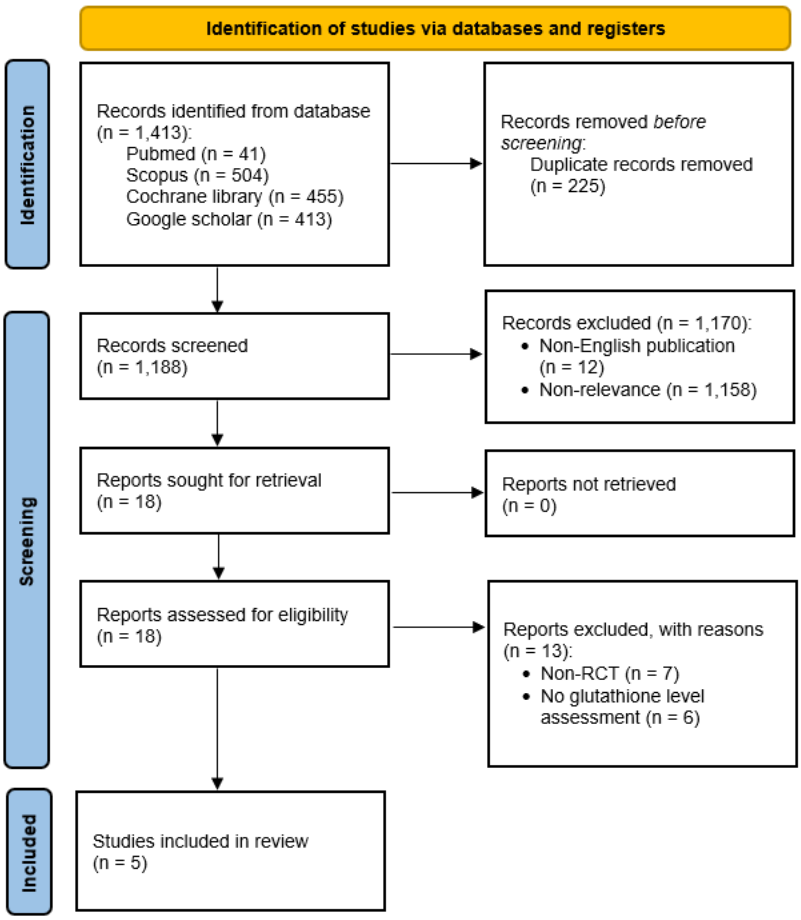

Figure 1 PRISMA flow diagram

Table 1 RCTs investigating the effects of glutathione supplementation on glutathione levels in the body

Authors, year	Participant, Age (years)	Main characteristics or Comorbidities	Intervention group(s) and control or placebo group(s)	Duration	Measurement methods	Result(s)	Side effects
Allen, & Bradley, 2011	40, 21-62 (mean = 40.7)	Healthy, non-smoking	G1 = 1,000 mg (500 mg twice a day) G2 = Placebo	4 weeks	Red blood cell by enzymatic recycling method	G1 vs G2: not significant	Mild adverse effects: Increased flatulence and loose stools (n = 5), flushing (n =2), and weight gain (n = 1)
Richie et al., 2015	54, 28-72 (mean = 46.6)	Healthy, non-smoking, no antioxidant supplementation for at least 1 month	G1 = 250 mg G2 = 1,000 mg G3 = Placebo	6 months	Whole blood, erythrocytes, plasma, lymphocytes, and exfoliated buccal mucosal cells by bicinchoninic acid procedure and spectrophotometry	G1 vs G3: not significant G2 vs G3: significantly increased in erythrocytes, plasma, lymphocytes, and exfoliated buccal mucosal cells ($p < 0.05$)	Mild adverse effects: colds, stomach virus, lightheadedness, back pain, hot flashes, soft stools, eye twitching, headaches, ear infection, urinary tract infection and constipation (G1 = 18, G2 = 19, G3 = 20
Lai et al., 2020	61, G1 = 62.39 ± 2.35 G2 = 56.40 ± 1.84 G3 = 62.86 ± 2.09 G4 = 55.0 ± 3.41	Liver cirrhosis patients	G1 = 500 mg G2 = 500 mg + vitamin B-6 50 mg G3 = vitamin B-6 50 mg G4 = Placebo	12 weeks	Plasma by respective commercial kits	G1 vs G4: not significant	No serious adverse effects
Søndergård et al., 2021	20, G1 = 61 ± 1 G2 = 59 ± 2	Obese male with and without type 2 diabetes	G1 = 1,000 mg (500 mg twice a day) G2 = Placebo	3 weeks	Whole blood by HPLC and spectrophotometry	G1 vs G2: not significant	Dryness in the mucous membranes (n = 1), itchy skin (n = 1), and flu-like symptoms including nausea, bloated stomach, aches in muscles and joints, increased urination (n = 1)
Kalamkar et al., 2022	360, G1 = 56 G2 = 55.5 G3 = 39.5	Healthy and type 2 diabetic patients with anti-diabetic therapy	G1 = 500 mg + anti-diabetic therapy G2 = anti-diabetic therapy alone G3 = Control	6 months	Erythrocytes by glutathione assay kit	G1 vs G2: significantly increased	-

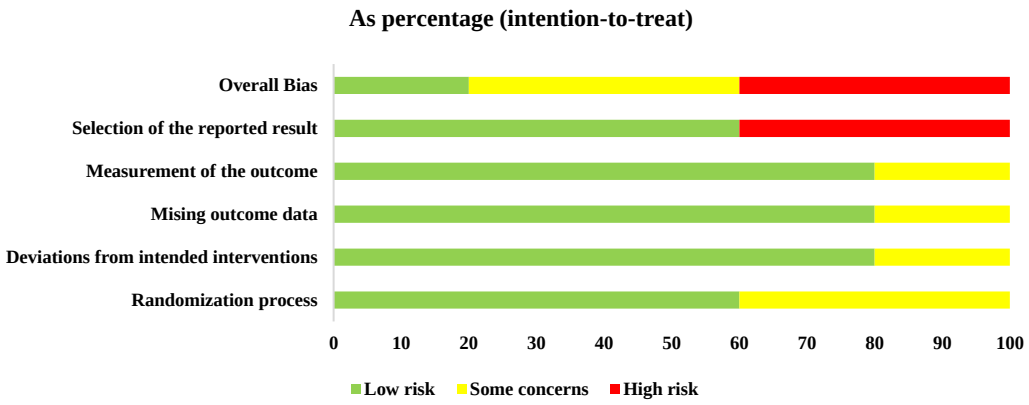

Figure 2 Quality assessment summary showed risk of bias of all included studies

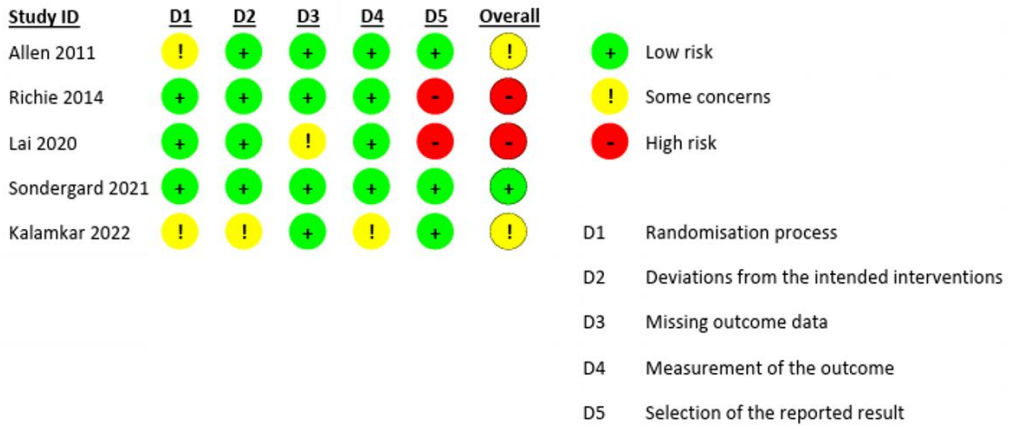

Figure 3 Quality assessment showed risk of bias in each included study

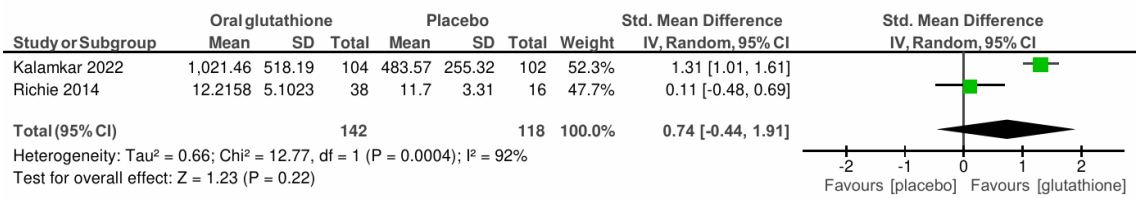

Figure 4 Forest plot showed meta-analysis of standardized mean difference of erythrocytes glutathione levels between glutathione supplementation group and placebo group
(IV, independent variable; SD, standard deviation)

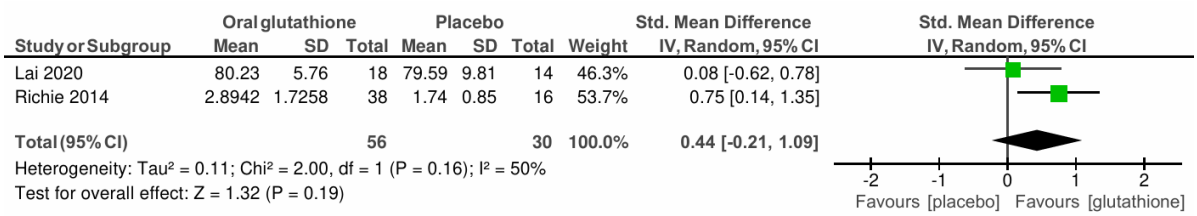

Figure 5 Forest plot showed meta-analysis of standardized mean difference of plasma glutathione levels between glutathione supplementation group and placebo group
(IV, independent variable; SD, standard deviation)

4.1 Quality Assessment of Included Studies

Quality assessment revealed that most studies had low risks of bias or some concerns across most bias domains. However, there was a high risk of bias in selection of the reported result due to multiple outcome measurements in Richie's and Lai's studies (Figures 2 and 3).

4.2 Meta-analysis on the Effect of Glutathione Supplementation on Glutathione Levels in the Body

Three studies were selected and analyzed in the meta-analysis. Some outcome data from two studies could not be retrieved (Allen, & Bradley, 2011; Søndergård et al., 2021). Before calculating the pooled effect size, we combined the two outcomes from Richie's study into a single outcome, as the methodology involved dividing participants into two intervention groups: one receiving 250 mg of oral glutathione per day and other receiving 1,000 mg per day (Richie et al., 2015). Subsequently, the meta-analysis was conducted and categorized based on the method of glutathione measurement, specifically in erythrocytes and plasma. The results did not show a statistically significant difference in glutathione levels between the intervention group and the placebo group for either erythrocyte [Standardized mean difference, 0.74, 95% CI (-0.44, 1.91); P = 0.22] and plasma glutathione levels [Standardized mean difference, 0.44, 95% CI (-0.21, 1.09); P = 0.19] (Figure 4 and Figure 5).

The results indicated a statistically significant level of heterogeneity among the studies regarding erythrocyte glutathione levels (P = 0.0004) with a high percentage of inconsistency index (I^2 = 92%). In contrast, no statistically significant heterogeneity was observed among the studies concerning plasma glutathione levels. The funnel plot assessing publication bias displayed a symmetrical distribution of effect size averages.

5. Discussion

Glutathione serves as an important antioxidant and collaborates with other substances to maintain cellular homeostasis. This balance is influenced by various factors, including lifestyle, nutrition, diseases, and health conditions (Ballatori et al., 2009; Forman et al., 2009; Lu, 2013; Lushchak, 2013; Vázquez-Meza et al., 2023). Therefore, glutathione levels in the body are dynamic and can fluctuate in response to these various factors. Several studies have assessed the therapeutic outcomes of glutathione supplementation by examining its end products and effects. These studies have revealed statistically significant improvements, including reductions in melanin indices and wrinkles (Arjinpathana, & Asawanonda, 2012; Weschawalit et al., 2017), decreases in serum alanine transaminase (ALT) levels in patients with non-alcoholic fatty liver disease (NAFLD) (Honda et al., 2017; Irie et al., 2016), and improvements of growth or increases in forced expiratory volume in one second (FEV1) in cystic fibrosis patients (Calabrese et al., 2015; Visca et al., 2015).

Although both studies included in the meta-analysis of erythrocyte glutathione levels reported statistically significant increases, the overall meta-analysis did not show a statistically significant difference between the intervention and placebo groups. This outcome may be attributed to the combination of results from the intervention group that received a lower dose of 250 mg of glutathione per day, which did not demonstrate a statistically significant difference in Richie's study (Richie et al., 2015). Some studies have demonstrated a dose-dependent effect of glutathione supplementation on outcomes. For example, Arjinpathana, & Asawanonda (2012) found the reduction in melanin indices was statistically significantly greater in subjects receiving 500 mg of oral glutathione compared to those receiving a placebo, whereas Weschawalit et al., (2017), using a lower dose of 250 mg, found no show a statistically significant reduction in melanin indices in either the intervention or placebo groups.

The statistical heterogeneity among the studies on erythrocytes glutathione levels is likely due to clinical and methodological heterogeneity, including differences in baseline characteristics (Age, underlying diseases, race, and lifestyle), sample sizes, glutathione supplementation protocols, and glutathione levels measurement methods.

The meta-analysis of plasma glutathione levels revealed no statistically significant difference between the intervention and placebo groups, a result influenced by the inclusion of Lai's study. This study, which examined the effects of glutathione supplementation in patients with liver cirrhosis, found no statistically significant differences not only in glutathione levels but also in other parameters such as oxidative stress and antioxidant capacities between the intervention and placebo groups. Factors such as the inadequate dose of glutathione (500 mg per day), and the pathological conditions in cirrhosis patients, including defective transsulfuration pathway, blood clotting cascade, and glutathione redistribution, were

considered responsible for the non-significant findings (Lai et al., 2020).

According to randomized controlled trials from the systematic review, achieving a statically significant increasing in glutathione levels in the body compared to the placebo group requires a dosage of 500-1,000 mg of oral glutathione per day for at least six months (Kalamkar et al., 2022; Richie et al., 2015). The duration of glutathione supplementation also affects the glutathione levels. For instance, Søndergård et al., (2021) evaluated effects of three weeks glutathione supplementation (1,000 mg per day) on glutathione levels and other markers, including insulin sensitivity. While the study found a statistically significant improvement in insulin sensitivity, it did not demonstrate a statistically significant increase in glutathione levels in the intervention group compared to the placebo group. In Allen's study, administration a dose of 1,000 mg of glutathione per day for four weeks did not demonstrate a statistically significant difference of all oxidative stress parameters, including glutathione levels, between the intervention group and placebo groups (Allen, & Bradley, 2011).

Furthermore, various factors influencing glutathione level in the body cannot be regulated solely through clinical criteria. In addition to lifestyle and health conditions or diseases, intracellular factors including genetic variation, enzymatic activities, transition metals, and antioxidant availability also affect glutathione metabolism and levels (Giustarini et al., 2023; Halliwell, 2024).

The meta-analysis of this study focused on glutathione levels in erythrocytes and plasma due to lack of a gold standard for glutathione measurement methods. Each study selected different methods based on its objectives, mostly in plasma and erythrocytes, as glutathione primarily accumulates in erythrocytes (Giustarini et al., 2008; Kleinman, & Richie, 2000). This contributed to the limitation of included studies in the meta-analysis.

Limitations of the study include small sample sizes and high heterogeneity among the studies, which restrict the generalizability of the results to larger populations. Furthermore, this study included only randomized controlled trials that used standard forms of glutathione supplementation, excluding other formulations designed to enhance absorption, such as oral dispersible film (Sharma, & Sharma, 2022) or liposomal glutathione (Sinha et al., 2018). Nevertheless, this study represents the first systematic review and meta-analysis to assess the effect of glutathione supplementation on glutathione levels in the body, revealing study methodological limitations in the included randomized controlled trials, including small sample sizes, and insufficient doses and durations of glutathione supplementation.

6. Conclusion

Glutathione supplementation is generally well-tolerated; however, it has not been shown to significantly increase glutathione levels in erythrocytes and plasma. Nevertheless, a dosage of 500 to 1,000 mg per day over a period of at least six months may result in an increase in overall glutathione levels in the body. Future randomized controlled trials should be designed with larger sample sizes, appropriate dosing and duration of glutathione supplementation, and extended follow-up periods to better assess the impact of glutathione supplementation on body glutathione levels.

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8. References

Allen, J., & Bradley, R. D. (2011). Effects of oral glutathione supplementation on systemic oxidative stress biomarkers in human volunteers. *Journal of Alternative and Complementary Medicine*, *17*(9), 827-833. https://doi.org/10.1089/acm.2010.0716

Arjinpathana, N., & Asawanonda, P. (2012). Glutathione as an oral whitening agent: A randomized, double-blind, placebo-controlled study. *Journal of Dermatological Treatment*, *23*(2), 97-102. https://doi.org/10.3109/09546631003801619

Ballatori, N., Krance, S. M., Notenboom, S., Shi, S., Tieu, K., & Hammond, C. L. (2009). Glutathione dysregulation and the etiology and progression of human diseases. *Biological Chemistry*, *390*(3), 191–214. https://doi.org/10.1515/BC.2009.033

Baudouin-Cornu, P., Lagniel, G., Kumar, C., Huang, M. E., & Labarre, J. (2012). Glutathione degradation is a key determinant of glutathione homeostasis. *Journal of Biological Chemistry*, *287*(7), 4552-4561. https://doi.org/10.1074%2Fjbc.M111.315705

Calabrese, C., Tosco, A., Abete, P., Carnovale, V., Basile, C., Magliocca, A., ... & Raia, V.

(2015). Randomized, single blind, controlled trial of inhaled glutathione vs placebo in patients with cystic fibrosis. *Journal of Cystic Fibrosis*, *14*(2), 203-210. https://doi.org/10.1016/j.jcf.2014.09.014

Forman, H. J., Zhang, H., & Rinna, A. (2009). Glutathione: Overview of its protective roles, measurement, and biosynthesis. *Molecular Aspects of Medicine*, *30*(1-2), 1-12. https://doi.org/10.1016/j.mam.2008.08.006

Giustarini, D., Milzani, A., Dalle-Donne, I., & Rossi, R. (2008). Red blood cells as a physiological source of glutathione for extracellular fluids. *Blood Cells, Molecules, and Diseases*, *40*(2), 174-179. https://doi.org/10.1016/j.bcmd.2007.09.001

Giustarini, D., Milzani, A., Dalle-Donne, I., & Rossi, R. (2023). How to Increase Cellular Glutathione. *Antioxidants (Basel, Switzerland)*, *12*(5), Article 1094. https://doi.org/10.3390/antiox12051094

Halliwell, B. (2024). Understanding mechanisms of antioxidant action in health and disease. *Nature reviews. Molecular Cell Biology*, *25*(1), 13–33. https://doi.org/10.1038/s41580-023-00645-4

Higgins, J. P., Savović, J., Page, M. J., Elbers, R. G., & Sterne, J. A. (2019). Assessing risk of bias in a randomized trial. *Cochrane Handbook for Systematic Reviews of Interventions*, 205-228. https://doi.org/10.1002/9781119536604.ch8

Honda, Y., Kessoku, T., Sumida, Y., Kobayashi, T., Kato, T., Ogawa, Y., ... & Nakajima, A. (2017). Efficacy of glutathione for the treatment of nonalcoholic fatty liver disease: an open-label, single-arm, multicenter, pilot study. *BMC Gastroenterology*, *17*(1), Article 96. https://doi.org/10.1186/s12876-017-0652-3

Irie, M., Sohda, T., Anan, A., Fukunaga, A., Takata, K., Tanaka, T., ... & Sakisaka, S. (2016). Reduced Glutathione suppresses Oxidative Stress in Nonalcoholic Fatty Liver Disease. *Euroasian Journal of Hepato-gastroenterology*, *6*(1), 13–18. https://doi.org/10.5005/jp-journals-10018-1159

Kalamkar, S., Acharya, J., Kolappurath Madathil, A., Gajjar, V., Divate, U., Karandikar-Iyer, S., ... & Ghaskadbi, S. (2022). Randomized clinical trial of how long-term glutathione supplementation offers protection from oxidative damage and improves HbA1c in elderly type 2 diabetic patients. *Antioxidants*, *11*(5), Article 1026. https://doi.org/10.3390/antiox11051026

Kleinman, W. A., & Richie Jr, J. P. (2000). Status of glutathione and other thiols and disulfides in human plasma. *Biochemical Pharmacology*, *60*(1), 19-29. https://doi.org/10.1016/s0006-2952(00)00293-8

Lai, C. Y., Cheng, S. B., Lee, T. Y., Hsiao, Y. F., Liu, H. T., & Huang, Y. C. (2020). Impact of Glutathione and Vitamin B-6 in Cirrhosis Patients: A Randomized Controlled Trial and Follow-Up Study. *Nutrients*, *12*(7), Article 1978. https://doi.org/10.3390/nu12071978

Lu, S. C. (2013). Glutathione synthesis. *Biochimica et Biophysica Acta (BBA)-General Subjects*, *1830*(5), 3143-3153. https://doi.org/10.1016/j.bbagen.2012.09.008

Lushchak, V. I. (2012). Glutathione homeostasis and functions: potential targets for medical interventions. *Journal of Amino Acids*, *2012*(1), Article 736837. https://doi.org/10.1155/2012/736837

Orlowski, M., & Meister, A. (1970). The γ-glutamyl cycle: a possible transport system for amino acids. *Proceedings of the National Academy of Sciences*, *67*(3), 1248-1255. https://doi.org/10.1073/pnas.67.3.1248

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., ... & Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *bmj*, *372*. https://doi.org/10.1136/bmj.n71

Richie, J. P., Nichenametla, S., Neidig, W., Calcagnotto, A., Haley, J. S., Schell, T. D., & Muscat, J. E. (2015). Randomized controlled trial of oral glutathione supplementation on body stores of glutathione. *European Journal of Nutrition*, *54*(2), 251-263. https://doi.org/10.1007/s00394-014-0706-z

Sharma, D. K., & Sharma, P. (2022). Augmented Glutathione Absorption from Oral Mucosa and its Effect on Skin Pigmentation: A Clinical Review. *Clinical, Cosmetic and Investigational Dermatology*, *15*, 1853–1862. https://doi.org/10.2147/CCID.S378470

Sinha, R., Sinha, I., Calcagnotto, A., Trushin, N., Haley, J. S., Schell, T. D., & Richie, J. P., Jr (2018). Oral supplementation with liposomal glutathione elevates body stores of glutathione and markers of immune function. *European*

Journal of Clinical Nutrition, *72*(1), 105–111. https://doi.org/10.1038/ejcn.2017.132

Søndergård, S. D., Cintin, I., Kuhlman, A. B., Morville, T. H., Bergmann, M. L., Kjær, L. K., ... & Larsen, S. (2021). The effects of 3 weeks of oral glutathione supplementation on whole body insulin sensitivity in obese males with and without type 2 diabetes: a randomized trial. *Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquee, Nutrition et Metabolisme*, *46*(9), 1133–1142. https://doi.org/10.1139/apnm-2020-1099

Sterne, J. A., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., ... & Higgins, J. P. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ (Clinical Research ed.)*, *366*, Article l4898. https://doi.org/10.1136/bmj.l4898

United States Food and Drug Administration. (2024). *GRN no. 293 Glutathione*. Retrieved April 8, 2024, from https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=grasnotices&id=293

Vázquez-Meza, H., Vilchis-Landeros, M. M., Vázquez-Carrada, M., Uribe-Ramírez, D., & Matuz-Mares, D. (2023). Cellular Compartmentalization, Glutathione Transport and Its Relevance in Some Pathologies. *Antioxidants (Basel, Switzerland)*, *12*(4), Article 834. https://doi.org/10.3390/antiox12040834

Visca, A., Bishop, C. T., Hilton, S., & Hudson, V. M. (2015). Oral reduced L-glutathione improves growth in pediatric cystic fibrosis patients. *Journal of Pediatric Gastroenterology and Nutrition*, *60*(6), 802–810. https://doi.org/10.1097/MPG.0000000000000738

Wang, H. L., Zhang, J., Li, Y. P., Dong, L., & Chen, Y. Z. (2021). Potential use of glutathione as a treatment for Parkinson's disease. *Experimental and Therapeutic Medicine*, *21*(2), Article 125. https://doi.org/10.3892/etm.2020.9557

Weschawalit, S., Thongthip, S., Phutrakool, P., & Asawanonda, P. (2017). Glutathione and its antiaging and antimelanogenic effects. *Clinical, Cosmetic and Investigational Dermatology*, *10*, 147–153. https://doi.org/10.2147/CCID.S128339

Witschi, A., Reddy, S., Stofer, B., & Lauterburg, B. H. (1992). The systemic availability of oral glutathione. *European Journal of Clinical Pharmacology*, *43*(6), 667–669. https://doi.org/10.1007/BF02284971

Zhang, H., Forman, H. J., & Choi, J. (2005). Gamma-glutamyl transpeptidase in glutathione biosynthesis. *Methods in Enzymology*, *401*, 468-483. https://doi.org/10.1016/S0076-6879(05)01028-1