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The Effectiveness of Glutathione on Skin Lightening: A Review

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Abstract

Glutathione is a thiol-tripeptide with a low molecular weight that is important for maintaining intracellular redox balance. Its antimelanogenic qualities have led to its promotion as a skin-lightening agent, in addition to its exceptional antioxidant properties. In some ethnic groups, it is commonly utilized for this purpose. There is, however, a discrepancy between the evidence supporting its efficacy and safety. The marketing gimmick surrounding its depigmenting properties could be a pharma-cosmeceutical company's marketing ploy. This article examines the different characteristics of glutathione, including its metabolism, mechanism of action, and scientific evidence to assess its usefulness as a systemic skin-lightening agent. Glutathione, in its reduced form, is found within cells and plays a crucial part in a variety of physiological functions. The direct and indirect suppression of the tyrosinase enzyme, as well as the switch from eumelanin to phaeomelanin production, are responsible for its skin-lightening effects. It can be taken orally, parent rally, or topically. Although intravenous glutathione injections are widely used, there is little proof that they are effective. Indeed, the Philippines' Food and Drug Administration has issued a public warning denouncing intravenous glutathione's usage for off-label applications such as skin whitening due to its negative consequences. There are now three randomized controlled trials that support topical and oral glutathione's skin-lightening impact and good safety profile. However, important questions such as treatment duration, skin-lightening impact lifetime, and maintenance regimens remain unsolved. To establish the importance of this chemical in hyperpigmentation and skin lightening diseases, more randomized, double-blind, placebo-controlled trials with bigger sample sizes, long-term follow-up, and well-defined efficacy outcomes are needed.

Keywords: Melanin, Hyperpigmentation, Hypopigmentation, Glutathione.

Introduction

Glutathione (-glutamyl-cysteinyl glycine) serves a variety of activities in the human body, hence identifying this small molecule is critical in modern medicine and pharmacy, every prokaryotic and eukaryotic cell produces it because it aids in the protection against oxidative stress, as well as detoxification and immune modulation. The body can protect itself against various infections, cancer growth, the liver can detoxify heavy metals, poisons, and other xenobiotics, and cells are not constantly destroyed. The thiol group (-SH) which is important for glutathione's biological functions, is a distinguishing feature of its structure. Glutathione can take a variety of

forms due to the existence of this group. Reduced (GSH) and oxidized (GSSG) glutathione are the most common types. S-nitrosoglutathione and GSSG-protein conjugates are two more common types. [1]

Glutathione is made up of three amino acids: glycine, cysteine, and glutamic acid or glutamate, and it is found in every cell in the body (Figure1) [2]. Its principal duty is to offer its electrons to other molecules in need, and it regenerates its electrons regularly. Glutathione play a critical role in chemical, mechanical, and electrical activities. The molecule glutathione is incredibly big. Many studies have shown that ingesting glutathione in pill or liquid form or injecting it into the blood stream intravenously, results in very little, if any, Glutathione reaching the cells, and thus having a negligible effect [3]. Glutathione is an endogenous peptide that works as an antioxidant and in other metabolic processes. Glutathione and glutathione sodium is used to prevent neurotoxicity caused by cisplatin or oxaliplatin; they've also been used to prevent other side effects of antineoplastic and radiation therapy, as well as a variety of other conditions such as heavy metal and other compound poisoning, liver disorders, corneal disorders, and eczema. Idiopathic pulmonary fibrosis and peripheral vascular diseases have also been treated with glutathione [4].

Many of the reactions we'll discuss later are critical for cell survival, and glutathione has been dubbed "the most important nonproteinthiol." Glutathione is a vital component for cellular survival, and there is probably no contradiction in broadening its role. While this latter viewpoint appears to reflect some scientific exaggeration, it is difficult to exaggerate the pivotal relevance of glutathione in the biochemistry of living cells [5]. The immune system performs best when lymphoid cells have a precisely balanced intermediate level of glutathione. Even minor variations in intracellular glutathione levels have a significant impact on lymphocyte activities. Because certain activities, such as the DNA synthesis response, are extremely sensitive to reactive oxygen intermediates, high amounts of the antioxidant glutathione are beneficial. Conversely, oxidative circumstances and low intracellular glutathione levels encourage certain signal pathways [6].

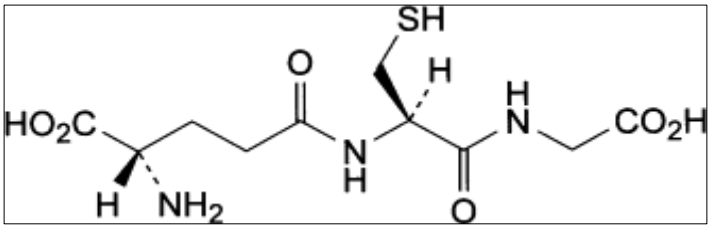


Fig.1. Glutathione Structure $C_{10}H_{17}N_3O_6S$

In general glutathione has many functions [5,7].

Antioxidant and reducing agent

- •Scavenger of free radicals.
- •Cell membrane protection.
- •Antioxidant and lipid peroxidation protection (higher levels of oxidized glutathioneGSSG).
- •Radiation and UV light protection; DNA repair.

•Protein and other molecular SH groups are maintained.
•Hydrogen peroxide, other peroxides, and free radicals are destroyed.

Xenobiotics detoxification

•Conjugation.
•Metal transport between ligands. Drug resistance is determined.
•Cysteine reservoir and transfer

Regulation of metabolites

•Substrate and cofactor
•Synthesis of proteins and nucleic acids. Synthesis of leukotrienes.
•Transport of amino acids.
•Ca2+ homeostasis (ATPase protection of –SH.
•Mitogenesis and cell-cycle control
•Immune system functions
• Thermo tolerance

Glutathione in Human

GSH levels in human tissues typically vary from 0.1 to 10 millimolar (mM), with the liver (up to 10 mM) and the spleen, kidney, lens, erythrocytes, and leukocytes having the highest concentrations. The concentration in the plasma is in the micromolar range (about 2-20 M).[29] UV and other forms of radiation; viral infections; environmental pollutants, household chemicals, and heavy metals; surgery, inflammation, burns, septic shock; dietary deficits of GSH precursors and enzyme cofactors are all examples of oxidative stresses that can deplete GSH. [8]

The glutathione redox cycle

The glutathione redox cycle is a biological process, Reduced glutathione (GSH) and oxidized glutathione (GSSG) are two inter convertible forms of glutathione, GSH is the most abundant intracellular form, acting as a powerful antioxidant and protecting cells from harmful chemicals and xenobiotics. GSH is constantly oxidized to GSSG by the enzyme glutathione peroxidase in this process [Figure2]. GSH is regenerated by the glutathione reductase enzyme, which reduces GSSG to maintain intracellular redox equilibrium.[1]

Glutathione depletion and supplementation in medical conditions

Many human disorders have been linked to low glutathione levels, according to extensive study in numerous fields, such as emphysema, asthma, allergy disorders, medication toxicity, metabolic disorders, cancer, chemotherapy, and human immunodeficiency virus-acquired immune deficiency syndrome are only a few of the conditions and causes. [6,7] There is little research on the role of glutathione supplementation in these disorders, the majority of the research has focused on autism and cystic fibrosis. [9,10]

The degree of inconstancy in a person's ability to provide glutathione, which is mostly owing to hereditary changeability in chemical components involved in its formation and recovery, is a factor influencing glutathione renown, glutathione s-transferase and gamma-glutamyltransferase are two enzymes that convert glutathione to glutamate and have received a lot of attention in the logical writing and internal clinical medicinal drug, one of those catalysts requires complement cofactors [11]. There may be a much bigger exceptional requirement for

glutathione when oxidative stress is elevated, there is a dearth of healthy food, or there is rapid harmful weight owing to exposure to environmental contaminants. [12,13]. Many chronic diseases have been linked to a drop in glutathione levels, which has led to the concept that raising glutathione levels might help prevent and/or attenuate disease development. A list of illnesses [14] and difficulties linked to glutathione dysregulation or depletion is shown below. [15]. Table 1 lists a few hypothesized disease conditions associated with low glutathione levels.

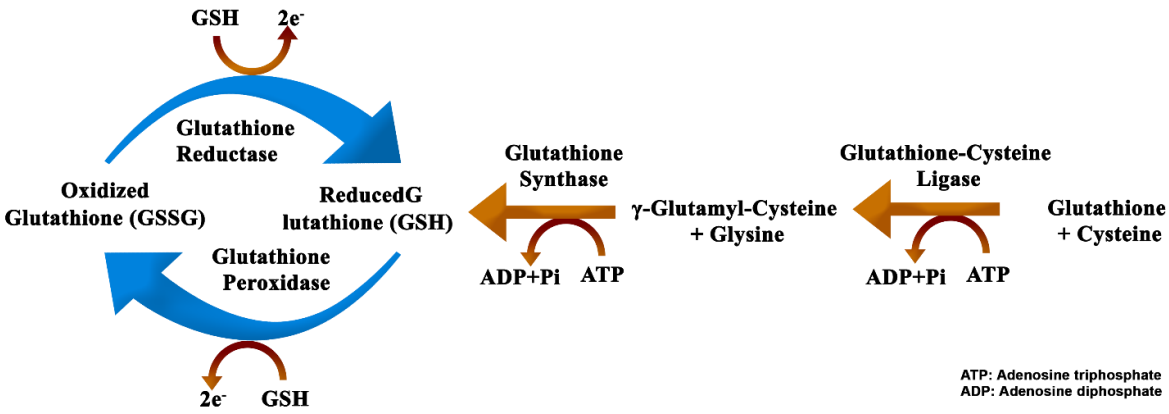


Figure2: The glutathione redox cycle, which shows how oxidized and reduced glutathione interact.

Natural foods that contain Glutathione

Glutathione is abundant and inabundant in wet fruit, vegetables, and nuts. Tomatoes, avocados, oranges, pecans, and asparagus are the most common foods that help the body build glutathione levels. Whey protein is another rich source of glutathione, and it has been shown to help cystic fibrosis patients enhance their basic glutathione levels.[32]

Human pigmentation and glutathione

Melanin is a polymer of different indole compounds generated from L-tyrosine in human skin by the Raper–Mason pathway of melanogenesis [Figure.3], with tyrosinase as the rate-limiting enzyme. The skin color is determined by the ratio of two different types of melanin found in the skin, black-brown colored eumelanin, and yellow-red pheomelanin, [33]. Lighter skin is correlated with a higher amount of pheomelanin, the most essential factor that promotes unfavorable hyperpigmentation is exposure to UV radiation. Increased tyrosinase activity is a critical cellular event. When cells are exposed to ultraviolet radiation, they produce an excessive amount of reactive oxygen and nitrogen species [34,35] By inhibiting these free radicals, oral antioxidants can help to prevent melanogenesis, the effect of a human skin extract containing an active sulfhydryl-containing substance was one of the first pieces of evidence demonstrating the link between thiols and skin. Tyrosinase suppression

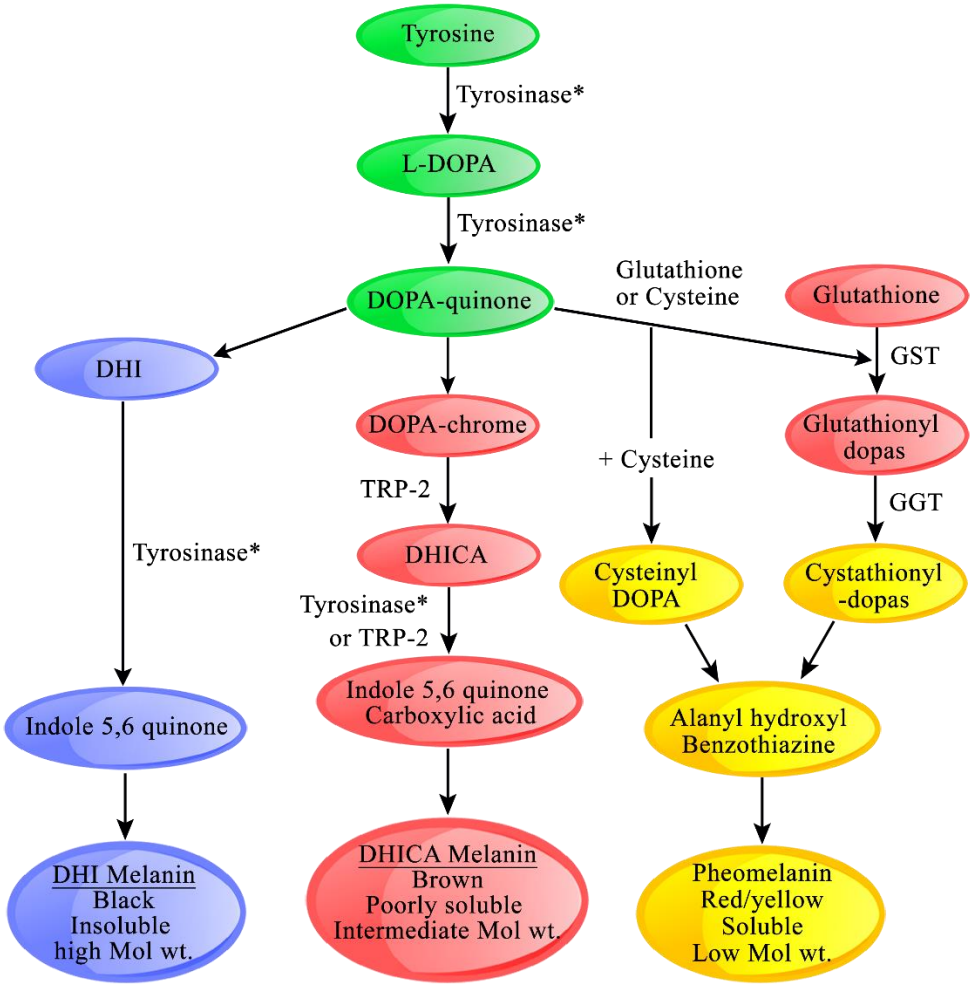
prevented melanin production. When this molecule is oxidized and inactivated by causes such as heat, radiation, or inflammation, it loses its inhibitory effect on tyrosinase, resulting in hyperpigmentation. This "sulfhydryl substance" was glutathione, according to Halprin and Ohkawara's physical and biochemical evidence. [36]

Table 1. Clinical conditions and sicknesses related to glutathione.

Disease	Reference
Aging and related disorders	**15,16**
Alzheimer's disease	**17**
Cancer	**18**
Chronic liver disease	**19**
Cognitive impairment	**20**
Cystic fibrosis	**21**
Diabetes, especially uncontrolled diabetes	**22, 23**
Human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS)	**24**
Hypertension	**25**
Infertility in both men and women	**26**
Systemic lupus	**27**
Mental health disorders	**28**
Multiple sclerosis	**29**
Neurodegenerative disorders	**30**
Parkinson's disease	**31**

Whitening of the skin

The desire to attain a skin tone lighter or fairer complexion in adults is increasing day by day. This craze exploits the implications of topical skin lightening agents and therapies containing hydroquinone, alpha, and beta hydroxy acids, tretinoin, arbutin, vitamin C serum, soy extract. These agents are used generally as skin lighteners on the face, neck, and other exposed parts of the body. Hence their effect is limited to the application site without any systemic skin lightening effect.[37].



DHI - 5,6-dihydroxyindole, **DHICA** - 5,6-dihydroxyindole-2-carboxylicacid
DOPA-3,4-dihydroxyphenylalanine, **GGT** - Gamma-glutamyl transpeptidase
GST - Glutathione-S-transferase: **L-DOPA** - Levo-DOPA;
TRP-2 - Tyrosinase-Related Protein 2

Figure 3: Steps of pheomelanin synthesis.

Vitamin E, Hydroquinone, Vitamin C serum, niacinamide (nicotinamide), arbutin, glycolic acid, kojic acid, and a few novel items including marine algae extracts, soy, pycnogenol, Boswellia, and others are available over-the-counter. All of the products are applied locally, and the results vary from one person to others. Systemic medicines such as an l-cysteine peptide, tranexamic acid, and other plant extracts are also available. Because of its quick action and popularity, glutathione has become a popular skin-lightening agent.[38,39]. Glutathione peptide is an antioxidant that detoxifies xenobiotics by combining the amino acids glutamate, cysteine, and glycine. [40]. Glutathione acts as a skin-lightening agent by inhibiting the tyrosinase enzyme, which aids in the formation of melanin. It also changes the production of eumelanin (which produces a dark brown color) to pheomelanin (which produces a yellow-red color), resulting in skin whitening. [41]. Glutathione comes in a variety of forms, including topical, oral, and injectable. [42]. When used consistently over a length of time, topical formulations demonstrate a considerable improvement

in skin tone. Tablets and solution versions of oral preparations are both available. The FDA considers the sublingual method to be safe because it is more accessible and requires smaller amounts. [43]. The needed amount is 20-40 mg/kg (i.e. 1 g to 2 g in two separate doses), and significant results can be evident in as little as three months. Intravenous doses (600-1200 mg once/twice a week) are known to cause additional side effects due to the risk of overdosing toxicities or the presence of additives in glutathione injection, Potentially fatal Stevens-Johnson syndrome and toxic epidermal necrolysis, kidney dysfunction, liver dysfunction, thyroid dysfunction, severe abdominal pain, and lethal complications such as air embolism or potentially fatal sepsis due to improper sterile IV administration are all common side effects of intravenous preparations. [44].

In nations like the Philippines, glutathione is a magical skin whitening' chemical. Glutathione's popularity has exploded in a short period of time all over the world. Many manufacturers and media campaigns backed its efficacy in treating hyperpigmentation problems including melasma, as well as a general skin lightening treatment [45]. Glutathione comes in two forms: reduced (GSH) and oxidized (GSO) (GSSG). The reduced version, GSH, appears to play a role in this unique molecule's depigmenting abilities. [46].

Recent studies on glutathione as skin lightening agent

Only a few research on the efficacy of oral, topical, and parenteral glutathione as a skin whitening agent have been published. Two trials on oral GSH were conducted in Thai women by Arjinpathana [46] and in Filipino women, by Handog et al [47]. Both trials involved administering 500 g/day of GSH in two divided doses to the study population, with the difference being that the latter study used buccal lozenges instead of oral capsules to increase glutathione systemic absorption, the pre-and post-treatment melanin indices were the primary efficacy outcome in both trials. Arjinpathana et al.[46] found a consistent drop in melanin indices in the GSH group individuals at all six sites tested, with a statistically significant reduction over placebo at two sites. Handog et al.[47] study revealed significant reductions in melanin index at both suns exposure and sun-protection areas in all 30 healthy Filipino women who took buccal lozenges instead of capsules of GSH, and moderate skin lightening in 90% of the subjects on a global evaluation. [48]. Another study by Watanabe et al. found that topical GSSG 2 percent lotion applied twice daily for 10 weeks produced transient skin whitening and indicated a statistically significant reduction in skin melanin index with glutathione compared to placebo, with no adverse pharmacological effects. [40] The tiny sample size of healthy participants, the exceedingly short study period with an even shorter follow-up, and the lack of detection of glutathione levels in the blood were all important limitations of these studies.[39,46,47]. Few studies support the use of intravenous glutathione. Despite a complete absence of evidence, manufacturers, distributors, skin clinics, and med spas have been advocating arbitrary dosage regimes for years [49]. Zubair et al [50] examined the efficacy and safety of intravenous GSH for skin tone lightening in 25 individuals in a

placebo-controlled study (1,200 mg given IV twice a week for 6 weeks in the treatment group versus normal saline in the control group), IV glutathione was not found to be an effective or long-lasting treatment for skin tone lightening in this investigation. The most serious side effect in the IV GSH group was liver impairment, which was not qualified nor quantified. The researchers also did not calculate the participants' baseline or post-treatment renal or thyroid function, both of which have been documented to be negatively affected by IV glutathione. [50]

Glutathione safety status

Glutathione-based oral dietary supplements are generally recognized as safe (GRAS) under Section 201(s) of the Federal Food, Drug, and Cosmetic Act of the United States Food and Drug Administration (US-FDA) [51]. In the United States, the Philippines, and Japan, there are no limits on its oral forms. In India and other Asian nations, oral formulations are offered as over-the-counter medications. The oral GSH dosage form has a limited bioavailability in humans, which is a major disadvantage, as a result, makers of GSH IV injections recommend using this mode of administration to quickly obtain therapeutic levels in the blood and skin, resulting in immediate skin lightening benefits. The recommended dose is 600-1200 mg, injected weekly or twice weekly, with no set net treatment time. However, there is still a scarcity of research on the efficacy of IV GSH. [41]

Limitations for intravenous injection of GSH

Outrageous sizeable fee of infusion vials is one of the convincing drawback to its usage. Different limits incorporate are absence of disbursed source supporting its viability as a skin easing up expert, indistinct component and length of IV infusions, absence of endorsement from US FDA and cautioning towards the usage of intravenous glutathione by the FDA of Philippines, and its introduced opposed results.[43]

Glutathione mesotherapy

Despite the dearth of published research on the efficacy and methods of utilizing glutathione solution as mesotherapy, dermatologists use it to treat melasma and other face melanoses. It can be used alone or in combination with ascorbic acid, vitamin E, tranexamic acid, and other ingredients [52]. Despite the promising findings, further proof and published data are needed to support the use of glutathione as a mesotherapy.

Recent research experience

GSH must have a sufficient intracellular concentration and be transported into melanosomes to block tyrosinase and shift melanogenesis from eumelanin to pheomelanin. Trans-melanosomal transit can be accomplished via a membrane channel or diffusion, both of which appear to be deficient for GSH, according to previous research. [53,54] GSH monoethyl ester (GSH-MEE), GSH diethyl ester (GSH-DEE), and GSH monoisopropyl ester (GSH-MIPE) were tested in vitro for antimelanogenic properties and cytotoxicity in three cell culture lines by Chung *et al,* Their findings revealed that GSH-MEE and GSH-MIPE have a considerable inhibitory effect on intracellular tyrosinase activity and melanin synthesis,

Additional cytotoxic action was discovered of GSH-DEE and GSH-MIPE, making them unsuitable for clinical application. The researchers advocated the creation of GSH-MEE, rather than GSH, as an efficacious and safe molecule for the treatment of hyperpigmentation, based on its in vitro efficacy and lack of cytotoxicity. However, further clinical and in vitro testing is required before conclusive conclusions can be drawn.[55]

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