Glutathione Under Scrutiny: infusion risks?

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Abstract

Skin lightening has long been influenced by socio-cultural perceptions that favour lighter skin tones, leading to widespread use of depigmenting agents. Across the years, many have been used, such as mercury, hydroquinone, and potent steroids. Glutathione, a naturally occurring tripeptide with potent antioxidant and anti-melanogenic properties, has gained popularity for its skin-whitening effects. It modulates melanogenesis by inhibiting tyrosinase activity, shifting melanin production from eumelanin to pheomelanin, and reducing oxidative stress induced by ultraviolet radiation. Glutathione is available in oral, topical, and parenteral forms. Evidence suggests that oral and topical formulations, particularly when combined or enhanced with micro-needling, are relatively safe and may improve skin tone and texture. However, intravenous glutathione remains controversial due to limited clinical evidence, lack of standardised dosing, transient effects, and reports of serious adverse events, including renal failure and severe cutaneous reactions. Despite this, unregulated promotion and self-medication persist. Robust, large-scale clinical trials are urgently needed to establish efficacy, safety, and ethical considerations before recommending glutathione, particularly intravenous formulations, for cosmetic skin lightening.

This paper will critically review the biological basis, clinical evidence, safety, and ethical implications of glutathione use for skin lightening, with particular emphasis on comparing oral, topical, and intravenous routes, highlighting the risks of unregulated cosmetic use, and guiding dermatologists toward evidence-based and safe practice.

Keywords: glutathione, skin lightening, intravenous, infusion, parenteral.

Introduction

There is considerable activity surrounding the use of glutathione in conjunction with vitamins, as well as other additives such as vitamin C, collagen, and various micronutrients, administered parenterally in the context of skin lightening, detoxification, and anti-aging. The promotion of it has occurred due to the strong commercial marketing as a magical wonder for whitening skin by certain pharmaceutical companies, on social media platforms. In Libya, it took a toll, and in many places worldwide, the dream of whiteness is a mystical thing. Furthermore, it is not licensed and not regulated by the Food and Drug Administration (FDA) or European Medicines Agency (EMA)(1-3).

Additionally, in certain nations and ethnicities, it is promoted as a wellbeing injection for detoxing and whitening and taken systemically, as an intravenous drip, and is widely offered in the UK by the aesthetic clinics, and in some countries, like the Philippines it's taken far more than any other nation, besides India, Pakistan, Singapore, Thailand, Malaysia, China, and Indonesia. I came across some of my Filipino patients taking it intravenously, with no evidence and is unlicensed for that use and it is administered by non-medically qualified beauticians, without consistent regulation. Further glutathione has some recent warning of serious side effects, such as anaphylaxis, kidney and liver problems which mandate a call for action by the decision makers and the relevant authorities.

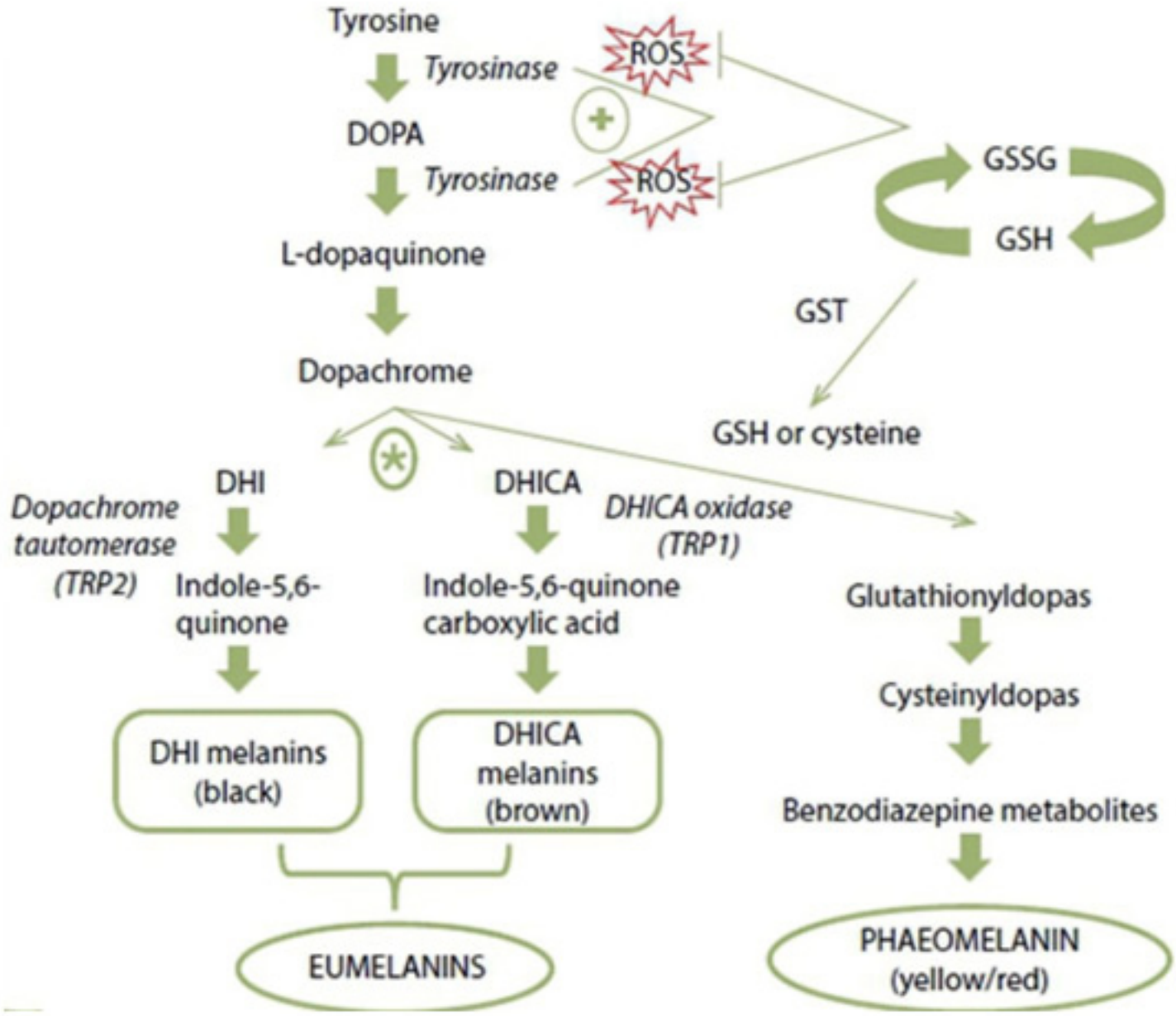
There has been preoccupation and obsession with whiteness in certain nations and in those with darker skin. The general tale is that a fairer complexion is beautiful, preferable, and alluring. Thus, many women and some men would revert to skin whitening, and thus marketing companies exploit that obsession. Across the years, many depigmentary therapies have been devised and utilised in different skin conditions, including for melasma and post inflammatory pigmentation (1).

Glutathione structure

Glutathione is a small, low-molecular-weight, water-soluble molecule. It's a tripeptide molecule composed of amino acids L-cysteine, glycine, and glutamate, which is synthesized intracellularly(6).

Glutathione is one of the most used antioxidant agents in humans (protects against ultraviolet induced damage and improves skin elasticity) that has anti-melanogenic properties and has gained widespread popularity. Also it shifts the process of melanogenesis from the darker eumelanin to the lighter molecules of phaeomelanin. It lessens melanin production and thus reduces hyperpigmentation, and reduces oxidation of tyrosinase, which is the crucial factor in melanin production, and modulates melanin production (Figure 1). Glutathione exists in two forms, the reduced (GSH) and the oxidized form (GSSG), in a balanced ratio GSH: GSSG, and the former is linked to the depigmentatory functionality, as it is intracellular with potent antioxidative properties (defends against toxic particles and prevents oxidative damage needed for cell survival), and is constantly oxidised to GSSG by the glutathione peroxidase enzyme. Any imbalance as a marker for oxidative stress, is reported in many diseases such as cancer, neurodegenerative disorders, cystic fibrosis, diabetes, anorexia, low birth weight neonates, and autism (6). Additionally, it plays a role in the body's defence system, scavenges free radicals, and reduces oxidative stress.

Figure 1: melanogenesis, David et al, 2016.



Human skin colour

Human skin colour is determined by the amount of melanin, which is synthesised from tyrosine, through the melanogenesis. The ratio of melanin found in skin, black-brown eumelanin and yellow-red pheomelanin, determines the skin colour, where lighter skin colour implies increased pheomelanin (Figure 1). This might lead to UV skin photosensitivity and DNA damage. GSH has the potential to lighten human skin, which is lower in black human skin than in white skin (6).

Ultraviolet exposure and heat cause hyperpigmentation, where tyrosinase activity increases, resulting in excessive amounts of reactive oxygen and nitrogen within cells (1).

The lightening effects of glutathione were an accidental discovery as a side effect of a larger dose of it, as it directly inhibits tyrosinase by chelating the copper site with the thiol group, and at the cellular level, transferring tyrosinase to premelanosomes, and by antioxidant effects indirectly inhibiting tyrosinase.

Glutathione scavenges the ultraviolet radiation-induced reactive oxygen generated in epidermal cells (2).

Medical conditions and glutathione

There are certain medical conditions where glutathione is depleted, such as emphysema, asthma, allergic disorders, drug toxicity, metabolic disorders, cancer, chemotherapy with cisplatin, human immunodeficiency virus, and acquired immune deficiency syndrome.

Glutathione forms and routes

Glutathione is administered in three forms, oral, topical, and parenteral, as a skin whitening agent. The generalised method was twice weekly for at least eight to ten weeks to notice the changes. The oral and the topical glutathione have shown some appealing positive results in terms of lightening and improving texture of the skin, especially if both were combined, and proven to be safe and effective as well as well tolerated, without any concerns. Additionally, microneedling shows enhanced effects of the topical glutathione as it enhances its penetration through the micro-tunnelling of the skin. Whereas the intravenous route is considered concerning and controversial and short-lived, as it fades after six months, besides the concerning side effects and no standardised dosing protocols.

Glutathione: Miracle or Myth?

Most of the studies were small samples conducted on healthy volunteers for a short period of time, with poor study design, no long-term follow-up, no serum level glutathione measurement, and some of the participants had experienced skin lightening.

Despite a lack of clinical evidence for their effectiveness and lasting skin whitening tone, manufacturers, distributors, spas, and clinics kept promoting and recommending them. Some had experienced various liver dysfunction and disorders, and had no pre-tests done to assess the progress and changes. Others reported risks are renal failures, severe fatal skin reactions like toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), systemic inflammatory response syndrome (SIRS), skin cancer which might be due to depletion and switch from brown melanin to red which increases sun induced skin cancer, skin aging, immune system suppression, severe abdominal pain, thyroid dysfunction, air embolism, and blood sepsis from untrained staff or use of counterfeit intravenous glutathione (1-3).

Additionally, some of those forms are available over the counter (OTC) and online for purchase. The manufacturer advised that the rapid skin whitening can be achieved by a high dose of 600-1200 mg, twice a week injection, with an undefined duration to keep the desirable changes. Furthermore, those injections are sold expensively. The only indication is to reduce the neurotoxicity associated with cisplatin chemotherapy.

Many patients are inclined to self-medicate with glutathione, lured by the manufacturers' claims and the aesthetician and the spa promotion (3).

Natural glutathione

Glutathione can be found in fresh fruits, vegetables, and nuts. Also, tomatoes, avocados, oranges, walnuts, and asparagus are other sources to increase the level of glutathione inside our body (3).

Discussion and Conclusion

Oral and topical forms are safe for cosmetic and therapeutic uses within specific guidelines and are well tolerated with minor side effects. Most reported assessments were done based on photography (6). Whilst skin brightening and lighter tones might improve individual socioeconomic status and opportunities, it risks reinforcing structural racism (3).

Unregulated IV glutathione products are considered debatable as they can cause life-threatening health issues, along with cross-reactions with other drugs, and pose significant risks. Non-prescription cosmetic infusions should be scrutinised. Further rigorous and robust research with clinical evidence is needed on a larger scale to evaluate the efficiency and effectiveness of those cosmetic infusions, to reach long-term safety with an optimised, thoroughly investigated dose before recommending it (4).

Patients should refrain from buying over-the-counter glutathione skin-lightening products, particularly those that may contain or be combined with mercury (6).

It would be sensible for dermatologists to refrain from processing such injections for skin lightening until rigorous further clinical trials and high-quality studies are conducted to establish a safe use of it. Urgent measures are required to protect consumers from potential adverse effects and complications associated with intravenous infusions (6). Additionally, raising awareness about its potential risks, where statutory remains elusive should be mandatory.

Finally, the psychosocial consequences of systemic skin lightening represent a complex and sensitive topic that is best addressed through a multidisciplinary approach involving dermatologists, social scientists, psychologists, and psychiatrists.

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