

Review Article

Glutathione for skin lightening for dermatologists and cosmetologists

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ABSTRACT

Glutathione is a potential antioxidant and its reduced form (GSH) has a good skin-whitening effect in humans through its tyrosinase inhibitory activity. Many physicians consider it as a Wonder drug for skin lightening and treatment of hyperpigmentation, especially with darker skin tones. Glutathione is available in topical, oral and injectable formulations. Topical and oral forms are considered to be safe. Intravenous form did not prove its safety and efficacy to till date. In this article, we shall review and discuss the current status of glutathione as a skin lightening agent and address the miscellaneous unanswered queries regarding the dosage, duration of use and longevity of accrued effects based on clinical evidence and recent insights into its antimelanogenic mechanism.

Keywords: Glutathione, Skin lightening, Dermatologists

INTRODUCTION

Desire to attain skin tone lighter or fairer complexion in adults is increasing day by day. This craze exploiting 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 face, neck and other exposed parts of the body. Hence their effect is limited to the application site without any systemic skin lightening effect.¹

Many products are available as the over-the-counter like vitamin E, Hydroquinone, vitamin C serum, niacinamide (nicotinamide), arbutin, glycolic acid, kojic acid and a few new products like marine algae extracts, soy, pycnogenol, Boswellia, etc. All the products are applied locally and their effect varies from person to person. Systemic products are also available like l-cysteine peptide, tranexamic acid, different plant extracts. Of all

these, glutathione has become a popular skin lightening agent because of its faster action and popularity.^{2,3}

Glutathione peptide is an antioxidant and is a combination of three amino acids glutamate, cystine, and glycine which detoxifies xenobiotics.⁴ As a skin lightening agent, glutathione inhibits tyrosinase enzyme which helps in synthesis of melanin. It also modifies the production of eumelanin (produce dark brown colour to pheomelanin (produce yellow-red colour), leads to lightening of skin.⁵

Glutathione is available naturally in fresh leafy vegetables, walnuts, oranges, whey protein, tomatoes and fresh fruits.^{6,7} Glutathione is available in different formulations like topical, oral and injectables.⁷ Topical formulations show significant improvement in skin complexion on continuous use for certain period of time. Oral preparations are available in the form of tablets and solution forms. Sublingual route availability is better and requires lower doses and is considered to be safe by

FDA.⁸ The required dose is 20-40 mg/kg (i.e. 1 g to 2 g in two divided doses) and significant effects are seen within 3 months. Intravenous doses (600-1200 mg once/twice in a week) known to show more adverse effects due to the chances of overdose toxicities or may be due to the additives present in glutathione injection. The common adverse effects related to intravenous preparations are 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 incorrect sterile method of IV administration.^{7,9}

Glutathione is a 'magical skin whitening' molecule in countries like the republic of Philippines. Glutathione has seen a rapid spread in its popularity across the globe in short duration of time. Many manufactures and media campaigns supported its outcome effects in treating the disorders of hyperpigmentation such as melasma, but also as general skin whitening agent.¹⁰

It is necessary to look into the literature on glutathione for detailed background, information regarding the basic and applied physiology of glutathione. Glutathione exists in a reduced form (GSH) and an oxidized form (GSSG). The reduced form, GSH, seems to be instrumental in the depigmenting properties of this unique molecule.¹¹

UPDATE ON GLUTATHIONE AS A SKIN-LIGHTENING AGENT

There were only few published studies that evaluated the efficacy of oral, topical and parenteral glutathione as a skin whitening agent. Two trails were conducted on oral GSH conducted in Thai population by Arjinpathana and in Filipino women by Handog et al, involved administering 500 g/day of GSH in two divided doses to the study population, the difference being the use of buccal lozenges instead of oral capsules in latter study to enhance systemic absorption of glutathione.^{11,12} The primary efficacy outcome in both the trails was to evaluate the pre- and post-treatment melanin indices. The study done by Arjinpathana et al, group showed a consistent reduction in the melanin indices at all six sites evaluated in the GSH group subjects, with a statistically significant reduction over placebo at two sites.¹²

Study conducted by Handog et al in 30 healthy Filipino women using buccal lozenges instead of capsules of GSH reported significant reduction in melanin index at both sun exposed and sun-protection sites in all the subjects and moderate skin lightening observed by 90% of the subjects on global evaluation.¹³

Another study by Watanabe et al, provided good evidence favoring efficacy of topical GSSG 2% lotion applied twice daily for 10 weeks in producing temporary skin whitening and also the study revealed statistically significant reduction of skin melanin index with

glutathione compared to placebo, with no adverse drug effects.⁴

The major limitation of these studies included were small sample size consisting of healthy volunteers, extremely short study period with an even shorter follow-up, and lack of measurement of blood levels of glutathione.^{4,12,13}

Evidences favoring the use of intravenous glutathione remain elusive. For years, manufacturers, distributors, skin clinics and med spas have been recommending arbitrary dosage schedules, despite complete lack of evidence.^{14,15} A placebo-controlled trial done by Zubair et al, studied the efficacy and safety of IV GSH for skin tone lightening in 25 patients (1,200 mg given IV twice a week for 6 weeks in the treatment group versus normal saline in control group). The findings of this study did not favor IV glutathione as an effective or lasting treatment for skin tone lightening. The major adverse effect reported in the IV GSH treated group was liver dysfunction, which was neither qualified nor quantified. The investigators also did not estimate baseline or post-treatment renal or thyroid function of the subjects, both of which were reported to be adversely affected by IV glutathione.¹⁶

SAFETY STATUS OF GLUTATHIONE

As per Generally Recognized as Safe (GRAS)" consistent with Section 201(s) of the Federal Food, Drug, and Cosmetic Act of the United States Food and Drug Administration (US-FDA), glutathione-based oral dietary supplements are safe.¹⁷ No restrictions are employed on its oral forms in the US, Philippines and Japan. Oral forms are available as the over-the-counter drugs in India and in other Asian countries. The major drawback of oral GSH dosage form is its low bioavailability in humans. This made manufacturers of IV injections of GSH to recommend this route of administration to achieve anticipated therapeutic levels in the blood and skin rapidly to yield instant skin whitening results. The recommended dose of 600-1200 mg, to be injected weekly or twice a week, with no specified net duration of the therapy. But, the literature evaluating the efficacy of IV GSH is still lacking.⁵

LIMITATIONS OF IV GSH

Extreme high cost of injection vials is on of the compelling deterrent to its use. Other limitations include are lack of published source supporting its efficacy as a skin lightening agent, undefined dose and duration of IV injections, lack of approval from US FDA and warning against the use of intravenous glutathione by the FDA of Philippines, and its reported adverse effects.⁸

RECENT INSIGHTS FROM RESEARCH

A reasonable intracellular concentration of GSH and its transportation into the melanosomes are essential for GSH to inhibit tyrosinase and change melanogenesis

from eumelanin to pheomelanin. Earlier reports revealed the facts that trans-melanosomal transportation can be achieved through a membrane channel or diffusion, both of which seem to be lacking for GSH.^{18,19} Chung et al recently evaluated in vitro antimelanogenic effects and cytotoxicity of GSH in three cell culture lines (GSH monoethyl ester (GSH-MEE), GSH diethyl ester (GSH-DEE), and GSH monoisopropyl ester (GSH-MIPE)).²⁰ The results of their research confirmed significant inhibitory effect of GSH-MEE and GSH-MIPE, on the intracellular tyrosinase activity and melanin production. GSH-DEE and GSH-MIPE established additional cytotoxic activity, interpreting them unsuitable for clinical use. The findings of in vitro efficacy and nonexistence of cytotoxicity of GSH-MEE, the researchers recommended the development of GSH-MEE, instead of GSH, as an efficacious and safe molecule for the treatment of hyperpigmentation. However further clinical and invitro evaluation is required to draw conclusive results.

CONCLUSION

Currently, there is only a little considerable evidence in favor of glutathione as a therapy for hyperpigmentation, and there are many unsolved controversies surround its use. The trails available to date have evaluated the role of glutathione in skin lightening administered through different modes. Although the safety of topical and oral GSH proved to be good, their efficacy especially long-term remains questionable. There is no perfect evidence to support or dampen the use if IV GSH as a therapeutic agent for skin tone improvement.

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