Review Article

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The Role of Glutathione as a Bleaching Agent in Whitening Skin: A Review

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ABSTRACT

Objective: To review and compare the efficacy of glutathione formulations as skin-whitening agents in adults participating in several clinical studies.

Methods: Using a MEDLINE search with the time frame specified up to March 2020 , seven clinical studies involving GSH use for lightening the skin were recognized and assessed for significance and validity.

Results: Four controlled clinical trials (GSH capsules: 60 healthy volunteers; 250 mg oral GSH capsules:60; 2% glutathione lotion: 30s healthy volunteers; GSH as wash:74 healthy volunteers) and a case series(GSH lozenges: 30 patients) showed a significant reduction in melanin index. A case series (GSH soap: 15 patients) revealed a skin-lightening effect based on photography. Only one placebo-controlled study on IV GSH (1200 mg) in 60 healthy volunteers demonstrated a poor effect of glutathione as a whitening agent.

Conclusion: The literature search revealed that glutathione is not useful enough as a skin-whitening agent, as it is only effective on some parts of the skin and did not present any long-lasting effect. Although the safety profile of topical and oral glutathione seemed to be good, long-term research studies employing better study design are required in order to evaluate the efficacy of this antioxidant.

Keywords glutathione, skin bleaching, skin whitening, hyperpigmentation.

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INTRODUCTION

A lighter skin tone is given much importance by most races.This stands especially true in the case of women of Asian or African descent who have Fitzpatrick skin types IV–VI. They try many oral and topical bleaching agents in order to attain a lighter skin tone. Chemical formulationscontaining substances such as hydroquinone, mequinol, tretinoin, kojic acid, soy extracts, glycolic acid, ascorbic acid, arbutin, as well as other new cosmeceutical agents areused as commondepigmentingsubstances.These are applied topicallyas single-agent or combination products.[1]Due to the need for skin lightening,some agents have been promoted, including glutathione, tranexamic acid, l-cysteine peptide, vitamin C, different plant extracts, and combinations of these compounds.[2]

Glutathione is a tripeptide that is synthesized intracellularly. It isformed of L-cysteine, glycine, and glutamate.[3,4]It has a largenumber of reducing equivalents, so it's considered as the main redox buffer in human cells.[5]Glutathione presentsintracellular either inanoxidized form (GSSG) or in a reduced state (GSH), and the maintenance of an optimal GSH:GSSG ratio in the cell is very important to avoid oxidative damage and ensure cell survival.[6] An imbalance in the glutathione level and its indication as anoxidative stress marker has been reported in many diseasessuch as cancer, neurodegenerative disorders, cystic fibrosis, HIV,[7] diabetes mellitus,[8] and autism[9,10] as well as in low-birth-weight neonates[11]and anorexia nervosa.[12]

In addition to being known as a potent antioxidant, glutathione is considered a skin-lightening agent.This effect came to light after the discovery of its anti-melanogenic effects. It scavenges oxidative free radicals, inhibits tyrosinase, and shiftsmelanogenesis from the darker eumelanin to the lighter phaeomelanin.[13]The reduced glutathione form appears to have a key role in supporting the depigmentingeffect of this unique compound. In addition to the twoforms of glutathione mentioned, the compound may undergo esterification to produce glutathione esters.[14]The possible side effects of glutathione usage include cutaneous eruptions, Stevens-Johnson syndrome, toxic epidermalnecrolysis, renal impairment, abdominal pain, and thyroid abnormalities. Intravenous administration of GSH may also be associated with complications such as fatal sepsis or air embolism due to improper/unsterile injections.[15] The objective of this review was to carry outa literature search of all academic reports pertaining to the efficacy and evidence of the various dosage forms of glutathione as a skin-whitening agent.

MATERIALS AND METHODS

We conducted MEDLINE searches for studies published up to March 2020. The search term was "glutathione and skinlightening." Inclusion criteria were cohort studies,meta-analyses, RCTs, and systematic reviews ofglutathione as a skin-whitening agent.Exclusion criteria were other indication reports of glutathione, articles not in English, studies on animals,and publications before 2010.

RESULTS

There were seven studies evaluating the efficacy of glutathione as a skin-lightening agent at the time this article was authored. These studies are explained in Table 1.

Table 1: Summary of recent studies on glutathione as a skin-whitening agent.

Glutathione dosage form	authors	year	Subject involved	Study design	method	outcome	limitations
intravenous	Zubair et al.[15]	2016	50 healthy Pakistani women Ages: 25-47 years	Open-label Placebo-controlled	Intravenous glutathione (1200 mg) or normal saline injected over 30 minute	this study showed poor outcomes of glutathione in terms of efficacy as well as cost-effectiveness	Blood GSH levels were not measured ,Small study population and short duration
oral	Arjinpathana and Asawanonda[16]	2012	60 healthy students Ages: 19-22 years	Randomized, doubleblind, placebocontrolled study	Oral glutathione (500 mg) or placebo capsules daily, in 2 divided doses for 4 week	Significant reduction in melanin indices (UV spots) as measured by VISIA (Canfield Scientific Inc., USA) at all six sites in subjects who received GSH v. controls	Small sample size ,Short duration of study Subjects: Healthy young adults ,No post-study follow up , Serum GSH levels not measured
	Handog et al.[17]	2015	30 healthy women Ages: 22–42 years	Open label, singe–arm pilot study	One buccal lozenge (500 mg) per day, for 8 weeks.	Melanin index reduction significant at all sites in buccal GSH group vs. placebo	Small study population and duration No control used and no follow-up Blood GSH levels were not measured
	Weschawalit & Asawanoda[18]	2016	60 healthy females 20-50 years old	Randomized, placebo controlled, three-arm study	250 mg/day of oral GSH, 250 mg/day of oral GSSG or placebo (dibasic calcium	Both GSH and GSSG caused decreased melanin indices, GSH more effective in wrinkle	Small study population and short duration

Only one – a placebo-controlled trial on intravenous glutathione –was conducted by Zubair et al.In this study, 25 Pakistani patients were given IV glutathione (1,200 mg) twice weekly for sixweeks and were compared with a control group in which the participants were given IVnormal saline.[15]

There were three trialson oral glutathione.One was conducted in the Thai population by Arjinpathana and Asawanonda, and it involved the administration of 500 mg/day of GSH as capsules, divided into two doses over four weeks, to 60 healthy students in medical college.The result was a significant reduction in indices of melanin in the group who took GSH.[16]

The second study is an open-label, single-arm pilot study. It was conducted by Handog et al. and included 30 healthy women in the Philippines with Fitzpatrick skintypes IV and V. In this study, buccal lozenges of GSHwere administered in doses of 500 mg/day, divided in two. The buccaldosageform was used to increase GSH systemic absorption. The results of this studyshowed a significant decrease in melanin indices at both sun-protected and sun-exposed sites in all the participants.[17]The last trial involving oral glutathione was conducted in 60 Thai healthy females,who were randomized into three equalgroups and givencapsulesof GSSG (250mg/d), GSH (250mg/d), or placebo for 12weeks.Thisrandomized, placebo controlled, three-arm studyrevealed that oral glutathione(in doses of250mg daily), in both oxidized and reduced forms,decreased melanin indiceseffectively.[18]

Three studies on topical GSH application were found. Watanabe et al. conducted a randomized, double-blind, placebo-controlled, matched-pair study, which included 30 healthy middle-aged Filipino women. In this study, a lotion containing 2% GSSG was applied to one side of the face and a placebo lotion was applied to the other side two times daily for 10weeks.This study saw a significant decrease in the skin melanin index inthe GSSG-treated part compared to the placebo-treated part.[19]

Another clinical trial on topical glutathione was a double-blind, randomized study, conducted by Kristiana et al. in Indonesia.In it, 74 healthy women (average age 33.3 ± 5.9 years) were each given doses of a day cream with sunblock, a night cream, and a face wash to be used twice daily under supervision. The participants were divided into threegroups.The women in the first applied GSH 0.1%, the second GSH 0.5%, and the third a placebo(without GSH). The results of this study showed that GSH 0.1% was significantly more effective compared to GSH 0.5% and placebo in lightening sun-exposed skin.[20]The pilot study conducted by Sriharsha et al.on15 Indian patients(15–70 years of age) with melanosisshowed that glutathione in soap form can decrease hyperpigmentation in 11 out of 15 patients after threemonths of use.[21]

DISCUSSION

Melanin is a skin pigment composed of eumelanin (blackish-brown pigment) and pheomelanin(a reddish-yellow pigment). Increase in the amount of pheomelaninmakesthe skin

lighter.[22]Theexposure to ultraviolet (UV) radiation leads to hyperpigmentation, which booststhe formation of free radicals between cells.[23,24]Orally administered antioxidants inhibit melanogenesis by controllingthese free radicals.The roleof glutathione as a skin-bleaching agent is carried out through the inhibition of the enzyme tyrosinase during the melanogenesis process, either by directly binding tothe copper-containing active site in the enzyme or by indirectly eliminating peroxidesand other free radicals.[25]

The literature search revealed inconclusive results on this subject.There were limited studies on the use of glutathione as a depigmenting agent, and there is need for it to be studied more extensively with respect to thehuman skin.Oral glutathione is characterized by low bioavailability.[25]As a result, manufacturers of IV injections of GSH "recommend" it to get the desired therapeutic blood level and,in turn, the "instant" skin-whitening effect.

Despite the fact that IV glutathione has been used in the past, there has been no long-term clinical trial assessing its efficacy till now. However, manufacturers of intravenous GSH recommend the administration of about600–1200 mg by injectionsonce or twice weekly without the determination of a specificduration of treatment.[26]The only study conducted by Zubair et al. did not favor the use of parenteral glutathione as effective form of treatment.Additionally, the study had a high dropout rate (9 out of 25).Furthermore,this study hada small sample size(25 patients in each group).In addition to the adverse effects of IV GSH that occurred in all the subjects in the GSH group, with 32% patients experiencing a disturbance in liver function,[15]the very high cost of GSH vials is a factor limiting its use.

Orally administered GSH reduces thepotentially adverse effects associated with parenteral (IV) GSH.The two studies on oral glutathione in this review revealed a considerable decrease in melanin indices.[16,18]The tolerance to oral GSH was excellent. Moreover,the popularity of oral administration of glutathionehas increased due to the idea that these can help achieve lighter appearance for the entire body.Limitations of the oral route trials include the decreased ability of the GSH molecule to pass the GIT tract, as it has to be converted into three amino acids before absorption.[27]

The systematic absorption of GSH can be enhanced through the administration of GSHas buccal lozenges, as seen in Handog et al.'s study. In this open-label study, a significant decline in melanin index was shown forboth sun-protected and sun-exposed skin in all the participants.[17]

Topical creams are slowly losing popularity, as their effects are restricted to the area of application.This has made way for oral lightening treatments as the preferred alternative. Oral glutathione treatments have increased in popularity due to the impression that they give the entire body a lighter appearance.

The literature search identified three studies on the topical application of glutathione. In Watanabe et al., a randomized, double-blind, placebo-controlled clinical trial,skin melanin

indices significantly reduced in the group receiving glutathione compared to the one receiving placebo.No adverse effects were reported.[19]Further study on topical glutathione was conducted by Kristiana et al., who also reported a significant skin-lightening effect from usingGSH as a wash.[20] The final study on topical glutathione revealed by the search was conducted bySriharsha et al. on patients with melanosis.The study revealed a reduction in hyperpigmentation when GSH was used insoap form on a sun-exposed area.[21]The use of topical glutathione has slowly declined, as the action of this form of glutathione is restricted to the area of application.

However, all the trialson both topical and oral glutathione had limitations such as the use of healthy volunteers, small sample sizes, short studyduration, non-measurement of glutathione serum level, and lack of long-term follow up. Therefore, better-designed clinical studies are required to determine the long-term safety and efficacy of glutathione as a skin-whitening agent and to ascertain its definite role in skin-whitening.

CONCLUSION

This literature review assessed recent clinical studies on the whitening effect of various GSH formulations.The evidence available is not convincing enough. Additionally, there are many controversies around theuse of glutathione. Although the use of GSH in topical or oral forms appears to be safe, the studies on their efficacy have many limitations. There is little evidence to encourage or discourage the use of IV GSH to combat hyperpigmentation.The adverse effect of the use of theIV route is a great concern.Additionally, regardless of the route of administration of GSH, the skin tone will return to the original after GSH administration is halted. As a result, more clinical studies with a better design, larger sample size, and longer-term follow up measuring GSH blood levels are required for better evaluation of the safety and efficacy of GSH use.

Conflict of Interest: None.

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