CLINICAL UPDATE

Intravenous glutathione for skin lightening: Inadequate safety data

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Background. Glutathione (GSH) is the most abundant naturally occurring non-protein thiol that protects mammalian cells from oxidative stress. Intravenous (IV) GSH for skin lightening is advertised by clinics in South Africa and internationally online, yet to date no published review on the subject exists.
Methods. We conducted a MEDLINE search (to 30 September 2015) of GSH use for skin lightening and of all indications in medicine, to evaluate its safety.
Results. Two controlled clinical trials (GSH capsules: 60 patients; 2% glutathione disulphide lotion: 30 patients) and a case series (GSH lozenges: 30 patients) reported a significantly decreased melanin index. A case series (GSH soap: 15 patients) reported skin lightening based on photography. Two systematic reviews of IV GSH for preventing chemo-induced toxicity and a third review of adjuvant therapy for Parkinson's disease altogether included 10 trials. Most trials reported either no or minimal GSH adverse effects, but all had treatment durations of a few doses (IV) or 4 - 12 weeks. No study reported long-term IV GSH use.
Conclusion. In spite of widespread reported use, there are no studies of IV GSH use for skin lightening or of its safety for chronic use (for any indication). The switch from brown to red melanin production may increase the risk of sun-induced skin cancers in previously protected individuals. Regulatory assessment of systemic GSH administration for cosmetic use by the Medicines Control Council seems urgently warranted to protect consumers from potential side-effects and from complications of IV infusions. This is especially concerning because of reports of GSH bought online. Effective topical GSH may be useful for hyperpigmented skin disorders, but this requires scientific scrutiny. The debate on the merits of cosmetic skin lightening is best handled by multidisciplinary teams.

S Afr Med J 2016;106(8):782-786. DOI:10.7196/SAMJ.2016.v106i8.10878

Dermatologists use depigmenting creams with various active ingredients in the treatment of melasma and post-inflammatory hyperpigmentation.[1] Skin lightening or bleaching refers to the cosmetic practice of applying depigmenting agents not as treatment for hyperpigmentation but with the deliberate aim of achieving a lighter skin colour. It is a practice that is common in many places (e.g. India, Africa and America) with pigmented populations and a history of improved social status with lighter complexion. Adverse effects are associated with active ingredients (mercury, hydroquinone and potent steroids) in depigmenting creams and are illegal in cosmetics in many countries. Further illegal ingredients in Africa have been shown to be imported from Europe (in spite of a European Union ban).[2]

Glutathione (GSH) was first discovered by Hopkins[3] in 1921 in yeasts, and subsequently in other tissues.[4] It is a tripeptide composed of L-cysteine, glycine and glutamate that is synthesised intracellularly.[5,6] It is considered the main redox buffer in human cells owing to its large amount of reducing equivalents,[7] and is an important enzyme cofactor that serves as a neuromodulator in the central nervous system. The tripeptide exists intracellularly either in an oxidised glutathione disulphide (GSSG) or reduced state (GSH), and maintaining an optimal GSH:GSSG ratio in the cell is critical for prevention of oxidative damage and for cell survival (Fig. 1).[8] An imbalance in GSH and its use as a marker of oxidative stress is reported in many diseases including cancer, neurodegenerative disorders, cystic fibrosis, HIV,[9] diabetes mellitus,[10] anorexia nervosa[11] and autism[12,13] and in low-birth-weight neonates.[14]

Reports of systemic skin lightening with GSH have appeared with increasing frequency on social media, and clinics advertise it online in many countries (Africa, the USA, Canada, Mexico, etc.). Our objective was to conduct a literature search to identify all academic reports of GSH use for skin lightening and all clinical trials of GSH use for all indications in medicine.

Methods

Two MEDLINE searches for studies published up to September 2015 were conducted. The search terms for the first were 'glutathione AND skin lightening', and for the second 'glutathione AND randomised controlled trial'. Inclusion criteria were any treatment report of GSH for skin lightening (or hyperpigmentation) and GSH for any randomised control trial (RCT) for the first and second searches, respectively. Abstracts were read independently by two authors to identify relevant articles.

Results

Nine articles were identified from the first MEDLINE search. Six publications mentioned GSH as part of reviews related to melanin (kojic acid in rats,[15] piceatannol inhibition of mushroom tyrosinase,[16] oral zinc sulphate murine hair hypopigmentation,[17] hydroquinone occupational exposure[18] (and toxicity for skin lightening)[19] and natural ingredient-containing treatments for hyperpigmentation.[20] A seventh article was an extensive review of biochemical mechanisms of how GSH causes depigmentation in cell cultures and laboratory animals.[21] Five clinical reports (4 published since 2012) of the use of GSH for skin lightening were identified (2 from the MEDLINE search and 3 from references). The first, a pharmacokinetic study of GSH in seven participants, did not measure skin lightening

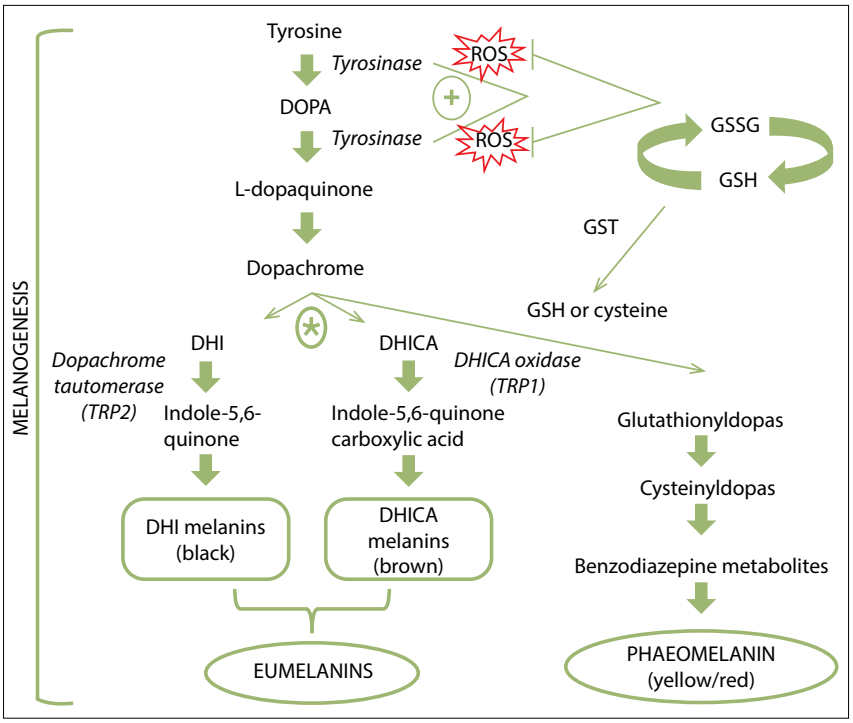

Fig. 1. GSH and its effect on skin lightening. Reactive oxygen species (ROS) have a direct activation effect on tyrosinase. Reduced GSH neutralises ROS formation and thus indirectly inhibits tyrosinase. At the dopachrome step of the melanogenic pathway, interaction of thiols such as reduced GSH and cysteine bind with dopaquinone to produce thioldopas and favour phaeomelanogenesis. GST catalyses binding of GSH and dopaquinone. (DOPA = dihydroxyphenylalanine; DHI = dihydroxyindole; DHICA = dihydroxyindole carboxylic acid.)*

or report side-effects.[22] A case series of 15 patients from India treated with a GSH-containing soap for melanosis of the face reported lightening (in 11/15 after 3 months) based on clinical photographs. However, no mention was made of how the conditions for photography were standardised or of follow-up on stopping treatment.[23] A controlled trial from Thailand tested 250 mg GSH capsules twice daily in two groups each of 30 medical students over 4 weeks. They reported a decreased melanin index measured at six body sites (but statistically significant only at two sites, namely the right side of the face (p=0.021) and the sun-exposed left forearm (p=0.036)).[24] Watanabe *et al.*[25] from Japan reported a significant reduction in the melanin index (mean (standard deviation), week 0: 272.77 (26.17); week 10: 243.47 (26.31)) in subjects treated with a GSSG-containing lotion measured with a Mexameter MX18 (Courage + Khazaka Electronic GmbH, Germany). Investigators and participants also subjectively scored GSSG-treated skin as lighter. The most recent study is an uncontrolled trial of 30 Filipino women. The authors reported a significant reduction in melanin index (measured with a portable mexameter) (p<0.0001) after 500 mg GSH lozenges were administered daily for 8 weeks.[26] None of the studies reported significant adverse effects or follow-up beyond the study period (Table 1).

Of the plethora of articles retrieved from the second MEDLINE search, we identified 28 systematic reviews of animal studies,[39-41] GSH-related genetic polymorphisms linked to various cancers (colorectal cancer,[42] leukaemia,[43,44] lung cancer,[45,46] bladder cancer,[47] gastric cancer,[48,49] prostate cancer,[50-53] adult brain tumours,[54] basal cell carcinoma[55]) and linked to other disorders (autism,[12,13] hypertension,[56,57] respiratory diseases,[58,59] cataract,[60] myelodysplastic syndrome,[61,62] glioma[63] and male idiopathic infertility.[64]) There were 9 RCTs identified from two systematic reviews of the use of GSH to reduce chemotherapy-induced toxicity (6 cisplatin, 2 axaliplatin, 1 platinum); most suggested less toxicity in GSH groups. A systematic review of GSH as an adjuvant therapy in Parkinson's disease identified one controlled trial[65] showing doubtful benefit. It was noteworthy that most studies did not report adverse events of GSH, and any reported were mild (Table 1).

Discussion

The idea of GSH-induced hypopigmentation may stem from early studies linking sulfhydral-containing compounds to the inhibition of melanogenesis or from early anecdotal observations in Parkinson's disease. Proposed mechanisms of its action include inactivation of the melanogenic enzyme, tyrosinase, influencing the switch from eumelanin to phaeomelanin.[66,67] During melanogenesis, tyrosinase is responsible for the conversion of L-tyrosine to L-DOPA and subsequently to dopaquinone, then the pathway bifurcates to produce eumelanin or phaeomelanin. At a critical point in the melanogenic pathway (asterisk, Fig. 1), thiols (cysteine and GSH) can react with L-dopaquinone to produce glutathionyldopa, or act as a reservoir of L-cysteine by conjugating with L-dopaquinone to produce cysteinyldopa. These two thioldopa substrates serve as a precursor to enhance the switch from eumelanogenesis to phaeomelanogenesis, resulting in lighter skin pigmentation.[68,69] This effect of GSH on skin pigmentation was reported half a century ago, with black human skin shown to exhibit lower levels of GSH than white skin.[70] In addition, GSH can act to lighten the skin directly through the quenching of free radicals and peroxides that have been shown to induce tyrosinase activity.[71] However, more evidence is needed to prove this unequivocally.

GSH therefore has the potential to lighten human skin. However, the only reliable safety data on GSH are of sporadic use during chemotherapy cycles, for a few weeks at most. There are no data on adverse effects of chronic high-dose GSH as used for skin lightening.

All chemotoxicity studies used injectable GSH. Reactive oxygen species are easily decomposed in aqueous solution; this may explain the novelty of drug delivery as lozenges, which may be more stable (although two participants complained about the taste). The oral route reduces potential adverse events associated with intravenous (IV) administration but is associated with low bioavailability. Effective topical GSH[25] may be useful for dermatologists treating hyperpigmentation, but it is worth noting that GSH as a thiol interacts with metalloid complexes that render it ineffective. Patients should be advised to avoid using GSH with over-the-counter skin lightening creams that may contain mercury.[1]

All identified published trials report mild or no side-effects of GSH use. However, study duration was a maximum of 12 weeks. We identified one case series that reported intolerable adverse effects leading to discontinuation of 5 mg oral GSH daily as adjuvant treatment for hepatocellular carcinoma (HCC). Seven of 8 patients died within

1 year. However, the very severe prognosis associated with HCC was a likely confounder.[72] The effect of long-term administration of high doses of GSH on cells or organ systems remains unclear. Furthermore, since GSH causes a switch from eumelanin to phaeomelanin, it may increase UV photosensitivity, DNA damage and skin cancers in previously protected populations.[73] Of major concern are

Table 1. Current list of human clinical trials associated with GSH

Reference	Country of origin Study type Indication	Subjects, *n* (sex), age GSH dose and duration Study duration	Outcomes	Adverse events
Skin whitening				
Hong *et al.*,[22] 2005	Korea Cases (uncontrolled) Pharmacokinetic study	7 (male), 22 - 23 yr 65.5 (SD 4.5) kg, 50 mg GSH/kg body weight IV over 10 min, 10 d	IV GSH oxidised to GSSG (half-life = 10 min) Loading dose = 1.69 g/kg Maintenance dose = 5.70 g/h/kg to reach extracellular concentration required to suppress intracellular ROS	None reported
Arjinpathana and Asawonda,[24] 2012	Bangkok, Thailand RCT (double-blind, placebo) Skin whitening	60 (18 male, 42 female), 19 - 22 yr 250 mg capsules GSH twice daily, 4 wk	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	Flatulence
Sriharsha *et al.*,[23] 2015	India Pilot study GSH soap: melanosis of the face	15, 15 - 70 yr 3 mo	Decreased hyperpigmentation in 11/15 patients after 3 mo	None reported
Watanabe *et al.*,[25] 2014	Ibaraki, Japan RCT (double-blind, placebo) Skin whitening	30 (female), 30 - 50 yr 2% GSSG lotion twice daily, 10 wk	Weeks 6 and 10: Melanin index sign lower GSSG v. placebo Keratin index sign lower GSSG v. placebo	Mild erythema of the face (*n*=1)
Handog *et al.*,[26] 2015	Manilla, Phillipines Single-arm trial (not blinded) GSH-containing lozenges Skin whitening	30 (female), 22 - 42 yr 500 mg daily, 8 wk	Decreased melanin index after 2 wk All subjects showed a significant decrease in melanin index from baseline (p<0.0001)	Sore gums (*n*=1) Undesirable flavour/texture of lozenge (*n*=1)
Chemotherapy drugs neuroprotection				
Cascinu *et al.*,[27] 1995	Italy RCT (double-blind, placebo) Prevent cisplatin toxicity in gastric cancer	50 GSH 1.5 g/m^2 in 100 mL saline IV over 15 min 600 mg GSH IM, days 2 - 5 15 wk	Neuropathy Week 9: 0 GSH v. 16 placebo Week 15: 4/24 GSH v. 16/18 placebo	None reported
Colombo *et al.*,[28] 1995	Italy Random, phase II Prevent cisplatin toxicity in relapsed ovarian cancer	33 50 mg/m^2 weekly ± 2.5 g/m^2 GSH, 9 wk	Higher (100% dose) cisplatin intensity was received by 56% GSH v. 27% control	None reported
Parnis *et al.*,[29] 1995	Australia RCT (double-blind, placebo) Prevent cisplatin toxicity in ovarian cancer	12 GSH 1.5 g/m^2 over 15 min CDDP 40 mg/m^2 over 2 h for 2, 3 or 4 consecutive days NR	No significant protection	None reported
Bogliun *et al.*,[30] 1992	Italy Placebo controlled Prevent cisplatin toxicity in ovarian cancer	33 CDDP total dose 500 - 675 mg/m^2 ± GSH 2.5 g/m^2 IV over 15 min, 1 wk	Less severe neurotoxicity after co-treatment with all methods	Similar in both groups except oliguria greater in placebo group
Smyth *et al.*,[31] 1997	United Kingdom RCT (double-blind, placebo) Prevent cisplatin toxicity in ovarian cancer	151 (female), 21 - 76 yr 6 cycles of 100 mg/m^2 ± 3 g/m^2 + GSH IV over 15 min, 3 wk	6 courses of cisplatin, 58% GSH v. 39% control Improved creatinine, GSH 74% v. 62% (p=0.006) GSH improved depression, emesis, neurotoxicity, hair loss, shortness of breath	None reported

Continued ...

Table 1. (continued) Current list of human clinical trials associated with GSH

Reference	Country of origin Study type Indication	Subjects, *n* (sex), age GSH dose and duration Study duration	Outcomes	Adverse events
Schmidinger *et al.*,[32] 2000	Austria RCT (blinding, pilot) GSH v. intensive hydration in cisplatin chemo regimen for solid tumours	20 80 mg/m^2, 4 wk GSH 5 g IV + 2 000 mL saline control + 4 000 mL saline + forced diuresis NR	Haemoglobin: GSH 10.7 mg v. placebo 9.5 mg (p=0.039) White cells: GSH 3.3 × 10^3/mL v. placebo 2.2 × 10^3/mL (p=0.004) Platelets: GSH 167 × 10^3/mL v. placebo 95 × 10^3/mL (p=0.02)	None reported
Cascinu *et al.*,[33] 2002	Italy RCT (double-blind, placebo) Prevent oxaliplatin toxicity in advanced colorectal cancer	52 GSH 1 500 mg/m^2 IV over 15 min prior to oxaliplatin 12 treatment cycles	Neuropathy Cycle 4: 7 GSH v. 11 placebo Cycle 8: 9/21 GSH v. 15/19 placebo Cycle 12: 3 GSH arm v. 8 placebo	None reported
Milla *et al.*,[34] 2009	Italy Oxaliplatin neurotoxicity in colorectal cancer treated with FOLFOX4 adjuvant regimen	27 GSH 1 500 mg/m^2 IV or saline solution before oxaliplatin infusion 12 treatment cycles	Reduced neurotoxicity GSH v. placebo (p=0.0037)	None reported
Leal *et al.*,[35] 2014	USA RCT (double-blind, placebo) Prevent platinum peripheral neuropathy	185 1.5 g/m^2 GSH IV or placebo over 15 min 18 wk	No statistically significant differences in peripheral neurotoxicity, degree of paclitaxel acute pain syndrome, time to disease progression or apparent toxicities	None reported
Neurodegenerative disorders				
Sechi *et al.*,[36] 1996	Italy Cases (uncontrolled) Parkinson's disease	9 600 mg GSH IV twice daily, 30 d, 4 mo	42% decline in disability, therapeutic effect lasted 2 - 4 mo	None reported
Hauser *et al.*,[37] 2009	USA RCT, pilot trial (placebo) Safety and preliminary efficacy in Parkinson's disease	21 1 400 mg GSH IV or placebo 3 times a wk, 4 wk 3 mo	Unified Parkinson's Disease Rating Scale (UPDRS) motor scores higher in GSH group v. placebo	No adverse events due to GSH
Mischley *et al.*,[38] 2015	USA Safety and tolerability of intranasal GSH in Parkinson's disease	30 600 mg/d of intranasal GSH v. placebo (saline) in 3 divided daily doses 3 mo	All groups met tolerability criteria	No adverse events due to GSH

NR = not reported; IM = intramuscular.

potentially severe complications (septicaemia, infective endocarditis and transmission of blood-borne infections) of IV administration of GSH by people with no health qualifications. Recent Food and Drug Administration warnings also point to a need for increased public awareness of potential harm.[74]

Conclusion

This brief review evaluates recent clinical studies on the use of GSH. Despite widespread use of IV GSH, no clinical report was identified. Large RCTs of long-enough duration and follow-up are warranted for the safe treatment of pigmentary disorders. The psychosocial impact of systemic skin lightening is a Pandora's box best addressed by multidisciplinary teams including social scientists, psychologists and psychiatrists.

Source of funding. Funded by the South African Medical Research Council.

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Accepted 11 April 2016.