A RANDOMISED, DOUBLE-BLIND, MULTIPLE-DOSE TRIAL OF THE EFFICACY OF A SUBLINGUAL GLUTATHIONE WAFER (LumeniX™/RadianiX™) AS A THERAPEUTIC SKIN HEALTH SUPPLEMENT

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Results summary

After 14 days
- ✓ Significant increase in skin luminosity and gloss by up to 60%
- ✓ Significant reduction in eye wrinkles and fine lines by up to 51%

After 28 days
- ✓ Significant increase in skin elasticity by up to 226%

After 8 weeks
- ✓ Significant increase in skin lightness by up to 12%
- ✓ Significant increase in skin smoothness with decrease in skin roughness by up to 71%

Based on a clinical trial of 34 female participants with signs of skin ageing on a regime of 200mg sublingual GSH wafers daily for 4 weeks followed by 100mg sublingual GSH wafers for 8 weeks

ABSTRACT

Glutathione (GSH) is a naturally occurring tripeptide. Literature reports show that GSH can cause skin lightening, improve skin gloss/luminosity and skin tone. Several routes of supplementing GSH for these skin treatment purposes are available including intravenous (IV), oral and topical administration.

A novel patented sublingual wafer containing GSH (LumeniX™/RadianiX™) was investigated in a randomised, double-blind, multi-dose trial for efficacy as a therapeutic skin health administration of LumeniX™/RadianiX™ wafers.

Objectives: The primary objectives of this study were to determine the changes in skin lightness, skin luminosity/ gloss, net skin elasticity, eye wrinkles and fine lines, skin roughness and skin discoloration following the sublingual administration of LumeniX™/ RadianiX™ wafers.

Methods: The 12-week study was conducted on 34 healthy females aged 30 to 65 years old with Fitzpatrick skin type IV or V at one clinical site in Sydney, Australia.

Results: Significant improvements were observed in skin lightness (up to 12%), skin luminosity and gloss (up to 60%), skin elasticity (up to 133%), skin smoothness (up to 27%) and decrease in eye wrinkles and fine lines (up to 51%) within 14 days of GSH therapy.

Conclusions: The authors concluded that the sublingual GSH wafers (LumeniX/RadianiX) were safe and clinically efficacious in healthy women with the ideal maintenance sublingual dose of 100mg GSH daily after a one month loading dose of 200mg GSH daily.

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INTRODUCTION

Melanin is a pigment present in the skin epidermis. Each person has a different amount of melanin in their skin. This variation is due to genetics and other factors, including environmental factors such as sunlight exposure. Melanin is a UV-absorbing agent, preventing the penetration of UV radiation from reaching the lower dermal cells which can result in sunburn.

Tanning is an indication that the skin is producing and releasing melanin. There are two types of melanin; eumelanin which results in a darker skin colour and pheomelanin which produces a lighter skin colour. The ratio of these two different types of melanin produced determines the skin colour[1]. Sunlight exposure (UV radiation) promotes the production of melanin, especially eumelanin, resulting in hyperpigmentation.

A lighter skin tone may be created by manipulating the skin's ratio of eumelanin and pheomelanin. Glutathione is an example of such agent used to alter this ratio. When used consistently over a period of time, GSH can result in a noticeably lighter skin tone[2,3,4].

The discovery of the GSH skin lightening effect was accidental. Pale skin was one of the side effects noticed in cancer patients treated with GSH for its antioxidant and its antitoxin properties during chemotherapy[5,6]

Topical, oral, and IV GSH are available as a nutraceutical product for skin lightening. The sublingual (SL) form is the most bioavailable compared to oral forms (tablet, capsule) due to the sublingual absorption bypassing the liver first pass metabolism and the hostile environment of the GI tract. An in vivo study by Daniela Buonocore et al[7] revealed a rapid and efficient uptake of GSH into the blood via the oral mucosa resulting in higher bioavailability. In another in vivo study by Bernard Schmitt et al[8], these researchers also showed increased plasma GSH levels in the SL group when compared to the oral GSH group. The differences between these two groups were statistically significant ($p < 0.05$). Oral administration of GSH is not considered optimal due to its very poor bioavailability.

Our SL wafer used a patented wafer matrix technology (WaferiX™) as the GSH carrier. This novel SL GSH wafer was prepared by freeze-drying an aqueous dispersion of GSH containing sodium carboxymethycellulose and amylopectin as the matrix formers. The novel wafer GSH formulation rapidly dissolves sublingually, releasing the GSH into the small saliva volume immediately, adjacent to the sublingual mucosal membranes, resulting in a direct SL absorption with higher bioavailability than other oral formulations.

This study aimed to explore the clinical effect of SL GSH on related skin conditions as a therapeutic skin health supplement.

METHODOLOGY

This study was a randomised, double-blind, multiple-dose study on the efficacy of a sublingual glutathione wafer (Lumenix™/ RadianiX™, commercially available products under two trademarks) as a therapeutic skin health supplement. The 12-week study was conducted on 34 healthy females aged 30 to 65 years old with Fitzpatrick skin type IV or V at one clinical site in Sydney, Australia.

The primary efficacy objectives included: (i) skin colour; (ii) skin gloss/luminosity; (iii) skin elasticity; (iv) eye wrinkles/fine lines (crow's feet) and (v) skin roughness.

Participants were instructed on how to administer the wafers under the tongue for maximum SL absorption. Food and drink were avoided within 10 minutes of administration and the wafers were administered twice daily (morning and evening).

Participants were blinded and randomised in a 1:1 ratio to one of the two cohorts each with seventeen (17) participants. Cohort 1 received

100mg GSH wafer (2 x 50mg GSH wafers plus 1 x placebo wafer) administered twice daily (total daily dose of 200mg) in Week 1 to Week 4. In Week 4 to Week 12, 50mg GSH wafer (1 x 50mg GSH wafer plus 1 x placebo wafer) were administered twice daily (total daily dose of 100mg). This will be referred to as the 200mg/100mg dosing regimen.

Cohort 2 received 150mg GSH wafer (3 x 50mg GSH wafers) administered twice daily (total daily dose of 300mg) in Week 1 to Week 4. In Week 4 to Week 12, 100mg GSH wafer (2 x 50mg GSH wafers) were administered twice daily (total daily dose of 200mg). This will be referred to as the 300mg/200mg dosing regimen.

Assessments were conducted at baseline (Day 0), Week 2 (Day 14), Week 4 (Day 28), Week 8 (Day 56) and Week 12 (Day 84) which was the end of study (+/- 3 days) or at early termination.

Participants were allowed to continue their current skincare regimen without introducing any new or different skincare products or facial treatments. Participants were also asked to avoid sun exposure or to use appropriate sun protection when outdoors (sunscreen, hat, protective clothing). Each participant was provided with product instructions (for use and storage) and a diary to keep track of product use. At each visit participants' compliance and any changes to concomitant medications were recorded.

INSTRUMENTAL MEASUREMENTS

Skin colour was assessed using a Mexameter® MX 18 (Courage + Khazaka electronic GmbH), skin elasticity was measured by Cutometer® Dual MPA 580 (Courage + Khazaka electronic GmbH), skin luminosity (gloss) was measured by Skin Glossymeter® GL 200 (Courage + Khazaka electronic GmbH) and skin brightness was measured by Skin Colorimeter® CL 400 (Courage + Khazaka electronic GmbH).

The skin properties were analysed by digital photographs of the face (front and side facial photographs) using a custom-made digital photography equipment (Canon EOS 60D DSLR camera). Each image was cropped and resized in GIMP to facilitate image analysis. After images were processed, they were imported into Image Pro Premier (IPP) for image analysis (assessment including eye wrinkles, skin discolouration, and skin roughness). The IPP provides values in percentage change ("change from baseline" and "percentage change from baseline").

STATISTICAL ANALYSIS METHODS

The instrumental and photos measures were transferred to SAS for analysis. Descriptive statistics were calculated and averaged over participants for each measure and visit. These averages were analysed inferentially using repeated measures analysis of covariance within a mixed model framework. Inferential statistical analysis was performed in order to assess if each parameter (the dependent measure) varied linearly over time. The Baseline value (Visit 1) of the measure, in addition to other demographic variables, were used as covariates within each measure.

Adjusted means, calculated as Least Squared Means in the analyses, are presented in the tables with probabilities less than 0.05 indicating significant differences between selected means. The adjusted means between the first and last visit were compared using a t-test to see if there was an overall change at the end of the study.

Change from Baseline was calculated, and descriptive statistics were also calculated for each measure. This includes number of observations (n), mean, percentage change, standard deviation (SD), minimum, median, and maximum values for each parameter's value and its change from Baseline.

STUDY POPULATION

A total of thirty-four (34) healthy female participants with Fitzpatrick Skin Type IV or V and with some signs of skin ageing (crow's feet, hyperpigmentation and uneven skin texture) whose written informed consent had been obtained, were screened and enrolled in the study.

RESULTS AND DISCUSSIONS

The average age of the thirty-four (34) female participants enrolled was 44 years (SD = 9.5), ranging from 31 years to 64 years old.

88% of participants had an ethnicity from Asia, 3% from the South Pacific/Papua with 9% from other regions. 24% of participants had normal skin, 18% had dry skin, 11% had oily skin and 47% had combination skin.

56% had 'Phototype IV' skin (olive, moderate brown; burns minimally, always tans well); 44% had 'Phototype V' skin (brown, dark brown; rarely burns, tans profusely).

The following efficacy parameters showed a statistically significant improvement compared to baseline: skin lightness (p = 0.03), skin luminosity and gloss (p = 0.04), eye wrinkles (p = 0.04), and skin roughness (p = 0.04).

Other parameters measured were changes to melanin and hyperpigmentation. While not statistically significant, the results showed a trend for improvement in these measurements.

High positive responder rates across all parameters

We analysed the percentage of participants who had a positive result to GSH therapy within the study period. The study showed an overall high positive responder rate of greater than 70% across all parameters. 100% of participants on the 200mg/100mg regime showed improvements to skin lightness, skin roughness and elasticity within 12 weeks.

Due to the high levels of positive response seen in participants on the 200mg/100mg regime across the parameters studied, we postulate that 200mg/100mg regime provides the body with optimal homeostatic GSH level. More supplementation may not be necessary as excessive GSH may be broken down or rechannelled to other cells. GSH has a very complicated pattern of involvement in diverse biological processes. Maintaining GSH homeostasis is of utmost importance for proper cells function.

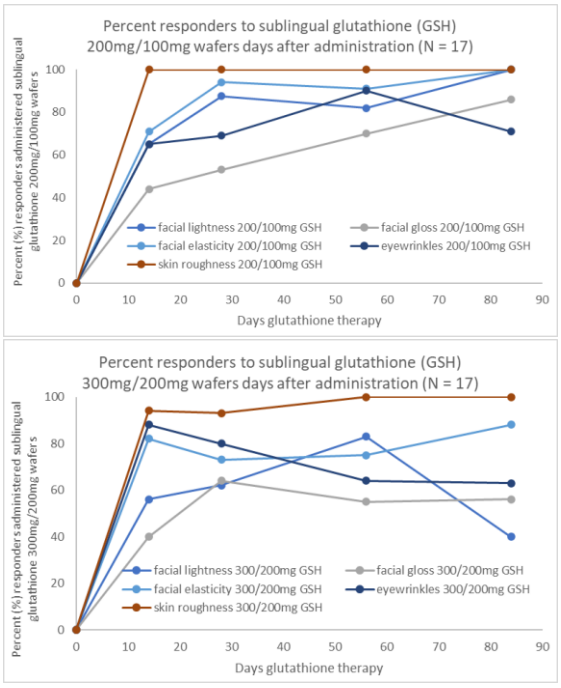

Fig 1. Graph of responder rates (%)for all study participants from baseline throughout end of study for each skin parameter

Skin lightness

SL GSH therapy resulted in a statistically significant improvement to skin lightness in all participants compared to baseline (p=0.03) (see Fig. 2).

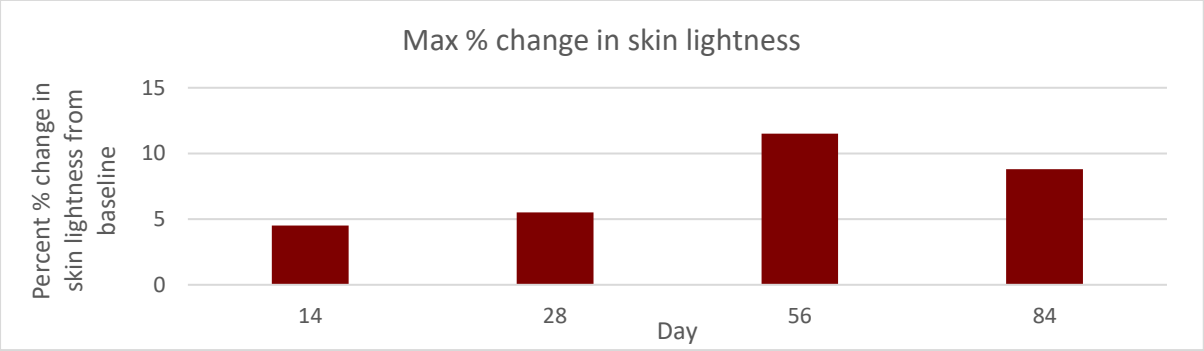

Fig 2. Graph of maximum percent changes for skin lightness for all study participants taking sublingual GSH from baseline to study completion

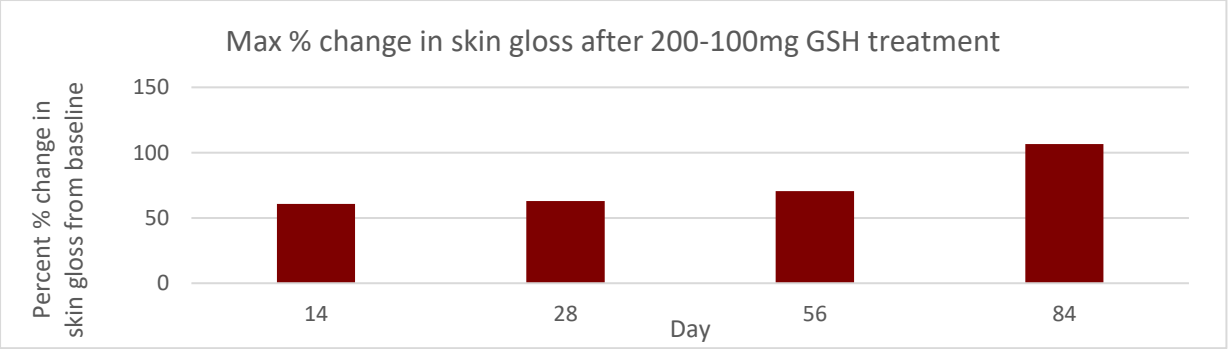

Fig 3. Graph of maximum percent change for skin gloss/luminosity for all study participants taking sublingual GSH from baseline to study completion

Within 14 days, 88% of participants on the 200mg/100mg regime experienced some skin lightening, increasing to 100% of all participants by 12 weeks.

The study measured skin colour on both the face and forearm. Skin lightening was observed on both the face and forearms of participants, indicating that SL GSH has the potential to be a whole-body skin lightening therapy compared to topical skin lightening products. Topical skin lightening products typically have short-lived effects and only impact the parts of the body on which they are applied. In contrast, the greatest mean improvement to skin lightening after SL GSH administration was observed at 12 weeks, suggesting that continued SL GSH administration may lead to greater improvements in skin lightness over a longer period of time.

Skin luminosity and gloss

SL GSH therapy resulted in a statistically significant improvement to skin luminosity/gloss in participants compared to baseline ($p = 0.04$) (see Fig. 3).

Participants on the 200mg/100mg regime achieved rapid and marked increase in skin luminosity and gloss of up to 66% after 4 weeks, increasing up to a remarkable 106% after 12 weeks. By 12 weeks, increased skin luminosity and gloss was observed in 84% of participants.

As with skin lightness, both faces and forearms showed increased skin luminosity and gloss.

Based on the mean data showing that maximum improvement was achieved after 12 weeks, continuous SL GSH therapy beyond the study period is expected to result in greater increase in skin luminosity and gloss.

The improvement in skin gloss in this study is in line with other GSH clinical studies[9, 10]. The mode of action of improvement in skin gloss is possibly by GSH inhibiting the tyrosinase enzyme as well as by reducing free radicals damaging the skin cells. Uneven skin gloss can be treated by either regulating melanin production or eliminating already pigmented cells or reducing cells damage caused by UV radiation.

Skin elasticity

SL GSH therapy resulted in a statistically significant improvement in skin elasticity in participants compared to baseline ($p = 0.03$) (see Fig. 4)

Participants on the 200mg/100mg regime achieved significant increase in skin elasticity of up to 226% after 4 weeks and 295% after 12 weeks. By 12 weeks, increased skin elasticity was observed in 100% of participants. Elastin is a fibrous protein found in the dermal skin layer and is responsible for skin elasticity. This study showed that GSH can increase the skin elasticity, most probably due to its antioxidant effect. Weschawalit et al[4] in their study, reported that GSH improves skin elasticity and reduces skin wrinkles in either sun-exposed or sun-protected areas and that GSH is superior to placebo in reducing skin wrinkles.

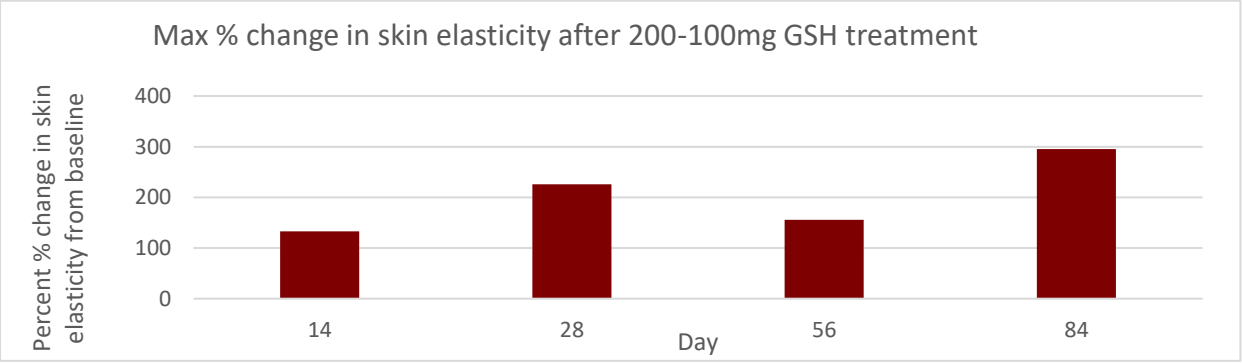

Fig 4. Graph of maximum percent change in skin elasticity for all study participants taking sublingual GSH from baseline to study completion

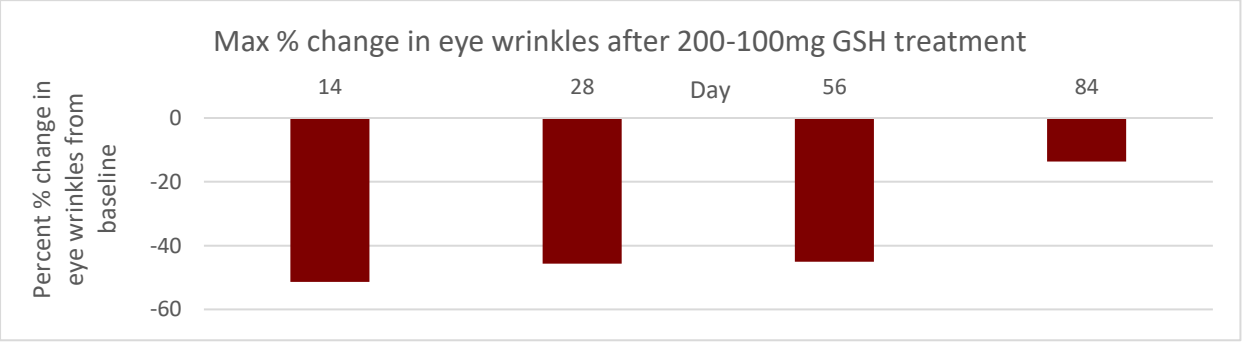

Fig 5. Graph of maximum percent change for eye wrinkles for all study participants taking sublingual GSH from baseline to study completion

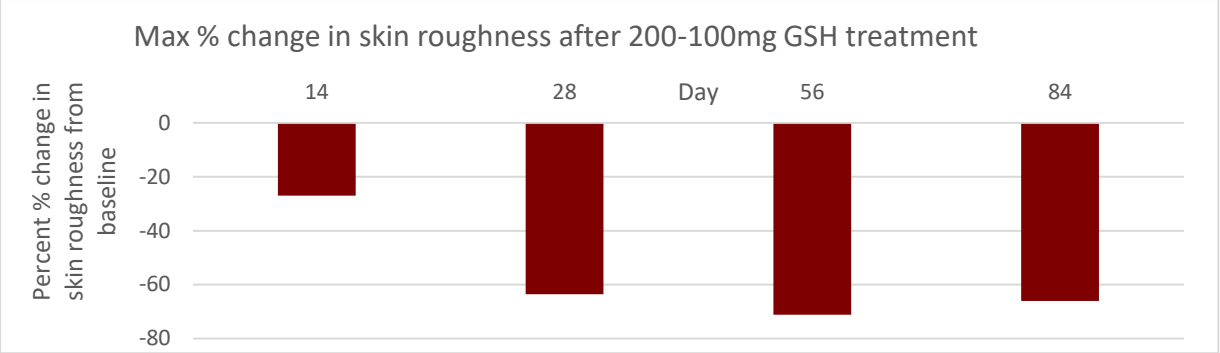

Fig 6. Graph of maximum percent change in skin roughness for all study participants taking sublingual GSH from baseline to study completion

Eye wrinkles

SL GSH therapy resulted in a statistically significant reduction in eye wrinkles and fine lines around the eyes compared to baseline (p = 0.04) (see Fig. 5).

In the 200mg/100mg regime group, 90% of participants responded positively to treatment at the 8 week mark. The greatest maximum change from baseline in this cohort was 51%, observed at day 14 of the study.

This study demonstrated that glutathione supplementation yields cosmetic benefits such as improvements to skin elasticity and reduction in skin wrinkles, especially around the eyes.

Free radical formation in the cells (cause by UV radiation), if left unchecked or not neutralised (by GSH supplementation) will damage the cells and tissues and may cause inflammation and skin wrinkles, especially around the eye. GSH being a powerful and most important intracellular antioxidant, reduces free radicals and inflammation, resulting in the improvement of the skin wrinkles and skin complexion as shown in this study. This confirms the finding that GSH is effective in reducing facial wrinkles in another study by Weschawalit et al[4].

Skin roughness

SL GSH therapy resulted in a statistically significant reduction in skin roughness compared to baseline (p = 0.04) (see Fig. 6)

Within 14 days, all participants on the 200mg/100mg regime had shown improvements in skin roughness. Within 4 weeks, there was a reduction of up to 64% in skin roughness, which increased to 71% by week 8.

GSH delays skin stiffening and decreases collagen loss from skin injury induced by UV radiation[11]. GSH also assists with skin cell renewal giving the skin a glowing appearance. The aging “dull” skin cells give the skin a rough appearance. GSH assists skin renewal by sloughing away dead cells and giving the new underlying cells a chance to rise to the surface[6]. This study has demonstrated that GSH can improve skin smoothness (or decrease skin roughness) shown by 100% of the participants in the 200/100mg protocol with 14 days of initiation of therapy and maintained till 12 weeks.

The Watanabe et al[12] study showed that GSH significantly increases the moisture content of the stratum corneum plus the suppression of wrinkle formation leading to the improvement in skin smoothness.

CONCLUSION

This study showed that GSH sublingual wafers are an effective therapeutic skin health supplement. Statistically significant positive results were observed for skin lightness, skin gloss, skin elasticity, eye wrinkles, and skin

roughness. All these parameters showed positive therapeutic results within 14 days of therapy with high positive responder rates.

The ideal initiation dose of GSH is 200mg daily for 28 days, followed by a maintenance dose of 100mg daily.

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