

Effectiveness of a Nutraceutical During Non-Ablative 1927 nm Fractional Laser on Patients With Facial Hyperpigmentation and Photoaging

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ABSTRACT

Background: Fractional lasers have been proven to treat hyperpigmentation and photoaging. Little research has been done on the effects of supplements on healing post-laser resurfacing. A nutraceutical could offer the benefit of faster healing of the skin and fewer side effects.

Objective: Evaluate the effectiveness of a nutraceutical associated with fractional 1927 nm laser in healing time and effectiveness on hyperpigmentation and photoaging.

Methods & Materials: A prospective, randomized, evaluator-blinded, pilot study included Fitzpatrick skin types I-III patients with hyperpigmentation and photoaging randomly assigned to two groups. Group 1 was laser treatment and Group 2 was laser treatment and nutraceutical. Results were compared with objective biometric TEWL (transepidermal water loss), mexameter, corneometer, and cutometer parameters. A blinded physician-evaluator and the subjects completed questionnaires to evaluate skin improvements.

Results: Twenty women were included. Eight in Group 1 and 10 in Group 2 completed the study. Group 2 presented a faster recovery of the skin barrier function post procedure. Three months after the procedure, Group 2 presented with significantly improved skin glossiness, hydration, and melanin rebound levels. Group 2 presented more overall aesthetic improvement determined by the patient and the blinded physician-evaluator.

Conclusion: The nutraceutical improved the results of the laser treatment.

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INTRODUCTION

As we develop, our normal body functions begin to slow down. There is a reduction in the number of fibroblasts, along with a significant loss in their biosynthetic capacity.¹ Consequently, the epidermis becomes atrophic and relatively acellular, with very minimal blood flow.²

Changes in melanocytes can indirectly change a person's skin tone. Disorders of hyperpigmentation are commonly seen in office-based dermatology practices worldwide.³ Melasma causes hyperpigmentation of the face or neck and can have severe adverse psychological and emotional effects on affected individuals.⁴

Pigmentary disorders are commonly seen in dermatology practices and can have a damaging psychosocial influence on patients.⁵ Furthermore, environmental factors, hormones, and sun exposure are also influential skin factors.

The primary contributors to the maturation process of the skin are environmental factors. Populations with Fitzpatrick skin types I, II, and III are more prone to prematuration of the epidermis.⁶ Fair skin tones are more prone to this because of their hypersensitivity

to the sun's rays, making these patients more prone to getting sunburns.⁷ When the epidermis is extra sensitive to ultraviolet radiation, over time, critical skin conditions may develop.⁸ The long-term effects of ultraviolet radiation include rhytides, actinic damage, malignant neoplasms, lentiges, and dyschromia.

Hyperpigmentation can be defined as an excessive flush of coloration or pigmentation in a tissue or specific area.⁹ Melanocytes in support with enzyme tyrosinase are accountable for the production and conversion of dopa to melanin.¹⁰ Measurement of stratum corneum hydration often involves the use of commercial devices to help determine proper treatment.¹¹ Melanin production and skin color are affected not only by keratinocytes but also by Langerhans cells, mast cells, and possibly by lymphocytes.¹⁰ Hyperpigmentation can occur in both the dermis and epidermis. Hyperpigmentation usually occurs in ethnic or darker skin tones due to the more concentrated melanin deposits.¹² Pigmentary disorders tend to disproportionately affect individuals with darker skin pigmentation.¹³ The melanin in these deposits protects the skin from photodamage, but cannot prevent them from becoming more vulnerable to postinflammatory dyspigmentation over time.¹⁴

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There have also been tremendous advances in the medical application of the laser in the past few decades.¹⁵ Some photoaging and hyperpigmentation treatment options would include neurotoxins, fillers, microdermabrasion, chemical peels, lasers, and non-ablative therapies.¹⁶ The therapy of hyperpigmentation is based primarily on accelerating epidermal turnover with removal of pigment in the superficial layers, down regulation of tyrosinase, delaying melanocyte proliferation, and inhibition of inflammation with decrease melanogenesis.¹⁰ Furthermore, the treatment of facial dyspigmentation requires persistence and diligence on the part of the dermatologist and the patient.¹⁷

Fractional photothermolysis combines the benefits of fully ablative lasers with significantly reduced downtime and fewer complications.¹⁸ The laser involves the emission of light into microscopic treatment zones, creating miniature columns of injury to the skin sparing the adjacent untreated skin. Fractional lasers have been known to treat a variety of pigmented lesions including hyperpigmentation and photoaging.¹⁹

The Fraxel Dual 1927 nm nonablative thulium laser allows for resurfacing, which can eliminate sun damage hyperpigmentation, melasma, and actinic keratosis safely in all skin types. This device delivers high-density microscopic thermal zones within treated skin using a wavelength with moderate to high water absorption.²⁰

Some nutricosmetics formulas claim to be rich in antioxidant enzymes that may prepare the body for laser treatments. Taken orally, nutricosmetics contain nutraceuticals, such as antioxidants and vitamins, which purport to support the function and the structure of the skin, enhancing the skin cosmetic aspect.²¹

GliSODin[®] Skin Nutrients' Skin Brightening Formula contains five active ingredients which enhance the healing and health of the skin. Superoxide dismutase (SOD) reduces the reactive oxygen species formation associated with oxidative stress.²² Oxidative stress, involved in many diseases, is defined as an impaired balance between reactive oxygen species production and antioxidant defences.²¹ This allows for secondary antioxidants to achieve their aimed cellular tasks. Borage seed oil contains essential fatty acids, calcium, and potassium.²³ The active ingredient in this oil assists in replenishing the skin at a cellular level. The leaves, stems and flowers of lemon balm are used medically due to high amounts of catechins, flavonoids, rosmarinic acid, tannins, and triterpenes.²³ Lycomato extracted from tomatoes gives a durable layer of photo protection to help support skin from sun exposure.²⁴ GliSODin patented defensive coating enables the body to safely absorb this powerful enzyme.²⁴

Since the 1990s, sales of nutricosmetics have increased dramatically to over 1 billion USD annually.²⁴ Dermatologists

should be aware of the theoretic actions of these products to guide patients to the best options.

This study aimed to evaluate the effectiveness of a nutricosmetic associated with fractionated 1927 nm laser in facial hyperpigmentation and photoaging.

MATERIALS AND METHODS

Study Design and Patients

This was a randomized, evaluator-blinded, open label, single-center clinical trial performed in the Dermatology Research Institute, Coral Gables, FL currently Skin Research Institute. Twenty women suffering from facial hyperpigmentation and photoaging were included in this study. An Ethical Committee approved the study. All patients were fully educated and gave written informed consent before the onset of the study.

The main inclusion criteria was the presence of facial hyperpigmentation and photoaging, Fitzpatrick phototype I to III, participants older than 40 years of age, agreement to maintain a normal skincare regimen, and avoidance of any facial procedures during the study. The main exclusion criteria were pregnancy and nursing.

The patients had their Fitzpatrick skin type recorded qualitatively with the colorimeter.

The greatest tool to determine Fitzpatrick skin types I, II, and III, is a colorimeter. A colorimeter can sometimes have trouble with determining Fitzpatrick skin types IV, V, and VI.²⁵ This tool works by expressing skin color as a coordinate in a color space (eg, L*a*b). Therefore, it can measure changes in skin color resulting from self-tanning products or make-up.²⁶

Each patient was randomly assigned to either of two groups. Each group received one laser treatment on their entire face. Group 1 received the laser treatment, while group 2 took Nutricosmetic pre and post formula vitamins orally for 15 days prior and post laser treatment, subsequently, followed by an additional Nutricosmetic formula, until the last study visit. Patients were monitored for consecutive 8 visits.

The melanin and erythema values were measured with the mexameter (Courage & Khazaka electronic GmbH, Cologne, Germany).²⁶ The mexameter is extremely useful in determining the existence of hyperpigmentation disorders.²⁷ We can determine these values with this tool because of the photodiodes that emit light of specific wavelengths into the skins surface, with the measurement rate of absorption and reflection determining the melanin content and erythema levels.²⁸

The transepidermal water loss was recorded with the TEWL meter (Courage & Khazaka electronic GmbH, Cologne,

Germany).²⁶ A TEWL meter measures the difference in these values to get a better sense of the skin barrier's functionality.²⁹

The corneometer (Courage & Khazaka electronic GmbH, Cologne, Germany) measured the general hydration of the face. The more hydration in the skin, the longer the charge can be retained. The "charge time" is then calculated and recorded.²⁸

The glossiness of the skin was measured with the Glossimeter (Courage & Khazaka electronic GmbH, Cologne, Germany).

The cutometer would measure the general elasticity of the face. This functions by measuring the elasticity of the upper skin by using negative pressure that deforms the skin mechanically.²⁶

Subjective evaluations were done during last visit by a blinded physician evaluator and by the subjects. Subjects completed a treatment satisfaction questionnaire and another questionnaire that they graded, on a scale from 0-10 (10= complete clearance of the hyperpigmentation).

Blinded evaluators completed the same treatment satisfaction questionnaire completed by the patients.

Statistical analyses were performed. The Student t-test was used to compare continuous variables before and after treatment and differences between groups. $P < 0.05$ was considered statistically significant.

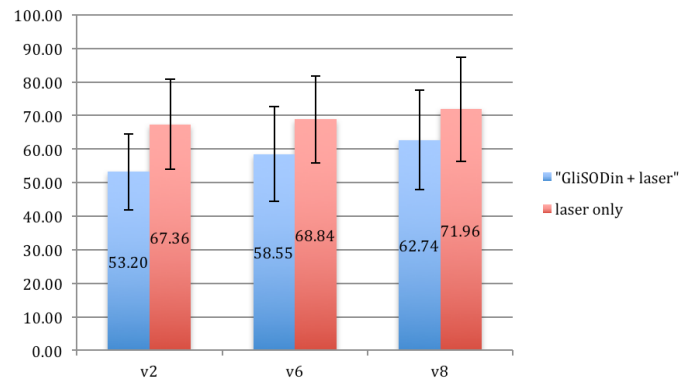
Visits

During their first visit, both groups had their medical history recorded and photographs were taken. Patients completed a urine test to ensure that they were not pregnant. They were also interviewed to find out medical history in regards to current medications they were taking. Patients signed the informed consent and were randomly assigned to Group 1 or Group 2.

If the patients were in Group 1 all the tests (erythema, glossiness, TEWL, melanin, corneometer, and elasticity) were done during the first visit immediately before their laser procedure. However, if the patients were in Group 2 they had all this information previously recorded, which allowed them to start the nutricosmetic formula that day and have their laser treatment 14 days later, during visit two. Visit one and two were combined for patients in Group 1.

During visit 2 the study physician provided the patient with a numbing compound to help minimize any discomfort that may be experienced from laser treatment. Each patient received a full face fractional resurfacing using the Fraxel Dual laser with a single 1927 nm wavelength treatment. Settings including energy, density, and number of passes remained consistent for all patients. Patients remained at the study center for 30 minutes

FIGURE 1. Corneometer Values.



GliSODin + laser skin hydration increased from baseline (v2) while laser only group remained stable.

following the completion of the study procedures. Half an hour after the laser treatment, the staff evaluated the treated area for any adverse events.

Visit 3 occurred 24 hours after the patient had their laser treatment (visit 2). During this visit the patient was asked about how they were feeling and about any medications or treatments that the patients had received since their last study visit. Photographs were taken and any adverse events were recorded. The same evaluations were performed visits 4 through 8 for both Groups 1 and 2.

Visit 4 took place 72 hours after visit 2. Visit 5 occurred a week after the laser treatment. Visit 6 was two weeks after visit 2 and subjects in Group 2 received another formula product. Visit 7 happened 30 days after the laser procedure. The final visit (visit 8) was 3 months after the laser treatment, and the subjects and blinded physician evaluator questionnaires were completed.

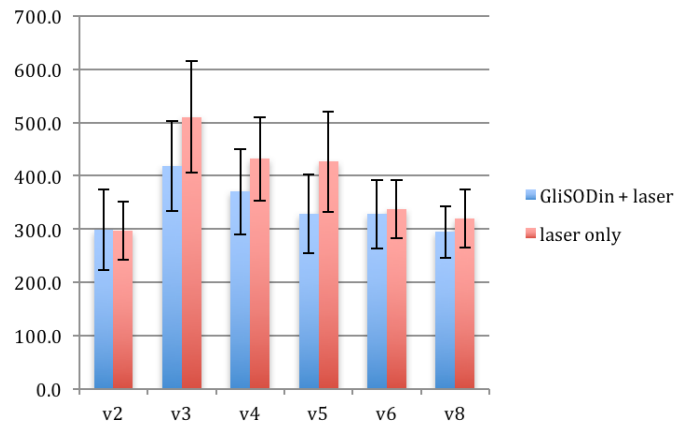
Treatments

The laser treatment (Solta Medical[®]) was performed by fractional 1927 nm with 10 mj and 40% coverage delivered in 8 passes. Same laser settings were used on all subjects, and treatment was performed on their entire face. All participants received only one laser treatment at visit 2.

Group 2 took the Advanced GliSODin Pre formula[®] 15 days prior to the laser treatment. Advanced GliSODin Post formula[®] was taken for 15 days post laser treatment followed by the brightening GliSoDin formula[®] until the last study visit.

RESULTS

Twenty female patients, 42 to 72 years old, with Fitzpatrick skin color I to III suffering from hyperpigmentation and photoaging were enrolled. Eighteen subjects completed the study, 10 on the nutricosmeceutical arm (Group 2) and 8 on the control

FIGURE 2. Skin erythema was significantly improved in Group 2 compared to Group 1 at 3 months post laser treatment (Figure 3).

Visit	P-value
V2	0.83515739
V3	0.00000142
V4	0.00010788
V5	0.00000002
V6	0.42851771
V8	0.01007022

arm (Group 1). Two patients were withdrawn from the study because they lost their follow-up visit.

The nutricosmetics were well tolerated by all participants. Regarding side effects, only two cases developed herpes simplex virus (HSV) on the lip after the laser procedure (one in each group).

Hydration levels measured by the corneometer increased significantly from the day of laser procedure to 30 days and 3 months, respectively, in Group 2 compared to the control group (Figure 1).

Erythema values were significantly reduced in the nutricosmetic group 24 hours, 72 hours, and 7 days post laser procedure compared to the control group (Figure 2).

Melanin values showed some rebound 3 months after the laser procedure, however the GliSODin laser group was not statistically significant while the control group showed a statistically significant rebound (Figure 4).

Increased levels of TEWL were noted in Group 1 24 hours after the laser treatment, Group 2 had normal TEWL at 24 hours after the laser procedure (Figure 5).

Subjects reported a high degree of satisfaction with the product by agreeing or very much agreeing that at the end of the study

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their skin looked more rested, healthy, fresh, revitalized, luminous, radiant, hydrated, moisturized, and nourished. On a scale from 0-10 (10= complete clearance), subjects in Group 2 reported 8.86±1.2 vs 6.21±1.3 in the laser alone group, respectively.

Blinded evaluators reported that the subjects in the nutricosmetic group had skin that looked more youthful, had more of an improved texture.

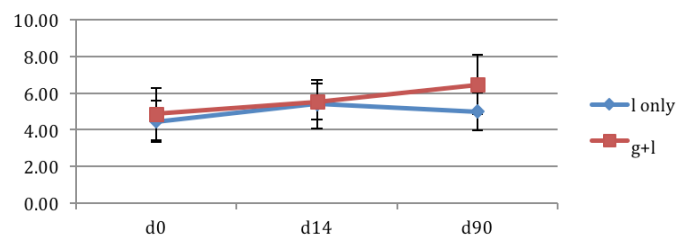
DISCUSSION

The nutricosmetics have been gaining popularity. Today's patients desire a more holistic approach to beauty. They believe oral supplements will increasingly become part of their daily beauty routine. Dermatologists should familiarize themselves with available products and carefully assess their quality before recommending nutricosmetics to their patients. This study evaluated the effectiveness of a nutricosmetic named GliSODin.

Isocell Laboratories based in Paris, France, developed GliSODin. Isocell Laboratories is a leading company in anti-aging medicine. They also are the owner of GliSODin's two US patents. GliSODin is a unique non-genetically modified melon extract naturally rich in superoxide dismutase (SOD).

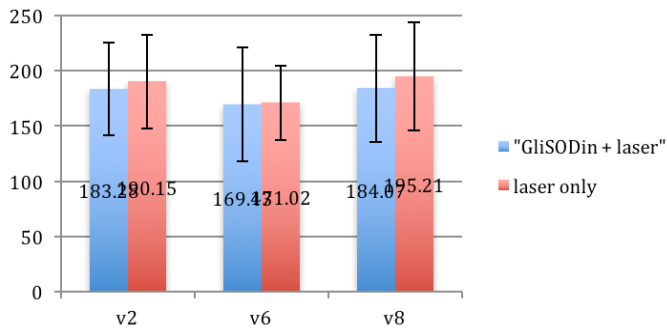
One of the main issues of nutricosmetics is its active ingredient. To ensure the nutrients reach the skin in a stable and active form it cannot be degraded by the intestinal cells of the gastrointestinal system. In 2004, Vouldoukis et al demonstrated that the combination of the antioxidant enzyme superoxide dismutase with wheat protein not only delayed their degradation during the gastrointestinal digestive process, but also promoted, in vivo, the cellular defenses by strengthening the antioxidant status.²³ GliSODin combines wheat protein to protect its SOD activity within the intestinal cells.²³

SOD, also known as the "Enzyme of Life," catalyzes our natural antioxidant defense system, boosts immunity, and reduces accelerated aging. SOD acts as the first line of defense against toxins and cellular breakdown caused by free radicals. The

FIGURE 3. Glossiness.

Day 90; $P < 0.0001$.

Melanin values rebounded 3 months after the laser procedure, however the GliSODin laser group was not statistically significant while the control group showed a statistically significant rebound (Figure 4).

FIGURE 4. Melanin values rebounded less than laser alone.

	P-value
Laser only/v6-v8	0.005902322
GliSODin+laser/v6-v8	0.111170922

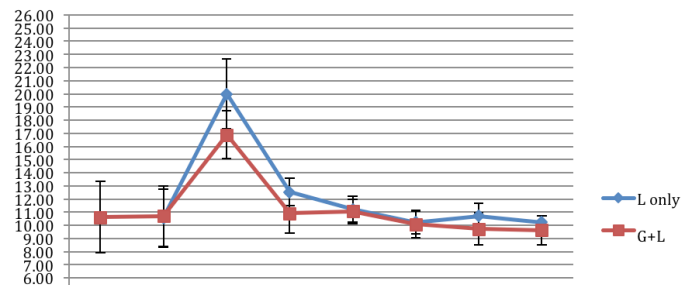
production of SOD decreases with age, causing an increase in susceptibility to free radical damage. An imbalance between free radicals and antioxidants can lead to an oxidative stress that can damage the structure and function of the skin, including hydration, elasticity, and structural integrity.

This study agreed with the idea that the reduction of the oxidative stress and consequently the improvement of the skin structure and function is produced by the intake of the nutricosmetic, in two aspects: skin glossiness and faster recovery after damage. The patients that received GliSODin in this study presented an improvement in skin glossiness and hydration level compared to the control group.

A study published recently by Goldberg and Cryslar suggested that GliSODin associated with tazarotene 0.1% to the treatment of facial photodamage is safe and provides significant clinical benefit with respect to improvement in facial overall photodamage, skin moisture and elasticity. The study done by Goldberg and Cryslar used the GliSODin Advanced Anti-Aging Formula.

There are six different formulas of GliSODin. The main nutraceutical is the superoxide dismutase in all formulas. Patients in this study used the GliSODin Advanced Pre & Post Formula that is specifically designed to assist patients through their recovery. The manufacturer claims, this formula prepares the body for treatment, boosts immune functioning to fight infection, reduces swelling and bruising, assists in wound healing, and speeds recovery time.

Erythema values were significant reduced in the nutricosmetic group 24 hours, 72 hours, and 7 days post laser procedure compared to the control group. Also, increased levels of TEWL showed impaired barrier function for patients in the control

FIGURE 5. TEWL.

24 hours; $P < 0.0001$.

group, while patients in Group 2 showed faster recovery of the skin barrier 24 hours post procedure (Figure 5). On the other hand, this study did not prove the ability that the nutricosmetic has to boost immune functioning, since there were equal number of HSV outbreaks (one in each group) post laser.

Another formula used in the study was the advanced skin brightening formula. The nutritional support that may enhance the results of skin resurfacing treatments providing the following benefits: soothes skin from the effects of the laser treatment, offers internal protection from UV rays, assists laser with pigment reduction, supports healing, maximizes results of facial rejuvenation procedures, and has tyrosinase enzyme inhibiting properties.³⁰

In this study, melanin values started to increase 3 months after the laser procedure in both groups, however in Group 2 it was not statistically significant while the control group showed a statistical significant rebound (Figure 4). The melanin 'rebound' may be due to the reexposure to UV radiation in our southern environment. The data suggests that the nutricosmetic may assist in conjunction with laser treatments in achieving longer reduction in pigmentation.

The study confirmed our hypothesis that the association of the nutricosmetic would enhance the results of the patients receiving Fraxel laser treatment, but larger studies are necessary in order to truly state that this would benefit all patients. Although nutricosmetics products have the potential to enhance standard dermatologic treatment regimens, it is important that clinical trials are performed in order to clarify the real effectiveness of them. As Bowe and Pugliese mentioned in a review they recently published, there is a paucity of clinical data.¹⁷

CONCLUSION

The results of this study suggest that the addition of the nutricosmetic GliSODin to the treatment of facial photodamage with fractional laser (1927 nm 10 mj) is safe and provides significant clinical benefit with respect to improvement of skin glossiness,

hydration, less melanin rebound values, reduction of erythema, and more rapid barrier recovery as measured by TEWL at 24 hours. Also, the results of the blinded physician-reported scales and patient-reported response to treatment suggested that the addition of the nutricosmetic can improve the overall skin appearance better than the use of the laser alone. Nonetheless, further investigation involving a larger study is necessary to truly state nutricosmetic would benefit all patients.

DISCLOSURES

The authors have no conflicts of interest to declare. The study was supported in part by Glisodin company, Isocell.

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