

Effect of Lumenato a Tomato derived oral supplement on improving skin barrier strength

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Abstract

Introduction: Improvement of skin barrier strength could lead to healthy and youthful appearance. “Beauty inside-out” approach using nutraceuticals such as tomato derived carotenoids to support skin barrier strength could be of benefit to the ageing population.

Method: A panel of 60 female subjects were provided with the Lumenato capsules (containing carotenoids) or placebo capsules as nutritional supplements for 3 months. Skin health and barrier function were observed using evaporimeter which measures trans epidermal water loss (TEWL). Barrier strength was determined by study of the number of strippings required to disrupt skin barrier and barrier repair was observed in terms of TEWL a few hours after barrier disruption. Cutometer was used to observe skin firmness and elasticity. Measurements were obtained before treatment and after 4 and 12 weeks of use.

Results: Results indicated a statistically significant improvement ($p < 0.05$) in skin barrier strength; a higher number of strippings were required to disrupt skin barrier after 12 weeks of supplement use. There was also a significant improvement in skin firmness and elasticity as observed with a cutometer.

Conclusion: Based on the confines and conditions of this study, oral supplementation with Lumenato resulted in significant improvement in skin barrier as well as skin firmness and elasticity.

KEYWORDS

carotenes, facial ageing, oral supplement, skin barrier

1 | INTRODUCTION

Skin is the primary interface between the body and the environment, and the skin epidermal barrier expresses diverse functions to maintain a balance with the dry ambient environment.¹ Any damage to this stratum corneum barrier function can lead to increased transepidermal water loss (TEWL) and increased susceptibility to penetration of toxic agents.

The stratum corneum is the primary permeability barrier between the internal body and the environment. It is composed of fibrous protein-enriched corneocytes (10–15 μm thick) and a lipid-enriched intercellular matrix consisting of stacked lipid layers composed of ceramides, cholesterol, and free fatty acids in a roughly molar 1:1:1 ratio. Lipid synthesis occurs in the viable nucleated keratinocytes of the epidermis, and the synthesized lipids are delivered via lamellar bodies to the interstices of the stratum corneum during epidermal

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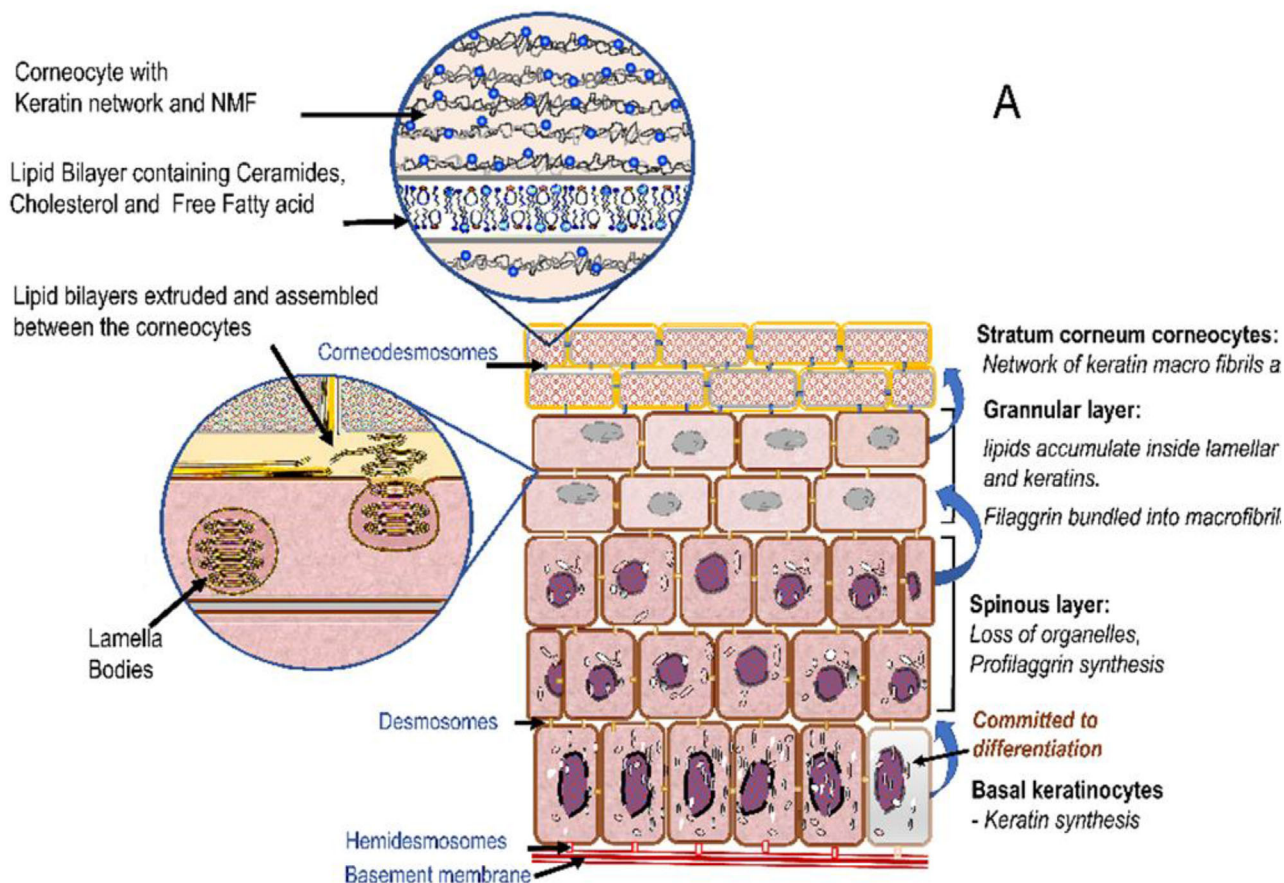


FIGURE 1 (A) Epidermal differentiation from basal keratinocytes to the spinous layer, the granular layer and ultimately the stratum corneum. (B) This continuous turnover is affected by accumulation of carotenoids from oral supplementation.

differentiation.² Water is not homogeneously distributed in the stratum corneum. Bulk of the water is situated intracellularly in the corneocytes, and a small fraction is situated adjacent to the lipid headgroups in the intercellular space.^{3,4}

1.1 | Epidermal differentiation

The epidermis is a stratified epithelium that undergoes continuous self-renewal in a basal to surface direction. Keratinocytes residing at the base of the epidermis undergo differentiation in stages expressed in the different layers of the epidermis⁵ (Figure 1).

The process of terminal differentiation begins when basal cells withdraw from the cell cycle and cease to adhere to the basement membrane. In the spinous layer the cells begin to lose their organelles and profilaggrin synthesis is triggered. As the cells transit into the granular layer, lipids are produced and accumulated inside lamellar bodies and keratins. Meanwhile, filaggrins are bundled into macrofibrils thus protecting the keratins from disintegrating enzymes (Figure 1).^{5,6}

The corneocytes of the stratum corneum contain a network of primarily keratin macrofibrils and mixture of multiple small hygroscopic compounds referred to collectively as *natural moisturizing factor*

(NMF).^{5,7} Intercellular lamellar lipid membrane is primarily composed of ceramides, cholesterol, and fatty acids. The final epidermal barrier is analogous to bricks and mortar structure, with the keratin macrofibrils and cornified envelopes of the corneocytes forming the bricks and the extruded lipids forming the mortar to seal together the cornified envelopes.^{8–10} This process of differentiation, from a mitotically active basal cell to a terminally differentiated squamous cell, is maintained throughout life as part of epidermal regeneration.^{11,12}

1.2 | Carotenoid oral supplementation and skin barrier

Carotenoids represent a large group of plant pigments that are consumed with fruits and vegetables. Carotenoids possess strong antioxidant properties^{13,14} as well as strong lipid radical scavenging and singlet oxygen quenching activities.¹⁵

Metabolism of carotenoids such as β -carotene takes place in a several organs, including the skin.¹⁶ Cutaneous carotenoids can be enriched in skin via oral administration of β -carotene and this supplementation is known to be effective in preventing induction of UV-induced erythema.^{17–20} Similar effects have been expressed in volunteers receiving a carotenoid-rich diet.^{21,22} Photoprotective action

of carotenoids against UV-induced damage to human skin^{23–25} may also contribute to defer skin aging,²⁶ possibly due to its antioxidant action.^{23–26}

Dietary supplements have been studied extensively for their potential impact on the skin barrier.^{27,28} Carotenoids absorbed from the gut are conveyed by lipoproteins in the bloodstream and then transported to the epidermis via scavenger receptor class B member 1 (SR-B1).²⁹ SR-B1 is a receptor that also facilitates uptake of cholesterol from HDL particles. It also regulates ceramide levels in skin thereby improving the barrier strength.³⁰ Skin is persistently exposed to environmental assaults from pollution and UV irradiation causing damage to the epidermal barrier which then contributes to accelerated aging by causing the skin to develop fine lines and wrinkles as well as loss of volume and elasticity. Strengthening skin barrier could reverse some of the signs of ageing and support healthier and more resilient skin. Supplementation with Lumenato would accumulate carotenoids in the skin thereby regulating cutaneous ceramide which is a major component of the stratum corneum lipid barrier.

Studies have shown that oral intake of carotenoids elevate the levels of skin filaggrin protein which contributes to building the skin barrier.³¹ In addition, the potent antioxidant activities of carotenoids accumulated in skin pose as a protective barrier against UV and environmental pollution.^{32,33} Oral administration of carotenoid-rich extract has also been shown to prevent the aging-related collagen I degradation in the dermis and thereby improve the extracellular matrix.^{34,35} A strong barrier allows improved skin hydration, smoothness, firmness, elasticity as well as reduction in fine lines and wrinkles.^{36,37}

This trial was designed to study the effect of oral supplementation with Carotenoids (Lumenato) on improvement of skin barrier as well as hydration and visible improvements in skin condition.

2 | MATERIAL

Material A: Lumenato Oral Supplement: soft gel capsule containing Oleoresin obtained from yellow tomato pulp. The supplement contains a proprietary mix of tomato carotenes standardized to 10 mg total carotenoids predominantly phytoene and phytofluene, as well as other naturally occurring tomato phytonutrients (Lycored Inc, Beer Sheva, Israel).

Material B: Placebo: Soft gel capsules containing pure glycerin.

The test materials submitted were determined to be safe for use in humans. The subjects were instructed to take one capsule per day with a meal. No adverse complaints were received from the subjects in this study.

3 | METHOD

This was a double-blind clinical study where the subjects as well as the investigator were not aware of the contents of the test materials.

3.1 | Subjects

A total of 69 subjects were recruited for the study out of which 59 completed the study. Eight subjects discontinued due to product unrelated causes.

The subjects were healthy women between the age of 35 and 55 interested in improving health and appearance of sensitive facial skin. They were recruited from a database of registered individuals interested in participating in clinical trials and were not enrolled in any other oral supplement or facial study. The subjects were dependable and able to follow directions as outlined in the protocol and anticipated being available for all study visits and willing to participate in all study evaluations.

The subjects were Caucasians or Latinos of Fitzpatrick skin types II, III, or IV with self-perceived sensitive skin and a baseline TEWL of $\geq 12\text{G/M}^2/\text{hour}$. Sensitive skin was defined as being sensitive to different topical products through different seasons resulting in any of the following: redness, irritation, itching, tingling, or edema. The subject had Glogau skin classification of Type 2.³⁸

The subjects signed an Informed Consent Form in conformance with 21 CFR Part 50: "Protection of Human Subjects" as well as a Photography Release Form, providing consent for the capture of digital images for use in relation to this clinical study. All subjects were free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Subjects who were pregnant, nursing, planning a pregnancy, or not using adequate birth control were excluded from the study. So were subject with a history of digestive problems; Chronic or relapsing inflammatory and/or allergic skin conditions such as atopic dermatitis, rosacea, psoriasis and alike including telangiectasias ("spider veins"), diagnosed adult acne or currently on treatment for adult acne or those who received facial irradiation within last year or are planning on undergoing facial irradiation during the study. Participants who were taking supplements containing carotenoids, lutein, melatonin or tryptophan, retinoids as well as those on blood thinners, sympathomimetics, antihistamines, vasoconstrictors, non-steroidal anti-inflammatory agents, and/or systemic or topical corticosteroids within 4 weeks prior to initiation of the study were also excluded.

The subjects were nonsmokers who refrained from using tanning salons or suntanning and did not undergo invasive facial procedures (injections, chemical peeling, etc.) 3 months before commencement and during the course of the study.

Participants with auto-immune skin diseases (e.g., scleroderma, psoriasis, lupus, epidermolysis bullosa, bullous pemphigoid, temporal arteritis) as well as a history of acute or chronic dermatologic, medical, and/or physical conditions which would, in the opinion of the Principal Investigator, preclude application of the test material and/or could influence the outcome of the study; were excluded from the study. Subject who had a history of skin cancer, currently undergoing treatment for active cancer of any kind as well as diabetics were also excluded from the study.

3.2 | Clinical assessment

On the first visit (T0), the subjects were examined by a trained technician to confirm the inclusion and exclusion criteria.

Before product use (T0) and in the visits after 4 (T4w) and 12 (T12w) weeks of product use, the technician conducted a clinical assessment, verification of compliance with the requirements of the study, verification of possible adverse events, discomfort sensations and confirmation of the correct use of the products. Subjects were instructed to contact the study coordinator at any time, in case they presented any complaints.

The subjects acclimated in a standard environment of 20--22°C temperature and humidity of 40%--60% for 15--20 min³⁹ and then the following measurements were obtained at T0, T4w, and T12w time points.

3.3 | Barrier integrity: Tewameter® measurements

Measurements of transepidermal water loss was performed by trained technicians using the Vapometer (Delfin Technologies Vapometer model SWL5, Kuopio, Finland). Measurements were obtained by applying the probe to the test area and resting it on the skin. The measurement indicated trans epidermal water loss (TEWL) in G/M²/hour where higher values indicate greater evaporation and hence a worse skin barrier.

D-Squame a 22 mm diameter, crystal-clear adhesive-coated disc was used to remove layers of the stratum corneum to simulate barrier disruption.⁴⁰ It has a homogenous layer of a medical-grade adhesive that safely removes superficial corneocytes and provides optimum visibility of adhering skin cells. A D-Squame Pressure Instrument was used to apply standardized pressure on the tape. The D-Squame discs were applied to the skin and the soft padded end of D-Squame Pressure Instrument was placed on the D-Squame and pressed downward for 2 s, then released. The D-squames were gently peeled off to remove loose layers of the stratum corneum.

TEWL measurements were obtained again after three consecutive strippings with D-squames. Strippings and TEWL measurements were continued until the skin barrier was disrupted as indicated by a value of TEWL of 18G/M²/hour or more. TEWL was plotted against number of strippings and using the linear equation the exact number of strippings to obtain a TEWL of 18G/M²/hour was calculated for each subject. Barrier repair was determined by measurement of TEWL, 3 h after the final stripping.

The same measurements were performed on the left and right malar areas of the face at baseline and after 4 and 12 weeks of product use.

3.4 | Cutometer

Cutometer® (dual MPA 580 2 mm probe by Courage and Khazaka Cologn, Germany) was employed to study the viscoelasticity of skin.

The Cutometer measures the vertical deformation of the surface of the skin as it is pulled by a vacuum suction (500 mm Hg) through a small probe aperture. From the resulting curve, several variables can be extrapolated including immediate, delayed, and final distention and immediate retraction.^{41,42} These variables estimate the elastic, viscoelastic, and purely viscous behavior of the skin.⁴²

The measurements were obtained under standard conditions of temperature and humidity (T = 20--22°C, humidity 40%--60%) and after a rest period of 15--20 min for each subject tested.³⁹

Measurements were automatically produced in triplicate. One Cutometer measurement was obtained from the randomized cheek at each designated time point. The following parameters were observed:

R0: Distensibility (Uf) This parameter looks at the maximum amplitude and represents the passive behavior of the skin to force. Decrease in this parameter indicates improvement in firmness.⁴³⁻⁴⁴

R1: The ability to return to the original form (Uf-Ua) (minimum amplitude after relaxation). The older the skin, the higher the number, thus decrease in this parameter indicates improvement in elasticity.⁴³⁻⁴⁴

R3: (Last max amplitude): Tiring effect (Fatigue) visible for repeated suction/relaxation. Repeated suction and release with the Cutometer provoke skin fatigue, resulting in decreased elasticity and increased maintenance of the deformed position. Tiring effects of the skin are visible, as the amplitude increases with each new suction. The last curve, compared to the maximum amplitude of the first curve is correlated with skin fatigue (laxity). Decrease in this parameter indicates improvement.⁴³⁻⁴⁴

3.5 | Statistical considerations

Using Excel package statistical package, descriptive statistical analysis was performed on all parameters pertaining to the primary and secondary objectives.

Comparisons were made between Baseline and 4 and 12-weeks use. Descriptive statistics (frequencies and percentages) summarized responses from the Study Product. A Students t test was conducted to determine statistical significance.

3.6 | Ethical considerations

The investigational test products, study protocol, Informed Consent Form, subject recruitment materials, and written study instructions were reviewed and approved by the Institutional Review Board prior to study initiation in accordance with Title 21 of the Code of Federal Regulations (CFR), Parts 50 and 56. This study was performed in accordance with the ethical principles based in the Declaration of Helsinki and its subsequent amendments, and in accordance with the International Council for Harmonization (ICH) Good Clinical Practice (GCP) guideline (ICH E6(R2), 2016), and applicable regulatory requirements.

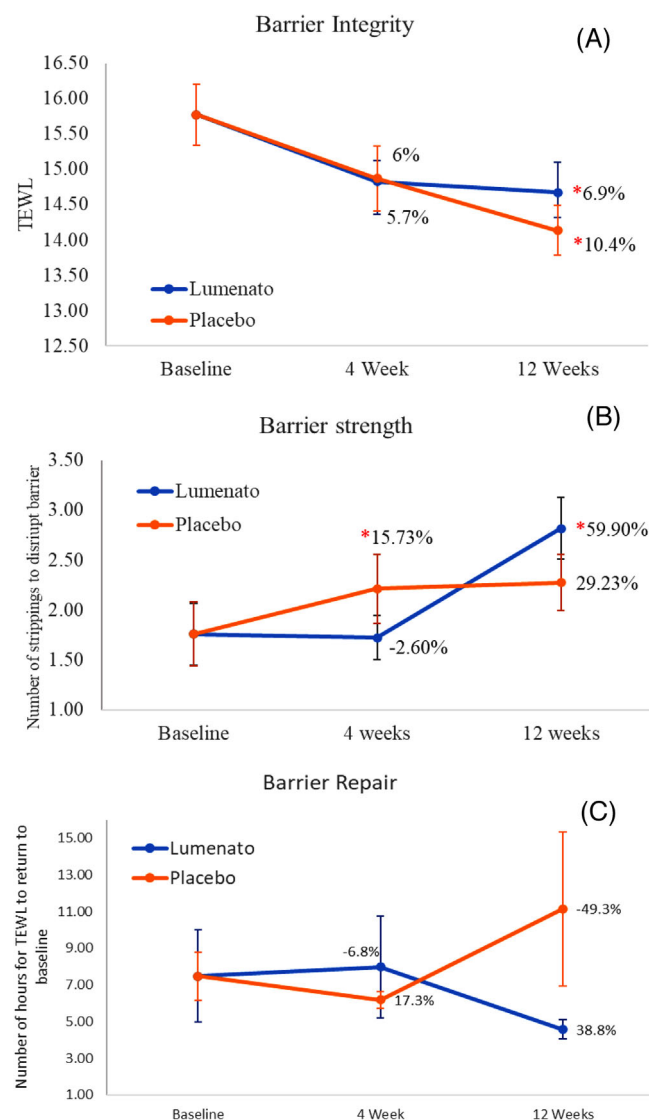


FIGURE 2 Skin barrier. There were 30 subjects in the supplement group and 29 in the placebo group. The error bars indicate standard error of the mean. Data were averaged and percentage difference and significance were calculated versus baseline. Statistical significance of one star indicates that the difference from baseline was a p value of less than 0.05. (A) TEWL of both groups reduced with treatment. (B) barrier strength in terms of the number of layers of stratum corneum removed with D-squam tape. After 12 weeks both groups required more strips to disrupt barrier; however, the group using the supplement showed a significant ($p < 0.05$) increase of 59.9%. (C) Barrier repair in terms of calculated number of hours for repair to baseline. Lumenato treatment appeared to accelerate barrier repair from about 7 h at baseline to about 4 h after 12 weeks treatment.

4 | RESULTS

Trans epidermal water loss (TEWL) measures barrier integrity and a reduction in TEWL indicates barrier improvement. As observed in Figure 2(A) there was a slight reduction in TEWL by about 6% after 4 weeks and a significant ($p < 0.05$) 6.9% after 12-week use of the sup-

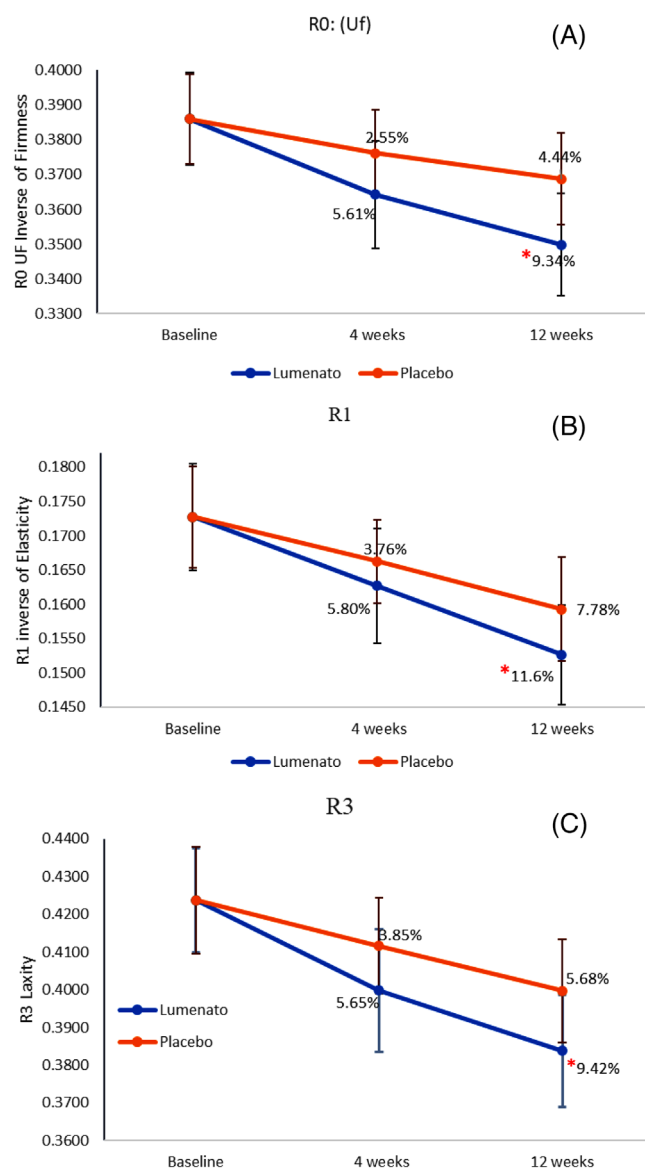


FIGURE 3 Cutometer measurement of skin firmness and elasticity. There were 30 subjects in the supplement group and 29 in the placebo group. The error bars indicate standard error of the mean. Statistical significance of one star indicates that the difference from baseline was a p value of less than 0.05. (A) R0 skin firmness; the Lumenato group exhibited a consistent reduction in this parameter over the course of the study. After 12 weeks use there was a significant improvement in skin firmness. The placebo group also exhibited a slight reduction. (B) R1 inverse of elasticity; there was 5.8% and a significant 11.6% ($p < 0.05$) improvement in skin elasticity after supplementation with Lumenato. The placebo also showed an improvement, but the difference was not statistically significant. (C) R3 skin laxity reduced by 5.6% and 9.42% ($p < 0.05$) after treatment with Lumenato for 4 and 12 weeks, respectively. The placebo also exhibited a slight improvement, but it was not statistically significant.

plement. However, the placebo group also exhibited a slight reduction of 6% (non-significant) and 10% after 4- and 12-week use, respectively.

Barrier strength as measured by the calculated number of strippings to disrupt skin barrier is presented in Figure 2(B). An increase in the number of strippings indicates that the barrier strength increased.

As observed, initially the placebo group appeared to exhibit a 15% improvement in 4 weeks (possibly due to temporary effect of glycerin in the placebo). This further increased to 29.23% after 12 weeks of use. The group that used Lumenato did not show a change after 4 weeks; however, after 12 weeks of use, this group exhibited a significant ($p < 0.05$) improvement of 59.9% in barrier strength. In this study barrier structure required more than 4 weeks to strengthen.

Barrier repair is presented in Figure 2(C) as the calculated number of hours for the stripped skin to return to baseline TEWL. The placebo appeared to exhibit a 17% improvement after 4 weeks of use; however, the repair process appeared to slow down after 12 weeks of use. The Lumenato group did not show much effect after 4 weeks, but after 12 weeks of use there was 38.8% faster repair in this group as compared to baseline.

4.1 | Firmness and elasticity

R0 looks at the maximum amplitude and represents the passive behavior of the skin to force (firmness). As observed in Figure 3(A) Skin firmness improved by 5.61% after 4 weeks and a significant ($p < 0.05$) 9.34% after 12 weeks of using Lumenato. The placebo also showed a slight improvement of 2.55% and 4.44% (non-significant) after 4 and 12 weeks of use, respectively.

R1 measurement indicates an inverse of elasticity (the ability to return to the original form). Older the skin has been reported to exhibit a higher R1.^{55,56} As observed in Figure 3(B), skin elasticity improved by 5.8% and a significant 11.6% ($p < 0.05$) after 4 and 12 weeks of using the Lumenato supplement. The placebo exhibited a slight effect of 3.76% and 7.78% after 4- and 12-week use, respectively.

The cutometer measures the skin in triplicate. Repeated suction/relaxation causes fatigue and R3 (Last max amplitude) measures tiring effect termed as laxity. This parameter is known to go up with age.^{55,56} As observed in Figure 3(C) there was a 5.65% reduction of this parameter after 4 weeks which continued to a significant ($p < 0.05$) reduction of 9.42% after 12 weeks of using Lumenato. The Placebo group also exhibited a reduction of 3.85% and 5.68% after 4 and 12 weeks of use, respectively; however, the difference was not statistically significant.

5 | DISCUSSION

Carotenoid ingestion in food has been reported to significantly increase serum as well as skin levels of carotenoids. Such an increase has been linked to protection from photodamage.⁴⁵ Skin epidermal barrier is a dynamic process of cell differentiation and turnover which is known to be strengthened with oral supplementation with nutrients such as tomato extract. Skin barrier, commonly measured in terms of TEWL was on average 16G/M²/hour which is slightly higher than normal facial skin and consistent with sensitive skin. TEWL dropped significantly from Lumenato use, but also to some extent in the placebo

group, which contains glycerin. Orally administration of glycerol has been shown to improve skin elasticity and barrier recovery.⁴⁶ Pathways for endogenous delivery of glycerol and metabolism in the skin involve the aquaporin-3 transport channel and lipid metabolism in the pilosebaceous unit.⁴⁷ It is possible that the initial boost in skin barrier observed in this study could be from the glycerin in the placebo. The placebo effect did not appear to maintain for the course of the study.

While TEWL in damaged skin is high, it does not increase with age,^{48–50} however, the aged barrier is perturbed more readily versus young subjects⁵⁰ and barrier recovery is slower in aged than in young subjects.^{50,51} In this study, sensitive skin individuals showed a significant improvement in barrier strength after consuming carotenoids from Lumenato supplement. Dietary carotenoids accumulate in the skin and regulate ceramide levels^{52,53} which strengthen the adhesion between the corneocytes of the stratum corneum, thus improving the strength of the skin barrier structure. In addition, the antioxidant properties of carotenoids such as those in Lumenato protect the stratum corneum from further damage.

This study indicates that skin barrier repair was faster with Lumenato supplementation. When the barrier function is damaged, a series of homeostatic systems is accelerated to recover it to its original level.⁵⁴ Lamellar bodies are immediately extruded into the intercellular domain between the stratum granulosum and stratum corneum to form a water-impermeable membrane.^{54,55} This is followed by an increase in the activity of enzymes involved in the biosynthesis of the lipids, cholesterol, ceramides, and free fatty acids of the stratum corneum lipid bilayer. Carotenoids in Lumenato may affect ceramide levels in skin thereby enhancing this repair process. In addition, oral administration of carotenoids elevates the levels of skin filaggrin protein which is instrumental in improving skin barrier.³¹ A strengthened barrier further improves skin hydration, smoothness, firmness elasticity as well as reduce fine lines and wrinkles.^{36,37} Skin hydration is an important parameter responsible for skin homeostasis and all deviations from normal hydration levels can result in significant changes in skin properties and functions. It is well known that lower hydration levels result in a lower elasticity of the skin⁵⁶ as well as faster skin aging and wrinkle creation.⁵⁷ Dry skin is more prone to mechanical failure, flakiness, irritation, and other problems.^{58,59} In this study there was a significant improvement in skin elasticity and frictional parameters after using Lumenato for 12 weeks.

Older individuals are more vulnerable to environmental insults and their cellular turnover and repair are much slower⁶⁰; however, as observed in this study, supplementation with Lumenato could reverse some of these effects associated with ageing. A healthy lifestyle is known to influence the extrinsic aging process, which is related to visible signs of aging. Healthy diet, containing significant fruits and vegetables, as well dietary enhancement with antioxidant rich supplements such as Lumenato can lead to a higher concentration of carotenoids in skin manifested as a slower rate of skin aging.^{61,62}

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DATA AVAILABILITY STATEMENT

Research data are not shared.

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