

ORIGINAL ARTICLE

Beauty from within: Improvement of skin health and appearance with Lycomato a tomato-derived oral supplement

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Email: elizabeth.tarshish@lycored.com**Abstract**

Background: Healthy and a youthful appearance is a common desire of the aging population. "Beauty from within" involves using nutrition and nutraceuticals to support skin function for reducing and reversing signs of aging such as wrinkles, pigmentary changes, skin laxity, and dullness. Carotenoids possess strong antioxidant and anti-inflammatory activities and are effective in improving skin barrier and could thereby stimulate "beauty from within" by providing endogenous support to reduce the expressions of aging.

Aim: This study was designed to determine whether 3-month supplementation with Lycomato would improve skin condition.

Method: A panel of 50 female subjects used Lycomato capsules as nutritional supplements for 3 months. Skin status was observed via questionnaires for the assessment of skin condition and expert visual grading of facial markers such as wrinkles, tonality, roughness, laxity, and pore size. Skin barrier was assessed using transepidermal water loss (TEWL). 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 as measured by TEWL after 12 weeks of consuming the supplement. There was also a significant improvement in skin tonality, lines and wrinkles, pore size, and skin firmness as observed by expert evaluation as well as subject self-assessment.

Conclusion: Based on the confines and conditions of this study, oral supplementation with Lycomato resulted in significant improvement in skin barrier. Visual appearance of lines and wrinkles, skin tonality, pores, smoothness, and firmness were considerably improved, and these improvements were found to be substantially discernible by the subjects.

KEYWORDS

carotenes, facial aging, lycopene, oral supplement, wrinkles

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1 | INTRODUCTION

1.1 | Skin structure

Human skin is a complex barrier organ that provides physical, chemical, and biochemical protection and helps regulate body temperature and prevent moisture loss.¹ The stratum corneum (SC), the outermost layer of the epidermis, is the definitive border that sharply separates the vulnerable organs and tissues of the body from the variable and sometimes hazardous environment. SC is 10–15 μm thick and consists of anucleated “dead” cells called corneocytes, which are filled with keratin filaments wrapped by a cornified envelope. These cells are surrounded by multilamellar lipid membranes, which are composed of cholesterol, free fatty acids, and ceramides (CERs; Figure 1). Together these provide efficient protection from desiccation and environmental challenge by regulating water flux and retention. The SC properties can be altered by changes in the skin environment² such as humidity and UV irradiation. Free radicals and other reactive oxygen species (ROS) from UV irradiation and environmental pollution damage biomolecules, and this damage results in premature aging of the skin.³

Aging skin has a thinner epidermis with flattened dermal ridges and thinner dermis with depleted collagen, thus resulting in weaker skin that is less resistant to shearing forces. The complex biochemistry of the dermis is also changed with age, and the delicate balance between enzymes that control renovation and repair of the dermal matrix is also disrupted.⁴

1.2 | Environmental stress and premature skin aging

Exposure of the skin to environmental pollutants, such as ultraviolet irradiation and ozone, generates reactive oxygen species (ROS), which accelerate apoptosis through mitochondrial membrane depolarization.^{5–8} Reactive oxygen species can alter DNA and cellular proteins and damage the cell membrane. Excessive reactive oxygen species upregulates the expression of matrix-metalloproteinases (MMP). MMPs increase collagen degradation in skin, thus contributing to the skin damage. Aging and the degenerative diseases associated with it have been declared to be attributed to the deleterious strikes of free radicals on cell constituents. Increased levels of free radicals can reach a critical level leading to oxidative stress,^{9,10} which can manifest as premature skin aging.^{11,12} Facial lines and wrinkles are the most examined expressions of aging. It has been reported that the furrows and wrinkles are deeper and denser in the skin of individuals with a low antioxidant level.^{13,14}

Skin aging is a continuous process heavily determined by the combined influences of intrinsic aging, the environment and lifestyle factors including diet. It is well known that balanced nutrition is essential for maintaining healthy skin, and certain nutritional deficiencies result in skin abnormalities; nevertheless, increasing evidence suggests that what we eat can affect our skin aging appearance^{15–18} Conversely, nutritional components of diet can be identified as possible modifiable environmental risk factors for premature skin aging.

Healthy and a youthful appearance is a common desire of the aging population. This is reflected by the billions of dollars spent

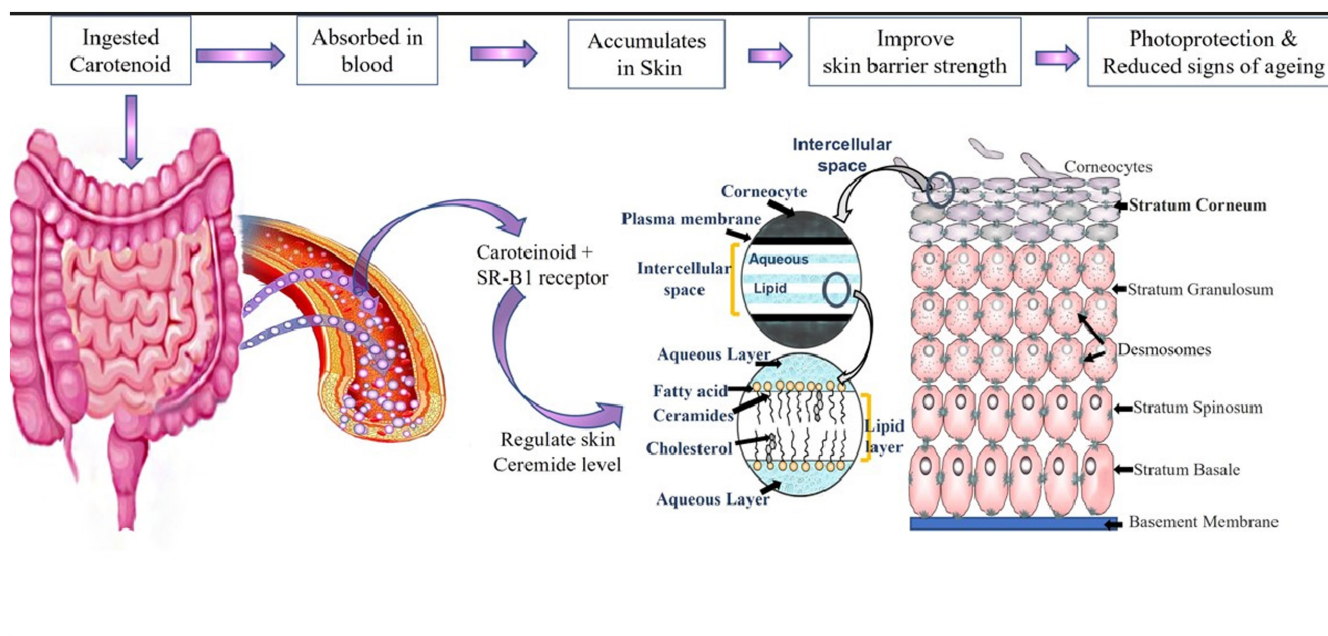


FIGURE 1 Carotenoids in the gut are conveyed by lipoproteins in the bloodstream and then transported to the epidermis via scavenger receptor class B member 1 (SR-B1) which is a multifunctional scavenger receptor that is known for facilitating uptake of cholesterol from HDL particles. It also regulates ceramide levels in skin thereby improving the barrier strength. Skin with a damaged barrier is susceptible to environmental assaults by pollution and UV irradiation which are key contributors to accelerated aging, causing the skin to develop fine lines and wrinkles as well as lose volume and elasticity.

each year on vitamins, minerals, botanical extracts, and antioxidants in an effort to maintain a youthful appearance of the skin and to promote overall well-being. “Beauty from within” approach using nutrition and nutraceuticals to support skin function is of high interest by the aging population.¹⁹ Antioxidants such as carotenoids tackle “beauty from within” by providing endogenous support to reduce the effects and expressions of aging.

1.3 | Carotenoids

Carotenoids constitute a large group of plant pigments that are routinely consumed with fruits, vegetables, and marine products as well as from supplementation. Due to their vast abundance, especially in plant-derived food, they are an integral part of the human diet. Although carotenoids have never been identified as being essential for humans as long as preformed vitamin A is available through the diet,^{20,21} there is increasing evidence of their important role in human health.

Absorption of carotenoids in the gut is reported to be mediated by simple diffusion as well as facilitated diffusion through cholesterol membrane transporters such as scavenger receptor class B member 1 (SR-B1) and a lipid receptor “cluster of differentiation 36” (CD 36).^{22,23} SR-B1 is a multifunctional scavenger receptor that is known for facilitating uptake of cholesterol from HDL particles. After absorption in the gut, the carotenoids are transported into the skin, by the same transporters, SR-B1 found in the epidermal basal layers. The epidermis is an active site of cholesterol accumulation and crucial for barrier function.²⁴ The SR-B1 also regulates ceramide levels in skin, thereby improving skin barrier strength.²⁵ Skin with a compromised barrier is left vulnerable to environmental assaults by pollution and UV irradiation, which are key contributors to accelerated aging. Skin aging is manifested as lines and wrinkles as well as loss of volume and elasticity. Strengthening skin barrier could reverse some of these signs of aging.

Carotenoid metabolism takes place in a wide variety of organs, including the skin.²⁶ Cutaneous carotenoids are known to be effective in preventing the induction of UV-induced erythema.²⁷⁻³¹ The mechanisms behind these phenomena are explained by antioxidant action of the carotenoids.³²⁻³⁴ Carotenoids have been reported to possess strong antioxidant properties^{35,36} as well as strong lipid radical scavenging and as a singlet oxygen quenching activities.³⁷ As antioxidants, carotenoids enhance the ability of the endogenous the antioxidant system to neutralize free radicals such as lipid peroxides, superoxide anions, and hydroxyl radicals, formed in skin after UV and visible light exposure.³⁸ Carotenoids scavenge photo-induced free radicals and antioxidants, thus protecting cellular target molecules such as the cell membrane. Free radicals cause inflammatory responses, and by scavenging these free radicals, carotenoids can suppress cellular inflammatory response. Inflammation is one of the foremost causative factors for visible signs of aging.^{37,39} Nutrition

rich in carotenoids is reported to prevent cell damage, premature skin aging, and skin cancer.³¹

1.4 | Measurement of skin condition

Facial aging signs are commonly assessed via visual grading by trained experts using valid and comprehensive grading systems. Several validated methods are available for credible and reliable measurement of skin aging signs.^{40,41}

Antiaging claims that address reversal of aging signs such as wrinkles often meet with skepticism and fierce inspection from regulators and competitors. For quantitative results, there is a myriad of sophisticated instruments used to support claims.⁴² However, this approach has been criticized since the changes measured by instruments can be too small to be perceptible by the consumers; thus, subject self-assessment is necessary to obtain a discernable valuation of product effect.⁴³ Furthermore, the final approval of consumers is what signifies the success of a product; thus, a combination of instrumental and subjective assessment can provide a complete picture of product effect. This clinical study was designed to examine the effect of a carotenoid supplement on improving signs of skin aging such as pigmentary discolorations, wrinkles, texture, hydration, and firmness as observed by expert visual grading and subject self-assessment. Skin barrier was assessed using instrumental measurements of transepidermal water loss (TEWL). In a previous study by⁴⁴ instrumental measurements were used to observe changes in skin after using a carotenoid supplement ingestion, while in another study⁴⁵ expert visual grading as well as subject self-assessment successfully perceived improvement in signs of skin aging after using oral supplement containing golden tomato extract for 12 weeks.

2 | MATERIALS

Lycomato™ soft gels were supplied by Lycored Ltd., Beer Sheva, Israel. The soft gels contained Lycomato™ tomato extract, standardized to provide 15 mg lycopene. The proprietary tomato extract contains additional fat-soluble natural tomato components such as phytoene, phytofluene, natural tocopherols, beta carotene, and phytosterols.

The subjects were provided with the Lycomato soft gels and instructed to swallow them once a day for 12 weeks.

3 | METHODS

3.1 | Subjects

This was an open-label study; both the study team and the participant knew what product they received for the duration of the study. A total of 56 female participants were recruited for the study out

of which 50 completed the study. Six subjects discontinued due to nonproduct-related reasons.

The subjects were healthy women between the age of 35 and 55 interested in improving health and appearance of normal facial skin recruited for the study. They were recruited from a database of registered individuals interested in participating in clinical trials.

3.1.1 | Inclusion

A total of 50 female subjects aged 35–55 completed the study. The subjects were classified as Fitzpatrick skin types II, III, and IV.⁴⁶

Subjects with baseline signs of facial skin aging as conformed by visual expert grading of photographs score ≥ 3 for fine lines and wrinkles (periorbital area), score ≥ 2 for global fine lines and wrinkles, score ≥ 2 for radiance, score ≥ 2 for pores and score ≥ 2 for skin tone evenness.

The subjects expressed interest in improving skin health and appearance, were willing and able to follow the procedures and restrictions of the study and understand the study requirements and activities in English, so they could provide informed consent. The participants agreed to refrain from changing their diet or lifestyle significantly for the duration of the study.

3.1.2 | Exclusion

Participants with Fitzpatrick skin types above 5 and those with known allergies or sensitivity to tomato and/or latex were excluded from the study. They were also excluded if they used hormonal therapies (including hormonal contraceptives); oral steroids within a month and retinoids within 2 months of study enrollment.

They were also excluded if they experienced chronic or relapsing inflammatory and/or allergic skin conditions such as atopic dermatitis, rosacea, psoriasis, and alike including telangiectasias (spider veins). In addition, the participants were not diagnosed or treated for skin cancer within the last year. They did not have active herpes infections or currently on treatment for herpes infections.

Within the last 6 months, the participants did not have cardiovascular conditions such as stroke, transient ischemic attack (TIA), or myocardial ischemia/infarction, recently on treatment for congestive heart failure, or currently having vasculitis or vascular conditions. They were not on potent anticoagulants such as low-molecular-weight heparin (LMWH), rivaroxaban, apixaban, or other prescription anticoagulants (excluding aspirin).

The participants were also excluded if they held current diagnosis of diabetes mellitus type I or II, chronic liver disease (excluding early-stage nonalcoholic fatty liver disease (NAFLD)); chronic kidney disease; autoimmune skin diseases (e.g., scleroderma, psoriasis, lupus, epidermolysis bullosa, bullous pemphigoid, and temporal arteritis). Also excluded were participants who are HIV positive, immunosuppressed or having chronic connective

tissue disorder affecting the skin (e.g., Ehlers–Danlos syndrome, Marfan's Syndrome, and osteogenesis imperfecta). Participants with a recent (<2 months prior to enrollment) diagnosis of a psychiatric condition were also excluded.

The subjects did not use oral contraception for 3 months before the screening visit and did not change her contraceptive method within the 3 months before the baseline visit nor did she plan to modify her contraception treatment within the duration of the study. Pregnant, lactating, or breastfeeding women (within the last 6 months) or those planning to become pregnant during the study period were also excluded from the study as were those experiencing perimenopausal or menopausal symptoms and/or had a hysterectomy and/or both of their ovaries removed.

Participants who currently take supplements containing carotenoids, lutein, melatonin, or tryptophan were excluded from the study. Those who made a change in oral supplements or medications targeting skin health within 2 months prior to enrollment were also excluded. In addition, they were excluded if they were on any other medication, condition, or disease that in the PI's opinion that may adversely affect the participant's ability to complete the study, substantially impact the study's integrity or may pose a significant risk to the participant.

Participants who received UV irradiation within last year or were planning on undergoing facial irradiation during the study were excluded; so were those with occupations or lifestyle that require significant daily exposure to the sun (defined as at least 1 h of continuous outdoor sun exposure). They did not have a sunburn and did not use tanning salons or tanning products in the last 3 months and did not plan a trip to the mountains or to a higher UV index region during the study period.

3.2 | Clinical assessment

On the first visit (T0), subjects were examined by an expert technician to confirm the inclusion and noninclusion criteria.

Before product use (T0) and during visits 4 (T4w) and 12 (T12w) weeks of product use, the expert 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.

3.3 | Expert grading assessments

Visual assessments were performed by a trained expert grader at the testing laboratory, using a 10-point ordinal scale where 0 was none and 9 was excessive for signs of the facial aging of the face.⁴⁰ Table 1 describes the parameters and the scale details. Clinical grading detailed in Table 1 was performed from photographs at each time point (T0, T4w and T12w).

TABLE 1 Clinical Efficacy Assessment attributes and scale.

Attribute	Type of grading	Scale
Fine lines (Periorbital)	Visual	0 = None 9 = Numerous, deep fine lines
Wrinkles (Periorbital)	Visual	0 = None 9 = Numerous, deep wrinkles
Wrinkles (global)	Visual	0 = None 9 = Numerous, deep Wrinkles
Fine lines (global)	Visual	0 = None 9 = Numerous, deep fine lines
Pore Appearance	Visual	0 = Small, not easily visible 9 = Large, easily visible
Brightness/Radiance/luminosity	Visual	0 = Radiant, Luminous, glowing appearance 9 = Dull/Matte and/or Sallow
Skin Tone Evenness	Visual	0 = Even, Healthy skin color 9 = Uneven, Discolored, Blotchy
Dark spot intensity	Visual	0 = None, no color difference present 9 = Intense/Deep color difference (dark brown/tan)
Skin texture/Smoothness (Visual)	Visual	0 = Smooth, even surface appearance 9 = Rough, uneven surface appearance
Firmness	Visual	0 = Very Firm, tight appearance 9 = Loose appearance

3.4 | Digital imaging

Digital photographs of the subjects were obtained for efficacy documentation purposes. Images of the subjects were acquired with a Nikon D850 digital camera and specific lighting from five positions (front, 3/4 and profile). Resulting images were delivered as JPEG files.

Images were obtained at the following time-points:

- T0—before investigational product use.
- T4w—after 4 weeks of investigational product use.
- T12w—after 12 weeks of investigational product use.

3.5 | Barrier integrity: Tewameter® measurements

Measurements of transepidermal water loss (TEWL) were performed by expert technicians using the Tewameter TM 300 equipment (Courage+Khazaka electronic GmbH, Koln Germany). Measurements were obtained by applying the probe to the test area, resting it on the skin. The measurement area was approximately 75 mm².

The measurement indicated the degree of water evaporation on the skin surface based on the sensitivity of hygrosensors. The scale used was G/m²/h, and higher reading values indicate greater evaporation and hence a worse skin barrier. The measurements were performed on the left or right malar areas of the face per a randomization at baseline and after 4 and 12 weeks of product use.

3.6 | Self-assessment questionnaire performed by the study subjects

Self-assessment of subject was performed in adherence to the “Standard Guide for Sensory Claim Substantiation”,⁴⁷ through the application of a questionnaire.

American Society for Testing and Materials (ASTM) standards organization has been developed for over a century and represents one of the greatest voluntary organizations for standards development in the world, being a reliable source of technical standards of material, products, systems, and services. Known by their high technical quality and relevance on market, ASTM standards have an important role in the infrastructure of the information guiding the study design, product manufacturing and commerce in global economy. The “Standard Guide for Sensory Claim Substantiation” is an ASTM standard that aims to disclose the good practices in sensory studies, approaching reasonable practices for executing sensory studies to validate product claims.

Subjective questionnaires allow the determination of the subjects' perceptions of the investigational product and its effects. Study subjects were instructed to assess the product through questionnaire after 4 and 12 weeks of using Lycomato. The subjects answered questions about their preference using a 5-point scale:

- 5—Strongly Agree.
- 4—Agree.
- 3—Neutral.
- 2—Disagree.
- 1—Strongly Disagree.

3.7 | Statistical considerations

Using Excel 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-week use. Descriptive statistics (frequencies and percentages) summarized responses from the Study Product. A Student's t test was conducted to determine statistical significance.

3.8 | Ethical considerations

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. The study was approved by Allendale IRB, Old Lyme, CT (approval number 4123PP).

No adverse reactions were reported during the study or in previous studies done with Lycomato.

4 | RESULTS

4.1 | Skin barrier: TEWL

As observed in Figure 2, there was an average reduction of 7.2% and 8.9% ($p < 0.05$) in TEWL of facial skin after using Lycomato for 4 weeks and 12 weeks, respectively, indicating a significant improvement in skin barrier after 12 weeks of use.

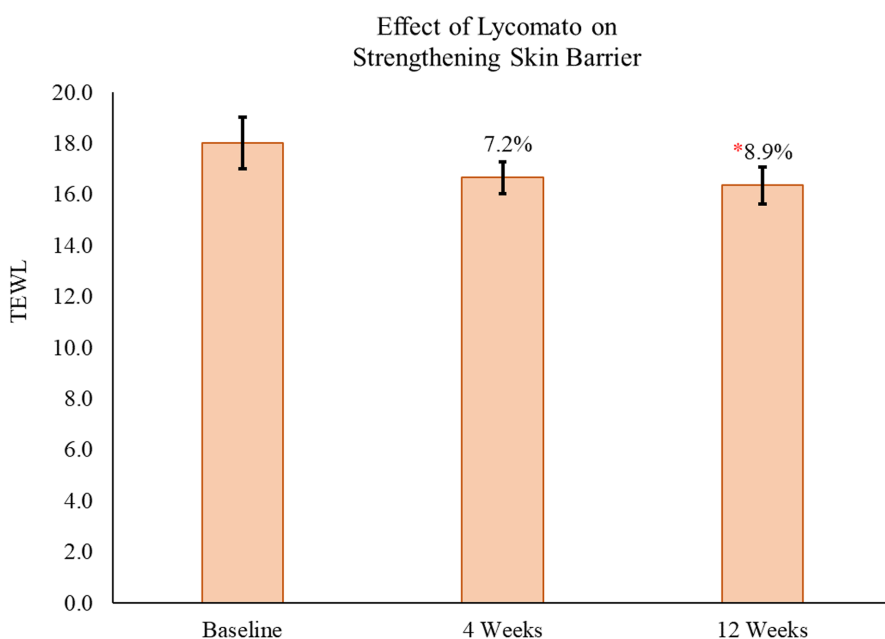


FIGURE 2 There was an average reduction of 7.2% and 8.9% ($p < 0.05$) in transepidermal water loss (TEWL) of facial skin after using Lycomato for 4 weeks and 12 weeks, respectively. The error bars represent standard error of mean.

4.2 | Expert visual grading

Facial lines and wrinkles were considerably reduced after using Lycomato as described in Figure 3. Periorbital fine lines reduced by 25% and 41.4% after 4 and 12 weeks of using Lycomato, respectively ($p < 0.001$; Figure 3B). Periorbital deeper wrinkles also reduced after the use of Lycomato with a 14.8% reduction after 4 weeks 26% ($p < 0.05$) after 12 weeks of use.

Global fine lines and wrinkles were also significantly reduced as observed visually after using Lycomato. There was a highly significant ($p < 0.001$) reduction of global fine lines after 4 weeks (31.5%) and 12 weeks (51%) of use. More pronounced global lines also reduced after 4 weeks with 17% ($p < 0.05$) reduction that improved further to 26% reduction ($p < 0.001$) after 12 weeks of use. Figure 3C shows improvement in marionette line after using Lycomato for 12 weeks. Figure 3D illustrates a reduction in the glabella lines and Figure 3E shows a smoothing of nasolabial line.

Skin Tonality indicates variation in tones and tints of the face described as brightness, radiance, luminosity, as well as evenness of skin color and contrast. As observed in Figure 4, skin tonality improved significantly after supplementation with Lycomato. Skin brightness and luminosity improved by 7.9% ($p < 0.05$) and 13.5% ($p < 0.001$) after 4 weeks and 12 weeks of use, respectively. Figure 4D illustrates improvement in skin luminosity after 12 weeks of use. Figure 4C illustrates reduction of under-eye dark circles after using the product for 12 weeks.

The skin tone was 11.14% ($p < 0.05$) less patchy after 4 weeks of use and improved further after 12 weeks with 18.3% ($p < 0.001$) improved evenness of skin tone. 62.26% of the population showed improvement after 4 weeks and 71.7% after 12 weeks.

Dark spots severity reduced slightly (4.8%) after 4 weeks of use and improved up to 11.9% ($p < 0.05$) after 12 weeks. This is illustrated

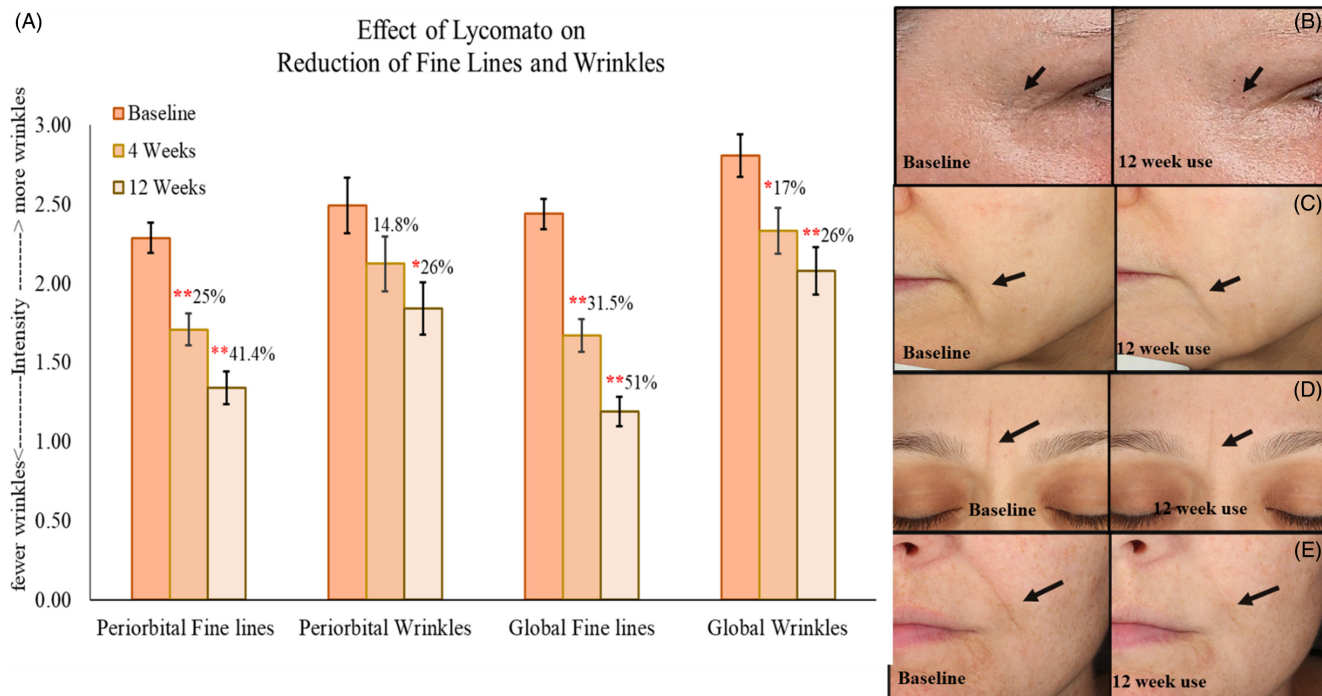


FIGURE 3 (A) Periorbital fine lines reduced by a highly significant ($p < 0.001$) 25% and 41.4% after 4 and 12 weeks of use of Lycomato, respectively. 77.36% of the population showed improvement after 4 weeks and 86.79% after 12 weeks. This is illustrated in (B). Periorbital deeper wrinkles also reduced after the use of Lycomato. There was 14.8% reduction after 4 weeks with 62.26% of the population showing improvement and a significant ($p < 0.05$) reduction of 26% after 12 weeks of use with 75.47% of the population showing improvement. Global fine lines and wrinkles also reduced significantly after using Lycomato. As observed in (C–E), there was a highly significant ($p < 0.001$) reduction of global fine lines after 4 weeks (31.5%) and 12 weeks (51%). 94.34% of the population showed improvement after 4 weeks and 98.11% after 12 weeks of use. There was also a reduction of 17% ($p < 0.05$) in more pronounced global lines after 4 weeks of use, which improved further to 26% reduction ($p < 0.001$). 58.49% of the population exhibited improvement after 4 weeks and 75.47% after 12 weeks of using Lycomato.

in Figure 4B, which shows significant reduction in skin discoloration after 12 weeks of use.

Figure 4E indicates a reduction in skin inflammation after 12 weeks of using Lycomato. Redness of the cheek area is considerably reduced in the photograph after 12 weeks of use.

Skin pores appeared to be reduced in size after using Lycomato (Figure 5). As observed by visual grading, there was 8.16% reduction after 4 weeks, which improved further to 21.7% after 12 weeks of use ($p < 0.001$). This reduction in pore intensity is illustrated in Figure 4B, which shows photograph of a face before and after 12-week supplementation with Lycomato. After 12 weeks of use, the pores appear less distinct.

Skin texture visibly improved significantly after using Lycomato (Figure 6). There was 7% ($p < 0.001$) improvement after 4 weeks and 10.8% ($p < 0.001$) after 12 weeks of supplement use. Improvement in skin texture is illustrated in Figure 6B. The skin appears smooth and lustrous after using the product for 12 weeks.

Skin firmness was defined as visual appearance of tightness vs lax skin (Figure 7). There was a significant improvement of 8.28% in skin firmness after 4 weeks ($p < 0.05$) and 14.4% ($p < 0.001$) after 12 weeks of supplement use.

4.3 | Subject self-assessment

Tonality

Subject self-assessment of skin tonality parameters is illustrated in Figure 8. As observed in the graph, the subjects observed improvement in all the skin tonality parameters; the average grading of all parameters was above 3, which is the point of neutrality. The subjects observed improvement after 4 weeks which increased further after 12 weeks, for all skin tonality parameters. After 12 weeks of use, the subjects noticed high improvement in skin brightness.

When asked if the test product improved the tone of skin with skin tone appearing more even, 31 out of 56 subjects noticed improvement with the product after 4 weeks of use while 22 subjects were neutral. Three subjects disagreed and the average score was 3.68. After 12 weeks of use, the average score increased to 3.9 with 33 subjects out of 50 (66%) noticing an improvement. Seventeen subjects were neutral and there was no disapproval.

Out of 56, a total of 36 (64.3%) subjects noticed a brighter skin tone after using the supplement for 4 weeks. Eighteen subjects were

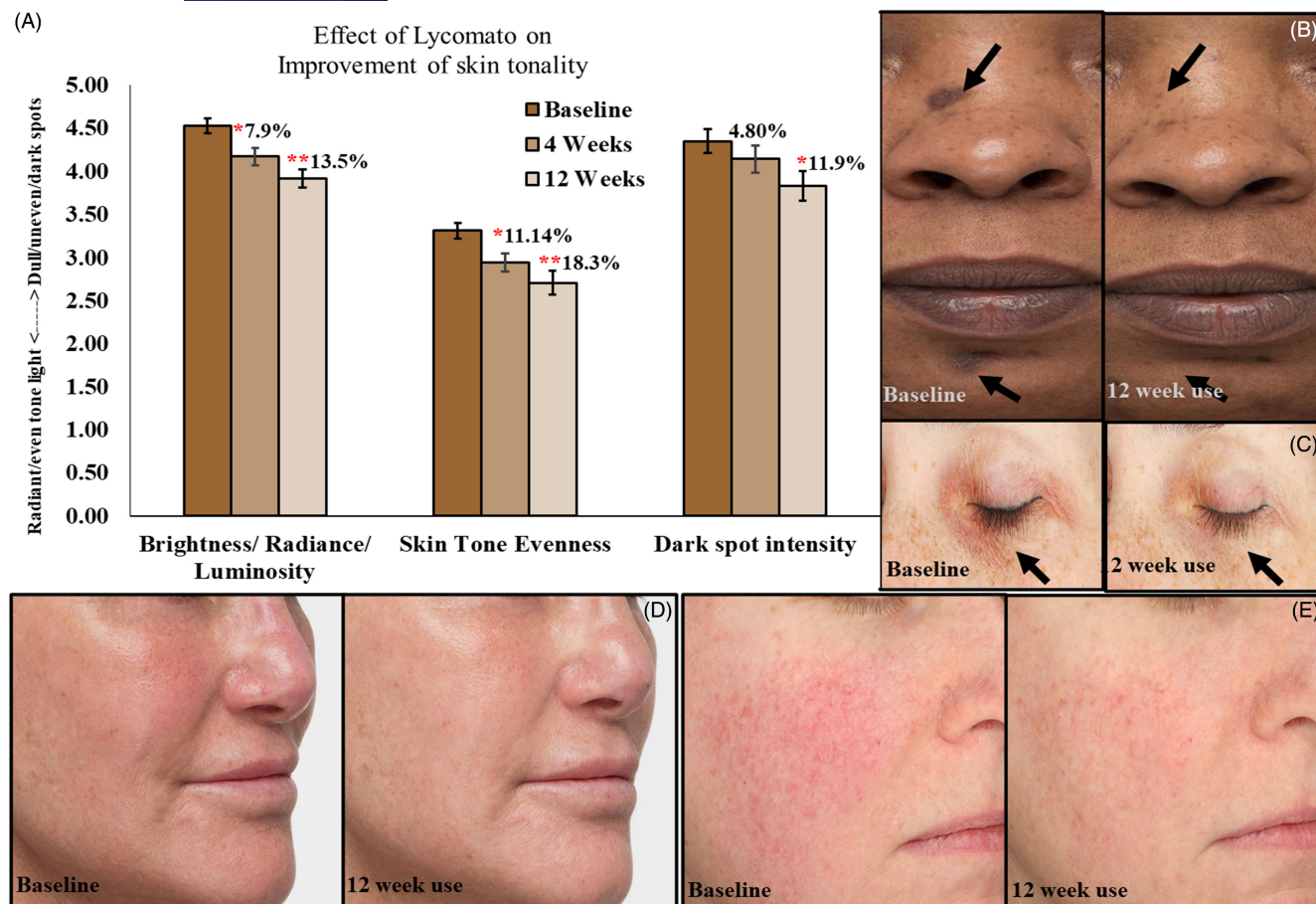


FIGURE 4 (A) Expert grading of skin tonality exhibited a significant improvement of 7.9% ($p < 0.05$) in brightness and luminosity after 4 weeks and 13.5% ($p < 0.001$) after 12 weeks of use. 64.15% of the population showed improvement after 4 weeks and 79.25% after 12 weeks. (C) illustrates improvement in the tonality of under-eye dark circles after using the product for 12 weeks. The skin tone was 11.14% ($p < 0.05$) evener after 4 weeks of use and even better after 12 weeks with 18.3% ($p < 0.001$) further improvement in evenness of skin tone. 62.26% of the population showed improvement after 4 weeks and 71.7% after 12 weeks. The intensity of dark spots reduced slightly (4.8%) after 4 weeks of use and continued to improve for 12 weeks at which point there was an 11.9% reduction ($p < 0.05$). 26.24% of the population exhibited lightening of dark spots after 4 weeks and 56.6% after 12 weeks. This is further illustrated in (B), which shows significant reduction of discolored marks after 12 weeks of use. (D) illustrates improvement in skin luminosity after 12 weeks of use, and (E) indicates a reduction in skin inflammation after use.

neutral while two subjects disagreed. The average score was 3.75, which increased to 4.08 after 12 weeks of use. After 12 weeks of use, 40 subjects out of 50 (80%) noticed a brightening of their skin tonality. Ten subjects were neutral, and there were no disapprovals.

Twenty-one subjects declared their *skin appears lighter* after 4 weeks of use. Thirty subjects were neutral. Five subjects disagreed, and the average score was 3.34. After 12 weeks of use, the average score increased to 3.66 with 25 approving subjects, 22 neutrals and three disapprovals.

Skin discoloration and uneven tone is a major concern for the aging population. When asked if the test product *reduced the appearance of dark spots (pigmentation spots)*, the average score was 3.13 after 4 weeks and 16 out of 56 subjects noticed improvement with the product while 31 subjects were neutral. Nine subjects disagreed. After 12 weeks of use, the average score improved to 3.42 where 21 subjects out of 50 (42%) noticed an

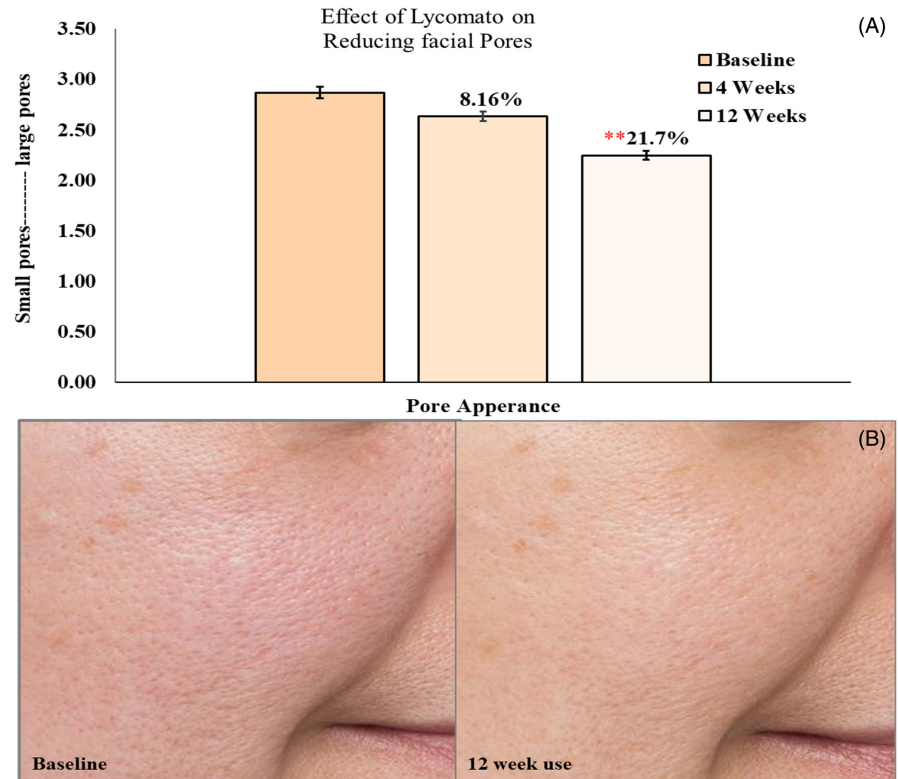
improvement. Twenty-four subjects were neutral, and 5 subjects did not notice any change in their facial pigmentation after using the supplement.

After using the supplement for 4 weeks, 16 out of 56 subjects noticed *improvement in skin redness*; 36 subjects were neutral, 4 subjects disagreed, and the average score was 3.25. The average score increased to 3.56 after 12 weeks of use at which time point 25 subjects out of 50 (50%) noticed an improvement. There were 24 neutral gradings and 5 subjects disapproved.

Firmness, elasticity, and tightness

When inquired if the subjects noticed an *improvement in skin elasticity* after using the product for 4 weeks, 30 out of 56 subjects noticed improvement while 24 subjects were neutral and two subjects disagreed (Figure 9A). The average score was 3.55, which went up to 4.16 after 12 weeks of use. At the 12-week time point,

FIGURE 5 (A) Expert grading of skin pores showed an 8.16% reduction after 4 weeks, which improved further to 21.7% after 12 weeks of use ($p < 0.001$). After 4 weeks 47.17% of the population exhibited an improvement, which increased to 68.81% after 12 weeks of use. (B) illustrates reduction in pore intensity after 12 weeks of product use.



44 out of 50 subjects (88%) noticed an improvement by allocating a score above 3, six subjects scored a neutral of 3, and there was no disapproval.

When asked if the supplement use *improved their skin's firmness*, the average score was 3.46 after 4 weeks of use and 27 out of 56 subjects noticed improvement with the product while 26 subjects were neutral. Three subjects disagreed. After 12 weeks of use, the average skin firmness score increased to 3.98. Thirty eight out of 50 (76%) subjects noticed an improvement in skin firmness, 11 subjects were neutral, and there was one disapproval.

Improvement in *skin's tightness* was observed by 21 out of 56 subjects after 4 weeks of use. Thirty-two subjects were neutral. Three subjects disagreed and the average score was 3.36., which increased to 3.94 after 12 weeks of use. Skin tightness improvement was noticed by 36 out of 50 subjects (72%), and there were 14 neutral scores after 12 weeks of supplement use.

Healthy and younger skin

The subjects were asked if their skin looks and feels younger/healthier after using the supplement (Figure 9B). After 4 weeks of use, the average score was 3.61 and 31 out of 56 subjects noticed improvement while 24 subjects were neutral. One subject disagreed. Remarkably, after 12 weeks of use, 42 out of 50 (84%) subjects noticed an improvement. Eight subjects were neutral, and there was no disapproval. The average score at this time point was 4.14.

When asked if the test product improved the overall appearance of skin; 36 out of 56 subjects noticed improvement with the

product, while 19 subjects were neutral. One subject disagreed and the average score was 3.71. After 12 weeks of use, the average score increased to 4.18 and 43 out of 50 (86%) of the subjects noticed an improvement. Six subjects were neutral with one subject in disagreement.

Dryness and texture

Generally, the subjects observed a much healthier/younger skin and better overall appearance of skin, which felt more hydrated and smoother (Figure 9C). After using Lycomato, there was a high approval score over 4 after 12-week use.

When asked if the subjects noticed improvement in skin dryness with more hydrated feel, 37 out of 56 subjects noticed improvement with the product after 4 weeks of use while 16 subjects were neutral. Three subjects disagreed, and the average score was 3.66. After 12 weeks of use, the average score was 4.12 and 40 out of 50 (80%) subjects noticed an improvement. Eight subjects were neutral and two disapproved.

Forty out of 56 subjects noticed improvement in skin texture having a smoother feel after 4 weeks of using the supplement. Fifteen subjects were neutral, one subject disagreed, and the average score was 3.8. After 12 weeks of use, 43 out of 50 (86%) subjects noticed an improvement while 6 subjects were neutral and one disapproved. The average score was 4.14.

Lines and wrinkles

The subjects observed some improvement in facial lines and wrinkles after using Lycomato (Figure 9D). *Fine lines and wrinkles* appeared to

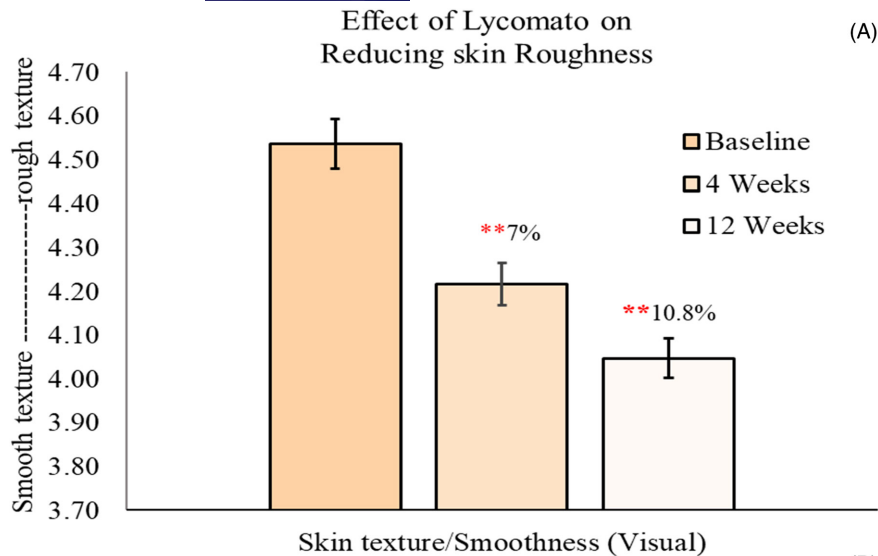


FIGURE 6 (A) Expert grading of skin texture showed a significant improvement of 7% ($p < 0.001$) after 4 weeks and 10.8% ($p < 0.001$) after 12 weeks of use. 66.04% of the population exhibited improvement after 4 weeks and 79.25% after 12 weeks of using Lycomato. (B) illustrates improvement in skin texture after using the product for 12 weeks; lines on the cheeks are softer and generally the skin looks smoother.

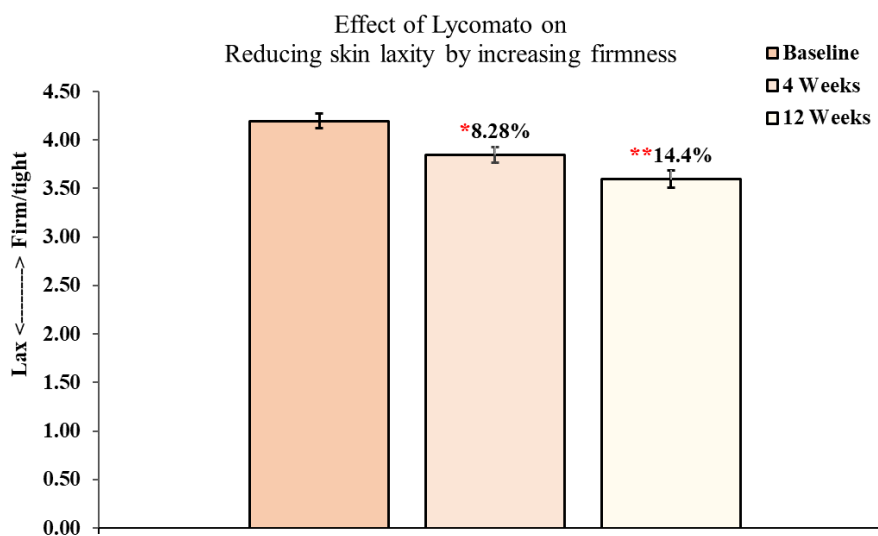


FIGURE 7 Visual appearance of tightness of lax skin was defined as skin firmness. Skin firmness improved by 8.28% after 4 weeks ($p < 0.05$) and 14.4% ($p < 0.001$) after 12 weeks of use. After 4 weeks of use, 67.92% of the population showed improvement, which increased to 77.36% after 12 weeks.

be somewhat improved as noticed by the subjects after 4 weeks of use when 18 out of 56 subjects (32.14%) noticed improvement with the product while 35 subjects were neutral. Three subjects disagreed, and the average score was 3.29. After 12 weeks of use, the average score was 3.76 and 30 out of 50 (60%) subjects noticed an improvement. Seventeen subjects were neutral, and three subjects did not notice a change.

Improvement in deep wrinkles was noticed by 12 out of 56 subjects (21.43%) after 4 weeks of use, while 39 subjects were neutral. Five subjects disagreed, and the average score was 3.14. After 12 weeks of use, 20 out of 50 (40%) subjects noticed an improvement in their deep wrinkles. Twenty-four subjects were neutral, and 6 subjects did not notice any change. The average score was 3.4.

FIGURE 8 Subject self-assessment of skin tonality. As observed in the graph the subjects observed improvement all the skin tonality parameters; the average grading of all parameters was above 3, which is the point of neutrality. The subjects observed improvement after 4 weeks, which increased after 12 weeks for all skin tonality parameters. After 12 weeks of use, the subjects noticed high improvement in skin brightness with over 80% of the subjects declaring improvement.

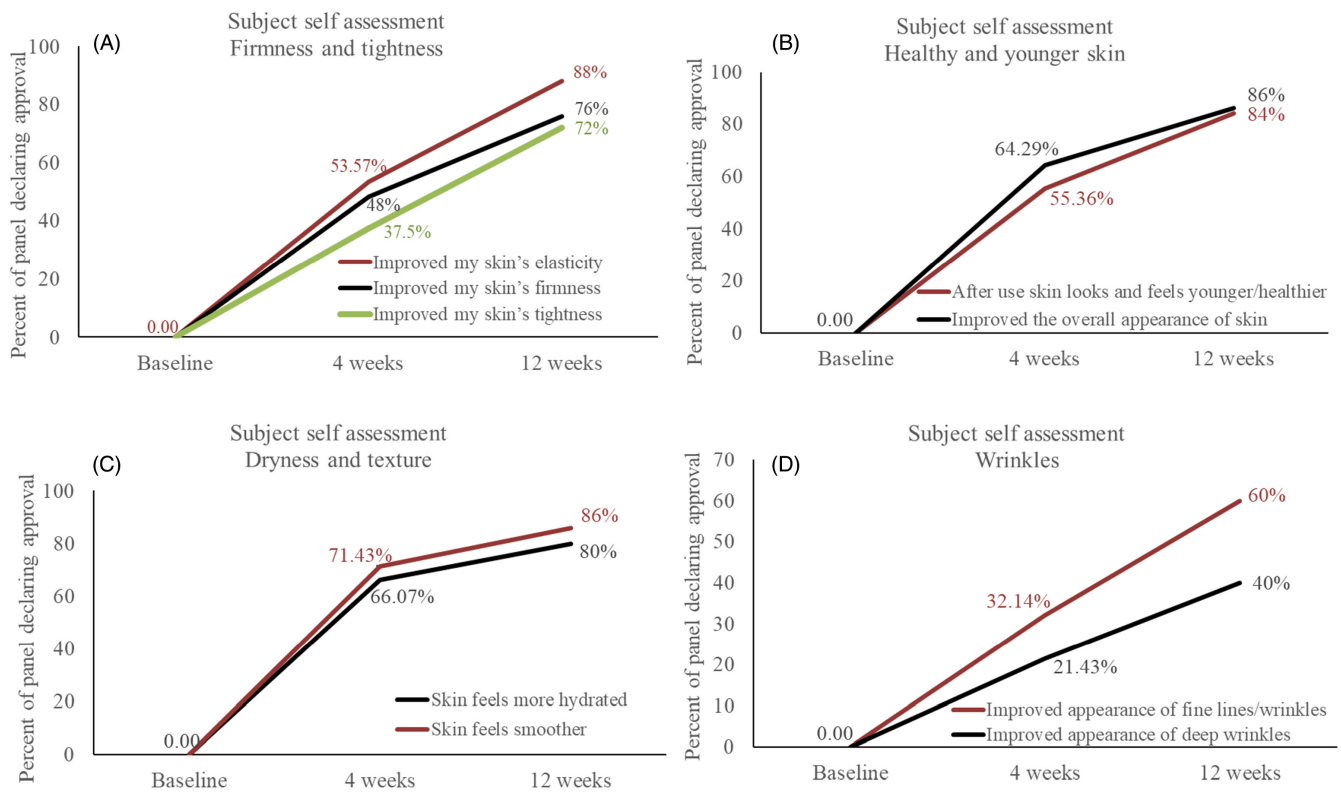
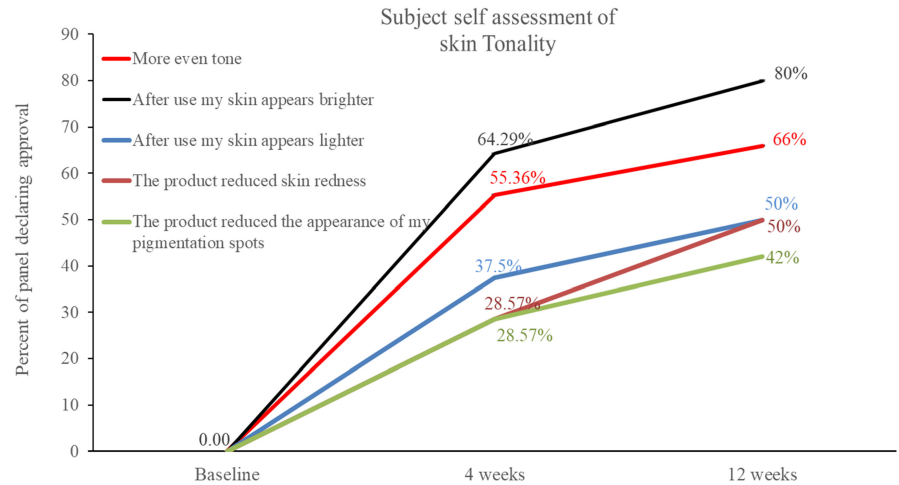


FIGURE 9 Subject self-assessment. (A) The subjects observed improvement in skin elasticity, firmness, and tightness. Skin elasticity improvement was noticed by 55.57% of the subjects after 4 weeks of use, which increased to 88% after 12 weeks. Skin Firmness improvement was noticed by 48.21% and 76% of the subjects after 4 and 12 weeks of use, respectively. 37% of the subjects noticed improvement in skin tightness after 4 weeks and 72% after 12 weeks of use. (B) The subjects observed a much healthier/younger skin and better overall appearance of skin after using Lycomato. Over 50% of the subjects noticed improvement after just 4 weeks of use, which increased to over 80% after 12 weeks of use (C) The subjects felt their skin to be further hydrated and smooth after using Lycomato. Over 60% of the subjects noticed improvement in skin hydration and smoothness after 4 weeks of use, which increased to over 80% after 12 weeks of use. (D) Improvement in fine lines and wrinkles was noticed by 32.14% of the population after using Lycomato for 4 weeks, which increased to 60% after 12 weeks of use. Deep wrinkles were improved in 21.43% of the subjects after 4 weeks and 40% after 12 weeks of use.

5 | DISCUSSION

Human skin, the largest organ of the body, constitutes the first line of defense from environmental assault and is important for protecting against water loss and regulation of body temperature. It is also

an "aesthetic" interface with physical attributes that form the basis of first impressions of a person's health and beauty.

Most ingredients for skin care are topical and intended for improving hydration, softening, strengthening barrier function or to deliver antioxidants for protection from the sun and pollution. However,

topical nutrients have limited capacity to penetrate the outer skin layers and also have a local effect and thus cannot provide nutrients to the full body. As a result, dietary supplementation is becoming increasingly important to complement for skin health and beauty.

Environmental pollutants and UV irradiation cause the generation of free radicals and oxygen species, which can accumulate and cause oxidative stress which has been linked to age-related changes in skin.⁴⁸ Oxidative stress triggers cellular damage pathways and causes senescence of cells, which may lead to photoaging.^{48,49} Skin contains protective antioxidants, defensive enzymes, and micronutrients derived from circulation; however, these particles can be depleted with age and exposure to the environment, thus requiring dietary supplementation for support.⁵⁰⁻⁵⁴ In this clinical study, oral administration of a mix of powerful antioxidants containing tomato carotenoids such as lycopene was found to be effective in improving skin quality, including reversal of some signs of aging such as wrinkles and skin tonality.

Carotenoids absorbed from the gut to the bloodstream are transported to the epidermis via the SR-B1 receptor,⁵⁵ which facilitates transport of carotenoids into the epidermis and regulates ceramide levels in skin, thereby improving the barrier strength of the skin²⁵ as observed in the current study.

Carotenoids accumulated in skin are able to offer photoprotection possibly via enhancement in barrier function against UV irradiation as well as protection of target molecules by scavenging photo-induced free radicals. In addition, carotenoids are known to suppress cellular inflammatory responses and repair UV-induced damage. Due to the hydrophobic nature of carotenoids, it is possibly incorporated into the cell membranes resulting in the prevention of lipid oxidation. Results of this study imply that all these aspects could collectively repair skin damage and thus reduce signs of aging including wrinkles, skin tonality, as well as skin roughness and laxity. The improvements were positively noticed by the subjects, indicating a significant benefit of Lycomato on skin.

Protective effects of oral carotenoids on human skin indicate their application in the field of dermatology as nutraceuticals, cosmeceuticals, and photo-protectants. Due to their antioxidant, and anti-inflammatory activities, the optimal supply of these supplements can increase dermal defense against ultraviolet irradiation and environmental pollutants, thereby contributing to better skin health and appearance expressed as "beauty from within."

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CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

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. The study was approved by Allendale IRB, Old Lyme, CT (approval number 4123PP). No adverse reactions were reported during the study or in previous studies done with Lycomato.

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