IFSCC 2025 full paper IFSCC2025-1809

Topical Application of Adaptogens Modulate the Brain-Skin Axis for Holistic Well-Aging

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1. Introduction

In recent years, the concept of holistic well-being has gained considerable traction in both scientific and consumer contexts, emphasizing the systemic connection of physiological and psychological health. Central to this paradigm is the brain-skin axis – a bidirectional communication network through which emotional and neurological states influence skin biology and vice versa [1]. The relevance of this axis is underscored by mounting evidence linking chronic psychological stress to premature skin aging, barrier dysfunction, inflammation, and altered pigmentation [2]. This neuro-immuno-cutaneous dialogue is mediated by cytokines, neuropeptides, and oxidative stress pathways, all of which represent therapeutic targets in the pursuit of well-aging interventions.

One particularly promising avenue in this field lies in interoception – the brain's perception and regulation of internal bodily states – which is increasingly understood to mediate both mood and skin health [3,4]. However, most available skincare products address either aesthetic or emotional well-being in isolation. There remains a substantial unmet need for integrated solutions that concurrently improve skin condition and mental state, particularly in the context of daily stressors.

To this end, the present study investigates the topical efficacy of a novel complex, GLMC, composed of Gyokuro-derived nootropic actives (rich in L-theanine and caffeine) and adaptogens from Lion's Mane and Cordyceps mushrooms, known for their neuroprotective and stress-modulating properties. The formulation was designed to synergistically enhance both brain-derived mood and engagement and skin physiological resilience.

To evaluate the full potential of GLMC in supporting skin resilience and emotional well-being, we selected a targeted set of *in vitro* assays designed to probe fundamental biological processes known to deteriorate under stress and aging. These included markers of inflammation, oxidative stress, metabolic vitality, vascular integrity, and cellular senescence – all of which play central roles in both skin health and the broader stress response. This approach allowed us to capture a comprehensive mechanistic picture of how GLMC supports cellular function and resilience.

In parallel, *in vivo* clinical studies were conducted to validate the relevance of these mechanistic findings in real-world conditions. Here, we assessed GLMC's impact on skin appearance, structural integrity, and psychological perception, including changes in mood and cognitive engagement. The four-week topical application protocol was chosen to reflect typical product use, with outcomes aligned to visible signs of aging – such as wrinkles, elasticity, and pigmentation – as well as user-reported shifts in mental state.

Together, these preclinical and clinical assessments provide converging evidence that GLMC acts on both the biological and sensory dimensions of the brain-skin axis. The results support its potential as a multifunctional cosmetic active that delivers measurable skin improvements alongside enhanced emotional well-being – positioning it as a next-generation solution for integrative skincare.

2. Materials and Methods

A multi-faceted approach was employed to determine the effect of GLMC on *in vitro* mechanisms and *in vivo* indicators of skin health and well-being. All data are displayed as averages and t-test analyses were performed with statistical significance accepted at $p \leq 0.05$. Pre-clinical experiments examined the anti-inflammatory, reactive oxygen species (ROS) scavenging, anti-pollution, anti-aging properties of GLMC in addition to the capacity of GLMC to enhance metabolic function and vascular integrity.

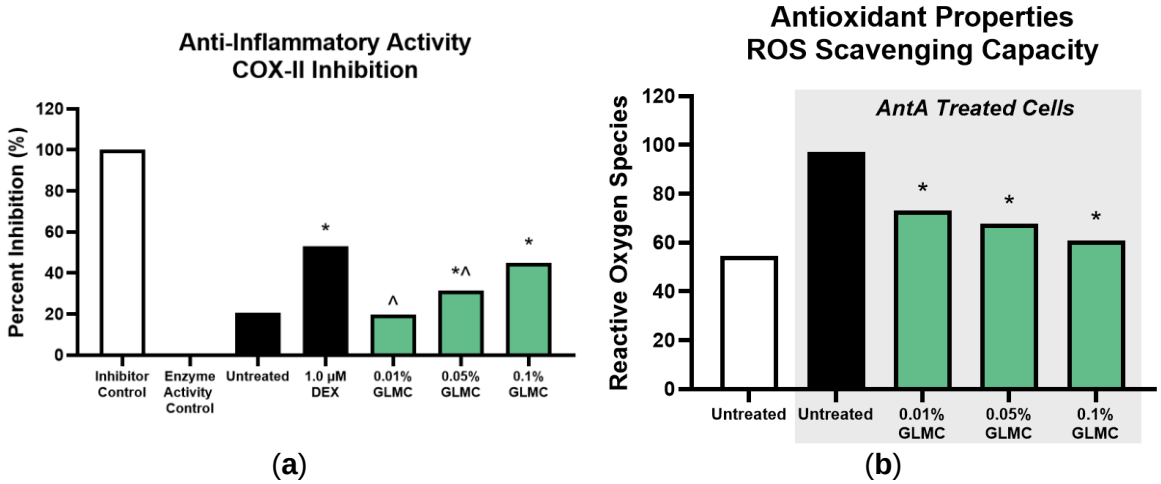
- The anti-inflammatory properties of GLMC was determined by COX-II inhibition. Dermal keratinocytes were grown to confluency and exposed to various concentrations of GMLC. After 72 hours, cell supernatants were collected and determined via ELISA.
- ROS scavenging capacity was determined by generating a supraphysiological level of mitochondrial- and non-mitochondrial-derived levels of oxidative stress by inhibiting complex III of the mitochondrial electron transport chain in fibroblasts with Antimycin A (AntA). Dermal fibroblasts were grown to confluency and exposed to various concentrations of GMLC. After 18 hours, cells were washed and incubated with 20 µM Hoechst and 5 µM CellROX™. Next, cells were washed and AntA (200 pM) was added to specific wells. After 30 minutes, fresh media was added to all wells, and fluorescence measurements were obtained (ex / em): Hoechst (361 nm / 486 nm), CellROX™ (545 nm / 565 nm). ROS levels are expressed as CellROX™ (ROS) divided by Hoechst (cell count).
- The anti-pollution properties of GMLC were determined by assessing cellular homeostasis after soluble pollutant exposure (i.e. cigarette smoke). Cigarette Smoke Media was generated by bubbling cigarette smoke through Complete Media via a manual syringe utilizing two second puffs with 30 second delays between puffs to model human smoking. Dermal fibroblasts were grown to confluency and exposed to various concentrations of GMLC. After 24 hours, Cigarette Smoke Media was added to all wells, except the Untreated Control. After exposure to cigarette smoke for 18 hours, cells were washed again and cellular viability was assessed via fluorescent measurements (560 nm / 590 nm).
- Mitochondrial membrane potential ($\Delta\Psi m$) was evaluated to assess the ability of GLMC to stimulate metabolic function via oxidative phosphorylation. Dermal fibroblasts were grown to confluency and exposed to various concentrations of GMLC. After 24 hours, cells were washed and incubated with JC-10 Dye Solution. $\Delta\Psi m$ was assessed with multiple fluorescent measurements (490 nm / 525 nm) and (540 nm / 590 nm). $\Delta\Psi m$ data (the 525/590 ratio) is expressed as a percent of untreated fibroblasts.
- 'Young' (passage 4) and 'aged' (passage 8) dermal fibroblasts were utilized to determine the anti-aging effects of GMLC. Cells were grown to confluency and exposed to various concentrations of GMLC. After 24 hours, cells were washed and incubated with 20 µM Hoechst

to enumerate cell counts (361 nm / 486 nm). Cells were washed, lysed, and incubated with a SPiDER-ßGal dye to determine β-galactosidase levels (535 nm / 580 nm). Normalized SA-β-gal activity is displayed as β-galactosidase levels divided by Hoechst cell counts.
- Endothelial permeability was utilized to determine the capacity of GLMC to increase vascular integrity. Dermal fibroblasts were grown to confluency and exposed to various concentrations of GMLC. After 48 hours, conditioned media was collected, combined with LPS, and added ontop of dermal microvascular endothelial cells. After 24 hours, endothelial permability was measured by optical density and data is relative to the Untreated Control.

Clinical studies were implemented to determine the impact of topical application with and without GMLC on acute and short-term mood states, skin hydration, barrier function, elasticity, and the appearance of neck wrinkles and undereye dark circles.Participants provided informed consent prior to clinical studies and Cetaphil® Moisturizing Cream for All Skin Types was utilized as the Base Lotion for all studies.
- The immediate active thinking properties of GLMC were evaluated by measuring Beta brainwave activity in 20 participants (25-50 years old). After sitting in a quiet room for 10 minutes to obtain baseline brainwave activity, the four randomly assigned test sites were identified on the volar forearm and order of condition application was randomized. Following stable Baseline measurements, the principal investigator physically applied 0.2 g of one condition to the respective test site for 30 seconds. After applying the first condition, brainwaves were monitored for 60 seconds without physical contact from the principal investigator. Once stable recordings were achieved, the principal investigator applied 0.2 g of the second condition to the respective test site for 30 seconds, this process continued until all test articles were applied. Absolute Beta brainwave activity during the 30 second application period were utilized for analysis and data is displayed relative to baseline activity.
- To determine short-term effects of GLMC application on mood, 20 male and female participants (22-54 years old) completed baseline mood surveys. Next, participants applied 0.2 g of 2.0% GLMC on one of their volar forearms for 30 seconds. 24 hours after application, participants completed the same surveys and again after one week of daily application. The pleasant Mood Index (Brief Mood Introspection Scale) provides an evaluation of mood in terms of pleasant or unpleasant. Higher scores indicate a more pleasant mood.
- The skin moisturizing and skin barrier function effects of GLMC application were determined by randomly assigning three test sites on the volar forearms of 18 male and female participants (23-45 years old) to the following conditions: Untreated Control, Base Lotion, and 2.0% GLMC in Base Lotion. Participants applied 0.2 g of each treatment to their volar forearm for 30 seconds. Moisturization and transepidermal water loss (TEWL) measurements were recorded at five specific time increments after application.
- The elastic enhancing aspects of GLMC was determined by randomly assigning four test sites on the volar forearms of 20 male and female participants (23-50 years old) and recording measurements once a week for four weeks with twice daily application. Elasticity is expressed as Younge Elasticity Modulus (MPa).
- The ability of GLMC to reduce neck wrinkles was assessed by evaluating neck wrinkle length of 10 male and female participants (23-70 years old). Measurements were obtained once a week for four weeks with twice daily application to randomly assigned sides of their necks.
- The ability of GLMC to reduce undereye discoloration was assessed by evaluating skin pigmentation (melanin) and undereye color intensity of 10 male and female participants (24-45 years old). Measurements were obtained once a week for four weeks with twice daily application of conditions to randomly assigned sides of their faces.

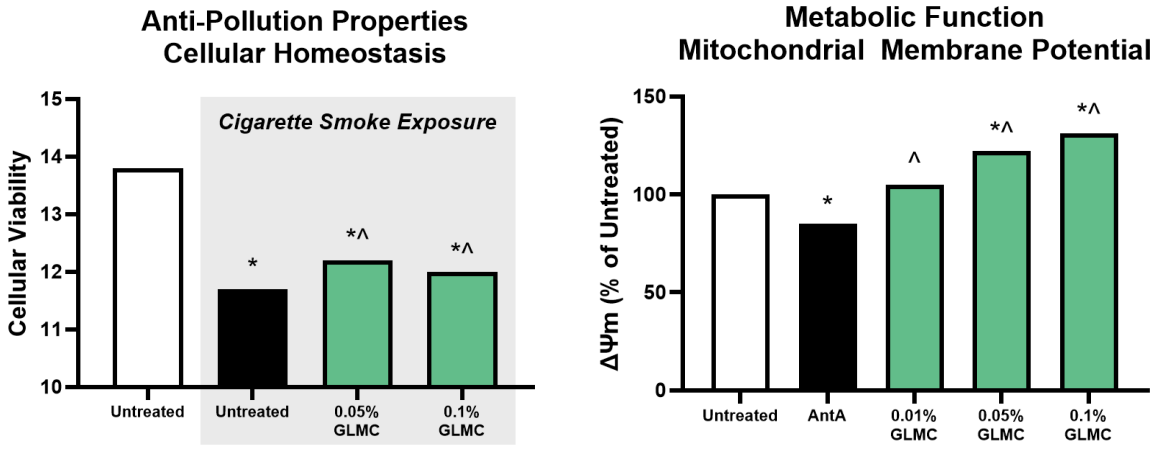
3. Results

Pre-Clinical Findings: With respect to anti-inflammatory properties, keratinocytes treated with 0.01%, 0.05%, and 0.1% GLMC inhibited COX-II by 20%, 31%, and 45%, respectively (Figure 1A). Potent antioxidant properties are illustrated with 0.01%, 0.05%, and 0.1% GLMC reducing AntA-induced ROS by 25%, 30%, and 37%, respectively (Figure 1B). GLMC demonstrated excellent anti-pollution properties by rescuing cigarette smoke-induced reductions in cellular viability by 4% and 3% at 0.05% and 0.1% GLMC concentrations, respectively (Figure 2A). GLMC reatins the capacity to augment metabolic function as illustrated by 0.01%, 0.05%, and 0.1% GLMC enhancing mitochondrial membrane potential by 5%, 22%, and 31%, respectively (Figure 2B). Strong anti-aging properties are illustrated with 0.05% and 0.1% GLMC reducing senescence activity by 8% and 13% in aged fibroblasts, respectively (Figure 3A). GLMC holds the capacity to strengthen vascular integrity as exhibited by 0.05% and 0.1% GLMC reducing endothelial permeability by 35% and 51%, respectively (Figure 3B).



(**a**) (**b**)

Figure 1. (a) Anti-inflammatory Effect of GLMC; * p ≤ 0.05 vs Untreated; ^ p ≤ 0.05 vs DEX. (b) Antixidant Effect of GLMC; * p ≤ 0.05 vs AntA.



(**a**) (**b**)

Figure 2. (a) Anti-Pollution Effect of GLMC. * p ≤ 0.05 vs Untreated; ^ p ≤ 0.05 vs Cigarette Smoke Untreated. (b) Effect of GLMC on Metabolic Function. * p ≤ 0.05 vs Untreated. ^ p ≤ 0.05 vs AntA.

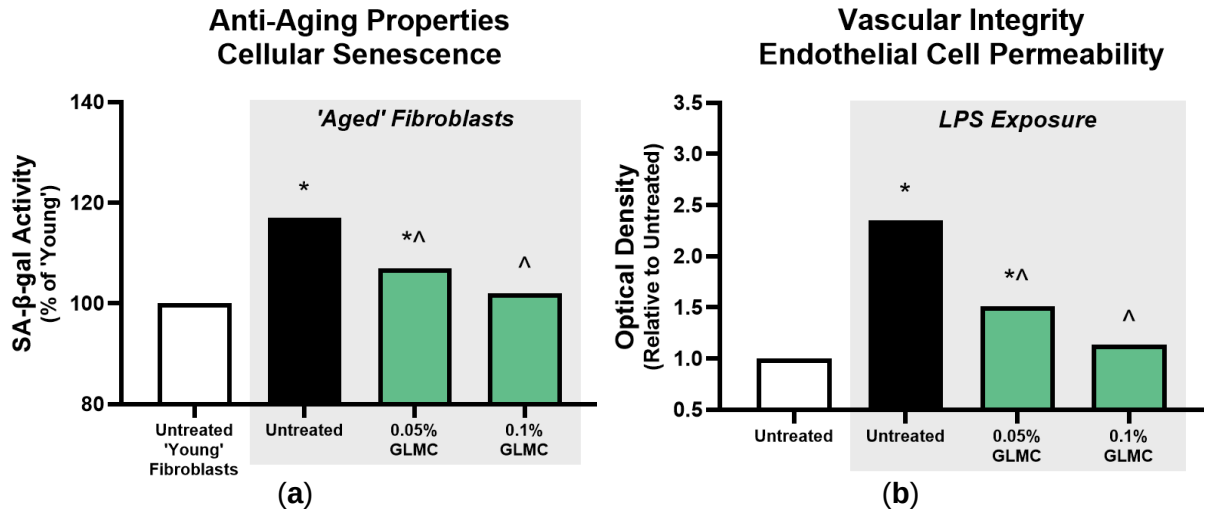


Figure 3. (a) Anti-Aging Effect of GLMC; * p ≤ 0.05 vs 'Young' Fibroblasts; ^ p ≤ 0.05 vs 'Aged' Fibroblasts. (b) Effect of GLMC on Vascular Integrity; * p ≤ 0.05 vs Untreated; ^ p ≤ 0.05 vs LPS-Exposed Untreated.

Clinical Findings: With respect to topical application of GLMC impacting acute and short-term mood states, we demonstrate GLMC augments Beta Brainwave Activity by 2% during application, whereas the Base Lotion reduced Beta Brainwave Activity by 1%, compared to baseline (Figure 4A). Moreover, GLMC enhanced pleasant mood by 6% 24 hours after a single application and 7% a week after twice daily application, compared to baseline (Figure 4B). A single application of GLMC enhanced skin moisturization by 57% and 51% after 8 and 24 hours compared to baseline, respectively, both of which were greater than Base Lotion (Figure 5A). Similarly, GLMC enhanced skin barrier function by reducing TEWL by 25% and 23% after 8 and 24 hours compared to baseline, respectively, both of which were greater than Base Lotion (Figure 5B). Likewise, twice daily application of GLMC enhanced skin elasticity by 4%, 6%, 7%, and 7% after 1, 2, 3, and 4 weeks, respectively, all of which were greater than Base Lotion (Figure 6A). Regarding neck wrinkles, twice daily application of GLMC reduced neck wrinkle length by 14% after 4 weeks, whereas no changes were observed with Base Lotion (Figure 6B). Moreover, GLMC improved undereye pigmentation as demonstrated by 2%, 2%, 3%, and 3% reductions in undereye melanin levels after 1, 2, 3, and 4 weeks of twice daily application, respectively, all of which were greater than Base Lotion (Figure 7A). Lastly, GLMC improved the appearance of undereye discoloration illustrated by 2%, 3%, 4%, and 5% reductions in undereye dark circle color intensity after 1, 2, 3, and 4 weeks of twice daily application, respectively, all of which were greater than Base Lotion (Figure 7B).

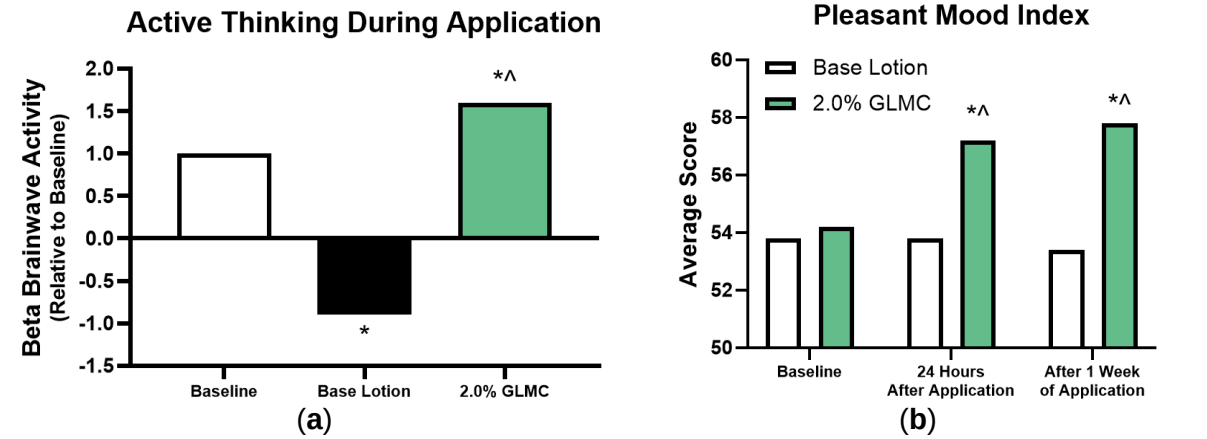


Figure 4. (a) Effect of GLMC on Active Thinking; * p ≤ 0.05 vs Baseline; ^ p ≤ 0.05 vs Base Lotion. (b) Effect of GLMC on Pleasant Mood; * p ≤ 0.05 vs Baseline within condition; ^ p ≤ 0.05 vs Base Lotion.

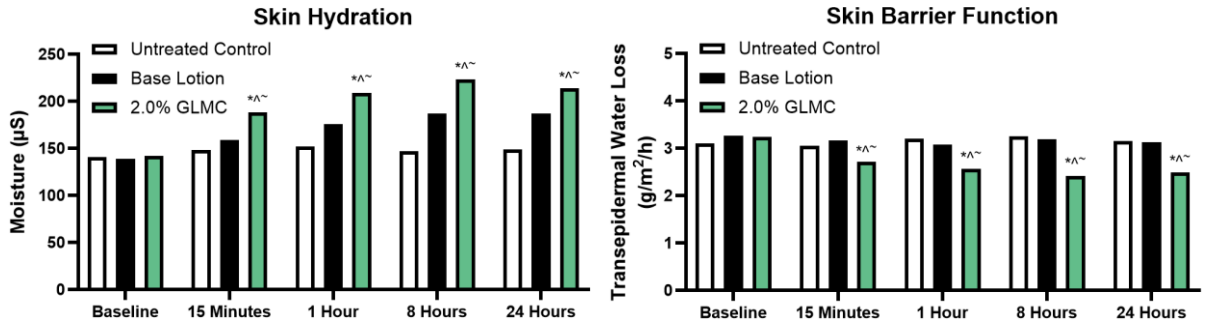


Figure 5. (a) Effect of GLMC on Skin Moisturization; * p ≤ 0.05 vs Baseline; ^ p ≤ 0.05 vs Untreated; ~ p ≤ 0.05 vs Base Lotion. (b) Effect of GLMC on Skin Barrier Function; * p ≤ 0.05 vs Baseline; ^ p ≤ 0.05 vs Untreated; ~ p ≤ 0.05 vs Base Lotion.

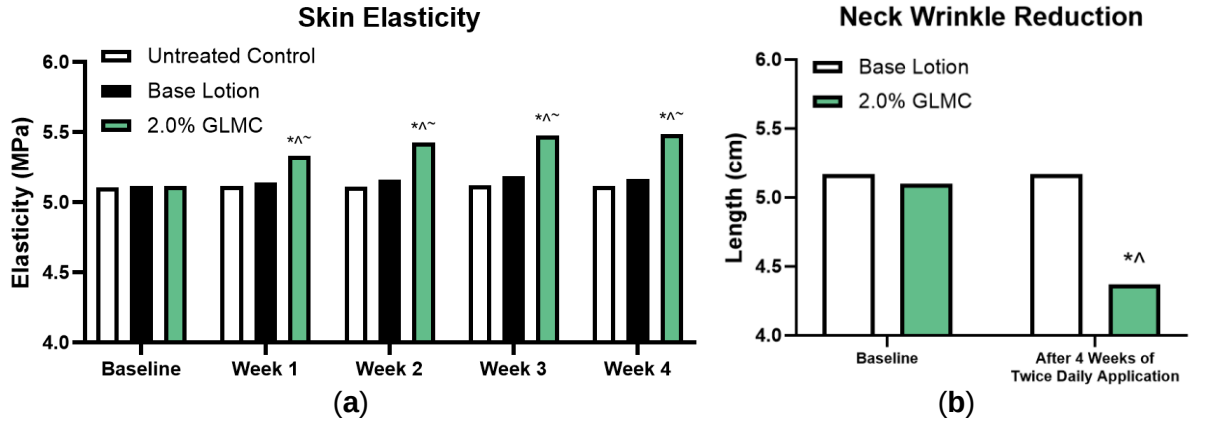


Figure 6. (a) Effect of GLMC on Skin Elasticity; * p ≤ 0.05 vs Baseline; ^ p ≤ 0.05 vs Untreated; ~ p ≤ 0.05 vs Base Lotion. (b) Effect of GLMC on Neck Wrinkle Length; * p ≤ 0.05 vs Baseline; ^ p ≤ 0.05 vs Base Lotion.

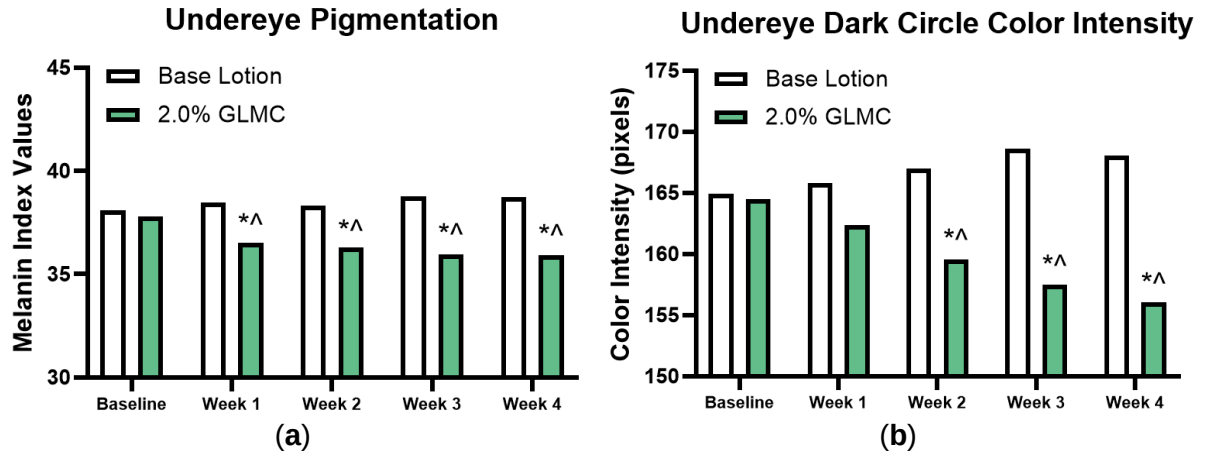


Figure 7. (a) Effect of GLMC on Undereye Pigmentation; * p ≤ 0.05 vs Baseline; ^ p ≤ 0.05 vs Base Lotion. (b) Effect of GLMC on Undereye Dark Circle Color Intensity; * p ≤ 0.05 vs Baseline; ^ p ≤ 0.05 vs Base Lotion.

4. Discussion

This study provides compelling evidence that the GLMC complex exerts targeted effects along the brain-skin axis by addressing key molecular mechanisms underlying stress-induced skin aging and impaired psychological well-being. *In vitro* analyses confirmed that GLMC

significantly inhibited cyclooxygenase-2 (COX-II) expression – by up to 45% – demonstrating robust anti-inflammatory activity. This is particularly relevant given the established role of COX-II inhibitors not only in dermatological applications but also in modulating neuroinflammatory pathways implicated in mood and psychiatric disorders [5].

Equally critical is GLMC's potent antioxidant activity, reducing Antimycin A-induced reactive oxygen species (ROS) by 37%. Oxidative stress is a known driver of both skin aging and cognitive decline, contributing to mitochondrial dysfunction and DNA damage [6]. The observed enhancement of mitochondrial membrane potential (ΔΨm) further suggests improved cellular bioenergetics, a key aspect of preserving skin vitality with age.

In addition to oxidative and metabolic stress, modern skin health is increasingly challenged by environmental aggressors such as airborne pollutants. These pollutants disrupt cellular homeostasis, promote inflammation, and accelerate visible aging signs. Our findings indicate that GLMC helps mitigate these effects, protecting dermal fibroblasts against pollutant-induced declines in viability. Taken together, these results position GLMC as a protective agent not only against intrinsic aging but also against environmental damage – a hallmark of modern exposome-based skincare.

Moreover, GLMC reduced markers of senescence in aged fibroblasts and significantly improved endothelial barrier function – reducing permeability by 51% – further supporting its capacity to enhance dermal structure and reduce vascular leakage, a factor implicated in under-eye dark circles and loss of skin tone [7].

Clinical outcomes confirmed these mechanistic findings with functional and visible improvements in skin texture, tone, and structural integrity as well as extended beyond the skin to psycho-sensory domains. Participants exhibited increased Beta Brainwave Activity, indicative of alterness and engagement, by 2% during application and reported mood improvements of 7% after one week of twice daily application. These effects reinforce the nootropic nature of the Gyokuro component (L-theanine and caffeine), as well as the adaptogenic profile of Lion's Mane and Cordyceps – ingredients known to support emotional balance and cognitive performance not only acutely during application, but also over time with repeated applications.

Notably, GLMC enhanced skin hydration and barrier function, as measured by increased moisturization and reduced transepidermal water loss (TEWL). These effects were statistically significant compared to both untreated controls and base lotion. Improved hydration supports the restoration of the stratum corneum, while reduced TEWL reflects a strengthened barrier – critical for resilience against irritants, dehydration, and inflammation. These benefits are particularly relevant for consumers exposed to urban stressors or experiencing age-related decline in skin barrier function.

A consistent improvement in skin firmness was observed, with elasticity increasing up to 7% over four weeks. Notably, neck wrinkle length decreased by 14%, while no change occurred in the control group. These effects likely stem from GLMC's *in vitro* impact on cellular senescence and endothelial integrity, supporting structural reinforcement in areas prone to visible aging.

Under-eye assessments revealed gradual but significant reductions in melanin levels and dark circle intensity—up to 3% and 5% respectively—outperforming the base lotion. These clinical

outcomes mirror GLMC's vascular-protective and anti-inflammatory mechanisms, suggesting improved microcirculation and reduced pigment deposition in the delicate periorbital region.

The synergistic efficacy of GLMC – across anti-inflammatory, antioxidant, metabolic, structural, and psychological dimensions – demonstrates its unique positioning as a neurocosmetic innovation. It meets growing consumer demands for multifunctional skincare that not only targets visible signs of aging but also promotes emotional well-being and resilience.

GLMC offers an integrative approach to well-aging, addressing the skin as both a barrier and a sensory organ. By modulating key aspects of the brain-skin axis, it delivers meaningful improvements in appearance, function, and user experience – making it a promising active for the next generation of holistic skincare.

5. Conclusion

This study provides compelling scientific validation for GLMC as a dual-function, neurocosmetic active that addresses the rising demand for holistic, well-aging skincare solutions. Through rigorous *in vitro* and *in vivo* evaluations, GLMC demonstrated multi-dimensional efficacy in modulating the brain-skin axis, offering both biological and perceptual benefits.

On the molecular level, GLMC significantly suppressed pro-inflammatory, scavenged excess ROS, and revitalized mitochondrial function.These mechanisms are crucial for maintaining cellular vitality under environmental and psychosocial stressors, aligning with evidence that oxidative stress and inflammation are primary drivers of skin and cognitive aging [6, 7]. The reduction in senescence markers and improved endothelial barrier function further indicate enhanced dermal resilience and vascular health – attributes critical for improving visible signs such as undereye dark circles and fine lines.

Clinical studies reinforced these mechanistic insights with concrete cosmetic and cognitive outcomes. Over a four-week period, users experienced statistically significant improvements in skin texture, firmness, hydration, and pigmentation, along with improved active thinking and emotional state. The reduction in wrinkle length and enhancement in mood ratings underscore the value of GLMC not only as a skin treatment but also as a contributor to emotional wellness.

What distinguishes GLMC is its integration of bioactive nootropics and adaptogens to simultaneously enhance cutaneous function and psycho-emotional balance. This positions the complex as a pioneering solution in the evolving category of neurocosmetics – products that not only beautify but also improve quality of life through scientifically grounded mechanisms.

In conclusion, GLMC is a novel, efficacious, and safe cosmetic ingredient that supports a comprehensive approach to skin aging and stress mitigation. It stands as a strong candidate for next-generation skincare formulations aimed at consumers seeking synergistic benefits for both outer appearance and inner well-being.

6. References

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