A novel combination of hyperpigmentation control agents to personalize treatments for all skin tones and their related disorders.

Frederic Flament[1], Marcelli Alves[2], Divya Agrawal[3], Gaurav Kumar[3], Reda Agnaou[3], Yashika Nikam[3], Rashmi Thakkar[3], Xavier Fastinger[3], Kwezi Molamodi[3], Valerie Jehan[1], Odette Jammayrac[1], Laurence Vesperini-Bouadjenek[1], Segolene Debeaumais[1], Eleonore Velly[1], Laurent Cordier[1], David Amar[1], Nathalia Ferro Oliveira[1], Janney Qiu[4], Yang Wang[4], Tracy Wang[4], Rose Zhang[4], Amie Sun[4], Gordon Huang[4], Linda Ding[4], Benoit Muller[1], Caroline Delaunay[1], Elisabeth Bouhadanna[5], Namita Misra[6], Emilie Warrick[6], Peggy Sextius[6]

[1] L'Oréal Research and Innovation, Chevilly-Larue, France.
[2] L'Oréal Research and Innovation, Rio de Janeiro, Brazil.
[3] L'Oréal Research and Innovation, Mumbai, India.
[4] L'Oréal Research and Innovation, Shanghai, China.
[5] L'Oréal, Clichy, France
[6] L'Oréal Research and Innovation, Aulnay-Sous-Bois, France.

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Abstract

Introduction: Hyperpigmentation disorders are very frequent, affecting the quality of life and may become a psychological burden for afflicted patients. Cosmetic regimens combined several mechanisms: antioxidative, tyrosinase inhibition, exfoliation, anti-inflammatory, photoprotection, etc. Despite these solutions, consumers, especially those with melanin-rich skins, are still looking for personalization in treatments answering more accurately their specific needs.

A new active ingredient, 2-Mercaptonicotinoyl Glycine (2-MNG) that intercepts melanin precursors, has recently been revealed in vitro, of high performances in controlling hyperpigmentation as well as in vivo in different phototypes and skin disorders.

Objectives: To identify whether this new mechanism of action, targeting melanin precursor could bring a major added value in the management of all skin tones and their related disorders when combined with other ingredients presenting other biological pathways.

A global evaluation platform aims to demonstrate efficacy of a new complementary combination of active ingredients

E-mail address: frederic.flament@loreal.com

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with different mechanisms of action, i.e. including 2-MNG, Niacinamide (inhibition of melanosome transfer, anti-inflammatory), Hydroxyethylpiperazine ethane sulfonic acid (exfoliation), 1,3,7-trimethyl-3,7-dihydro-1H-Purine-2,6-dione (anti-inflammatory) and Lipohydroxy acid (exfoliation) in an inclusive and diverse population in term of ages and phototypes.

Material & Methods:

i) 3D human reconstructed skin model was treated by the association for 8 days. The tissue structure and viable melanocytes were observed by HE, DOPA and TRP1 staining. Melanin quantification was assessed by multiphoton microscopy and Fontana Masson staining. Mean values were compared with DMSO as vehicle through Mann-Whitney U test ($p<0.05$).

ii) A standardized 6 week clinical protocol, randomized, double-blind and interindividual trial, was designed to assess the skin lightening performance of the combination during and after UV Daylight(UVDL)-exposure versus its vehicle without ingredients, i.e. capacity to prevent and correct from skin tone darkening induced by UVDL-exposure.

iii) A real-life controlled and open clinical study has been designed on 88 Brazilian women from all phototypes (I–VI) and presenting different disorders (solar lentigo, post-inflammatory hyperpigmentation, PIH, etc.) and aged 18–60 years to assess the potentialities of the new combination on a very diverse population. The subjects applied the treatment twice daily, before the SPF product application, for eight weeks. The evaluations were performed before treatment and 56 days post applications.

Results:

i) A significant decrease of melanin production by 27% in density and volume versus the vehicle, without any impact to epidermis quality and viability of melanocytes was observed.

ii) A significant efficacy versus induced darkening has been measured on both phases (anti-pigmentating and depigmenting) with a ΔE after 6 weeks of 3.02 for the formula vs. 4.61 for the vehicle.

iii) The results showed a prevalence of PIH higher in phototypes from III to VI, whereas the prevalence of solar lentigo was more frequent in lighter phototypes. Nonetheless, all skin tones clusters presented a significant statistical improvement for the visibility of the evaluated spot in versus baseline.

Conclusion: The new combination of hyperpigmentation controlling agents has demonstrated its functionality and visible clinical performance in all phototypes and disorders from a real-life study in a diversely pigmented population. This innovation opens new fields of personalization and efficacy for women and men worldwide, especially consumers with melanin-rich skins.

1. Introduction

Latin America and Brazil boast a diverse populace with rich tapestry of all skin phototypes. Pigmentary disorders in Brazil represent a significant portion of dermatological consultations, comprising 8.5% of all visits, making them the third most common reason for seeking dermatological care in the country (Cestari et al., 2014). Melasma alone is highly prevalent affecting almost 10% of women in Latin America among other pigmentation disorders (Taylor, 2003; Hexsel et al., 2009).

Hyperpigmentation is a common dermatological condition of the skin, results in skin darkening and uneven skin tone

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due to aberrant production and deposition of melanin in the epidermis and /or dermis. This occurs as a result of various internal and external factors including hormonal changes, injury, inflammation, acne, eczema, UV exposure, certain medication, etc. Hyperpigmentation might be acquired, congenital or inherited (Jimbow K, and Minamitsuji Y, 2001). Various commonly observed hyperpigmentation disorders include melasma, post-inflammatory hyperpigmentation, ephelides, lentigines, and many more (Nautiyal, Avni and Sarika Wairkar, 2021). Cutaneous insult and inflammation contributing to damage of basal layer of epidermis, results in increased production and redistribution of melanin and transfer to keratinocytes (Bohm Marcus, 2021) (Vashi and Kundu, 2013).

Hyperpigmentation can cause a significant negative impact on the self-image and the quality of life of people (Wang, Rebecca F., et al, 2023). A large international survey with 48,000 respondents from 34 countries showed that 50% of the population reports having at least one pigmentation disorder, which significantly impacted the quality of life of respondents and lead to stigmatization (Passeron et al., 2024).

After years of historical practices of skin lightening common among ethnic people, some methods still exist. Skin lightening for cosmetic reasons is associated with profound negative impacts on well-being, and adverse effects on the skin, resulting in immense challenges for dermatologists. Despite current regulations, lightening agents continue to dominate the cosmetic industry (Pollock, Samara et al, 2021). These ingredients not only target global facial skin lightening, but are also used for pigmentation resulting from PIH, melasma, ephelides, Lentigines, etc. (Pollock, Samara et al, 2021). Ingredients like hydroquinone target tyrosinase, a key enzyme in melanin production. However, these often lack efficacy or pose safety concerns which makes it unusable in cosmetics (Zolghadri, Samaneh, et al, 2023). Finally, depending on the skin's basic color, the pigmentary response of the skin to different stimuli can vary greatly. This translates clinically into very different localized hyperpigmentation in terms of location, nature, pigmentation intensity, shape and persistence, and it has been shown that the more melanin concentrated the skin, the more likely it is to develop this type of pigmentary disorders. The challenge for cosmetics research is therefore both important and complex: important because this is a subject that directly addresses people's well-being, and complicated because we need to identify the best combination of ingredients to address pigmentation disorders in all their physiological complexity, integrating the diversity of people and skin tones. Thus, there is a need for effective, safe, and environmentally friendly alternatives that can answer all the complexity of skin tone management.

For this purpose, based on all the pigmentation knowledge and the mechanisms involved in the appearance of pigmentary disorders, we propose to evaluate a unique innovative optimal combination for its benefit on the reduction of localized hyperpigmentaions in various skin tones.

A high-throughput screening method was used to identify potent melanin inhibitors. 2-MNG from a family of thiopyridones was selected based on its efficacy, safety, predicted skin penetration and low environmental impact. It exhibits superior efficacy to 4-n-butylresorcinol, a known tyrosinase inhibitor. Unlike traditional tyrosinase inhibitors, it also demonstrates a distinct mechanism for suppressing melanogenesis. It directly interacts with melanin precursors, effectively preventing their incorporation into growing melanin polymers (Sextius et al. 2024). This interaction hinges on the molecule’s thiol group, which exhibits a high affinity for the o-quinone moiety present in various melanin precursors, including: Dopaquinone (DOPAQ), DHICAquinone and DHIqunione. 2-MNG effectively competes with cysteine and glutathione for DOPAQ, forming stable 6-MNG-DOPA adducts, thus inhibiting the production of eumelanin and pheomelanin.

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By trapping these reactive melanin precursors, 2-MNG reduces the potential for oxidative stress and cellular damage within melanocytes. Formation of stable, excretable adducts with melanin precursors suggests that its action is likely confined to melanocytes, minimizing off-target effects. It also preserves melanocyte integrity and doesn't increase oxidative stress within cells. Safety studies found no evidence of skin irritation or other adverse effects associated with 2-MNG use.

While not all melanin synthesis is inhibited, 2-MNG performs its role without affecting the morphology, dendricity and viability of melanocytes. Hence, melanin in skin continues its photoprotective role along with active control of dark spots thus managing an even skin tone (Sextius, Peggy, et al, 2024).

A study was conducted on 33 individuals with Phototype III, IV and V where, effectiveness of 2-MNG in preventing both immediate pigment darkening (caused by UVA radiation) and delayed tanning (caused by UVB radiation) was investigated. It was found to effectively reduce both immediate skin darkening and delayed tanning. Both 0.5% and 1% concentrations were successful in reducing immediate skin darkening and preventing new melanin formation compared to a control substance. 1% concentration showed even better results than the 0.5% concentration (de Dormael, R., et al, 2024).

Under this standardized, randomized, double-blinded clinical protocol, thanks to a Bayesian Network Analysis method, results were compared across studies (Muller, Benoit, et al, 2024), to rank 14 different skin-pigmentation modulating molecules. Results showed that 2-MNG was the most effective at both preventing and reducing pigmentation, outperforming common ingredients like hydroquinone, kojic acid, and arbutin.

Pigmentation management solutions can include several mechanisms like antioxidation, melanin inhibition, exfoliation, anti-inflammatory, photoprotection, etc. Hence a unique formulation base that covered most mechanisms was created for holistic action. This research investigates efficacy of the novel multi-active formula containing 2-MNG, Glycolic Acid and Niacinamide.

This study was done with the objectives of validating the efficacy of this formulation in preventing hyperpigmentation through a multi-faceted approach. The aim was to demonstrate the formula's ability to deliver clinically measurable improvements in skin brightening and dark spot reduction. It was also to quantify its effectiveness in achieving visible results, a critical factor for consumer acceptance and satisfaction. The formulation's suitability as a comprehensive solution was evaluated for skincare and skin tone management in diverse populations with varying degrees of sun exposure, specifically focusing on the Brazilian context.

2. Materials and Methods

A platform to select an optimal combination of ingredients in skin tone and hyperpigmentation management from in vitro to in vivo and describe its potentialities for all skin phototypes. The sequence consists in three successive steps:

Step 1: In vitro testing was done on 3D human reconstructed skin models. These were treated by the association for 8 days. The tissue structure and viable melanocytes were observed by H&E, DOPA and TRP1 staining. Melanin quantification was assessed by multiphoton microscopy and Fontana Masson staining. Mean values were compared with DMSO as vehicle through Mann-Whitney U test ($p<0.05$). The 3D cell culture was derived via the standard Epidermal Reconstructed Pigmented (ERP) skin model. After the maturation of 3D skin model after 6th day of seeding,

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it was subjected for QC assessment. The QC approved models were selected and grouped for application of different products – a) Only 2-MNG (50um, 100um, 150 um), b) 2-MNG, Glycolic Acid, Niacinamide serum with and without 2MNG – 50 and 100 um, c) 2MNG + Niacinamide – (150+150) and (100+2604), d) Niacinamide (100 um, 150 um, 2604 um), and e) controls (Lucinol, DMSO). To further elucidate the depigmentation effects of the 10% Glycolic Bright combo, we employed Multiphoton Microscopy (MMP) to understand the distribution of Melanin in the tissues. For this, a series of 100 images for visualization and 50-100 rapid 2D XZ images for quantification per sample were acquired, encompassing both the treated and control groups.

Step 2: A standardized 6-week clinical protocol, randomized, double-blind and interindividual trial, was designed to assess the skin lightening performance of the combination during and after UV Daylight (UVDL)-exposure i.e. capacity to prevent and correct skin tone darkening induced by UVDL exposure. 30 Chinese subjects aged 21-60 years with Phototype III, ITA 28 ° < ITA° < 41 ° ±2 ° on back were chosen for this study. A standard dose of 4 mg/cm2 was applied on the minizones on the back. In this study the selected association with 2-MNG, glycolic acid, niacinamide was analyzed with 7% Vitamin C as a standard reference for validation for the study. A baseline measurement on D0 was done in the pre-treatment phase (D1-D07) followed by product application for 5 days. Anti-pigmentation phase: D08-D12: UV Exposure of 0.5 MED was given for 4 consequent days with consistent product application thrice a day. From D12 – D40, subjects continued product application twice per day for the first week and once per day for following weeks through this extended period The Global Brightening phase is considered as from D8-D40 to assess globally the brightening efficacy. Pigmentation measurements were taken by Chromameter® and analyzed using ΔE of UV-exposed area and non-exposed area.

Study 3: A clinical study across several phototypes performed in Brazil had the objective of assessing the anti-spot efficacy of 2-MNG, Glycolic acid & Niacinamide serum used in real life conditions under dermatological control through clinical and instrumental evaluation. The study included 88 female participants, aged 18- 60 years, Phototypes I–VI, with different hyperpigmentation (Melanosis, PIH/PIE, stubborn dark spots). Study protocol followed a 14 days washout phase before beginning the treatment, from D0-D56 days serum was applied twice-daily on the face and 3weeks relapse at the end without the treatment again. A SPF30 product was used across the study duration in accordance with consumer habits followed in Brazil. Clinical and instrumental evaluations were performed on D0, D7+/-2, D14+/-2, D28 +/-3 and D56+/-3. The evaluations were performed by trained dermatologists using a 10-point scale.

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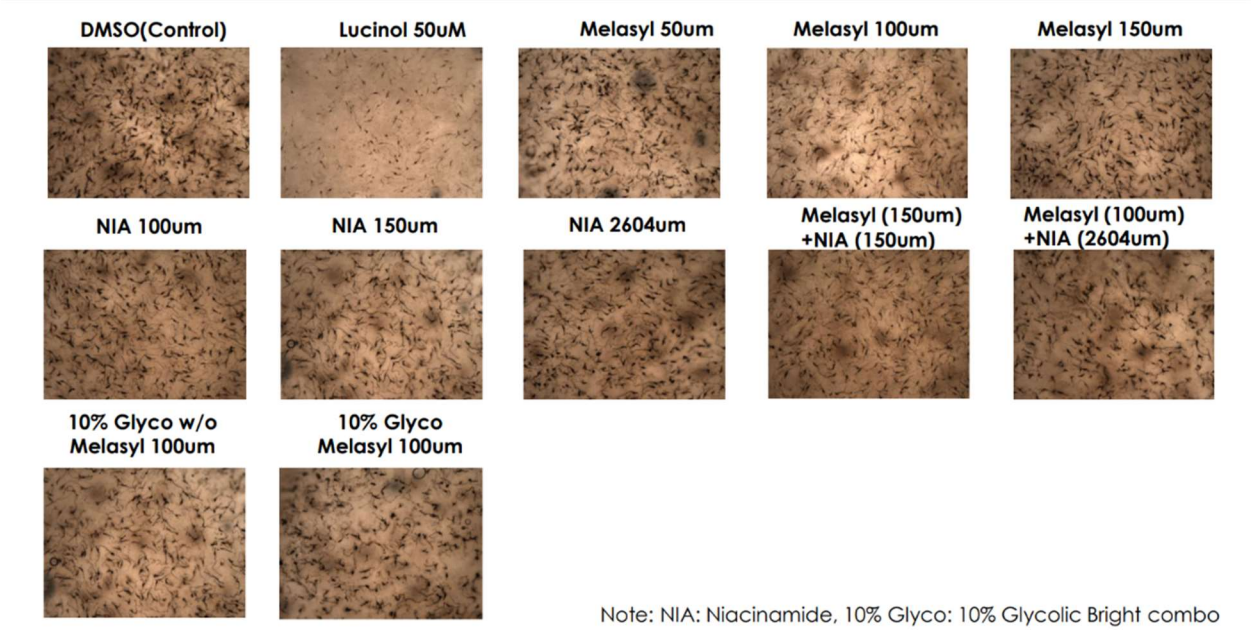

Fig.-1 Normal morphology of ERP Cells and Melanocytes shown across treatments of 2-MNG, the new formulation of 2-MNG+Niacinamide and Glycolic acid, only Niacinamide, and Lucinol and DMSO controls.

3. Results & Discussion

3.1. Study 1 – In vitro 3D Epidermal Reconstructed Pigmented (ERP) skin model

H&E staining, performed to assess tissue morphology and epidermal differentiation, revealed no abnormalities in either tissue structure or melanocyte morphology across all treatment groups. Similarly, DOPA staining, a sensitive and specific marker for melanocytes, demonstrated normal melanocyte morphology, with no marked alterations in size, shape, or number (Figure 1). Fluorescent TRP1 staining confirmed these observations, indicating no significant changes in melanocyte numbers across the epidermal sheets (Figure 2). These findings suggested that the tested formulation did not impact the baseline melanocyte population.

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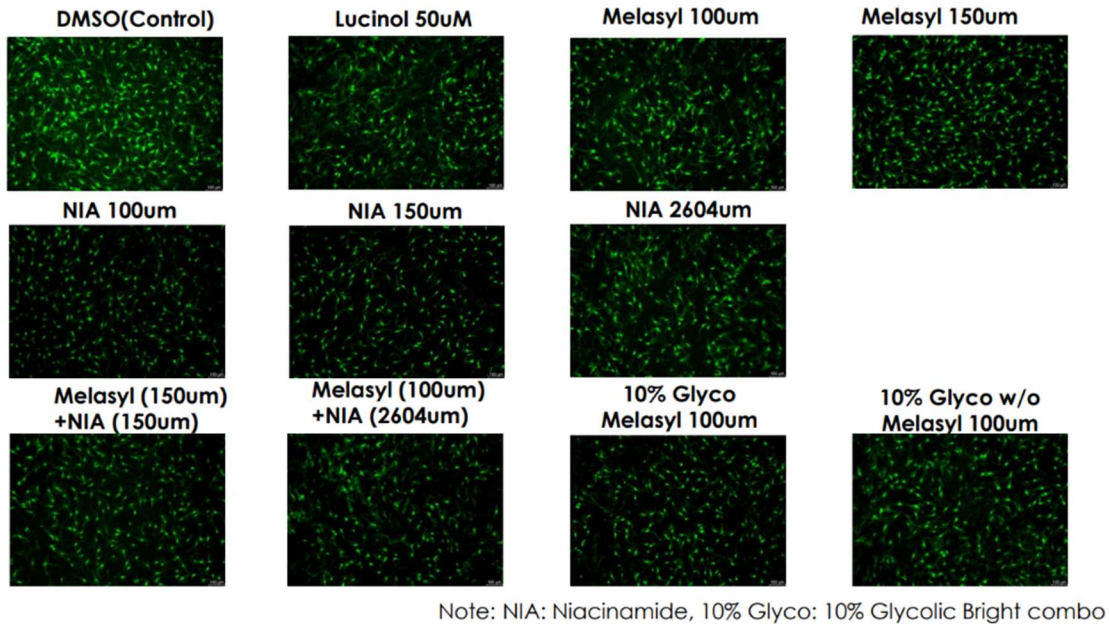

Fig.-2 Fluorescent TRP1 staining to validate the HEM morphology.

Image analysis of Fontana-Masson stained sections revealed a pronounced depigmenting effect in treated 3D skin models compared to the DMSO control group. Notably, 2-MNG concentrations of 100 µM and 150 µM elicited rapid depigmentation, surpassing the effects of niacinamide (Figure 3). The combination of 2-MNG and niacinamide produced the most substantial melanin reduction, as evidenced by very light staining. Quantitative analysis demonstrated a significant 27% decrease in melanin content (measured by both density and volume) with no detrimental effects on melanocyte viability or epidermal integrity. 2-MNG at 100 µM is more effective on depigmentation than NIA 100 µM by 15.3%, based on the 3 groups results (Figure 4).

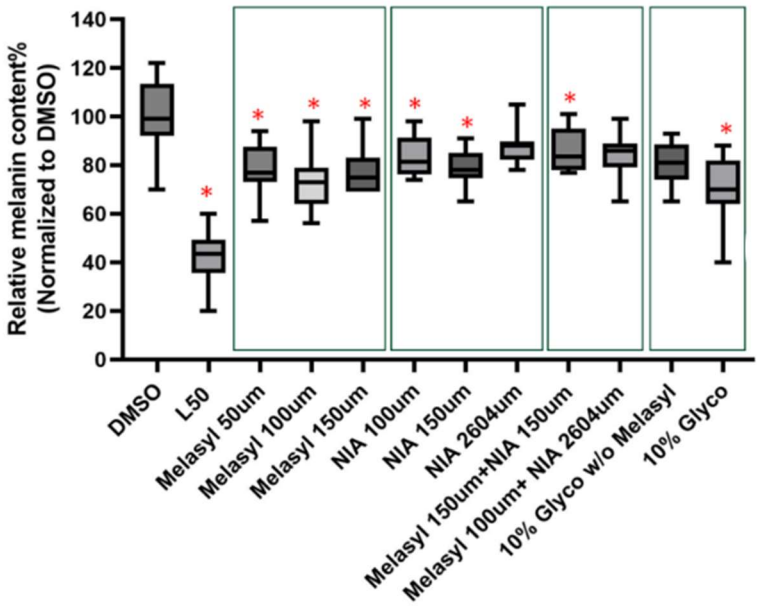

Fig.-3 Relative Melanin Content (%) across 3 groups.

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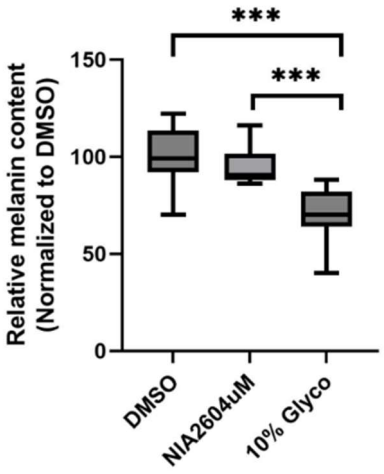

Fig.-4 Relative Melanin Content comparison between Niacinamide and Glycolic Acid+2-MNG+Niacinamide association.

The Multiphoton Microscopy analysis of the cells showed a significant reduction in both melanin volume and density in the ERP models treated with the 10% Glycolic Bright combo compared to the DMSO control group. This decrease was quantified as a 27% reduction in melanin volume, density (Figure 5), and distribution (Figure 6), highlighting the efficacy of the 10% Glycolic Bright combo in disrupting melanin accumulation within the epidermal layers.

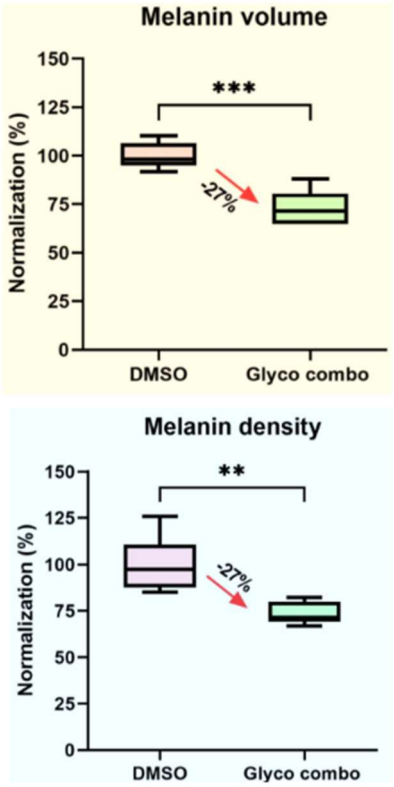

Fig.-5 Decrease in Melanin volume and Density by 27% in the new formulation 10% association.

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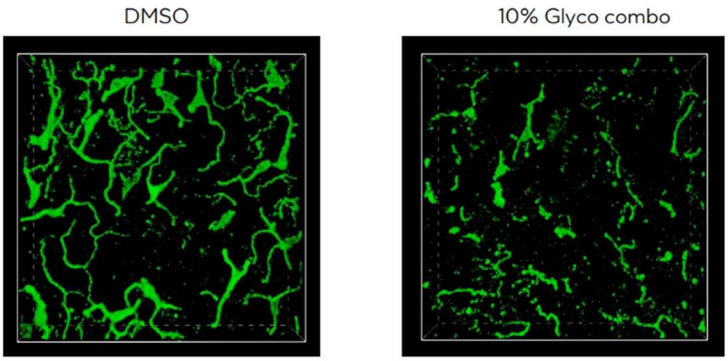

Fig.-6 Decrease in Melanin distribution in the DMSO control and 10% association treated group.

3.2. Study 2 – UV-Induced Pigmentation Chinese Clinical Study

The selected association with 2-MNG, glycolic acid, niacinamide exhibited a significant reduction in UV-induced pigmentation, as evidenced by a downward trend in ΔE values over the 40-day study period. Notably, both formulations demonstrated efficacy from D12 onwards, following 4 consecutive days of UV exposure and consistent product application ($p<0.05$). This finding highlights the enhanced efficacy of the new serum formulation incorporating 2-MNG in both preventing and reducing UV-induced pigmentation.

3.3. Study 3 – Brazilian Clinical Study

Clinical assessments conducted by trained dermatologists revealed a significant reduction in dark spot severity over the 8-week study period for all spot types evaluated. Statistically and clinically significant improvements were observed in spot color, contrast, intensity, and visibility/size. Additionally, positive changes were noted in skin radiance, clarity, and overall hyperpigmentation. Notably, PIH/PIE on the whole face exhibited significant improvement across all time points.

Figure 7 shows a significant improvement in skin tone evenness across all phototypes by week 8 (D56) ($p<0.05$). There was a significant increase in skin radiance (18.7%) across all phototypes by week 8 ($p<0.05$). A notable enhancement in skin clarity (14.8%) across all phototypes by week 8 ($p<0.05$). A substantial reduction in facial global hyperpigmentation (19.4%) across all phototypes by week 8 ($p<0.05$). Clinically visible improvements in PIH/PIE on the whole face as early as week 1 (D7) for phototypes I-II, week 2 (D14) for phototypes III-IV, and week 4 (D28) for phototypes V-VI ($p<0.05$).

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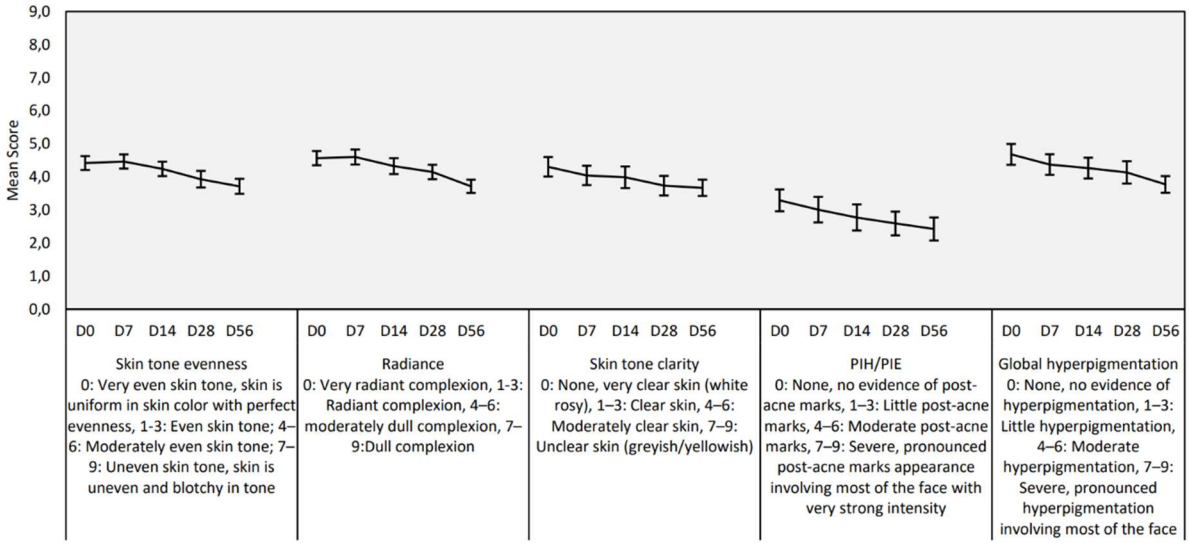

Fig.-7 Clinical evaluation by skin parameters (global face), Error bars: 95% CI

Figure 8 shows the significant improvement in color contrast (45.9%) and intensity of spot color (41.4%) of PIH/PIE spots by week 8 (D56) ($p<0.05$). A significant improvement in color contrast (38.2%) and intensity of spot color (26.4%) of Melanosis lentigo spots by week 8 (D56) ($p<0.05$). Improvement in color contrast (29.5%) and intensity of spot color (25.8%) of stubborn spots by week 8 (D56) ($p<0.05$). Improvement in spot size for PIH/PIE (40.35%), Melanosis lentigo (19.57%) and stubborn spots (20.27%) by week 8 (D56) ($p<0.05$) through image analysis.

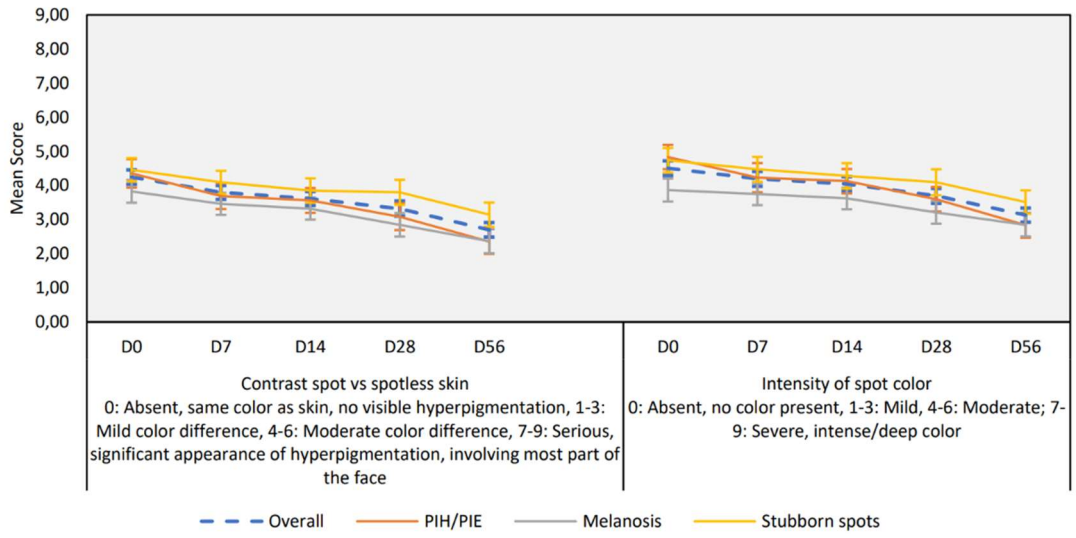

Fig.-8 Clinical evaluation by skin parameters (global face), Error bars: 95% CI

Global Face Image analysis revealed that the Luminance (L*) Increased by 4.15% at D56 ($p<0.001$) compared to baseline. The Redness (a*) component decreased by 1.77% at D28 ($p<0.001$) compared to baseline whereas the Yellow Component (b*) decreased by 6.75% at D56 ($p<0.001$) compared to baseline. The respective changes in the parameters correlate to increased luminance, brightness of the skin, even skin tone and improved radiance of the skin.

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Skin Clarity as quantified by ITA° increased by 12.71% at D56 ($p<0.001$) compared to baseline. The overall spot whitening component as measured by Individual Whitening Angle increased by 4.12% at D56 ($p<0.001$) compared to baseline, correlating to the increase in spot brightening.

The Spot analysis on color parameters by Chromameter to quantify Delta measurements of spots versus the adjacent skin revealed the action of this formulation in effectively targeting improving skin and spot brightness, whitening. Luminance (Delta L*) showed a significant difference at D56 (decreased by 20.78%, $p<0.001$), with the spot area showing a higher increase in luminance than the adjacent area. This statistically significant value for Delta L* signifies the spot being brighter than adjacent skin due to reduction in pigmentation. Redness (Delta a*) showed a significant difference at D56 (decreased by 10.41%, $p=0.005$), with the spot area showing a higher decrease in redness compared to the adjacent area. The Yellow Component (Delta b*) showed a significant difference at D28 (decreased by 17.90%, $p<0.001$), with the spot area showing a higher reduction in yellowness compared to the adjacent skin. Skin Clarity (Delta ITA°) showed a significant difference at D56 (decreased by 13.26%, $p<0.001$), with the spot area showing a higher increase in skin clarity compared to the adjacent skin. The Delta E change gave a significant decrease at D56 (decreased by 12.31%, $p<0.001$), indicating the skin tone is becoming more homogeneous.

4. Conclusion

This comprehensive investigation, encompassing both in vitro and in vivo assessments across diverse populations, substantiates the efficacy of the novel serum formulation comprising 2-MNG, glycolic acid, and niacinamide in addressing hyperpigmentation concerns. The formulation effectively attenuated melanin production in 3D skin models, achieving a significant 27% reduction in melanin density and volume without compromising melanocyte viability or epidermal integrity.

Clinical evaluations further underscored the serum's efficacy, demonstrating statistically significant improvements in both the prevention and reduction of hyperpigmentation. Notably, the serum achieved a color difference (ΔE) of 3.02 after 6 weeks of treatment, compared to 4.61 for the control group, highlighting its potent impact on skin tone evening. Importantly, the serum's *in vivo* efficacy transcended individual skin tone and hyperpigmentation type. Visible improvements in the appearance of affected areas were consistently observed across all study groups, regardless of whether the primary concern was post-inflammatory hyperpigmentation, more prevalent in darker skin tones, or solar lentigo, more common in lighter skin.

This serum formulation, featuring the innovative 2-MNG, represents a significant advancement in skincare, specifically addressing the needs of the diverse Brazilian population. Its compelling combination of efficacy, safety, and accessibility for individuals across a spectrum of skin tones holds immense potential for Brazil, where sun exposure and melanin-rich skin are prevalent. By effectively addressing hyperpigmentation concerns, this formulation has the potential to significantly improve the quality of life for a large segment of Brazilian society, empowering individuals to embrace their natural beauty.

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