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Evaluation of a Dermocosmetic Serum for Managing Hyperpigmentation Disorders in Phototypes IV-VI Individuals From South Africa and Argentina

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ABSTRACT

Background: Hyperpigmentation disorders are a distressing condition, especially for individuals with skin of color who are at higher risk. Often treated topically, a significant advancement in this field was Kligman's depigmenting trio, inhibiting melanogenesis, providing anti-inflammatory benefits, and promoting epidermal renewal.

Aims: Evaluate a serum (Pigmentbio C-Concentrate, NAOS, LABORATOIRE BIODERMA), inspired by Kligman's trio's mode of action.

Methods: Clinical studies were conducted on phototype IV–VI subjects in South Africa and Argentina. Subjects applied the serum nightly for 84 days. Clinical assessments were performed on days 0, 28, 56, and 84, with instrumental skin color evaluation in Argentina. The burden of hyperpigmentation was assessed at baseline and D84 using the Dermatology Life Quality Index (DLQI, South Africa) or the Melasma Quality of Life Questionnaire (MELASQoL, Argentina).

Results: In South Africa, clinical assessments showed a significant reduction in the number (−15%), intensity (−32%), and size (−13%) of hyperpigmented elements within 28 days. The Argentinian study similarly reported significantly decreased intensity (−18%), visibility (−32%), and contrast (−29%) of hyperpigmented elements on D28, alongside improved complexion homogeneity (+17%). In both studies, maximum improvements occurred on D84. These results were supported by instrumental assessments of skin luminance and pigmentation of hyperpigmented areas (L*: +5%, ITA°: +53% on D84), and color difference between hyperpigmented and non-hyperpigmented areas (ΔE: −16% on D84). Participants also reported a reduced burden of hyperpigmentation (DLQI: −92%; MELASQoL: −33%).

Conclusion: Replicating the complementary activities of Kligman's trio, the serum effectively reduces hyperpigmentation and its associated burden in individuals with darker phototypes.

1 | Introduction

Hyperpigmentation disorders are common dermatological conditions characterized by localized hyperpigmented areas resulting from an excessive melanin production [1]. Although these conditions can affect individuals of all skin types, they are notably more prevalent among individuals of Hispanic, Asian, African, etc. origin, who typically exhibit darker skin

tones and fall within Fitzpatrick skin types IV, V, and VI [1]. Hyperpigmentation is particularly conspicuous on darker skin complexions due to the pronounced contrast it creates with unaffected areas, making it one of the leading reasons individuals seek dermatological intervention [2]. While generally not life-threatening, hyperpigmentation impacts self-esteem, personality development, social interactions, and overall quality of life for those affected [3].

The three most prevalent hyperpigmentation disorders among individuals with skin of color are post-inflammatory hyperpigmentation (PIH), melasma, and solar lentigines. PIH results from inflammation-induced overproduction of melanin, manifesting as macules or patches with irregular contours that appear brown when localized in the epidermis and gray-blue when situated in the dermis [4]. Common causes are acne vulgaris and pseudofolliculitis barbae. Without treatment, it can persist for months or even years. Melasma is characterized by persistent and recurrent hyperpigmented irregular macules, typically located on sun-exposed facial areas [5]. Its etiology is complex and multifactorial, involving exogenous factors, most notably ultraviolet and visible light exposure [6]. Endogenous factors also play a significant role; beyond genetic predisposition, melasma's prevalence among women is largely influenced by estrogen and progesterone [6]. Finally, solar lentigines are pigmented, macular, and well-circumscribed lesions that accumulate with age in individuals with a history of chronic sun exposure [7]. Although most frequent in fair-skinned populations, solar lentigines are the predominant hyperpigmentation disorder in Asian populations [8]. These lesions would result from UVB-induced overexpression of the tumor necrosis factor-alpha (TNF-α), ultimately leading to sustained melanogenic activation [8]. While UV radiation is the principal etiological factor, environmental pollutants may also contribute to their formation, suggesting a more complex pathogenesis than previously understood [9].

Topical treatments are the most commonly used approach for managing hyperpigmentation disorders, though systemic medications and minimally invasive dermatological procedures, particularly chemical peels and laser therapy, are also effective [10]. While these methods are suitable for individuals with fair skin tones, those with skin of color require particular attention due to an elevated risk of post-inflammatory pigmentation disorders. Consequently, topical treatments are often the preferred option. A notable advancement in this field has been the development of the depigmenting efficacy of a combination of hydroquinone, tretinoin, and dexamethasone, commonly referred to as Kligman's depigmenting trio [11]. Although variations of this formulation exist, hydroquinone often remains a core ingredient owing to its high efficacy [12]. However, concerns over its side effects have prompted several countries to prohibit the sale of over-the-counter hydroquinone-containing preparations [13]. To expand access to depigmentation products, non-hydroquinone alternatives have been developed. Ingredients such as mequinol, retinoids, kojic acid, azelaic acid, and various natural compounds have demonstrated efficacy, albeit sometimes requiring longer treatment durations [14].

Despite advancements, there remains a demand for novel hydroquinone-free topical cosmeceuticals that are both effective in treating various hyperpigmentation disorders and well tolerated, particularly by individuals with skin of color (Fitzpatrick types IV, V, and VI). To address this need, we have recently developed a novel serum, drawing inspiration from the synergetic properties of the ingredients found in Kligman's depigmenting trio. It incorporates three key ingredients, each aimed at providing complementary effects: inhibiting melanogenesis, providing anti-inflammatory benefits, and promoting epidermal turnover. Here, we report on the results of two clinical evaluations of this new serum, conducted in South Africa and Argentina, alongside in vitro experiments that show how the three main ingredients account for the observed effects.

2 | Materials and Methods

2.1 | Investigated Product

The product evaluated in this study is a novel depigmenting serum (Pigmentbio C-Concentrate, NAOS, LABORATOIRE BIODERMA). A breakdown of its composition is provided in Table 1.

2.2 | Clinical Evaluation of Serum Efficacy

The efficacy of the serum was assessed in two clinical studies: one conducted in South Africa and the other in Argentina. Both were open-label, intra-individual studies carried out under the supervision of dermatologists. They involved healthy subjects presenting with recent (less than three years old) dark spots, lentigines, melasma, or post-inflammatory hyperpigmentation of mild to moderate intensity.

In South Africa, the study involved 39 subjects, two of whom only attended the D0 visit, leaving 37 subjects for analysis (4 males and 33 females; mean age ± SD: 41.1 ± 11.3) with Fitzpatrick skin types IV ($n = 1$), V ($n = 24$), and VI ($n = 12$). In Argentina, the study included 31 subjects (5 males and 26 females; mean age ± SD: 41.0 ± 10.5) with Fitzpatrick skin types IV ($n = 27$), V ($n = 2$), VI ($n = 1$), and one undetermined.

For three months, all subjects applied five drops of the serum each evening to their cleansed face, neck, chest, or hands, depending on the location of dark spots. Throughout the study, subjects were instructed to avoid prolonged sun exposure. In cases of unavoidable exposure, they applied the provided SPF50+ sunscreen.

2.3 | Ethics

The clinical evaluation conducted in South Africa was approved by Pharma-Ethics under the reference RC2022/PIGCC/ZA. According to the Argentinian cosmetic regulation, no IRB approval was required for the clinical evaluation. Both studies adhered to the principles of the Declaration of Helsinki and complied with Good Clinical Practices. Participants received detailed information regarding the study, and all provided written informed consent before enrolment.

TABLE 1 | Ingredients list for the depigmenting serum.

Properties	Ingredients (INCI names)
Formulation water	Aqua/water/eau
Core active ingredients	*Andrographis paniculata* leaf extract Saccharide isomerate *Glycyrrhiza glabra* (Liquorice) root extract
Additional depigmenting ingredients	Ascorbyl glucoside Niacinamide
Keratolysis	Glycolic acid Salicylic acid
Skin hydration and protection	Glycerin Tocopheryl acetate Mannitol Xylitol Rhamnose Fructooligosaccharides *Laminaria ochroleuca* extract
Cream base (texturing and protection ingredients)	Propanediol Dipropylene glycol Propylheptyl caprylate Sodium hydroxide Ammonium acryloyldimethyltaurate/Vp copolymer Sorbitan sesquioleate Pentylene glycol Xanthan gum Sodium citrate Lysine Azelaic acid Sodium metabisulfite Tocopherol Caprylic/Capric triglyceride Fragrance

2.4 | Clinical, Instrumental, and Quality of Life Assessments

In both clinical studies, evaluations were performed at four time points: days 0, 28, 56, and 84.

In the South African study, clinical assessments included the number of dark spots or post-inflammatory hyperpigmentation lesions, their intensity (graded on a 0, low intensity, to 6, high intensity, scale), and their size (in millimeters). On days 0 and 84, a Dermatological Life Quality Index (DLQI) was calculated based on replies (0, no impact, to 3, high impact) to a ten-item questionnaire. The resulting score ranged from 0 (no impact) to 30 (high impact).

In the Argentinian study, a trained investigator rated, at each visit, the intensity of dark spots or post-inflammatory hyperpigmentation lesions (graded on a 0, low intensity, to 6, high intensity, scale), their visibility (0, low visibility, to 9, high visibility, scale), and their contrast with adjacent non-pigmented skin (0, low contrast, to 9, high contrast, scale). The investigator also rated complexion homogeneity (0, low homogeneity, to 9, high homogeneity, scale). Instrumental assessments were conducted at each visit, measuring the CIE L*, a*, and b* parameters in a skin zone with hyperpigmented elements and a non-hyperpigmented adjacent area (CR-400 Chroma Meter, Konica Minolta, Japan). The analysis focused on the L* parameter, representing skin luminance, the Individual Typology Angle (ITA = [Arc tan ((L*-50)/b*) $\times 180/\pi$]), a measure of skin pigmentation, and ΔE ($\Delta E = \sqrt{\left(L_2^* - L_1^*\right)^2 + \left(a_2^* - a_1^*\right)^2 + \left(b_2^* - b_1^*\right)^2}$) quantifying the color difference between a hyperpigmented and adjacent non-hyperpigmented skin areas. Finally, the impact of skin hyperpigmentation on the quality of life was evaluated using a ten-item Melasma Quality of Life Questionnaire (MELASQoL) [15]. Responses, ranging from 1 (not bothered at all) to 7 (bothered all the time), resulted in a total score between 10 and 70.

2.5 | Expression of Endothelin-1 in Isolated Keratinocytes

Isolated human keratinocytes were irradiated, or not, with 20 mJ/cm^2 of UV-B (312 nm). Following irradiation, cells were incubated in a culture medium (EpiLife Medium, Sigma-Aldrich, MI, USA) supplemented, or not, with 0.001% of andrographolide. The andrographolide was introduced from a 0.1% DMSO stock solution, and the culture media of the controls were similarly supplemented with 0.1% DMSO.

After 48 h of incubation, endothelin-1 release into the culture medium was quantified using an ELISA assay (R&D Systems, UK) and normalized to the total protein content.

2.6 | Phorbol Myristate Acetate Induced Prostaglandin E2 Expression in Isolated Keratinocytes

Isolated human keratinocytes were incubated or not with varying concentrations of hydrocortisone (2 to 50 g/L) or glabridin (250×10^{-6} to 31×10^{-6}%). After a two-hour pre-treatment, the culture medium (EpiLife Medium, Invitrogen, MA, USA) was supplemented with 10 mg/L of phorbol myristate acetate (PMA) to induce an inflammatory response. After 24 h, the prostaglandin E2 inflammation mediator released in the culture medium was quantified using an ELISA assay (Cayman Chemical, MI, USA).

Glabridin being liposoluble, the stock solution was dissolved in 1% ethanol. All solutions of glabridin evaluated were adjusted to a 0.005% final concentration of ethanol and compared to a PMA control supplemented with ethanol (0.005% final concentration).

2.7 | Statistical Analysis

The results are reported as mean ± standard deviation (SD). After assessing data distribution using the Shapiro–Wilk test ($\alpha < 0.1$), the results from clinical evaluations of

hyperpigmentation, instrumental quantification of skin luminance and pigmentation, as well as DLQI and MELASQoL scores were analyzed using Wilcoxon's Signed Rank tests, comparing results of a time point to those of baseline. The results from in vitro experiments were analyzed using paired Student's *t*-tests.

In all analyses, significance was set at $p < 0.05$ with $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

3 | Results

3.1 | Clinical Evaluation of the Depigmenting Serum in South African Subjects

The clinical evaluation of the depigmenting serum in South African subjects applying the serum once daily demonstrated a significant reduction in all assessed parameters (number, intensity, and size) of dark spots or post-inflammatory hyperpigmentation over the study period (Figure 1A–C). Regardless of the parameter, reductions were already significant as early as 28 days after treatment initiation (number: −15%, $p = 0.002$; intensity: −32%, $p < 0.001$; and size: −13%, $p = 0.002$). Maximum improvements were observed by the end of the evaluation period (number: −46%, $p < 0.001$; and size: −30%, $p < 0.001$; intensity results being not exploitable due to an error in the scoring scale used).

Quality of life assessments, as measured by the Dermatological Life Quality Index (DLQI; Figure 1D), revealed that hyperpigmentation initially had a moderate impact (4.4 ± 5.9). By the end of the application period, this impact was drastically reduced (−93%, $p < 0.001$), with scores indicating that hyperpigmentation had almost no effect on the quality of life (0.3 ± 0.6).

3.2 | Clinical Evaluation of the Depigmenting Serum in Argentine Subjects

Daily application of the serum led to improvements across all clinically evaluated parameters (Figure 2A–D). Improvements were already significant after 28 days of use (intensity: −16%, $p = 0.001$; visibility: −32%, $p < 0.001$; contrast: −29%, $p < 0.001$; and complexion homogeneity: +18%, $p = 0.001$). Maximum improvements were observed by day 84 (intensity: −37%, $p < 0.001$; visibility: −45%, $p < 0.001$; contrast: −44%, $p < 0.001$; and complexion homogeneity: +26%, $p < 0.001$).

Instrumental analysis of the L* color parameter, representing skin luminance, demonstrated modest improvements in skin zones without hyperpigmentation (Figure 2E). A significant increase was first noted after day 56 (+2%, $p < 0.008$), reaching a maximum of +3% ($p = 0.005$) by day 84. In adjacent skin areas presenting hyperpigmentation, a significant increase in skin luminance was already evidenced by day 28 (+2%, $p < 0.001$), reaching a maximum by day 84 (+5%, $p < 0.001$).

The Individual Typology Angle (ITA), which combines the L* (skin luminance) and b* (green-blue color) parameters to quantify skin pigmentation, showed significant increases in both hyperpigmented and adjacent non-hyperpigmented skin areas (Figure 2F). For both, the increase was already significant after 28 days, yet reaching only +4% ($p = 0.040$) in non-hyperpigmented zones but +24% ($p < 0.001$) in hyperpigmented skin areas. The maximum increase in ITA occurred by the end of the study, with a +18% ($p < 0.001$) increase in non-hyperpigmented areas and +53% ($p < 0.001$) in hyperpigmented skin zones.

Furthermore, the ΔE parameter that assesses the color difference between hyperpigmented and adjacent non-hyperpigmented skin areas (Figure 2G) significantly decreased after 84 days (−16%, $p = 0.04$).

Finally, quality of life assessment using the MELASQoL questionnaire revealed an 18% decreased impact between D0 and D28 ($p = 0.04$), decrease reaching 23% ($p = 0.002$) by D56 and 33% ($p < 0.001$) by D84 (Figure 2H).

3.3 | In Vitro Assessment of the Inhibition of Melanogenesis

A key component of Kligman's depigmenting trio is hydroquinone that provides a strong anti-melanogenesis activity. In the serum, hydroquinone is replaced by andrographolide, a compound extracted from the leaves of *Andrographis paniculata*.

To assess the effect of andrographolide on melanogenesis, we monitored the expression of endothelin-1, a key regulator of UV-B induced melanogenesis, by quantifying its amount in keratinocyte culture medium. As shown in Table 2, the addition of andrographolide to the culture medium significantly reduced the amount of endothelin-1 released by keratinocytes, even in the absence of UV-B irradiation (−82%, $p < 0.001$). Upon UV-B irradiation, keratinocytes present the expected increase in endothelin-1 release, but this release is reduced by 65% in the presence of andrographolide ($p < 0.001$).

3.4 | In Vitro Assessment of Anti-Inflammatory Properties

Hydrocortisone is the ingredient providing the anti-inflammatory effect in Kligman's depigmenting trio. We substitute it with glabridin, the main constituent from the hydrophobic fraction of the root extract of Licorice (*Glycyrrhiza glabra* L.). Assessment of its anti-inflammatory effect was evaluated using phorbol myristate acetate (PMA)-induced prostaglandin E2 (PGE2) inflammation mediator expression in isolated human keratinocytes (Figure 3).

Compared to untreated keratinocytes, PMA treatment leads to a significant increase in PGE2 release (+291%, $p = 0.008$). Pretreatment with 50 and 2 mg/L of hydrocortisone decreases PGE2 release (−48% for both, $p = 0.045$ and $p = 0.034$, respectively), which is not the case with 10 mg/mL.

Addition of 0.005% ethanol to the PMA control—the ethanol concentration present when testing glabridin decreases PGE2 release. Yet, compared to this control, all concentrations of glabridin tested further reduce PGE2 release from −75% when present at 31×10^{-6}% ($p = 0.026$) to −80% at 250×10^{-6}% ($p = 0.021$).

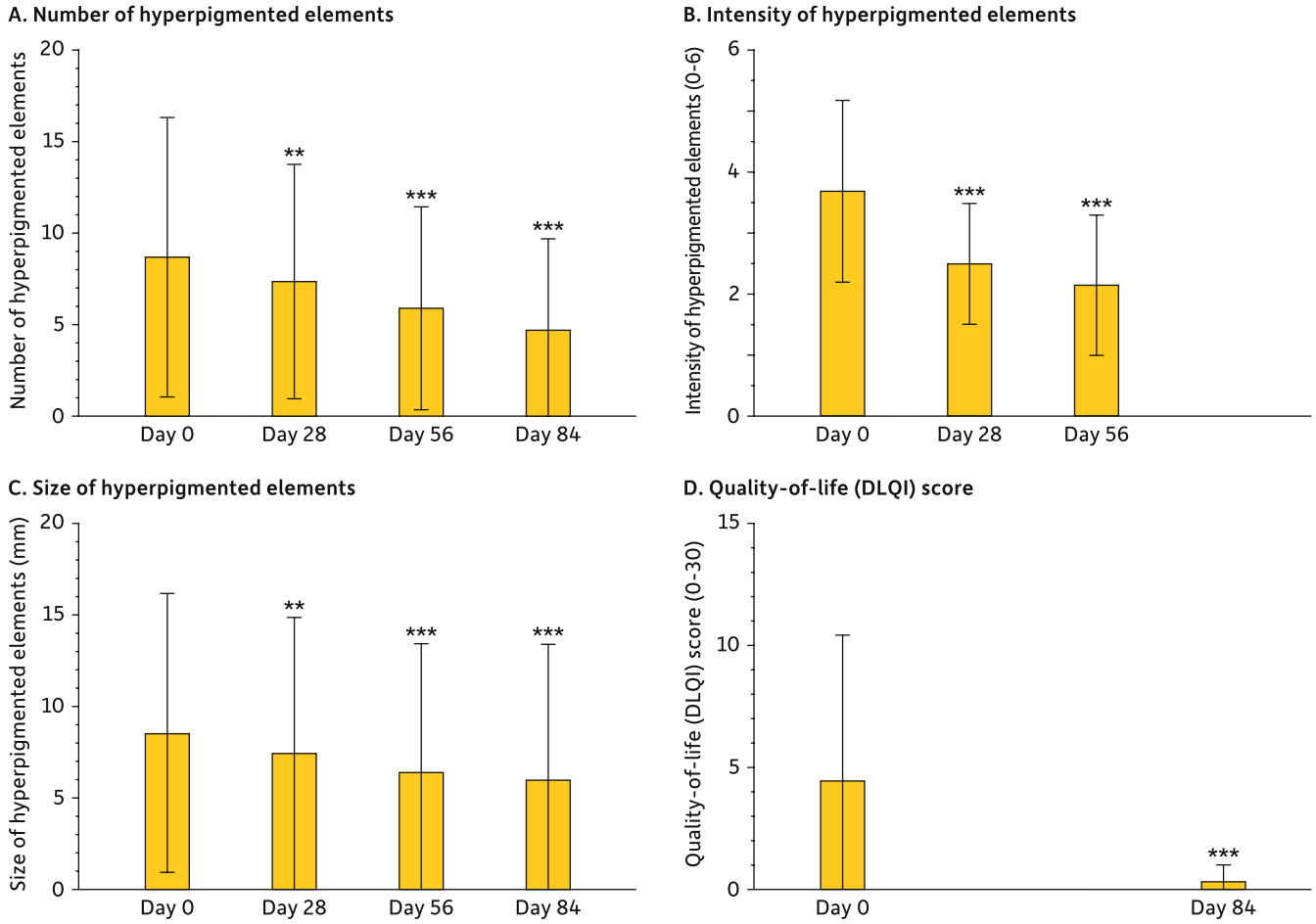

FIGURE 1 | Severity of dark spots or post-inflammatory hyperpigmentation elements in subjects from South Africa applying once-daily the serum. (A) Number of hyperpigmented elements, (B) intensity of hyperpigmented elements, (C) size of hyperpigmented elements, and (D) quality-of-life (DLQI) score. Significant differences are reported versus day 0 with **: $P < 0.01$, and ***: $P < 0.001$.

4 | Discussion

Using different evaluation methods, the studies conducted in South Africa and Argentina independently demonstrated the consistent efficacy of the depigmenting serum in individuals with skin of color. Clinical assessments in the South African study indicated a reduction in the number, intensity, and size of dark spots or post-inflammatory hyperpigmentation within 28 days. Similarly, the Argentinian study revealed that the intensity, visibility, and contrast of these hyperpigmented elements decreased over the same period, while complexion homogeneity improved. Besides, the skin color difference between hyperpigmented and non-hyperpigmented adjacent skin zones was reduced after 84 days. In both studies, maximum improvements were observed at the end of the evaluation period. The clinical results were further supported by the instrumental assessments of skin luminance and pigmentation conducted in Argentina.

Importantly, participants also perceived these improvements, leading to a reduced burden of their hyperpigmentation disorder. This was reflected in assessments using the generalist DLQI questionnaire in South Africa and the more specific MELASQoL questionnaire in Argentina.

The efficacy of the serum can be attributed to its formulation, which centers on three core ingredients designed to emulate the properties of Kligman's depigmenting trio [11]. These ingredients are the *Andrographis paniculata* leaf extract, the *Glycyrrhiza glabra* (Liquorice) root extract, and saccharide isomerate.

Andrographis paniculata is a widely recognized medicinal plant traditionally used in Asia to treat a large variety of disorders and diseases [16]. Its principal bioactive compound, andrographolide, exhibits multiple biological activities, including anti-inflammatory, anti-tumor, anti-diabetic, cardiovascular protective, neuroprotective, and hepatoprotective effects [17]. Previous analyses have shown that andrographolide reduces endothelin levels [18], a finding further confirmed by our in vitro experiments. Endothelin is a peptide that plays a critical role in modulating various biological processes, including melanin synthesis [19]. Furthermore, andrographolide is a direct inhibitor of melanin synthesis inhibitor [20]. Consequently, we incorporated an andrographolide-rich *Andrographis paniculata* leaf extract to promote a melanogenesis-reducing effect, similar to that provided by hydroquinone in Kligman's trio.

While andrographolide also possesses anti-inflammatory properties [21], the ingredient included in the serum to support the

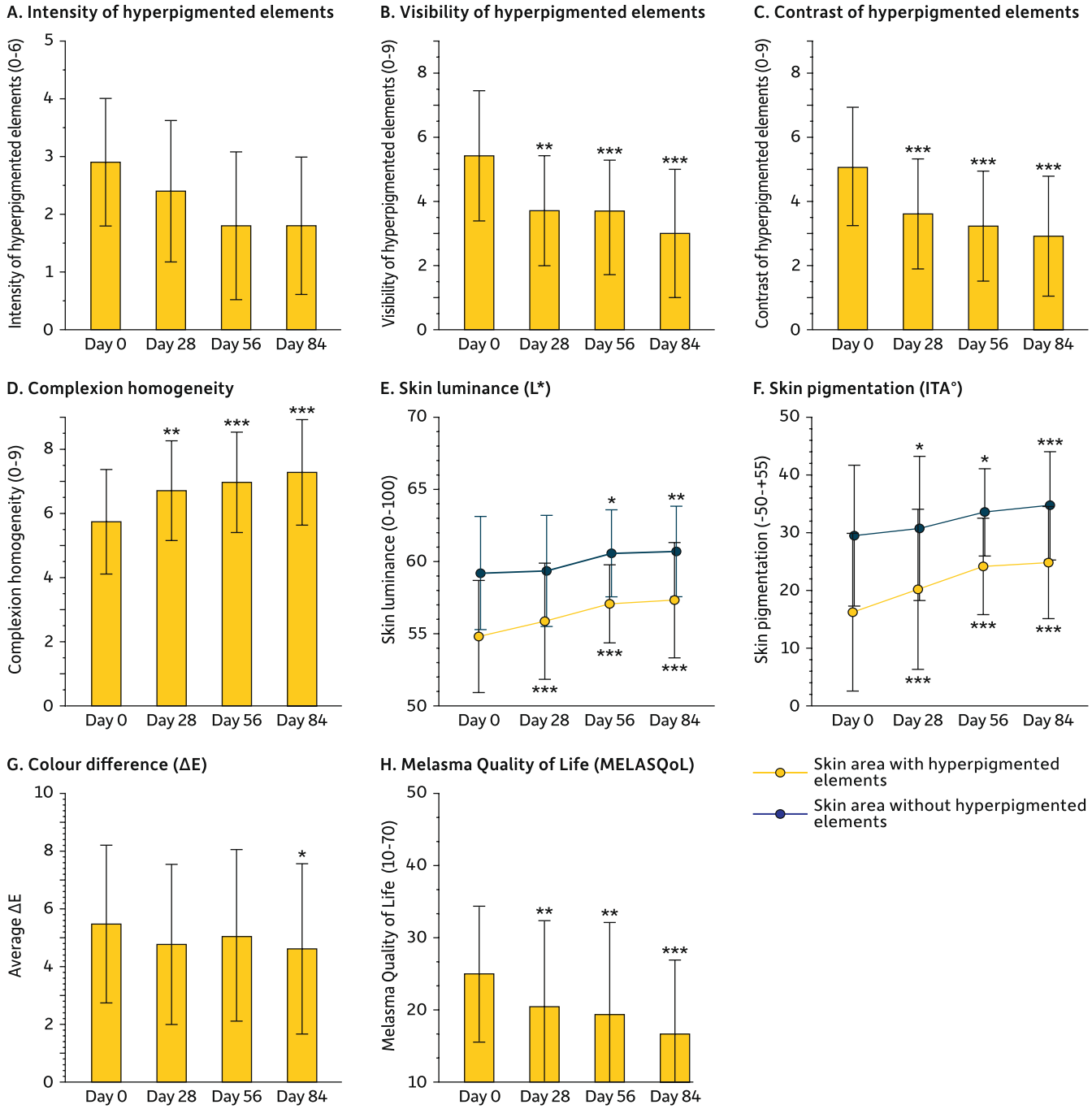

FIGURE 2 | Severity of dark spots or post-inflammatory hyperpigmentation elements in subjects from Argentina applying once-daily the serum. (A) Intensity of hyperpigmented elements, (B) visibility of hyperpigmented elements, (C) contrast of hyperpigmented elements, (D) complexion homogeneity, (E) skin luminance, (F) skin pigmentation, (G) color difference between hyperpigmented and adjacent non-hyperpigmented skin areas, and (H) Melasma Quality of Life (MELASQoL) score. Skin luminance and pigmentation are presented for a hyperpigmented skin zone and a non-hyperpigmented adjacent skin area. Significant differences are reported versus day 0 with *: $P < 0.05$, **: $P < 0.01$, and ***: $P < 0.001$.

TABLE 2 | Effect of andrographolide on the secretion of endothelin-1 by non-UV-irradiated and UV-irradiated human keratinocytes.

	Non-UV-irradiated		UV-irradiated	
Conditions	**Control**	**Andrographolide**	**Control**	**Andrographolide**
Mean ± SD	139.8 ± 9.1	24.7 ± 4.4 ***	194.4 ± 10.1	69.0 ± 10.2 ***

Note: Significance is versus the corresponding untreated control with ***: $p < 0.001$.

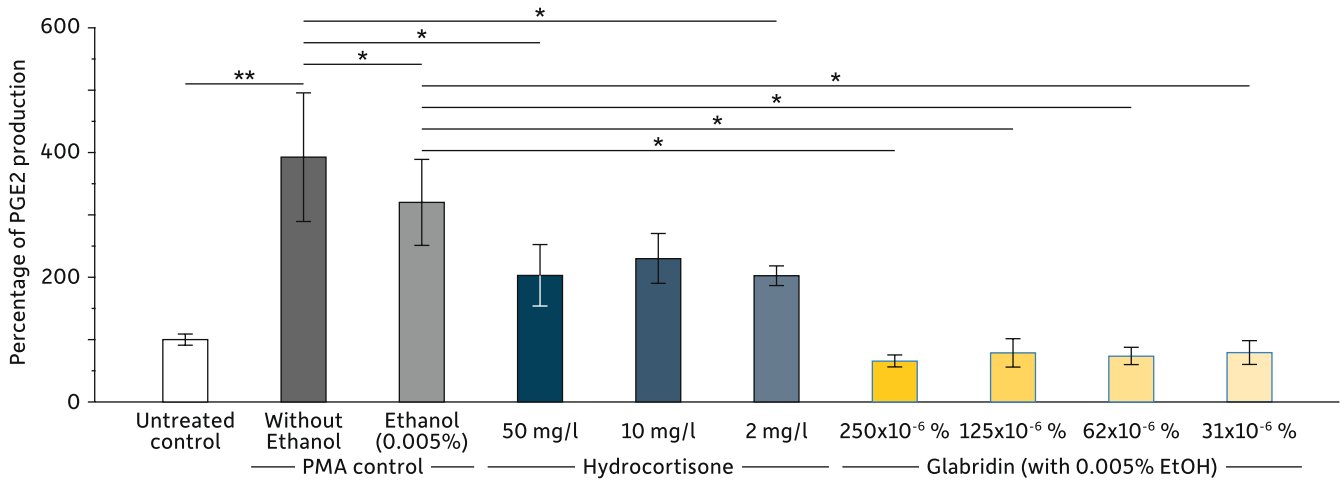

FIGURE 3 | Effect of hydrocortisone and glabridin on PMA-induced expression of PGE2 by keratinocytes. Results are presented as relative expression compared to untreated controls with *: $P < 0.05$ and **: $P < 0.01$.

anti-inflammatory effect of hydrocortisone is a *Glycyrrhiza glabra* root extract. This extract contains over 95% glabridin, a prenylated isoflavonoid with a wide range of biological activities [22], including the inhibition of melanogenesis [23], Yet, a key characteristic of glabridin, influencing several of its bioactivities, is its anti-inflammatory properties [22]. Our in vitro experiments demonstrated that glabridin, even at low doses, effectively inhibits PGE2, a major inflammatory mediator, surpassing the inhibition achieved with hydrocortisone.

Beyond andrographolide and glabridin, additional ingredients in the serum should contribute to inhibiting melanogenesis and controlling inflammation. The formulation also includes ascorbyl glucoside, a stabilized form of ascorbic acid that is enzymatically converted into active ascorbic acid upon cellular entry [24]. Ascorbic acid is a well-established depigmenting agent, inhibiting tyrosinase, the rate-limiting enzyme in melanin synthesis [25]. It also reduces o-quinone intermediates, preventing the formation of new melanin and lightening existing oxidized melanin [25]. The serum also contains niacinamide, another multifunctional vitamin with diverse cosmetic properties [26]. Unlike ascorbic acid, niacinamide does not inhibit tyrosinase activity but instead reduces melanosome transfer to keratinocytes and downregulates melanogenesis-related signaling pathways. Additionally, niacinamide possesses anti-inflammatory properties, inhibiting the secretion of pro-inflammatory cytokines [26]. Thus, ascorbyl glucoside and niacinamide complement the skin-lightening and anti-inflammatory effects of andrographolide and glabridin.

The third component of Kligman's trio promotes epidermal turnover, a function typically ensured by retinoic acid. In the serum, this role is fulfilled by saccharide isomerate. This galactose- and N-acetyl glucosamine-rich sugar complex is produced from a planktonic microorganism native to a coastal river (Brittany, France) [27]. According to manufacturer's unpublished data, it enhances skin barrier function by stimulating keratinocyte differentiation and epidermal renewal. This renewal process is further supported by the serum's mild peeling action ensured by glycolic acid and salicylic acid. These two acids are commonly used in high concentrations to treat various skin conditions, including post-inflammatory hyperpigmentation and melasma [28]. They induce a superficial exfoliation that triggers skin regeneration, ultimately improving skin's texture and appearance. Present at low concentrations in the serum, these two acids reduce the stratum corneum cohesion, eliminating dead skin cells and stimulating epidermal regeneration.

While a more thorough evaluation of the roles of the ingredients and their relative contribution to the serum's efficacy would be valuable, further clinical studies would also be beneficial. Although hyperpigmentation disorders constitute a major concern for individuals with skin of color, assessing the serum's efficacy in lighter skin types remains important. Moreover, the evaluation process would have benefited from standardized criteria to ensure comparability of results across studies, as well as from a comparative assessment against a control cream. However, conducting such a study using a split-face design might be challenging, as the effectiveness of the product could result in visible differences, potentially affecting participant adherence.

5 | Conclusions

Inspired by the principles of Kligman's depigmenting trio, the serum incorporates natural ingredients (andrographolide, glabridin, and saccharide isomerate), multifunctional vitamins (ascorbic acid and niacinamide), and gentle exfoliating agents. This formulation largely explains the clinical study results, demonstrating the serum's effectiveness in reducing hyperpigmentation and its associated burden in individuals with phototypes IV–VI from South Africa and Argentina.

Author Contributions

Conceptualization: A.P.F., S.V., S.B.-V., E.P.-M. Methodology: A.P.F., S.V., S.B.-V., A.F., S.T., E.P.-M. Formal analysis: S.B.-V., B.C. Resources: S.M.H.-K., A.P.F., S.V., A.F., S.T. Data curation: A.P.F., S.B.-V. Writing – original draft preparation: S.B.-V., A.G., A.F. Writing – review and editing: S.M.H.-K., A.P.F., S.V., S.B.-V., B.C., A.G., E.V., E.P.-M. Supervision: S.B.-V., A.G., S.T., E.V., E.P.-M. Project administration: E.V., E.P.-M. All authors have read and agreed to the published version of the manuscript.

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Ethics Statement

The clinical evaluation conducted in South Africa was approved by Pharma-Ethics under the reference RC2022/PIGCC/ZA. According to the Argentinian cosmetic regulation, no IRB approval was required for the clinical evaluation. Both studies adhered to the principles of the Declaration of Helsinki and complied with Good Clinical Practices. Participants received detailed information regarding the study, and all provided written informed consent before enrolment.

Conflicts of Interest

S.B.-V., B.C., A.G., A.F., S.T., E.V., and E.P.-M. are employees of NAOS. S.M.H.-K. and A.F.P. received personal fees from NAOS during the conduct of the study.

Data Availability Statement

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

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