

Aprilia Karen Mandagie

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CPM-HA WITH GYLYCEROL IMPACT ON MELANOGENESIS: A STUDY OF UVB-DRIVEN PIGMENTATION

Author:

Aprilia Karen Mandagie^{1,2}, Devina Karen Wibowo³

1. Dermatology Venereology Department Medical Faculty of Soegijapranta Catholic University.
Semarang Indonesia
2. Dermatology Venereology Skin Essential Clinic Semarang Indonesia
3. Medical Faculty of Diponegoro University, Semarang Indonesia

ABSTRACT

Background: Melanin, a pigment produced by melanocytes during the polymerization and oxidation stages of melanogenesis, can also increase in response to damage and inflammation. UVB-induced light is the most significant factor in this process. It is caused by light emissions that elevate levels of Reactive Oxygen Species (ROS), which, in turn, impact melanogenesis and lead to increased melanin production. CPM-HA is a type of Hyaluronic Acid (HA) filler used in aesthetic procedures to restore lost volume, smooth wrinkles, enhance facial contours, and is believed to reduce hyperpigmentation.

Objective: This study aimed to analyze the effectiveness of CPM-HA with glycerol in reducing melanin production in C57BL/6 mice, induced by UVB light and identified through histopathological images.

Methods: Utilizing a post-test only control group design and basic random sampling for the sampling method, this study implemented an appropriate experimental design. The study consisted of three groups (two intervention groups and one control group).

Results: The findings of UVB exposure indicate a significant increase in melanin pigmentation across all groups. Additionally, the results of CPM-HA with glycerol are notable, suggesting that CPM-HA with glycerol effectively reduces melanin levels in C57BL/6 mice exposed to UVB light.

Conclusion: This study concludes that CPM-HA with glycerol at a dose of 0.1 cc is effective in reducing melanin production in C57BL/6 mice caused by UVB light.

Keywords: CPM-HA with glycerol, melanin, C57BL/6 mice, UVB, histopathology.

INTRODUCTION

Skin quality is related to health, attractiveness, and youth and is intensively studied. A recent publication validated a scientific scale of skin quality and defined six relevant parameters for aged female facial skin: elasticity, wrinkles, skin roughness, pigmentation, erythema, and pore size.

As we all know, ultraviolet light is considered one of the important factors that induce the onset and worsening of melasma. Studies have found that UV irradiation can promote the release of histamine from skin mast cells, which has been shown to play a role in melanin production and can stimulate the proliferation and migration of melanocytes. On the other hand, ultraviolet light can stimulate keratinocytes to produce a variety of cytokines, including nerve growth factor, stem cell factor, alpha melanocytotropic hormone, vascular endothelial growth factor, and basic fibroblast growth factor, which are involved in the development and progression of melasma. During ultraviolet light irradiation of the skin, human keratinocytes can secrete the melanocyte cytokine SCF, which binds to the c-Kit receptor on melanocytes, leading to hyperpigmentation. In addition, repeated exposure to ultraviolet light can cause damage to the basement membrane zone, increased mast cell numbers, and solar elastosis in melasma lesions. Studies have shown that visible light is closely related to the onset of melasma. Visible light (blue-purple) can induce hyperpigmentation through specific sensors in melanocytes.

The skin is the body's primary protective organ, with its barrier function being the most critical. In melasma, this barrier is severely compromised, leading to disruptions in epidermal lipid metabolism, decreased water content, destruction of the basal layer, changes in dermal elastic fibers, local inflammation, and vascular hyperplasia. Ultraviolet (UV) radiation plays a central role in this pathogenesis by reducing lipid synthesis, triggering excessive melanin production, inducing oxidative stress, and increasing transepidermal water loss (TEWL). These factors collectively disrupt the skin barrier's stability, leading to uneven pigmentation. This evidence underscores that impaired skin barrier function is a fundamental aspect of melasma development.

Skin hyperpigmentation is a dermatological problem that not only has clinical implications but also affects the psychosocial wellbeing of sufferers. This condition occurs when melanocytes produce excessive melanin, creating dark patches that can reduce self-confidence and quality of life (Irfanti et al., 2021). In Southeast Asia, the prevalence of hyperpigmentation reaches 40%, with melasma cases disproportionately affecting women of reproductive age (Wit et al., 2022). This phenomenon reflects the complexity of the issue, which extends beyond skin health to sociocultural factors in which even-toned skin is considered the standard of beauty.

Conventional therapies for hyperpigmentation currently face a dilemma between efficacy and safety. Primary depigmenting agents such as hydroquinone (4%), kojic acid, and topical retinoids, while effective, often cause significant side effects with long-term use (H et al., 2015). Hydroquinone, considered the gold standard, has been associated with serious side effects, including skin irritation, contact dermatitis, and exogenous ochronosis (Gandana et al., 2024). This situation highlights the urgent need for innovative therapies that not only target melanogenesis but also prioritize patient comfort and long-term wellbeing.

Hyaluronic acid (HA) binds to the CD44 receptor, which is expressed by dermal fibroblasts and reduces the overexpression of MMP1. HA can also bind to the CD44 receptor on

36 keratinocytes, stimulating their growth, survival, and migration, thereby accelerating epidermal regeneration. Similarly, the interaction of HA with CD44 receptors on keratinocytes promotes the formation and release of lamellar bodies into the epidermal extracellular space, thereby maintaining epidermal hydration and exfoliation levels. Epidermal melanocytes also express CD44 receptors, and sulfated GAGs enhance the melanotic phenotype of these cells through binding to CD44 receptors. Under physiological conditions, melanocytes are surrounded by a hyaluronic acid layer that prevents them from synthesizing and releasing cytokines and chemokines. Ultraviolet radiation promotes HA hydrolysis by hyaluronidase and melanocytes, thereby releasing these pro-inflammatory factors. It is well established that pro-inflammatory factors, especially cytokines, play a crucial role in the development of decreased skin collagen levels, decreased skin thickness, and dry, wrinkled skin.

In vitro studies show that HA prevents the release of inflammatory cytokines by keratinocytes induced by ultraviolet radiation and ionizing radiation. Overall, this evidence shows that the HA biopolymer has a skin-rejuvenating effect through interaction with the CD44 receptor, supporting dermal fibroblast proliferation and the release of extracellular matrix proteins (type I and III collagen, sulfated GAGs, elastin), and preventing the release of inflammatory cytokines by epidermal melanocytes and keratinocytes. Microinjections of hyaluronic acid (HA) have been shown to improve skin quality significantly.

Skin pigmentation involves several steps, namely melanocyte activation, melanin synthesis, melanosome transport to the dendritic tips of melanocytes, and melanosome transfer from melanocytes to surrounding keratinocytes. It has been shown that vitamin C inhibits melanin synthesis by reducing tyrosinase activity. Vitamin C also disrupts the transport of melanosomes to the dendritic tips of melanocytes, as this vitamin reduces the expression of transport proteins from these melanosomes (such as kinesin). All these findings indicate that both vitamins support the activation of dermal fibroblasts and, consequently, the synthesis of new extracellular matrix proteins; they maintain keratinocyte proliferation, enabling adequate epidermal renewal, as well as the lipid content of the epidermal stratum corneum, which contributes both to epidermal renewal and to maintaining skin hydration levels; they prevent the degradation of HA surrounding melanocytes, prevent the release of inflammatory cytokines, and reduce melanin synthesis and melanosome transport to the tips of melanocyte dendrites, which has a depigmenting effect. All these changes can contribute to a more rejuvenated skin appearance.

Glycerol, a simple polyol, has shown significant potential to mitigate inflammation across various biological contexts. Recent studies highlight the complex biochemical role played by glycerol, particularly in inflammatory mechanisms and metabolic responses. Glycerol serves as a systemic biomarker of infection, suggesting that elevated glycerol levels may indicate metabolic adaptation in inflammatory bowel diseases, such as ulcerative colitis (Huang et al., 2024). Research shows that glycerol creates a stimulus for barrier repair, potentially through its hygroscopic properties that affect water flux. The relationship between glycerol and inflammatory markers underscores its therapeutic implications, suggesting that glycerol concentrations reflect underlying pathological changes and may guide treatment approaches.

The implications of glycerol in systemic inflammatory responses emphasize its role in overall metabolic dysregulation that often accompanies chronic diseases (Gong & Bai, 2025). The relationship between glycerol and inflammatory markers across various metabolic scenarios

supports the hypothesis that glycerol levels may reflect systemic inflammation and, in turn, guide therapeutic interventions. Glycerol not only acts as a humectant that helps improve skin hydration and accelerate barrier recovery, but also appears to stabilize the internal structure of the skin, including the stability of important components such as CPM (Core Permeability Mechanism) and HA (Hyaluronic Acid).

Additionally, glycerol has anti-inflammatory properties that help relieve UV-B-induced inflammation, thereby reducing damage and improving overall skin barrier function. Thus, glycerol functions as a multifunctional agent that repairs the barrier, stabilizes key skin components, and reduces UV-induced inflammation.

Research findings indicate that Microinjection HA effectively restores melanin levels in UVB-induced hyperpigmentation mouse models to levels comparable to those in standard conditions (Hidayat et al., 2016; Santos et al., 2023). These findings are consistent with previous in vitro studies reporting that carboxymethylated β -glucan (CPM) inhibits melanogenesis by downregulating tyrosinase and MITF expression (Chandra & Norawati, 2023). This success not only confirms its effectiveness in more complex biological systems but also addresses the existing gap in in vivo data, which has been limited until now.

Microinjection HA must be differentiated from HA filler in its indication, as it is injected over a larger area into the skin without building up much volume. Cross-linked Microinjection HA has relatively long durability within the tissue, and its hygroscopic property can provide a moisture depot, thereby improving cell turgor, tissue tension, and physiological processes in the extracellular matrix.

The advantages of the Microinjection HA formulation stem from its dual approach. In addition to CPM's depigmenting effect, the presence of hyaluronic acid (HA) provides crucial anti-inflammatory and moisturizing benefits. This aligns with studies highlighting the roles of compounds such as glycerol (Li et al., 2023) and HA in creating an optimal skin environment for recovery by reducing inflammation and oxidative stress after UVB exposure. Thus, this combination not only targets the causes of hyperpigmentation but also improves overall skin health, making it a safer and more comprehensive therapeutic candidate compared to conventional agents.

Based on the above description, the urgency of this research lies in the high prevalence of hyperpigmentation (40% in Southeast Asia), which has a significant impact on psychosocial wellbeing, as well as the limitations of conventional therapies such as hydroquinone, which has serious side effects. The current state of the art shows that the innovative Microinjection HA formulation offers a dual approach: downregulation of tyrosinase and MITF via CPM, and anti-inflammatory and optimal hydration effects of HA via interaction with the CD44 receptor, which not only targets melanogenesis but also improves overall skin health. Therefore, the objective of this study is to comprehensively validate the efficacy and safety of the Microinjection HA formulation as a safer and more effective alternative therapy for hyperpigmentation, while also laying the foundation for future cosmeceutical development.

RESEARCH METHOD

This study is an experimental study with a Posttest-Only Control Group Design aimed at determining the effect of Microinjection HA on melanin in hyperpigmented mice. The study was conducted at the Stem Cell and Cancer Research Laboratory in Semarang, with ethical approval. The sample consisted of 30 male C57BL/6 mice, randomly divided into three groups: the baseline group (healthy, untreated), treatment group 1 (hyperpigmentation + HA), and treatment group 2 (hyperpigmentation + HA + glycerol). Hyperpigmentation was induced by UVB exposure for 14 days, and the treatment was administered as a single intradermal injection, followed by incubation for 7 days before termination and tissue sampling.

Data analysis began with univariate analysis to describe the variables' characteristics. Bivariate analysis was performed using the One-Way ANOVA test to determine significant differences among the three groups, after first conducting prerequisite normality and homogeneity tests. If the ANOVA results were significant ($p < 0.05$), the Tukey HSD Post Hoc Test was used to identify which groups were different. If the data did not meet the parametric requirements, the Kruskal-Wallis non-parametric test was used, followed by the Mann-Whitney test. All analyses were performed using SPSS version 26 software.

Results and Discussion

Table 1 Results of the Prerequisite Test

Group	Normality Test	Homogeneity Test	One-Way ANOVA Test
Control	0,094		
HA	0,082	0,212	0,003
HA Glycerol	0,528		

Based on the results of the prerequisite analysis test, all data groups were normally distributed ($p > 0.05$). The results of the homogeneity test showed that the variance of data between groups was homogeneous ($p = 0.212 > 0.05$). The One-Way ANOVA test showed a statistically significant difference between the three groups ($p = 0.003 < 0.05$).

Table 2 Tukey Test Results

Group A	Group B	Mean Difference	Values- p	Description
Control	HA Glycerol	-148.900	0.004	Significant
Control	HA	-24.900	0.822	Not Significant
HA Glycerol	HA	-124.000	0.016	Significant

Based on Table 2 of the Tukey test results, there is a significant difference among the three groups. The comparison between the Control Group and the HA Glycerol Group showed a significant difference in mean of -148,900 (p -value=0.004), as did the comparison between the HA Glycerol Group and the HA Group, which was also significant with a difference in mean of -124,000 (p -value=0.016). In contrast, the comparison between the Control Group and the HA Group with an average difference of -24,900 was not significant (p -value=0.822). These

results indicate that the HA Glycerol treatment provides a statistically superior effect compared to the other two groups. This superiority is due to glycerol's role as a synergistic humectant, which forms an occlusive film on the skin surface. This layer has a dual function: preventing the evaporation of water bound by hyaluronic acid while maintaining skin hydration for an extended period. Meanwhile, the non-significance of the results between the single HA group and the control group indicates that without a stabilizing agent such as glycerol, HA's ability to maintain hydration is limited because the water molecules it binds are prone to evaporation.

Discussion

This study comprehensively investigated the therapeutic effects of HA Glycerol on UVB-induced skin hyperpigmentation in a mouse model. The results provide strong evidence supporting the effectiveness of this intervention. Preliminary analysis confirmed that data from all groups met the prerequisites for parametric statistics, with normality tests indicating normal distribution ($p > 0.05$) and Levene's test confirming homogeneity of variances between groups ($p = 0.212$). Fulfillment of these basic assumptions validated the use of the One-Way ANOVA test, which then revealed a statistically significant difference in melanin levels between the three groups studied ($p = 0.003$). This finding provides a solid basis for further analysis to identify the source of these differences.

Based on the Tukey test results for the three treatment groups, a clear, tiered pattern of effectiveness was observed. This post-hoc analysis revealed that the HA Glycerol treatment was the most superior interaction, showing a highly statistically significant difference compared to the other two groups. Compared with the Control group, the HA Glycerol treatment produced an average difference of -148,900 ($p = 0.004$; $p < 0.01$), indicating a very significant impact on the measured parameters. Similarly, compared with the HA group, the HA Glycerol treatment still showed superiority, with an average difference of -124,000 and a p-value of 0.016 ($p < 0.05$), confirming that the HA Glycerol formulation is more effective than the HA method.

The findings of this study show that there is no statistically significant difference between the control and HA groups ($p = 0.822$). These results not only show that HA reduces melanin but also effectively restores melanin levels to normal physiological levels, similar to those in healthy skin. The clinical implications of these findings are enormous. This shows that the administered dose works with precision, without causing hypopigmentation (a condition in which melanin becomes too low), but restores the skin to its normal condition. The ability to restore skin homeostasis, rather than simply inhibiting a pathological process, indicates the potential for a restorative rather than merely suppressive therapeutic modality.

Hyperpigmentation disorders are characterized by increased melanin production in melanocytes of the skin and hair follicles. This increase in melanin is due to melanin's role in the pigmentation process. Research by Putri (2020) indicates that continuous exposure to UVB light stimulates melanogenesis, leading to excess melanin production and hyperpigmentation. Melanocytes function as the site for melanin production and distribution. This is also consistent with research by Sarkar et al., (2021), which states that UVB radiation is a significant risk factor for hyperpigmentation by inducing DNA damage, as evidenced by increased expression of proteins involved in melanin formation, such as MITF.

22 The results of the study show that intradermal administration of the HA Glycerol formula successfully restored melanin levels in UVB-induced hyperpigmentation mouse models to levels comparable to those of normal skin (baseline). This finding is consistent with previous studies by Hidayat et al., (2016) and Santos et al., (2023), which reported the effectiveness of the combination of carboxymethylated β -glucan (CPM) and hyaluronic acid (HA) in inhibiting melanogenesis in vitro. The suspected mechanism is CPM's ability to modulate the expression of tyrosinase and MITF (Chandra & Norawati, 2023), which are key regulators of melanin synthesis. Thus, the Tukey HSD test results showing no significant difference between the experimental group and the baseline confirm that HA not only inhibits but also restores hyperpigmentation to normal physiological levels.

40 The success of this therapy may also be attributed to the potential anti-inflammatory effects of the formulation components, particularly HA and possibly glycerol, as mentioned in the background. Research by Huang et al. (2024) and Li et al. (2023) highlights the role of glycerol in mitigating inflammatory responses and improving skin barrier function. Although glycerol was not part of the variables tested in this study, the moisturizing and soothing properties of HA in the HA Glycerol formula are strongly suspected to contribute to creating an optimal skin environment for recovery, reducing oxidative stress, and ultimately supporting depigmentation efficacy. This is particularly relevant given that UVB-induced hyperpigmentation often involves inflammatory processes. Thus, the dual approach of HA Glycerol, which targets both the melanogenesis pathway and overall skin health, makes it a promising and safer therapeutic candidate compared to conventional agents such as hydroquinone.

Improved skin hydration and elasticity have already been discussed for microinjection treatment with CPM-HA20G. The ancillary function of glycerol in CPM-HA20G results in an enhanced, earlier onset of a skin-hydrating effect, as already reported by Hertz-Kleptow et al. Other cross-linked CPMHA products do not use glycerol as an additional additive. The results are consistent with those of a previous study using CPM-HA20G. These parameters improved over the study period. Previous studies on CPM-HA20G and NASHA also showed increasing improvements in gross elasticity.

Of particular importance for clinical recommendations and use is that three consecutive treatments—4 weeks apart—resulted in a stronger, more pronounced treatment response than a single treatment. Clinically, a single treatment can be recommended for patients with mild loss of skin elasticity and firmness, whereas patients with a more pronounced decrease in viscoelastic properties should undergo three consecutive treatment sessions to improve skin fatigue and firmness gradually.

Several hypotheses can explain the results described. An important factor in the improved skin firmness parameter R0 (Uf) and the skin fatigue parameter R3 could be the hygroscopic properties of HA and the hydrophilic properties of glycerol, which serve as a moisture depot, thereby improving cell turgor, tissue tension, and physiological processes in the extracellular matrix.^{8,9} Considering that CPM-HA20G is a viscoelastic fluid in its rheological characteristics, where the viscous properties (G'') exceed the elastic properties (G'), it could be assumed that these predominantly viscous properties were measured within the tissue by the suction method and therefore may influence the measured biophysical viscoelastic parameters.

37 This study has limitations, including the use of a mouse model with a relatively short observation period (7 days post-treatment), which cannot guarantee long-term therapeutic

stability or confirm the same results in human skin. The sample size was limited and focused on one main parameter (melanin content). Furthermore, this study was unable to identify specific molecular mechanisms, such as interactions at the CD44 receptor level or the expression of key proteins, including MITF and tyrosinase, that underlie the superior efficacy of conventional HA compared with microinjection formulations. For future research, it is highly recommended to conduct studies with more extended follow-up periods to validate the durability of the treatment effects. Future research should also include histological and biomolecular analyses to map in detail how the two HA formulations affect inflammatory and melanogenesis pathways at the cellular level. Clinical trials in humans with a broader range of skin types and hyperpigmentation conditions are needed to confirm the generalizability of these findings and to evaluate the long-term safety and comfort of both therapeutic modalities.

Conclusion

Based on the results of the study, it can be concluded that the Glycerol HA formulation was significantly superior at normalizing melanin levels in the UVB-induced hyperpigmentation mouse model compared to the control and HA groups, with statistically significant differences observed in the Tukey test ($p=0.004$ and $p=0.016$). At the same Time, the HA treatment did not show a significant difference from the control ($p=0.822$). The effectiveness of HA Glycerol is strongly suspected to be due to the dual role of glycerol as a synergistic humectant that forms an occlusive layer to maintain longer hydration and its potential anti-inflammatory effect that creates an optimal environment for skin recovery, thereby not only inhibiting melanogenesis but also restoring skin homeostasis to normal physiological conditions without causing hypopigmentation.

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