

Clinical Efficacy and Safety of a Multimodality Skin Brightener Composition Compared With 4% Hydroquinone

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ABSTRACT

There are numerous common skin disorders involving hyperpigmentation, including solar lentigines, postinflammatory hyperpigmentation, melasma, freckles, and dyschromia from photoaging. While these conditions are of an aesthetic nature, there is great interest in newer, safer, and more effective treatment modalities. Topical hydroquinone (HQ) has been the gold standard of skin lighteners for many years. However, regulatory authorities around the world are now questioning its safety. A randomized, double-blind, half-face study was conducted in females having moderate to severe facial hyperpigmentation to assess the efficacy and tolerability of 3 new skin brightener formulations containing SMA-432, a prostaglandin E_2 inhibitor, compared with 4% HQ. Each subject was assigned 2 of the 4 test materials and was instructed to apply the product on the assigned side of the face twice daily for 12 weeks. Evaluation visits were conducted at baseline and at 4, 8, and 12 weeks. At each visit, subjects were evaluated by a blinded investigator for clinical efficacy and tolerability using grading scales. Standardized digital photography and Chroma Meter assessments were also taken. Self-assessment questionnaires were completed at weeks 4, 8, and 12. Sixty-eight Caucasian subjects (136 half faces) completed the study. All test materials significantly reduced Overall Hyperpigmentation and improved the Investigator's Global Hyperpigmentation Improvement rating at weeks 4, 8, and 12 compared with baseline. SMA-432 exhibited a dose-dependent improvement in hyperpigmentation. There were no major tolerability issues with any of the test materials. Self-assessments were generally favorable for all test materials. At the completion of the trial, subjects rated one of the tested multimodality brightener compositions as the most favorable product and 4% HQ as the least favorable. This study demonstrated that the new non–HQ-containing skin brightener formulations were as effective and equally well tolerated as the gold standard, 4% HQ, in females with facial hyperpigmentation.

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INTRODUCTION

The amount and type of melanin pigments, which are polymers produced inside the melanosomes, determine skin color.[1,2] While there is tremendous diversity worldwide in the color of human skin, uniform or even skin color (particularly across the face) in an individual is considered a sign of health, attractiveness, and youthfulness and, as such, is aesthetically desirable.[3,4] Skin issues involving hyperpigmentation typically arise because of injury and/or advancing age. Exposure to sunlight is the most common cause of hyperpigmentation and is likely a postinflammatory response to ultraviolet (UV) damage to the skin.[5,6] Inflammation may lead to hyperpigmentation via several mechanisms, including direct stimulation of melanocytes by inflammatory mediators and reactive oxygen species (ROS) and release of endocrine inducers of pigmentation such as α-melanocyte-stimulating hormone.[6] The resulting melanin production provides protection against future insult, as melanin has both UV absorption and ROS scavenging activities.[7]

Altered production of cutaneous melanin causes problems of an aesthetic nature. Such disorders of hyperpigmentation, including melasma, postinflammatory hyperpigmentation, solar lentigines, freckles, and dyschromia from photoaging, are very common in humans, and there is a broad interest in newer, more effective treatment modalities. Traditionally, the gold standard topical agent for skin lightening was hydroquinone (HQ) 4%, until regulatory agencies around the world began questioning its safety.[8,9] Adverse effects, including skin irritation, contact dermatitis, and exogenous ochronosis may occur with use of this compound. The US Food and Drug Administration has initiated studies to better understand the long-term safety of topical HQ and has not made a determination on its safety[10]; however, many user interest groups have taken the position that products containing HQ should not be used because of potential safety concerns. As a result, there exists a large and growing market for alternative products that effectively lighten the skin.

While there are an ever-increasing number of cosmetic skin-lightening and skin-brightening products in the marketplace, the overwhelming majority lack any clinical studies to support their claims. Most often, manufacturers will utilize in vitro studies (such as tyrosinase inhibition) as a support for efficacy or utilize testimonials from satisfied users.

Employing a unique combination of skin-lightening and proprietary ingredients that address various pathways involved in melanin production and control, 3 formulations were devel-

FIGURE 1. All 4 products demonstrated significant reductions in Overall Hyperpigmentation scores at all visits compared with baseline (all *P*<.001). At week 12, there were no significant differences between BR1, BR3, and 4% hydroquinone (HQ) (*P*>0.13).

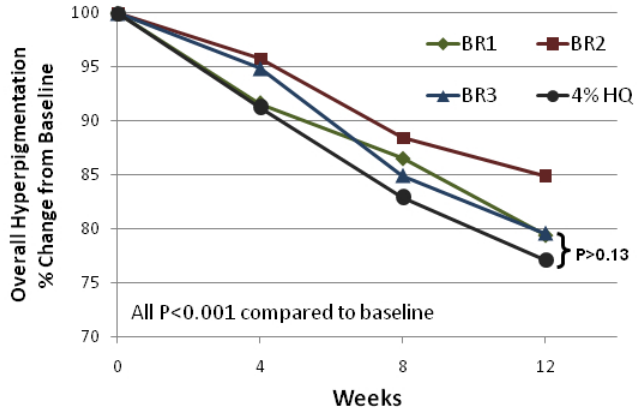
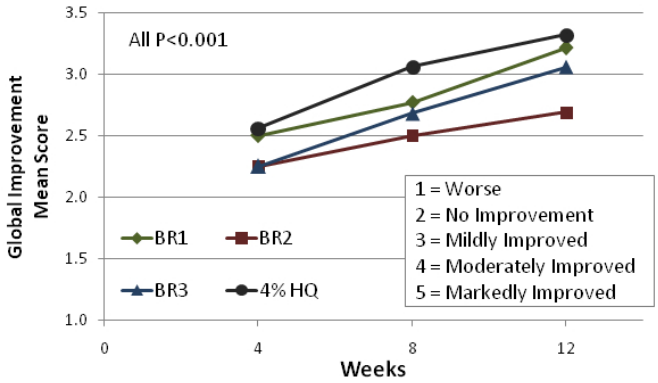


FIGURE 2. All 4 products showed significant improvements in the Investigator's Global Hyperpigmentation Improvement score at all visits compared with baseline (all *P*<.001). HQ, hydroquinone.



oped and tested for safety and efficacy compared with HQ using a randomized, double-blind, half-face clinical design model.

MATERIALS AND METHODS

The criteria for participation in the study included female subjects in good general health between the ages of 30 and 65 years with moderate to severe facial hyperpigmentation as determined by clinical examination. Subjects were required to have a baseline score of 4 to 9 on both sides of the face from the Overall Hyperpigmentation scale and to be willing not to apply any other topical products (skin lightening, retinoids, benzoyl peroxide, steroids, α- or β-hydroxy acids) to the facial area or to use any systemic retinoids throughout the duration of the study. Subjects were provided standard skin-care products (facial cleanser, moisturizer, and SPF 30 physical sunscreen) to use during the course of the study.

Institutional Review Board approval was obtained for this study. The study was conducted according to ethical and regulatory principles from the International Conference on Harmonisation. Before treatment, the subjects provided informed consent.

The complexity of biochemical processes of melanin formation and distribution necessitates a comprehensive approach to manage pigmentary disorders. Table 1 describes the composition of the multimodality skin brightener formulations used in this study, which contained multiple ingredients designed to address these numerous aspects of melanin formation and removal, and melanocyte activation. Three test formulations (BR1, BR2, and BR3) and a generic 4% HQ cream were studied to compare efficacy and tolerability in subjects with moderate to severe facial hyperpigmentation. Subjects were assigned 2 of the 4 test materials and were instructed to apply them on the assigned side of the face (left or right) according to a predetermined, randomized half-face design. Test materials were applied twice daily, morning and evening. Both the subject and the investigator were blinded to the assigned test materials.

The study was conducted over a 12-week period from June 2011 to October 2011 in Dallas, TX, and consisted of evaluation visits at baseline, week 4, week 8, and week 12. Subjects arrived at the clinic having removed all makeup at least 20 minutes before the visit. Subjects participated in the following assessments at each visit:

Clinical Efficacy

An investigator evaluated the face (right and left) of each subject for the following parameters using a grading scale (with half points allowed):

- Overall Hyperpigmentation: 0 = none, 1 to 3 = mild, 4 to 6 = moderate, and 7 to 9 = severe
- Investigator's Global Hyperpigmentation Improvement: 1 = worse, 2 = no improvement, 3 = mild improvement, 4 = moderate improvement, 5 = marked improvement

Tolerability

An investigator assessed each subject for erythema and scaling using a 4-point scale (0 = none, 3 = severe). In addition, subjective parameters, including burning/stinging, itching, tightness, and tingling, were assessed by the subjects.

Chroma Meter

A Chroma Meter (CR-400, Konica Minolta, Tokyo, Japan), in conjunction with a computer was used to instrumentally assess skin color. A single measurement was taken on the right and left sides of each subject's face on a hyperpigmented area selected by the expert grader. The location was recorded on a facial diagram to ensure consistency of measurement location at each visit.

Digital Photography

Digital photographs using a Nikon camera (Canfield VISIA-CR camera system, Fairfield, NJ) were taken of the right and left sides of the face of each subject with standard and cross-polarized lighting conditions to document changes in facial hyperpigmentation.

TABLE 1.

Composition for Skin Brightener Products 1, 2, and 3 With Suggested Biochemical Pathway of Action[a]

Pathway	Ingredients	Reference	BR1	BR2	BR3
Reduce Melanocyte Activation					
Reduce free radicals	Tetrahexyldecyl ascorbate	16	√	√	√
Reduce inflammatory cytokines	SMA-432	17	0.5%	0.1%	0.5%
Reduce Melanin Synthesis by Limiting Tyrosinase Availability					
Tyrosinase transcription inhibition	Retinol	18	√	√	√
Tyrosinase degradation	Linoleic acid	19	√	√	√
Tyrosinase transfer inhibition	SMA-013	20	0.1%	0.1%	–
Competitive tyrosinase inhibition	Glabridin	21	√	√	√
Competitive tyrosinase inhibition	Hexylresorcinol	22	√	√	√
Reduce Melanin Transfer to Keratinocytes					
Reduce melanocytic dendrite formation	Niacinamide	23	√	√	√
	SMA-432	17	√	√	√
Remove Epidermal Melanin					
Accelerate keratinocyte turnover	Retinol	24	√	√	√

[a]A checkmark indicates that the ingredient is present in the formula at a therapeutically relevant concentration.

Self-Assessment Questionnaires

Subjects completed a self-assessment questionnaire regarding various skin parameters on the right and left sides of the face.

Statistical Analysis

Clinical grading scores and Chroma Meter measurement values at week 4, week 8, and week 12 were compared with baseline scores/values using a paired *t* test. The average percent change from baseline was calculated for all parameters at each post-baseline visit. Comparisons among the test materials were performed using analysis of variance with paired comparisons using Fisher's least significant difference. All differences were considered to be statistically significant at the $P<.05$ level.

RESULTS

Seventy-five Caucasian female subjects were enrolled in the study. Of those, 68 subjects (136 half faces) completed the 12-week study and were included in the analysis. Of the 136 half faces, BR1 = 35, BR2 = 34, BR3 = 33, and 4% HQ = 34. Demographic information on the 68 subjects is presented in Table 2.

Efficacy Assessments

The mean Overall Hyperpigmentation score at baseline for all subjects was between 5 and 5.5 (moderate). Figure 1 shows a statistically significant reduction in Overall Hyperpigmentation score for all treatment groups when compared with baseline. BR1 and BR3 produced a reduction statistically equivalent to 4% HQ at 12 weeks ($P>.13$). BR1 appears to have a faster onset of action, with greater improvement at 4 weeks as compared with BR3. This may be attributed to the activity of SMA-013, a targeted inhibitor of tyrosinase transfer, present in BR1 but not in BR3. SMA-432, an inhibitor of prostaglandin E_2, shows a dose-dependent reduction in hyperpigmentation as seen when compared with BR1 and BR2, which contain 0.5% and 0.1% SMA-432, respectively.

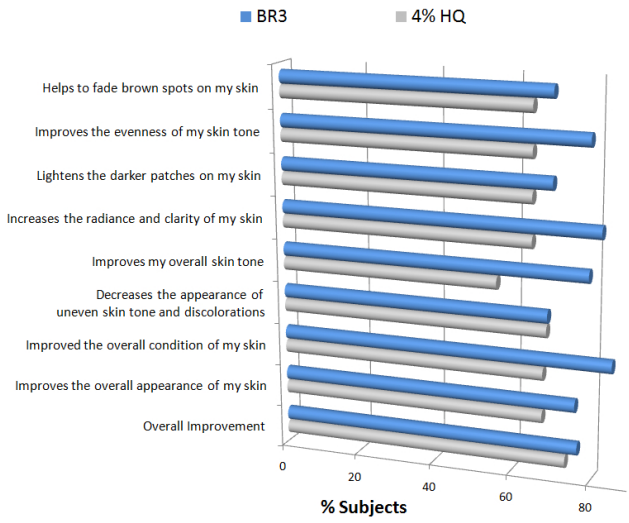
A similar trend is seen in rating of Global Improvement from baseline. As seen in Figure 2, SMA-432 exhibits a dose response, strongly indicating a significant contribution of this patented ingredient in the combination product. In addition, BR1 shows improvement that is statistically equivalent to that seen with 4% HQ.

The most relevant data from the Chroma Meter measurements related to changes in L^* values (skin-tone brightening). Analysis of the change from baseline scores indicated a statistically significant improvement in L^* for BR1, BR2, and BR3 at week 8.

Tolerability

There was significantly greater erythema observed for all products at week 4 compared with baseline. However, by week 12, there were no significant differences in erythema for any products compared with baseline. Scaling was not an issue for any of the formulations. In subject assessments, mean scores for

FIGURE 3. Subject self-assessment questionnaire results at week 12, reflecting the percentage of subjects who responded "strongly agree" or "agree." HQ, hydroquinone.



burning/stinging were mild or below at weeks 4 and 8 for BR1, BR2, and BR3. Subjects also reported transient and intermittent skin tightness with BR1 and BR2. Itching and tingling were of minor or no concern to subjects for all formulations.

Self-Assessment Questionnaires

The self-assessment questionnaires were generally favorable for all 4 products. After completion of the 12-week trial, subjects were asked to indicate overall satisfaction with the treatment. BR3 was the most favorable product, and 4% HQ was the least favorable product. Figure 3 is a comparison of subject responses to BR3 and 4% HQ. Significant improvements in melasma and mottled pigmentation are seen in photographs of the subjects at 12 weeks compared with baseline, as shown in Figures 4 and 5.

DISCUSSION

Humans seem to be preoccupied with altering their natural skin color, either making it darker or lighter. Skin pigmentation depends on the amount and type of melanin synthesized by the melanosomes. Melanin, particularly eumelanin (brown-black pigment), protects underlying tissues from harmful UV radiation.[7,11,12] Even considering the biological importance of melanin, there are differing perceptions regarding the "ideal" skin color according to various cultures around the world. In Western society, tanned skin has recently been perceived as a healthy look, despite warnings about the consequences of excessive UV exposure.[12] However, in the Eastern world, a light complexion is more desirable, as it is regarded as equivalent to youth and beauty.[13] Not only does skin lightness affect perceptions of a woman's beauty in Asian cultures, it also affects social standing, job and marital prospects, and even earnings potential.[13] Whitening and lightening skin products have

TABLE 2.

Study Subject Demographics	
Age, years	
Range	33-65
Mean	52.2
Fitzpatrick skin type	
I	5.9%
II	48.5%
III	45.6%

achieved dramatic growth and are among the best-selling product categories in the Asian beauty industry. The desire for fair skin is not, however, limited to Asian cultures. It is a global phenomenon also seen in African, South American, and Middle-Eastern cultures. Skin whitening is a rapidly growing segment of the global beauty industry. Today, skin-lightening products are used worldwide for their ability not only to lighten darker complexions, but also to control age-related hyperpigmentation.

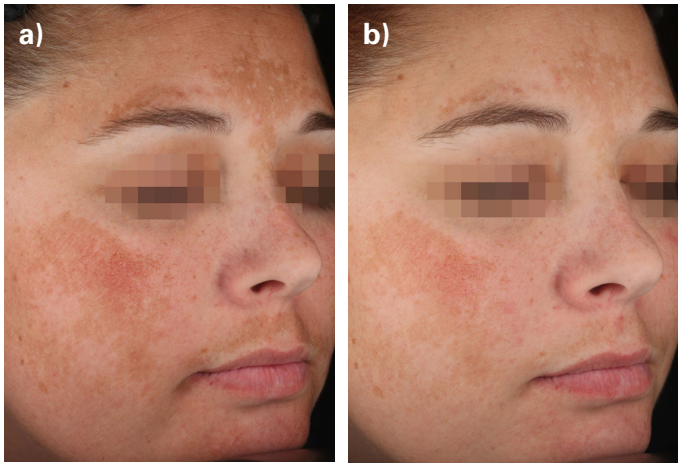
Concerns about the safety of topical HQ have resulted in its removal from certain European and Japanese markets and potential withdrawal in the US market. These actions led to a host of new skin lighteners being added to the cosmetic marketplace as "safe" alternatives. The majority of these products lack any clinical evidence to demonstrate that they can lighten hyperpigmented human skin.

Some of these new alternative products to HQ employ a related agent, arbutin. This β-D-glucopyranoside derivative of HQ is available in both natural and synthetic forms. Studies have shown that following oral ingestion, arbutin is metabolized and excreted in humans as HQ, HQ glucuronide, and HQ sulfate.[14] Normal skin microflora (*Staphylococcus epidermidis* and *Staphylococcus aureus*) can hydrolyze arbutin, converting it to HQ.[15] Thus, these arbutin-containing skin lighteners are not HQ free.

Inadvertent exposure to UV radiation plays a major role in melanin control during execution of clinical studies. Studies conducted over winter months tend to exaggerate the benefits of skin brighteners; therefore, studies assessing efficacy of skin brighteners should be conducted during the summer months to simulate worst-case scenarios.

The 3 skin brightener formulations were developed based on an understanding of the pathway for melanogenesis and employ a combination of ingredients that intervene with differing components of this pathway. These include suppression of tyrosinase production, enhancement of tyrosinase degradation, prevention of tyrosinase transport to melanosomes, inhibition of tyrosinase activity, and inhibition of melanosome transport. Other ingredients provide anti-inflammatory, antioxidant, and exfoliant properties. This

FIGURE 4. Thirty-five-year-old female with Fitzpatrick skin type III at baseline **a)** and after 12 weeks **b)** of twice-daily application of BR3.



multimodality approach delivers a truly comprehensive cosmetic solution to management of pigmentary conditions that provides efficacy comparable to a well-established prescription product.

CONCLUSIONS

The results of this blinded and controlled, half-face clinical use study indicate that the 3 skin brightener formulations and 4% HQ cream were all effective in reducing pigmentation after 4, 8, and 12 weeks of use, based on investigator assessments. A dose-dependent response was observed for proprietary skin-brightening agent SMA-432. There were no major tolerability issues with any product. At study completion, subjects reported highest satisfaction with BR3 and lowest satisfaction with 4% HQ. This new skin lightener has been clinically demonstrated as an effective non–HQ-containing product.

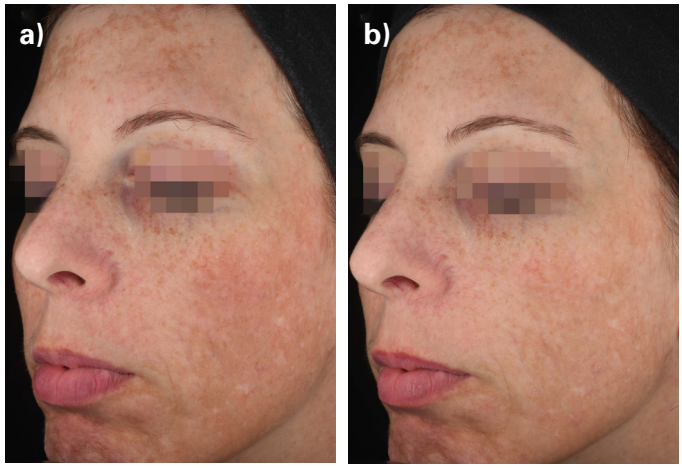
DISCLOSURES

Financial support for this study was provided by SkinMedica, Inc. Ms. Makino, Mr. Garruto, and Dr. Mehta are employees of SkinMedica, Inc. Mr. Gotz is a consultant for SkinMedica, Inc.

REFERENCES

1. Yamaguchi Y, Brenner M, Hearing VJ. The regulation of skin pigmentation. *J Biol Chem.* 2007;282(38):27557-27561.
2. Costin GE, Hearing VJ. Human skin pigmentation: melanocytes modulate skin color in response to stress. *FASEB J.* 2007;21(4):976-994.
3. Matts PJ, Fink B, Grammer K, Burquest M. Color homogeneity and visual perception of age, health, and attractiveness of female facial skin. *J Am Acad Dermatol.* 2007;57(6):977-984.
4. Fink B, Grammer K, Matts PJ. Visual skin color distribution plays a role in the perception of age, attractiveness, and health of female faces. *Evol Hum Behav.* 2006;27:433-442.
5. Clydesdale GJ, Dandie GW, Muller HK. Ultraviolet light induced injury: immunological and inflammatory effects. *Immunol Cell Biol.* 2001:79(6):547-568.
6. Ortonne JP, Bissett DL. Latest insights into skin hyperpigmentation. *J Invest Dermatol Symp Proc.* 2008;13(1):10-14.
7. Krol ES, Liebler DC. Photoprotective actions of natural and synthetic melanins. *Chem Res Toxicol.* 1998;11(12):1434-1440.
8. Nordlund JJ, Grimes PE, Ortonne JP. The safety of hydroquinone. *J Euro Acad Dermatol Venereol.* 2006;20(7):781-787.
9. Levitt J. The safety of hydroquinone: a dermatologist's response to the 2006 Federal Register. *J Am Acad Dermatol.* 2007;57(5):854-872.

FIGURE 5. Thirty-six-year-old female with Fitzpatrick skin type III at baseline **a)** and after 12 weeks **b)** of twice-daily application of BR3.



10. US Food and Drug Administration Web site. Hydroquinone studies under the National Toxicology Program (NTP). http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm203112.htm. Accessed August 7, 2012.
11. Brenner M, Hearing VJ. The protective role of melanin against UV damage in human skin. *Photochem Photobiol.* 2008;84(3):539-549.
12. Tran TT, Schulman J, Fisher DE. UV and pigmentation: molecular mechanisms and social controversies. *Pigment Cell Melanoma Res.* 2008;21(5):509-516.
13. Li EPH, Min HJ, Belk RW, Hosei JK, Bahl S. Skin lightening and beauty in four Asian cultures. *Adv Consum Res.* 2008;35:444-449.
14. National Toxicology Program. Arbutin review document. http://ntp.niehs.nih.gov/files/arbutin.pdf. Accessed March 2, 2012.
15. Bang SH, Han SJ, Kim DH. Hydrolysis of arbutin to hydroquinone by human skin bacteria and its effect on antioxidant activity. *J Cosmet Dermatol.* 2008;7(3):189-193.
16. Panich U, Tangsupa-a-nan V, Onkoksoong T, et al. Inhibition of UVA-mediated melanogenesis by ascorbic acid through modulation of antioxidant defense and nitric oxide system. *Arch Pharm Res.* 2011;34(5):811-820.
17. Sonti S, Mehta R, Holtz R. Mechanistic studies on novel anti-inflammatory molecule used in the treatment of facial redness. *J Invest Dermatol.* 2011;131(suppl 1):069.
18. Sato K, Morita M, Ichikawa C, Takahashi H, Toriyama M. Depigmenting mechanisms of all-trans retinoic acid and retinol on B16 melanoma cells. *Biosci Biotechnol Biochem.* 2008;72(10):2589-2597.
19. Ando H, Wen ZM, Kim HY, et al. Intracellular composition of fatty acid affects the processing and function of tyrosinase through the ubiquitin-proteasome pathway. *Biochem J.* 2006;394(Pt 1):43-50.
20. Data on file. SkinMedica, Inc.
21. Yokota T, Nishio H, Kubota Y, Mizoguchi M. The inhibitory effect of glabridin from licorice extracts on melanogenesis and inflammation. *Pigment Cell Res.* 1998;11(6):355-361.
22. Tasaka K, Kamei C, Nakano S, Takeuchi Y, Yamato M. Effects of certain resorcinol derivatives on the tyrosinase activity and the growth of melanoma cells. *Methods Find Exp Clin Pharmacol.* 1998;20(2):99-109.
23. Navarrete-Solís J, Castanedo-Cázares JP, Torres-Álvarez B, et al. A double-blind, randomized clinical trial of niacinamide 4% versus hydroquinone 4% in the treatment of melasma. *Dermatol Res Pract.* 2011;2011:379173.
24. Bellemère G, Stamatas GN, Bruère V, Bertin C, Issachar N, Oddos T. Anti-aging action of retinol: from molecular to clinical. *Skin Pharmacol Physiol.* 2009;22(4):200-209.

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