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EFFICACY AND TOLERABILITY OF A SKIN BRIGHTENING/ANTI-AGING COSMECEUTICAL CONTAINING RETINOL 0.5%, NIACINAMIDE, HEXYLRESORCINOL, AND RESVERATROL

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Efficacy and Tolerability of a Skin Brightening/Anti-Aging Cosmeceutical Containing Retinol 0.5%, Niacinamide, Hexylresorcinol, and Resveratrol

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ABSTRACT

Consumers are increasingly interested in over-the-counter skin care products that can improve the appearance of photodamaged and aging skin. This 10-week, open-label, single- center study enrolled 25 subjects with mild to moderate hyperpigmentation and other clinical stigmata of cutaneous aging including fine lines, sallowness, lack of clarity, and wrinkling. Their mean age was 53.4±7.7 years. The test product contained retinol 0.5% in combination with niacinamide 4.4%, resveratrol 1%, and hexylresorcinol 1.1% in a moisturizing base. Subjects were provided a skin care regimen including a cleanser, hydrating serum, moisturizer, and an SPF 30 sunscreen for daily use. The test product was applied only at night.

The use of this skin brightening/anti-aging cosmeceutical was found to provide statistically significant improvements in all efficacy endpoints by study end. Fine lines, radiance, and smoothness were significantly improved as early as week 2 ($P<.001$). By week 4, hyperpigmentation, overall skin clarity, evenness of skin tone, and wrinkles showed statistically significant improvement compared to baseline. Mild retinoid dermatitis including flaking and redness occurred early in the study as reflected by tolerability scores. By week 10, subjects reported no stinging, itching, dryness, or tingling.

The results of this open-label clinical study suggest that a topical cream containing retinol 0.5% in combination with niacinamide, resveratrol, and hexylresorcinol is efficacious and tolerable for skin brightening/anti-aging when used with a complementary skin care regimen including SPF 30 sun protection.

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INTRODUCTION

Sallowness, roughness, uneven pigmentation, coarse lines, and wrinkles are all visible signs of photoaging. Prescription retinoids such as tretinoin and tazarotene have demonstrated efficacy for treating photoaged skin in numerous clinical trials studies.[1-3] Clinical benefits include smoother skin, reduction in lines and wrinkles, and more even skin tone. The use of prescription retinoids in some patients is limited by their propensity to cause skin irritation including redness and flaking.

The gold standard for skin lightening is hydroquinone (HQ) 4%. Available only by prescription, patients have limited access to HQ 4% and often seek lower cost over the counter options. Additionally, consumer concerns about the safety of hydroquinone leave many looking for lightening products that may be perceived as more "natural" and gentle on the skin.

Excellent skin lightening results are obtainable by combining synergistic individual components. Examples include the well-known Kligman formulation for the treatment of melasma which contained tretinoin 0.1%, HQ 5.0%, and dexamethasone 0.1%.[4] The commercialized product TriLuma® Cream, (Galderma Laboratories, Fort Worth, Texas) includes tretinoin 0.05%, HQ 4.0%, and fluocinolone acetonide 0.01%. Clinical studies demonstrated that this product is an effective skin lightener improving hyperpigmentation in patients with melasma.[5] TriLuma was approved by the FDA in 2002 for the treatment of moderate to severe melasma and is now commonly used off-label to treat photoaged skin.

The brightening/anti-aging test product evaluated in this study contains the synergistic combination of retinol (ROL) 0.5%, niacinamide 4.4%, resveratrol 1%, and hexylresorcinol 1.1%. Collectively, these ingredients act on the melanin pathway in different ways at the same time, improving the product's effect as a skin lightening agent. Additionally, these ingredients have been shown to confer significant anti-aging benefits.

ROL is a non-prescription retinoid that has been shown to improve aging skin, but is associated with less irritation than prescription alternatives.[6] ROL is oxidized into retinaldehyde (RAL) in the skin then further oxidized into retinoic acid or tretinoin, which is the biologically active molecule. Kang et

al demonstrated that application of retinol to human skin induced epidermal hyperplasia and stimulated cellular retinoid binding proteins (CRBP) with minimal irritation.[7] In a clinical study of 36 elderly subjects, topical ROL 0.04% was applied to sun-protected skin on the arms up to 3 times per week for 24 weeks.[8] At study end, fine wrinkling scores were significantly improved with ROL ($P<.001$). ROL was also shown to increase glycosaminoglycan (GAG) expression significantly ($P=.02$) and procollagen I expression ($P=0.049$). ROL has also been shown to improve dyspigmentation in patients with photoaging.[9] Mechanisms include a downregulation of melanin synthesis via inhibition of tyrosinase expression and enhanced removal of epidermal melanin by acceleration of keratinocyte turnover.[10,11] In view of the multi-mechanistic benefits for treating photoaged skin and its favorable tolerability profile, many now view retinol as the ideal retinoid.

Niacinamide is an amide of vitamin B3 (niacin) and a valued cosmeceutical ingredient with wide ranging benefits on skin appearance. Niacinamide has been shown to improve skin sallowness, reduce wrinkling, inhibit sebum production, reduce pores size and confer photoprotection.[12] Niacinamide is shown to suppress glycation, or the Maillard reaction, that leads to the cross-linking of sugars to proteins. This inhibition subsequently reduces and improves age-related skin yellowing.[13-15] A unique advantage of niacinamide as an anti-aging agent is that it promotes the biosynthesis of ceramides thus improving barrier function.[16] Niacinamide is known to act as a skin lightener by inhibiting the transfer of melansomes from melanocytes to keratinocytes.[17] In a double-blind, randomized, split-face, 8-week clinical trial, topical niacinamide 4% was shown to have comparable efficacy to HQ 4% for skin lightening in patients with melasma, but with better tolerability.[18]

Resveratrol is a naturally occurring polyphenolic antioxidant found in grapes, berries, and peanuts. Decades of study have demonstrated that resveratrol is an important anti-aging molecule that affects a variety of metabolic pathways and cellular mechanisms. Resveratrol promotes mitochondrial biogenesis and reduces mitochondrial oxidative stress.[19] A unique characteristic of resveratrol is its dual antioxidant function. It scavenges free radicals while at the same time upregulating transcription of enzymatic antioxidants via the Nrf2 pathway.[20] Resveratrol and other stilbene polyphenols have been shown to inhibit tyrosinase thus have significant potential as skin lightening agents.[21] In a vehicle-controlled clinical study, topical resveratrol was shown to prevent tanning following exposure to artificial UVR and to lighten hyperpigmented spots.[22]

Hexylresorcinol is a commonly used anesthetic and antiseptic. It is found in over the counter products such as throat lozenges, mouthwashes and topical antiseptics. Hexylresorcinol is also gaining favor as a cosmetic ingredient, as it acts as a skin lightening agent by inhibiting tyrosinase.[23] Recent studies on a hexylresorcinol containing, HQ free, skin lightener demonstrated effective skin lightening, and was shown to inhibit melanogenesis in vitro and reduce UV-induced hyperpigmentation.[24]

The objective of this 10-week, open-label, single-center study was to examine the efficacy and tolerability of a retinol-based skin brightening, anti-aging combination product. The efficacy of these complementary ingredients was enhanced by delivering the actives using a patented OmniSome technology. This multi-layered, non-phospholipidic, time released delivery system stabilizes ingredients like retinol, enhances skin delivery and improves tolerability. The test product was formulated in a moisturizing base containing dimethicone, PEG-12 and glycerin.

MATERIALS AND METHODS

This single-center study was conducted by Stevens and Associates (Dallas, Texas). Based on a telephone screening, women ages 35 to 65 were scheduled for a clinical screening. Inclusion criteria were clinically determined mild to moderate hyperpigmentation (eg, age spots, sun spots, melasma) with a score of 3-6 (mild to moderate) on a scale where 0= none and 9= severe. Twenty-two subjects with Fitzpatrick skin types I-IV qualified for the study.

TABLE 1.

Clinical Grading of Efficacy Parameters		
Parameter	**0 =**	**9 =**
Hyperpigmentation	Even skin color, no hyperpigmentation	Pronounced hyperpigmented appearance
Fine lines	None	Numerous, deep fine lines
Overall appearance	Excellent	Poor
Radiance	Radiant, luminous appearance	Dull/matte and or/sallow appearance
Clarity	Extremely clear, bright, translucent skin appearance	Dull/flat matte skin appearance
Skin smoothness (tactile)	No palpable skin roughness, drag and/or surface bumps/depressions	Significantly (severe) palpable skin roughness, drag, and/or surface bumps/depressions
Skin tone evenness	Even, natural, and healthy skin color	Uneven, discolored appearance
Wrinkles	None	Numerous, deep wrinkles

TABLE 2.

Subject Disposition	
	All Subjects (n)
Enrolled Subjects	25
Completed Subjects (PP Population)	22
Discontinued Subjects	3
Reason for Discontinuation	
Subject requested withdrawal	1
Investigator decision	1
Lost to follow-up	1

Clinical evaluations of efficacy and tolerability were conducted at baseline and weeks 2,4,6,8, and 10. Grading of efficacy parameters (hyperpigmentation, fine lines, overall skin appearance, radiance, clarity, skin smoothness, skin tone evenness, and wrinkles) took place at each visit. A 10-point scale where 0= none, best possible condition;1-3= mild; 4-6= moderate,7-9= severe, worst possible condition was used for grading (Table 1).

Tolerability was assessed at each clinical evaluation by means of investigator objective grading of erythema, dryness/scaling and peeling, and subjective burning, stinging, itching, dryness, tightness, or tingling of facial skin. Tolerability evaluations were made by clinical grading and subjective assessments measured on a 3-point scale where 0=none; 1= mild; 2= moderate; and 3= severe.

Subjects also completed self-assessment questionnaires regarding their perceptions of their facial skin texture, evenness of tone, appearance of brown spots, brightness and redness, fine facial lines, healthy appearance, firmness, moisturization, and overall appearance. Questionnaires also asked about subject opinions of the test material including scent, texture, after-feel, mildness, application experience, and likelihood of purchasing the product.

Digital photography including 3 full-face views were made at each clinical evaluation using a Nikon D7000 digital SLR camera. The VISIA CR-photostation with a Canon Mark II 5D digital SLR camera was used under standard lighting 1,2,3,4, cross-polarized, parallel polarized, and UV spot lighting at baseline and weeks 6 and 10.

Subjects were provided with a pre-weighed unit of the test brightening/anti-aging product as well as a facial wash, hydrating serum with glycerin, a moisturizing broad spectrum sunscreen with SPF 30, and an evening hydrator. In the mornings, subjects were instructed to cleanse with the provided facial wash, then to apply a dime-size amount of hydrating serum followed by the moisturizing sunscreen with SPF 30. In the evenings, subjects cleansed as above, then applied a dime-size amount of the test product (avoiding the eye area and the neck), followed by application of a nickel size amount of the evening hydrator to the full face. Subjects were reminded to apply the test material for a minimum of 2-3 times per week for the first 2 weeks.

RESULTS

Demographics

A total of 25 subjects met the inclusion criteria and were enrolled, and 22 completed the study per protocol (Table 2). The 22 subjects had a mean age of 53.4 ± 7.7 years. All subjects were female, and 50% were Caucasian, 27.7% Asian, and 27.3% Hispanic or Latino. The majority had Fitzpatrick skin type III (54.5%), with 22.7% having Fitzpatrick type II, and 22.7% Fitzpatrick type IV.

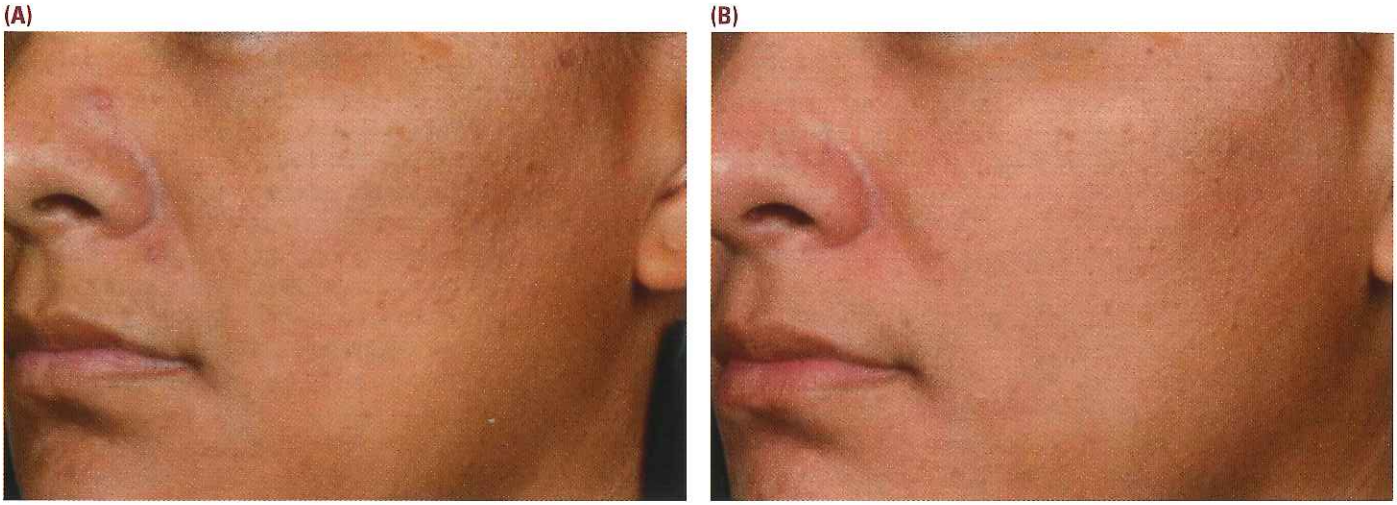
Efficacy

Use of the brightening/anti-aging 0.5% retinol product and a regimen of supporting skin care products produced improvements in all efficacy parameters. Fine lines, radiance, and skin smoothness all showed statistically significant improvement as early as week 2. By week 4, hyperpigmentation, overall skin clarity, and skin tone/evenness showed statistically significant improvement as did wrinkles by week 6. Table 3 shows mean

TABLE 3.

Mean Change in Efficacy Scores from Baseline to Week 10		
Parameter	Mean Baseline Score	Mean Score at Week 10
Hyperpigmentation	5.00 ± 0.83	4.25 ± 0.72
Fine Lines	4.39 ± 0.89	3.43 ±0.85
Overall Appearance	5.30 ±0.90	4.43 ± 0.84
Radiance	5.43 ± 0.50	4.30 ±0.45
Clarity	6.02 ± 0.82	4.66 ± 0.47
Tactile Skin Smoothness	4.43 ± 0.73	3.09 ± 0.48
Skin Tone Evenness	5.68 ± 0.80	4.64 ± 0.62
Wrinkles	4.84 ± 1.36	4.25 ± 1.29

FIGURE 1. Subject 001: (A) Baseline photographic assessment. (B) Week 10.



scores at baseline and week 10 for all efficacy endpoints. Figures 1, 2, and 3 depict 3 subjects at baseline and week 10.

Tolerability

As would be expected with the introduction of a retinol-containing product to a facial skin care regimen, some patients experienced mild retinoid dermatitis. A statistically significant increase (worsening) over baseline was observed for dryness/scaling at weeks 2 and 6, burning at week 2, and dryness/tightness at week 8. However, mean scores throughout the study were <1, reflecting mild severity. By week 10, mean scores =0 for stinging, itching, dryness/tightness, and tingling.

Self-Assessment Questionnaires

Self-assessment questionnaires reflected a statistically significant improvement in appearance of brown spots, skin brightness, appearance of facial lines, and skin firmness as early as week 2. As shown in Table 4, use of the brightening/anti-aging retinol 0.5% combination product and supporting skin care products resulted in statistically significant improvement in all subject self-assessments by week 10. Results from the self-assessment questionnaire revealed a statistically significantly higher proportion of favorable to unfavorable responses regarding product characteristics (ie, scent, texture, after-feel) as well as the experience of product application, overall product mildness, and desire to purchase the product.

Adverse Events

A total of 8 patients experienced adverse events (AEs) and, of those that did occur, all were considered non-serious and all resolved during the study. Most of the AEs that were considered related to the test product were of mild severity and included

FIGURE 2. Subject 002: (A) Baseline photographic assessment. (B) Week 10.

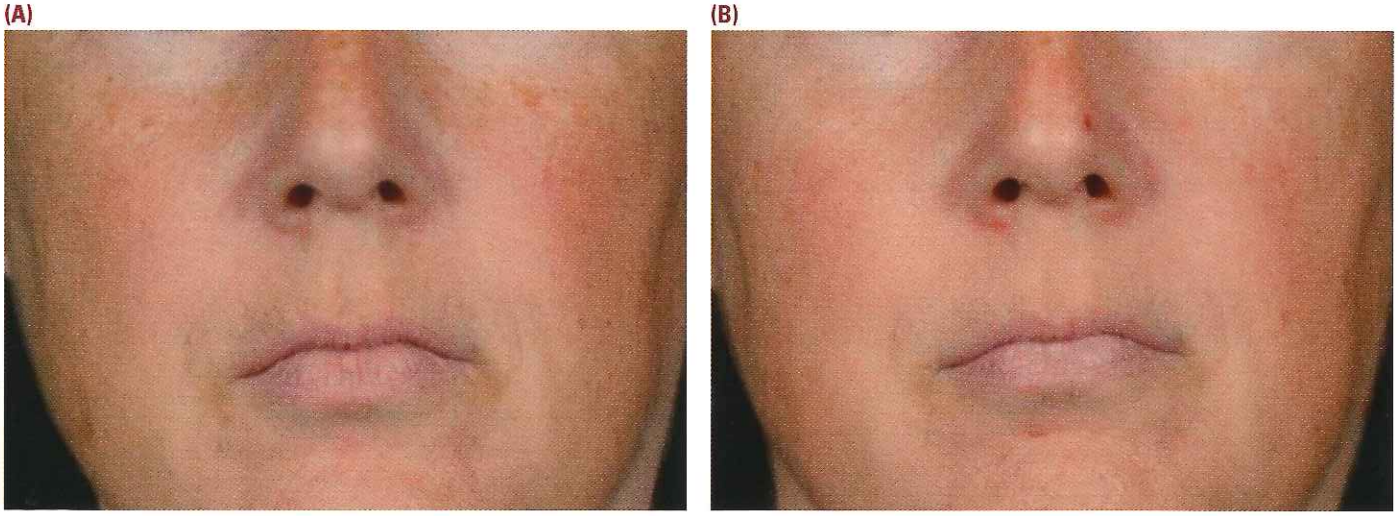
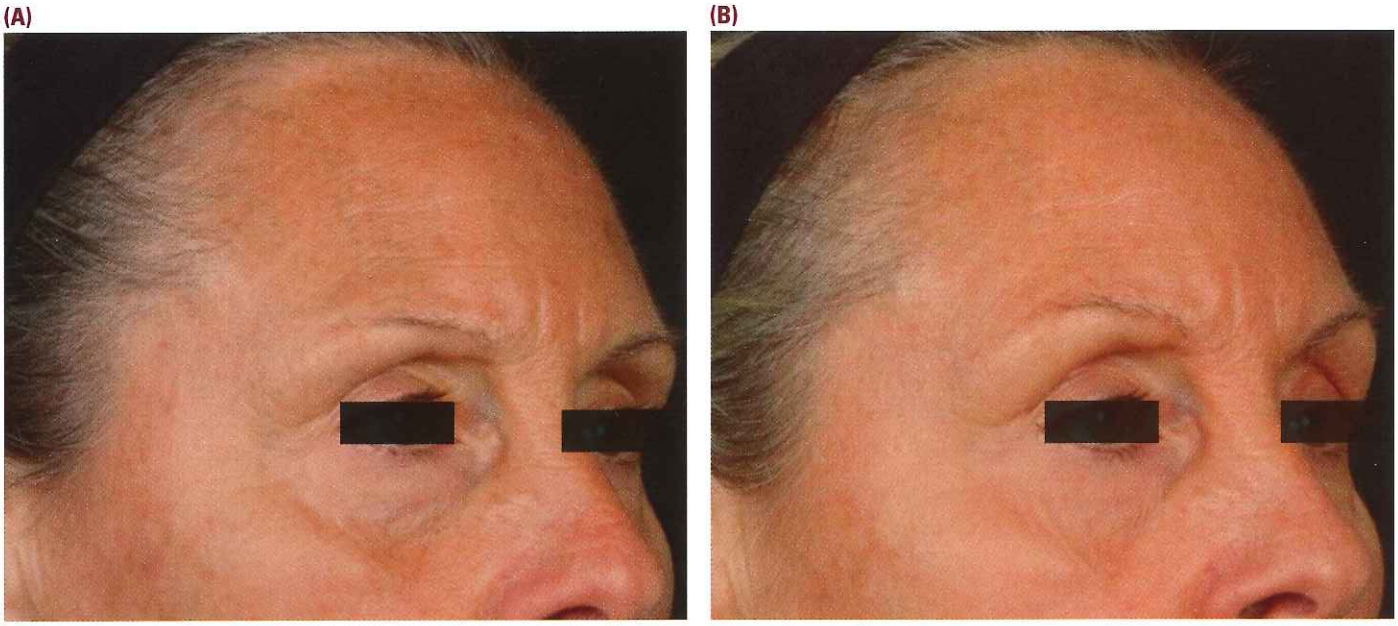


FIGURE 3. Subject 003: (A) Baseline photographic assessment. (B) Week 10.



dry skin, skin exfoliation, burning, and erythema. One subject experienced moderate facial burning pain, dry skin, erythema, and swelling beneath both eyes. This subject was withdrawn from the study by the investigator.

TABLE 4.

Results of Self-Assessment Questionnaires					
Inquiries (Skin Condition)	Week 2	Week 4	Week 6	Week 8	Week 10
Appearance of Brown Spots	X	X	X	X	X
Skin Brightness	X	X	X	X	X
Skin Texture	--	X	X	X	X
Evenness of Skin Tone	--	X	X	X	X
Skin Redness	--	--	--	--	X
Appearance of Facial Fine Lines	X	X	X	X	X
Healthy Appearance of Skin	--	X	X	X	X
Skin Firmness	X	X	X	X	X
Skin Moisturization	--	--	--	--	X
Overall Appearance of Skin	--	X	X	X	X

X Indicates statistically significant improvements

CONCLUSION

The development of effective skin rejuvenating products is complex and requires the proper combination of active ingredients and delivery systems. In this study, a skin brightening/anti-aging topical treatment with retinol 0.5% in combination with niacinamide 4.4%, resveratrol 1%, and hexylresorcinol 1.1% delivered using OmniSome was found to provide significant improvement in a variety of skin aging parameters including hyperpigmentation. Tolerability of the test product was good, with expectable mild retinoid dermatitis in several participants. The use of a complementary skin care regimen including cleanser, hydrating serum, moisturizing sunscreen SPF 30, and nighttime hydrating cream simulates the at-home experience typical of consumer use.

DISCLOSURES

The authors have served as advisory board members for PCA Skin.

REFERENCES

1. Kligman AM, Grove GL, Hirose R, Leyden JJ. Topical tretinoin for photoaged skin. *J Am Acad Dermatol.* 1986;15:836-59.
2. Olsen EA, Katz I, Levine N, et al. Tretinoin emollient cream: a new therapy for photodamaged skin. *J Am Acad Dermatol.* 1992;26:215-24.
3. Lowe NJ, Gifford M, Tanghetti E, et al. Tazarotene 0.1% cream versus tretinoin 0.05% emollient cream in the treatment of photodamaged facial skin: a multicenter, double-blind randomized, parallel group study. *J Cosmet Laser Ther.* 2004;6:79-85.
4. Kligman AM, Willis J. A new formula for depigmenting human skin. *Arch Dermatol.* 1975;111:40-8.
5. Taylor SC, Torok H, Jones T et al. Efficacy and safety of a new triple-combination agent for the treatment of facial melasma. *Cutis.* 2003;72:67-72.
6. Kligman LH, Gans EH. Re-emergence of topical retinol in dermatology. *J Dermatol Treat.* 2000;11:47-52.

7. Kang S, Duell EA, Fisher GJ et al. Application of retinol to human skin in vivo induces epidermal hyperplasia and cellular retinoid binding proteins characteristic of retinoic acid but without measurable retinoic acid levels or irritation. *J Invest Dermatol.* 1995;105:549-56.
8. Kafi R, Kwak SR, Schumacher WE, et al. Improvement of naturally aged skin with vitamin A (Retinol). *Arch Dermatol.* 2007;142:60612.
9. Tucker-Samaras S, Zedayko T, Cole C, et al. A stabilized 0.1% retinol facial moisturizer improves the appearance of photodamaged skin in an eight-week, double-blind, vehicle-controlled study. *J Drugs Dermatol.* 2009;8:932-36.
10. Bellemere G, Stamatas GN, Bruere V et al. Antiaging action of retinol: From molecular to clinical. *Skin Pharmacol Physiol.* 2009;22:200-9.
11. Sato K, Morita M, Ichikawa C, et al. Depigmenting mechanisms of all-trans retinoic acid and retinol on B16 melanoma cells. *Biosci Biotechnol Biochem.* 2008;10:2589-97.
12. Berson D, Osborne R, Oblong JE, et al. Niacinamide: A topical vitamin with wide-ranging skin appearance benefits. In: Patricia K. Farris (ed). *Cosmeceuticals and Cosmetic Practice.* 1sted. London, England, John Wiley & Sons Ltd, 2013:103-12.
13. Bissett DL, Miyamoto K, et al. Topical niacinamide reduces yellowing, wrinkling, red blotchiness, and hyperpigmented spots in aging facial skin. *Int J Cos Sci.* 2004;26:231-38.
14. *Bissett DL, Oblong J, Berge C. Niacinide: A B Vitamin that improves aging facial skin appearance. Dermatol Surg.* 2005;31:860-866.
15. Hui AM, Dabagh B. Topical niacinimide. In: Sivamani, Jagdeo J, Elsner P, Maibach H. *Cosmeceuticals and Active Cosmeceuticals,* Third Ed. CRC Press, Taylor & Francis Group, LLC. 2015:117-126.
16. Tanno O, Ota Y, Kitamura N, Katsube T, Inoue S. Nicotinamide increases biosynthesis of ceramides as well as other stratum corneum lipids to improve the epidermal permeability barrier. *Br J Dermatol.* 2000;143:524-31.
17. Hazozaki T, Minwall , Zhuang J et al. The effect of niacinamide on reducing cutaneous pigmentation and suppression of melanosome transfer. *Br J Dermatol.* 202;147:20-31.
18. Navarrete-Solis J, Castanedo-Cazares JP, Torres-Alvarez B et al. A double-blind, randomized clinical trial of niacinamide 4% versus hydroquinone 4% in the treatment of melasma. *Dermatol Res Pract.* 2011;Published online 2011;July 21.doi: 10.1155/2011/379173.
19. Farris PK, Krutmann J, Le YH, Krol Y. Resveratrol: a unique antioxidant offering a multi-mechanistic approach for treating aging skin. *J Drugs Dermatol.* 2013;12:1389-94.
20. Kode A, Rajendrasozhan S, Caito S, et al. Resveratrol induces glutathione synthesis by activation of Nrf2 and protects against cigarette smoke-mediated oxidative stress in human lung epithelial cells. *Am J Physiol Lung Cell Mol Physiol.* 2008;294:L478-88.
21. Ohguchi K, Tanka T, Ito T, et al. Inhibitory effects of resveratrol dreivatives from dipterocarpaceae plants on tyrosinase activity. *Biosci Biotechnol Biochem.* 2000;67:1587-158.9
22. Ryu JH, Seok JK , An SM et al. A study of the human skin-whitening effects of resveratrol triacetate. *Arch Dermatol Res.* 2015;307:239-247.
23. Ortiz-Ruiz CV, Bema J, Rodriquez-Lopez JN et al. Tyrosinase-catalyzed hydroxylation of 4-hexylresorcinol, an antibrowning and depigmenting agent: A kinetic study. *J Agric Food Chem.* 2015;63:7032-40.
24. Makino ET, Mehta RC, Banga A, et al. Evaluation of a hydroquinone-free skin brightening product using in vitro inhibitionof melanogenesis and clinical reduction of ultraviolet-induced hyperpigmentation. *J Drugs Dermatol.* 2013;12:s16-s20.

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