

Evaluation of a Kojic Acid, Emblica Extract, and Glycolic Acid Formulation Compared With Hydroquinone 4% for Skin Lightening

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Hydroquinone has been the standard prescription agent for skin lightening; however, its use recently has become controversial. Hydroquinone is banned in Europe and parts of Asia because of potential long-term consequences, including carcinogenesis when orally consumed. These concerns have stimulated research to develop alternative skin lightening agents with efficacy comparable to hydroquinone but with a better safety profile. This double-blind study examined the skin lightening ability of a topical formulation containing kojic acid, emblica extract, and glycolic acid compared with prescription generic hydroquinone cream 4%. Eighty multiethnic participants with mild to moderate facial dyschromia were randomly assigned to use the study product or hydroquinone 4% twice daily for 12 weeks to evaluate product efficacy, tolerability, and safety using investigator assessment, participant assessment, and dermospectrophotometry. Study results demonstrated efficacy parity between the study product and hydroquinone 4%. Thus this novel skin lightening preparation is an alternative to hydroquinone 4% for participants with mild to moderate facial dyschromia.

Cutis. 2010;86:153-158.

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This study was supported by an educational grant from L'Oréal.

Dr. Draelos is a consultant for and received a research grant from L'Oréal. Ms. Yatskayer, Ms. Bhushan, and Drs. Pillai and Oresajo are employees of L'Oréal.

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The standard prescription treatment of facial dyspigmentation is topical hydroquinone.¹ Hydroquinone has been part of the dermatologic armamentarium for many years, predating the advent of the US Food and Drug Administration. In recent years, its safety has been questioned. Hydroquinone is banned in Europe and parts of Asia.² Concern arose when rodents fed hydroquinone experienced carcinogenesis.³ Hydroquinone, a phenolic compound chemically known as 1,4-dihydroxybenzene, functions by inhibiting the enzymatic oxidation of tyrosine and phenol oxidases. It covalently binds to histidine or interacts with copper at the active site of tyrosinase. It also inhibits RNA and DNA synthesis and may alter melanosome formation, thus selectively damaging melanocytes. These activities suppress the melanocyte metabolic processes, inducing a gradual decrease of melanin pigment production.⁴

Hydroquinone is a highly unstable compound that undergoes rapid oxidation when exposed to air, causing skin irritation.⁵ When hydroquinone oxidizes, it changes from a creamy white color to yellowish brown and finally to dark brown. Oxidized hydroquinone is not efficacious in skin lightening. Issues regarding the safety of topical hydroquinone arise because it is a strong oxidant that is rapidly converted to the melanocyte toxic products *p*-benzoquinone and hydroxybenzoquinone. These by-products may cause depigmentation.

Safety concerns posed by regulatory agencies worldwide created the need for a nonhydroquinone topical skin lightening agent. Although

hydroquinone is the most efficacious substance for lightening skin, research aimed at developing other skin lightening ingredients with efficacy comparable to hydroquinone has progressed. One approach to enhancing the skin lightening effect of various ingredients is to combine them in formulations to maximize efficacy.

The most popular skin lightening agent used in combination formulations in the Orient is kojic acid, chemically known as 5-hydroxy-2-(hydroxymethyl)-4-pyrone.⁶ It is a chelation agent produced by several species of fungi, especially *Aspergillus oryzae*, and is a by-product of malted rice fermentation used to manufacture sake.⁷ It also is a well-known skin lightening ingredient that inhibits tyrosinase activity by binding to copper.^{8,9} To increase the skin lightening activity of kojic acid, it may be combined with glycolic acid as a penetration enhancer.

Kojic acid efficacy also can be increased by adding other skin lightening agents, such as arbutin, aleosin, ascorbic acid, soy extracts, or *N*-acetylglucosamine. One proposed combination is to add an aqueous extract from *Emblica officinalis*, also known as Indian gooseberry or amla. *Emblica* has antioxidant and skin lightening properties.¹⁰ Tannins from *emblica* inhibit melanogenesis, as demonstrated in human melanocyte cultures.¹¹

A successful skin lightening alternative to hydroquinone should remove existing pigment from the skin, decrease melanin synthesis, and prevent melanin transfer to the keratinocytes. Most of the currently marketed products do not achieve all of these goals. This research examined the skin lightening effect of a new formulation containing kojic acid, *emblica* extract, and glycolic acid by comparing it with hydroquinone cream 4% in multiethnic participants with mild to moderate facial dyschromia.

Materials and Methods

Eighty multiethnic participants (White, Hispanic, Asian, Middle Eastern, and light to medium skin tone black individuals) aged 25 to 60 years with mild to moderate facial dyschromia were recruited in this single-center, 12-week, double-blind study. Suitable forms of facial dyschromia included melasma and lentigines. The study was approved by an institutional review board and participants provided written informed consent. Participants were instructed to use only the provided study cleanser and study sunscreen. Forty participants were randomized to apply the study product (kojic acid, *emblica* extract, and glycolic acid formulation) twice daily to the entire face, and the remaining 40 participants

applied generic hydroquinone cream 4% twice daily to the entire face. Neither the dermatologist investigator nor the participants knew the identity of the product assignments.

Participants with any dermatologic disorder that might interfere with the accurate evaluation of facial dyschromia were excluded. Other exclusion criteria included participants who were pregnant, planning a pregnancy, or breastfeeding; used any topical facial medication, topical retinoid, or other cosmeceutical preparation within 2 weeks of study enrollment; and had a prior hypersensitivity reaction to the ingredients in any study products.

Investigator grading was performed at baseline, week 4, week 8, and week 12 on a 4-point ordinal scale (0=none; 1=mild; 2=moderate; 3=severe). Efficacy evaluation parameters included skin texture/smoothness, clarity, even tone, dark spot size and intensity, hyperpigmentation, radiance, and overall appearance. Tolerability was simultaneously assessed regarding burning/stinging, erythema, peeling, and dryness on the same 4-point scale.

Participants were asked to assess skin feel, tone, discolorations, radiance, and youthful appearance on a 9-point Likert scale ranging from disagree completely to agree completely. These assessments were made at baseline, week 4, week 8, and week 12.

Pigment lightening was assessed as compared with baseline. Observational data were confirmed with bioinstrumentation at baseline, week 4, week 8, and week 12. A dermospectrophotometer reading on the melanin scale was used to assess improvement in facial pigmentation at an investigator-selected target site noted on a facial map at baseline for reproducibility. One well-demarcated target site of observable pigmentation was chosen to increase the accuracy and reproducibility of the dermospectrophotometer readings. The investigator selected the target site based on the following criteria: representative of pigmentation on the entire face, easy access by the dermospectrophotometer, and sufficient size to cover the entire aperture of the dermospectrophotometer. Duplicate readings were taken at each evaluation and averaged based on the standard methodology currently used for dermospectrophotometer application in the skin care industry. Because of the multiethnic nature of the study population, longitudinal comparison for both treatment groups was made by comparison with baseline.

Results

Seventy-nine of 80 participants completed the 12-week study; 1 participant was lost to follow-up. No adverse events or adverse experiences occurred

Table 1.

Investigator Skin Attribute Assessment^a

Attribute	Week 4		Week 8		Week 12	
	Study Product, %	HQ 4%, %	Study Product, %	HQ 4%, %	Study Product, %	HQ 4%, %
Lack of skin texture/smoothness	-12	-20 ^b	-40 ^c	-39 ^c	-66 ^c	-67 ^c
Lack of clarity	-13	-19 ^b	-28 ^c	-32 ^c	-32 ^c	-38 ^c
Lack of even tone	-7	-11	-20 ^b	-26 ^c	-33 ^c	-31 ^c
Dark spot size	0	-3	-8	-5	-19 ^b	-20 ^b
Dark spot intensity	-2	0	-12	-5	-24 ^c	-25 ^b
Hyperpigmentation	-7	-8	-20 ^b	-20 ^b	-31 ^c	-34 ^c
Lack of radiance	-11	-18 ^b	-38 ^c	-31 ^c	-49 ^c	-50 ^c
Overall appearance	-6	-11	-28 ^c	-27 ^c	-38 ^c	-41 ^c

Abbreviation: HQ, hydroquinone.

^aPercentage improvement in each skin attribute compared with baseline analyzed longitudinally for the study product (kojic acid, emblica extract, and glycolic acid formulation) and HQ cream 4% to demonstrate parity. Assessments were made on a 4-point ordinal scale by the dermatologist investigator (0=none; 1=mild; 2=moderate; 3=severe).

^b $P < .05$.

^c $P < .001$.

during the study. Compliance was determined from weekly diaries and all participants who completed the study were included in the final data analysis. The investigator and participant data were analyzed with a Mann-Whitney test for nonparametric data with significance defined at $P \leq .05$. The dermospectrophotometer data were analyzed with a t test.

Investigator Assessment—The investigator assessed the efficacy criteria of skin texture/smoothness, clarity, even tone, dark spot size and intensity, hyperpigmentation, radiance, and overall appearance (Table 1). At week 4 there was a statistically significant improvement in skin texture/smoothness ($P = .016$), clarity ($P = .005$), and radiance ($P = .003$) observed in the hydroquinone 4% treatment group compared with baseline, but no changes were noted with the study product. By week 8, highly statistically significant improvement was seen in skin texture/smoothness, clarity, radiance, and overall appearance with both hydroquinone 4% and the study product ($P < .001$). In the hydroquinone 4% treatment group at week 8,

statistically significant improvement also was seen for even tone ($P < .001$) and hyperpigmentation ($P = .010$). For the study product at week 8, statistically significant improvement also was seen for even tone ($P = .003$) and hyperpigmentation ($P = .007$). Continued highly statistically significant improvement was seen at week 12 with both hydroquinone 4% and the study product for skin texture/smoothness, clarity, even tone, hyperpigmentation, radiance, and overall appearance ($P < .001$). In the hydroquinone 4% treatment group at week 12, statistically significant improvement also was seen in dark spot size ($P = .015$) and dark spot intensity ($P = .003$). In the study product group at week 12, statistically significant improvement also was seen in dark spot size ($P = .021$) and dark spot intensity ($P < .001$). No statistically significant difference between the pigment lightening abilities of hydroquinone 4% or the study product was seen at weeks 8 or 12.

The Figure demonstrates the representative results of a participant with extensive lentigines from photodamage before and after 12 weeks of



Participant with extensive lentiginos from photodamage before (A) and after 12 weeks of treatment with the study product containing kojic acid, emblica extract, and glycolic acid (B).

treatment with the study product. Photographically, the participants using hydroquinone 4% and the study product achieved similar results.

Tolerability—The investigator assessed the tolerability criteria of burning/stinging, erythema, peeling, and dryness. There was no statistically significant change in burning/stinging, erythema, peeling, or dryness with either study product or hydroquinone 4% as assessed by the investigator after 12 weeks of use. No irritant or allergic contact dermatitis occurred during the course of treatment. Fifteen participants using hydroquinone 4% complained of a foul smell. Ten participants noted stinging associated with the study product, but no participant discontinued the study because of this symptom.

Participant Assessment—The summary of the participant self-assessment questionnaire is shown in Table 2. Overall, both products were equally rated by the participants. No statistically significant differences were observed longitudinally at weeks 4, 8, and 12 within product groups or between product groups, which may reflect the qualitative and subjective nature of the self-assessment.

Instrumental Assessment—The dermospectrophotometer was used to determine if skin lightening occurred in a target site identified at baseline. The readings were taken in duplicate at each visit and averaged. Because of the multiethnic nature of the study population, the best analysis was believed to be a longitudinal comparison of both study groups.

Dermospectrophotometer readings must be compared with baseline for each participant and evaluated as change from baseline because the absolute reading has no meaning. No statistically significant skin lightening occurred at week 4 in either treatment group. By week 8, both the hydroquinone 4% ($P=.012$) and study product ($P<.001$) groups demonstrated statistically significant pigment lightening. This improvement in pigmentation continued into week 12 with hydroquinone 4% and study product both showing statistically significant pigment lightening of the target spot as measured by the dermospectrophotometer ($P<.001$).

Comment

Discoloration of facial skin is the most common cosmetic complaint worldwide. There are many different types of facial dyspigmentation. One form, common in individuals of all Fitzpatrick skin types, is the presence of solar lentiginos on the cheeks. Dyspigmentation also may take the form of mottled hyperpigmentation on the upper outer forehead, lower lateral jawline, and upper lip. This type of pigmentation, known as melasma, is seen in post-pubertal women of all ages and all skin colors but is more common in lighter-skinned individuals. It can be induced by the normal female production of estrogen, ingestion of birth control pills, or pregnancy. This research examined the effect of a kojic acid, emblica extract, and glycolic acid skin lightening preparation compared with hydroquinone 4%

Table 2.

Participant Self-assessment^{a,b}

Attribute	Study Product			Hydroquinone 4%		
	Week 4	Week 8	Week 12	Week 4	Week 8	Week 12
Skin feels exfoliated	6.0	5.0	7.0	6.0	5.0	6.0
Skin texture feels smoother	5.5	6.0	7.0	6.0	6.0	7.0
Skin tone appears more even	5.0	5.0	6.0	5.6	6.0	7.0
Skin discolorations appear diminished	5.0	4.8	6.0	5.0	6.0	7.0
Skin appears more radiant	5.0	5.1	6.0	5.5	6.0	6.0
Skin appears clearer	6.0	5.1	7.0	6.0	6.0	7.0
Product improves the overall appearance of skin	6.0	5.2	6.0	6.0	6.0	7.0
Skin appears younger looking	5.0	5.0	5.5	5.0	6.0	7.0
Skin appears younger looking by this many years	2.6	2.3	3.3	2.7	2.7	3.8

^aAssessed on a scale of 1 (disagree completely) to 9 (agree completely). Values represent average Likert scale score.

^bNo statistically significant differences were noted between the study product (kojic acid, emblica extract, and glycolic acid formulation) and hydroquinone cream 4%.

in the treatment of facial dyschromia (melasma and lentigines).

The findings indicate that the study product was well-tolerated with a few participants experiencing some stinging, which is probably due to the glycolic acid in the formulation. The products were equally effective in all Fitzpatrick skin types. In addition, the study product showed parity with hydroquinone 4% after 8 and 12 weeks of use. However, hydroquinone 4% did demonstrate faster pigment lightening after 4 weeks of application than the study product, according to the investigator assessment. The participants' ratings showed parity between both the study product and hydroquinone 4% at week 4. This discrepancy may be due to the more critical evaluation of the dermatologist investigator compared with the evaluation of the naïve participants.

There are dermatologic challenges in conducting pigment lightening studies that should be discussed. Not all pigmentation on the face is of the same severity and not all melanin is deposited at the same depth within the skin, which means

that the investigator must make a visual average of overall improvement while visible dyspigmentation may remain on the face. In addition, participant sun exposure can cause problems in demonstrating product efficacy. For this reason, the study was limited to 12 weeks and was run in only one season, thus avoiding an increase in casual sun exposure from winter to spring or a decrease in casual sun exposure from summer to fall. The response of the skin to pigment lightening preparations can vary by Fitzpatrick skin type and by age. This study enrolled a balanced population to realistically evaluate the efficacy of the study product. Additionally, no currently available skin lightening preparation produces dramatic results. For this reason, the study product was compared with hydroquinone, the currently accepted standard for skin lightening. The results of this study should be evaluated with these considerations.

This research is a start in the development process of formulations to replace hydroquinone. The study product containing kojic acid, emblica extract, and glycolic acid could be a suitable alternative

to hydroquinone 4% in treating mild to moderate facial dyschromia.

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