

# The Combination of Glycolic Acid and Hydroquinone or Kojic Acid for the Treatment of Melasma and Related Conditions

ALICIA GARCIA, BS  
JAMES E. FULTON, JR, MD, PhD

**BACKGROUND.** Melasma continues to be a difficult problem. Although the cause is genetic, the condition is aggravated with sunlight, birth control pills, and pregnancy. Although hydroquinone is effective and has been available for years, a new product, kojic acid, has the advantage of being pharmaceutically more stable and, also, a tyrosinase inhibitor.

**OBJECTIVE.** To evaluate on melasma and related conditions two similar formulations of glycolic acid/hydroquinone and glycolic acid/kojic acid. The therapeutic index of the two formulations is examined.

**METHODS.** Thirty-nine patients were treated with kojic acid on one side of the face and hydroquinone in a similar vehicle on the other side of the face. The results were documented by a clinical

investigator and with Wood's light examination combined with ultraviolet light photography.

**RESULTS.** Fifty-one percent of the patients responded equally to hydroquinone and kojic acid. Twenty-eight percent had a more dramatic reduction in pigment on the kojic acid side; whereas 21% had a more dramatic improvement with the hydroquinone formulation. These results were not statistically different. The kojic acid preparation was more irritating.

**CONCLUSION.** Both glycolic acid/kojic acid and glycolic acid/hydroquinone topical skin care products are highly effective in reducing the pigment in melasma patients. Both formulations should be available to the dermatologist to satisfy the patient's preferences. *Dermatol Surg* 1996;22:443-447.

Perhaps there is no more difficult disease to treat in dermatology than melasma. Although the predisposition to melasma is inherited and probably present at birth, the condition does not become manifest until the female hormone estrogen begins to circulate at adolescence. High levels of estrogen during pregnancy or from birth control pills also aggravate the condition. Excessive sun exposure is another common precipitating factor. Usually, the problem develops from the combination of genetics, hormones, and sun.<sup>1,2</sup> These multifactorial causes make treatment difficult. These melanocytes contain estrogen receptors that continually stimulate the cells to become hyperactive.<sup>3</sup> Topical treatments may temporarily blanch the skin but the condition often returns. While it is easy to remove the melasma temporarily with a facial peel, new melanocytes will migrate out of the hair follicles, repave the surface, and new pigment will develop. The melasma may actually be aggravated by this stimulus.<sup>4</sup>

The most useful treatments have been the alcohol gels of hydroquinone. These gels inhibit tyrosinase, the enzyme that converts tyrosine to melanin, and the chronic use of these lotions result in a bleaching of the skin.<sup>5,6</sup> However, excessive use will produce ochronosis in certain individuals,<sup>7</sup> and the oxidation of the hydro-

quinone will result in a brown discoloration of the lotion. These difficulties have led to the search of better formulations and newer compounds. The alcohol gels of hydroquinone augmented with glycolic acid provide more potent bleaching formulas. The glycolic acid decreases the stratum corneum barrier function and accelerates the turnover of the skin. This addition augments the effectiveness of the hydroquinone.<sup>8,9</sup> Another tyrosinase inhibitor is kojic acid (Figure 1). This compound is present in *Aspergillus oryzae* fungus. When

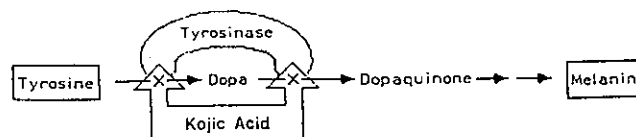
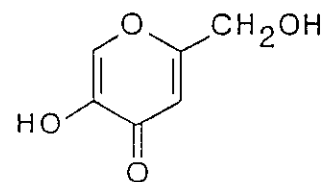


Figure 1. Kojic acid.

*In private practice.*

Address correspondence and reprint requests to: James E. Fulton, Jr, MD, PhD, 1617 Westcliff Drive, Suite 100, Newport Beach, CA 92660.

Table 1. Formulas

	Hydroquinone	Kojic acid
Padimate O	4%	4%
Glycolic acid	5%	5%
Propylene glycol	10%	10%
Hydroquinone	2%	-
Kojic acid	-	2%
Sodium bisulfite	0.1%	-
Alcohol gel	q.s.	q.s.

extracted, this acid has been suggested for the treatment of melasma; however, no published reports are available to review. Our study is designed to document the benefits of a hydroquinone/glycolic alcohol gel on one side of the face versus the application of a similar formula containing kojic acid on the other side of the face. The patients applied the two formulas on the left or right side of the face twice daily for the 3 months of the study. Results were monitored by a clinical investigator and with the ultraviolet (UV) detect camera. This camera is equipped with a special UV filter that accentuates the appearance of the pigment.<sup>10</sup> The camera provides

Table 2. Melasma (39 Patients)

General Data	
No. Females	38
No. Males	1
Age range	24-80 years
Average age	37 years
Aggravating Factors	
Sun	69%
Hormones	28%
Pregnancy	31%
Genetic	28%
Other	10%
Clinical Patterns	
Malar	91%
Mandibular	11%
Central face	31%
Other	6%
Wood's Light Examination	
Epidermal	86%
Dermal	5%
Indeterminate	9%
Results Better with:	
Kojic acid	28%
Hydroquinone	21%
Equal	51%

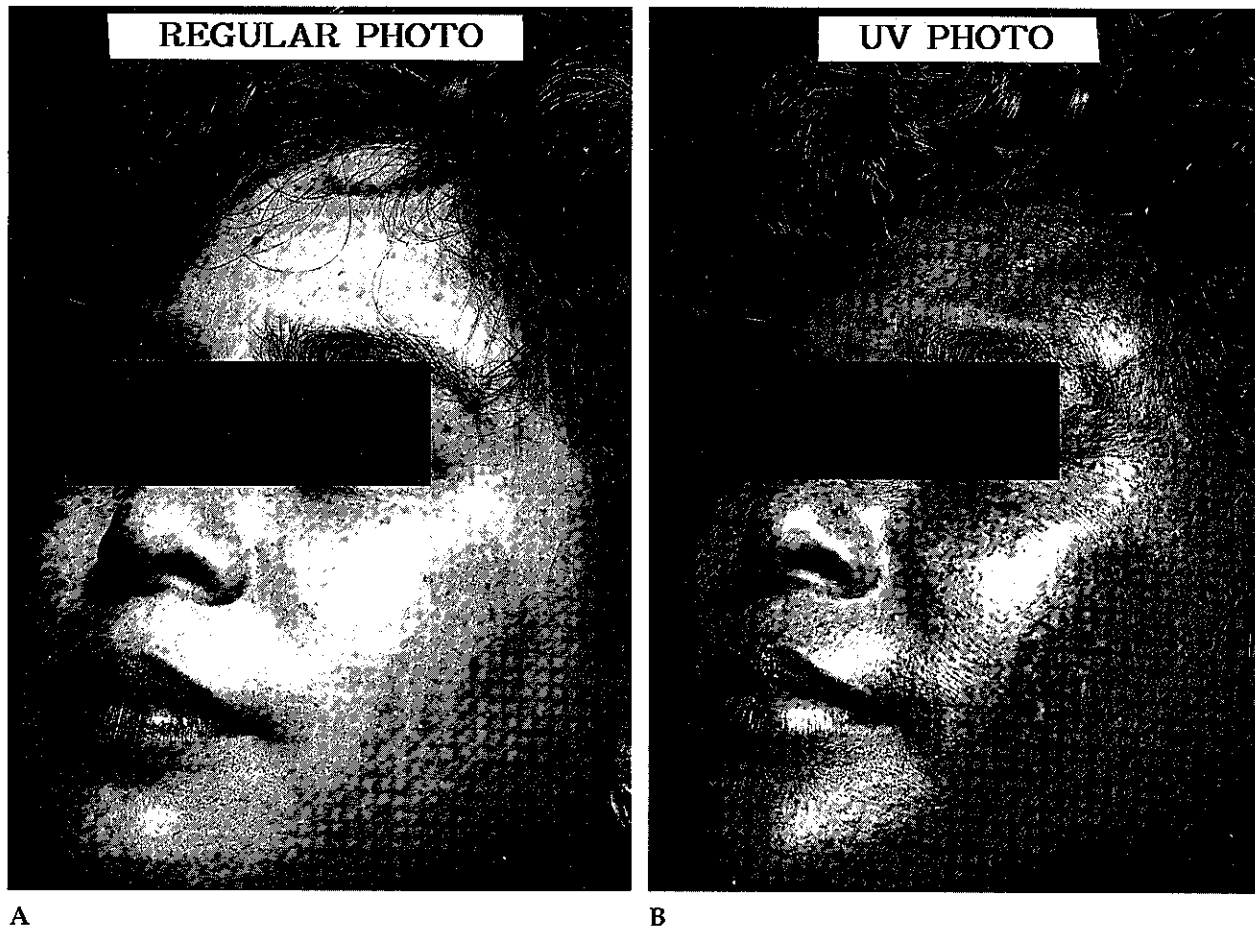


Figure 2. Melasma of the malar area. A) Regular photo. B) Note the more dramatic appearance documented with the UV detect camera.



**Figure 3.** After 3 months of treatment, the melasma on the left side (kojic acid side) is more diminished than the melasma on the right (hydroquinone) side.

objectivity to the evaluation and correlates well with the impressions of the patient and the investigator. The results of this 3-month evaluation are collated in this paper.

## Methods

Thirty-nine patients with hyperpigmented patches on the face were chosen for the study. The extent of their hyperpigmentation was monitored with the Wood's light and the UV detect camera. Their photograph was taken on a fix-staged table with standard film (400 ASA Tri-X film) with and without the use of the UV filter (UV Detail Camera, Faraghan Studio, Philadelphia, PA).

The test formulations were formulated identically, except the antioxidant, sodium bisulfite, was eliminated from the kojic mixture (Table 1). These formulations were stored in opaque bottles. The patients were randomly assigned to apply one of the gels to the right side of the face and the other gel to the left side of the face. Applications were begun once daily. If no excessive peeling or irritation developed, the application rate was increased to two times daily. The desired exposure level resulted in the appearance of a slight rosy red hue to the skin and a slight peel. Repeat photos were taken on a monthly

basis to document the progress of the two bleaching formulas. The impressions of the patients and clinical evaluator were also surveyed. These two opinions were compared with the photographs and an overall percent reduction of pigment was calculated for the left and right face. Results were tabulated for statistical analysis.

## Results

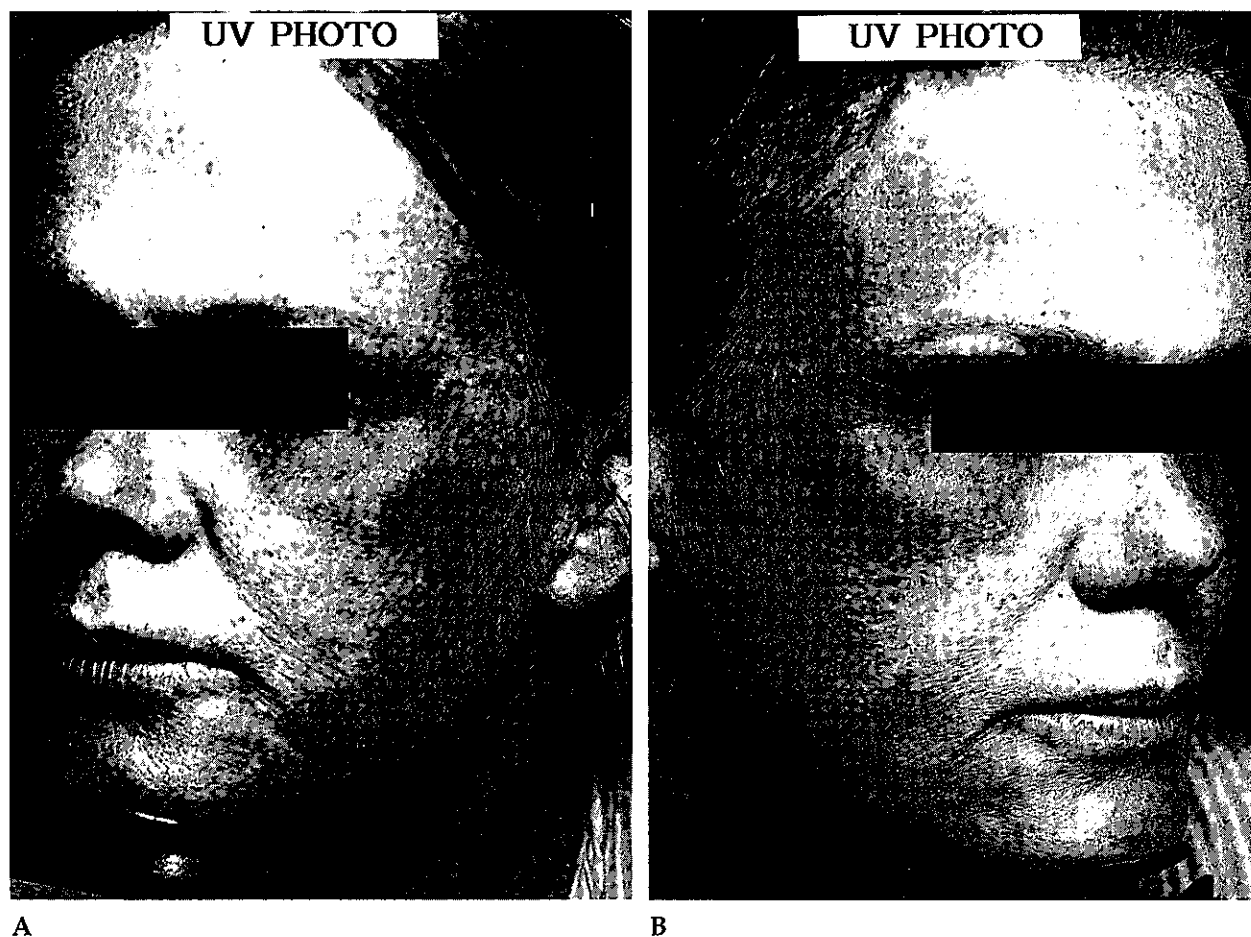
Thirty-nine patients completed the 3-month study (Table 2). Thirty-eight were female and one was male. The age range was 24-80 years of age. The average age was 37 years. Although the melasma tendency was genetic in these patients there were aggravating conditions. In 69% of the cases sun was a factor. In 38% birth control pills flared the problem, and in 31% the condition became apparent during or following a pregnancy. Ninety-one percent had malar lesions, 11% had mandibular lesions, and 31% had central facial involvement. Eighty-six percent were positive to Wood's light examination, 5% were negative and thought to have dermal involvement, and 9% were indeterminate (Figure 2).

The therapeutic benefits began to appear after 4 weeks. All 39 received some improvement after 3 months of treatment (Figure 3). The overall reduction in pigment varied from 10% to 90%. None of the patients was completely clear of hyperpigmentation in their follow-up UV photos. The average overall reduction in pigment intensity in the 39 subjects was 58%. Fifty-one percent of the patients had an equal reduction on both the kojic acid and the hydroquinone side (Figure 4). Twenty-one percent had a more dramatic reduction on the hydroquinone side, and 28% had a more reduction on the kojic side. The difference in pigment reduction between kojic acid and hydroquinone was not significant ( $P > .05$ ).

There were side effects related to the irritancy of the product formulation. Every patient had some burning and desquamation during the initial accommodation phase. The kojic acid formulation was more irritating. However, none of the patients discontinued treatment. Several had to decrease the frequency of applications to every other day or so until accommodation was achieved. Then they applied the gels twice daily. Two patients noticed a slight darkening during the accommodation phase. This disappeared during the subsequent treatment period.

## Discussion

Both formulas are effective in the reduction of the pigmentation from melasma. The kojic acid had the advantage of not oxidizing in the skin care lotion. However, it was a more irritating and a more expensive raw mate-



**Figure 4.** After 3 months of treatment, A) the reactive hyperpigmentation on the left side (hydroquinone side) is more diminished than the B) pigmentation on the right side (kojic acid side).

rial. Hydroquinone had the advantage of being an accepted pharmaceutical and less expensive. The majority of patients could not tell the therapeutic difference between the two formulations. Twenty-eight percent of the patients did better with kojic acid, and 21% did better with hydroquinone. These results were not statistically significant ( $P > .05$ ). The therapeutic results did not correspond to the clinical pattern. The molar mandibular or central facial regions responded equally well. However, the patients with a positive Wood's light examination responded quicker and more dramatically than those with a Wood's light negative pattern.

The dermatologist should have both formulations available. As discussed, the majority of patients will respond equally well to both preparations. However, many patients have already tried hydroquinone and need a new formulation to stimulate interest in a new therapeutic program. The kojic acid formulation is as effective as the hydroquinone. Some patients feel the increased desquamation with this acid has additional therapeutic benefits. The improved long-term pharmaceutical stability of the kojic acid preparation is also an

advantage for those patients who dislike the brown discoloration of the lotion. The availability of both formulations allows the dermatologist to have an alternative. It will be interesting to discover how these formulations will eventually compare to the other new pigment inhibitors such as azelaic acid or *N*-acetyl-4-5-cysteaminyphenol.<sup>11,12</sup>

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