

# Going Beyond Hydroquinone: Alternative Skin Lightening Agents

Nicole C. Syder, BA; Nada Elbuluk, MD, MSc

Disorders of hyperpigmentation—melasma, postinflammatory hyperpigmentation, lichen planus pigmentosus, erythema dyschromicum perstans, and pigmented contact dermatitis, among others—are common and challenging to treat. Although they can affect individuals of all skin types, they most commonly are seen in skin of color; in fact, dyspigmentation is one of the most common chief concerns for which individuals of color see a dermatologist.<sup>1,2</sup>

For many years, hydroquinone (HQ) was one of the main options available for use as a lightening agent. Although effective, it has the risk of causing irritant dermatitis, potentially leading to further dyspigmentation, in addition to the risk of ochronosis with long-term use. It remains an important and useful treatment for pigmentary disorders, but there are numerous other lightening agents that also can be considered in the treatment of disorders of hyperpigmentation.

Herein, we provide recommendations for traditional and newer non-HQ lightening agents that can be considered when treating disorders of hyperpigmentation.

## Traditional Non-HQ Lightening Agents

**Retinoids**—Retinoids are topical vitamin A derivatives that have been used safely and effectively for decades in the treatment of pigmentary disorders. Retinoids have multiple mechanisms of action in improving pigmentation. In addition to impeding tyrosinase induction, they inhibit pigment transfer to keratinocytes and lead to accelerated pigment loss due to epidermal shedding.<sup>3</sup> Over-the-counter formulations include retinol, retinaldehyde, and adapalene. Prescription formulations include tretinoin and tazarotene in different strengths and vehicle formulations.<sup>4</sup>

**Glycolic Acid**—Glycolic acid is derived from sugarcane and is considered an  $\alpha$ -hydroxy acid that leads to rapid desquamation of pigmented keratinocytes.<sup>5</sup> Glycolic acid can not only be used in chemical peels but also in topical creams. It is the most common  $\alpha$ -hydroxy acid peel and is sometimes paired with HQ and other topical lightening agents for increased penetration. Glycolic acid peels are available in concentrations of 20% to 70% and can be used at various depths. When used incorrectly, it can cause redness, burning, and even skin discoloration; however, when used at the proper concentrations and depth according to Fitzpatrick skin type, there typically are no notable adverse effects, and clinical results are favorable.

**Kojic Acid**—Kojic acid is a natural metabolite derived from fungi and is widely used in Asian countries. It works by inhibiting the catecholase activity of tyrosinase<sup>6</sup> and typically is available in concentrations of 1% to 4%. A study suggested that a concentration of 1% or less typically is safe to use for prolonged periods without adverse effects. Although not more effective than HQ as a monotherapy, kojic acid has been shown to have improved efficacy when used in combination with other lightening agents.<sup>7</sup>

**Azelaic Acid**—Azelaic acid works by inhibiting tyrosinase, mitochondrial oxidoreductase activation, and DNA synthesis. It preferentially targets heavily pigmented melanocytes and possesses anti-inflammatory and antibacterial properties.<sup>8</sup> A 20% concentration of azelaic acid was compared to HQ 4% for the treatment of melasma, and results revealed that the liposomal form of azelaic acid was considerably more tolerable than HQ 4% and also more effective.<sup>9</sup>

**Licorice Extracts**—Licorice extracts have been safely used in several cosmeceutical skin lightening products.<sup>10</sup>

From the Department of Dermatology, Keck School of Medicine, University of Southern California, Los Angeles.

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Correspondence: Nada Elbuluk, MD, MSc, Department of Dermatology, Keck School of Medicine of USC, 830 S Flower St, Ste 100, Los Angeles, CA 90017 (nada.elbuluk@med.usc.edu).

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The main active compounds in licorice root are glabridin and liquiritin, which work to disperse melanin. These compounds often are used topically at concentrations of 10% to 40%. A study by Amer and Metwalli<sup>11</sup> found that topical liquiritin produced a reduction of pigmentary intensity, with 80% of patients showing an excellent response, which was described as no difference between the previously pigmented area and the normal skin surrounding it.

**Aloesin**—Aloesin is a low-molecular-weight glycoprotein found in aloe vera plants. Its mechanism of action includes competitive inhibition of the dihydroxyphenylalanine oxidation site, resulting in the inhibition of tyrosinase.<sup>12</sup> It often is combined with arbutin for an enhanced lightening effect.

**Niacinamide**—Niacinamide is a form of vitamin B<sub>3</sub> that works by suppressing the transfer of melanosomes to keratinocytes.<sup>13</sup> In addition to its skin lightening effects, it also is photoprotective and antimicrobial, and its tolerability and safety have led to its inclusion in many cosmetic and prescription products.<sup>14</sup>

**Ascorbic Acid**—Ascorbic acid affects the monophase activity of tyrosinase, thus reducing the synthesis of melanin. It also serves as an antioxidant in the skin by preventing the production of free radicals that can induce melanogenesis.<sup>15</sup> Although it tends to be well tolerated with a low adverse effect profile, its relative instability and varying permeability can present a challenge. It is less effective as a monotherapy, so it often is combined with other lightening ingredients for greater efficacy.

**Corticosteroids**—Topical corticosteroids are anti-inflammatory and impact melanogenesis, though the mechanism of action of the latter has not been fully elucidated.<sup>16,17</sup> Low- to mid-potency topical steroids often are used in conjunction with skin lightening products to diminish irritation and decrease inflammation.<sup>18</sup> However, prolonged use of corticosteroids can lead to cutaneous adverse effects such as striae, hypopigmentation, and acne, as well as systemic side effects if there is sufficient absorption over time.

**Soybean Extracts**—Soybean extracts contain serine protease inhibitors that reduce the transfer of melanosomes into keratinocytes by inhibiting the PAR-2 (protease-activated receptor 2) pathway.<sup>19,20</sup>

**Ellagic Acid**—Ellagic acid is found in common plants such as eucalyptus and strawberry as well as green tea.<sup>21</sup> It works as an antioxidant and decreases melanogenesis through inhibition of tyrosinase activity.

**Paper Mulberry**—Paper mulberry extract comes from the roots of the *Broussonetia papyrifera* tree and functions by inhibiting tyrosinase activity. It is widely used in South Africa and Europe.<sup>22</sup>

**Resveratrol**—Resveratrol is an ingredient extracted from *Morus alba* L and functions as an antimelanogenic agent by directly inhibiting tyrosinase as well as transcriptional and posttranscriptional processing of tyrosinase.<sup>23</sup> It also holds antiproliferative, anti-inflammatory, and

antioxidant properties and has widely been used for anti-aging and skin lightening purposes.<sup>24</sup>

### Newer Non-HQ Lightening Agents

**Silymarin**—Silymarin (also known as milk thistle [*Silybum marianum*]), is a polyphenolic flavonoid that possesses anticarcinogenic, antioxidant, and anti-inflammatory properties. It prevents melanin production in a dose-dependent manner by inhibiting levodopa (L-dopa) oxidation activity of tyrosinase and also reduces the expression of tyrosinase protein.<sup>25</sup> In combination with vitamins C and E and hexylresorcinol, silymarin has been found to reduce the effects of photodamage, brighten skin, improve evenness and lines, as well as improve global facial appearance.<sup>26</sup>

**Malassezin**—Malassezin is an indole produced by *Malessezia furfur* yeast and has recently been investigated for melanogenesis suppression. Grimes et al<sup>27</sup> assessed the efficacy of topical malassezin in 7 patients with facial hyperpigmentation applied twice daily for 14 weeks. Punch biopsies were taken at weeks 0, 8, 14, and 22. Biopsies from weeks 8 and 14 demonstrated reduced epidermal melanin compared to baseline in all participants; however, at 22 weeks, biopsies showed no difference in melanin content compared to baseline, indicating a temporary process induced by the malassezin.<sup>27</sup> More clinical studies are needed to investigate this further.

**N-acetyl-glucosamine**—N-acetyl-glucosamine is an aminosaccharide that inhibits the glycosylation of tyrosinase as well as its function in melanogenesis.<sup>28</sup> It is synthesized and included in topical products for wound healing, rhytides, moisturization, and pigmentation disorders.

**Topical Tranexamic Acid**—Tranexamic acid traditionally has been used orally for the treatment of menorrhagia but also has been found to be beneficial as a therapy for hyperpigmentation and erythema. Tranexamic acid interferes with plasmin activity, thus indirectly inhibiting melanogenesis while also inhibiting angiogenesis by targeting vascular endothelial growth factor (VEGF) receptors.<sup>29</sup> It also leads to an increase in the levels of  $\beta$ -endorphin and  $\mu$ -opioid receptors as well as the expression of estrogen receptor  $\beta$  on the surface of mast cells.<sup>30</sup> Its oral benefit led to the development of topical formulations, typically in 2% to 5% concentrations. It has proven particularly beneficial in the treatment of melasma due to its effects on improving pigmentation, erythema, and skin barrier function.<sup>31</sup> Topical tranexamic acid has a relatively high safety profile, with minor side effects such as transient skin irritation and erythema being reported.<sup>32</sup>

**Cysteamine**—Cysteamine inhibits tyrosinase, peroxidase, and chelating copper ions necessary for melanogenesis. It has proven to be effective in treating melasma and chronic severe postinflammatory hyperpigmentation when used in a 5% cream formulation.<sup>33,34</sup> Lima et al<sup>35</sup> were the first to compare the effects of topical cysteamine to HQ in the treatment of facial melasma. They found

that the mean reduction in modified Melasma Area and Severity Index score was 24% for cysteamine and 41% for HQ after 60 days. There were no severe adverse effects with either treatment group.<sup>35</sup>

## Final Thoughts

Hydroquinone remains the gold standard for treatment of hyperpigmentation; however, its side-effect profile and risk of ochronosis with long-term use has ushered in various other safe and effective skin lightening agents that can be used as monotherapies or in combination with other lightening agents. Many of these products also can be used effectively with procedural treatments such as chemical peels, lasers, and microneedling for enhanced absorption and efficacy. As newer agents are developed, additional well-designed studies will be needed to determine their safety and efficacy in different skin types as well as their role in the treatment of pigmentary disorders.

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