

Topicals for Facial Hyperpigmentation

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Facial hyperpigmentation is among the most common signs of photoaging. Many patterns can be seen. Focal hyperpigmentation in the form of small lentigines across the lateral cheeks usually begins at about 25 to 30 years of age, depending on cumulative sun exposure, with continued accumulation of lesions throughout life. Hyperpigmentation can also present in the form of melasma, with reticulated pigment over the sides of the forehead, lateral jawline, and upper lip. Lastly, hyperpigmentation can present as overall darkening of the skin from a combination of melanin pigment, fragmented elastin fibers, and residual hemosiderin. Topical treatments for hyperpigmentation are problematic. A successful treatment must remove existing pigment from the skin, shut down the manufacture of melanin, and prevent the transfer of existing melanin to the melanosomes. No available topical agent is able to accomplish all these functions. This article examines the various mechanisms of action for the topical hyperpigmentation formulations that have been identified in the US prescription and over-the-counter (OTC) markets.

Prescription Hyperpigmentation Topical Agents Hydroquinone

Hydroquinone remains the gold standard for hyperpigmentation treatment in the United States. This substance is actually quite controversial, having been removed from the OTC markets in Europe and Asia. Concern arose because oral hydroquinone has been reported to cause cancer in mice when ingested in large amounts. While oral consumption probably is not related to topical application, hydroquinone remains controversial, because it actually is toxic to melanocytes. A phenolic compound chemically known as 1,4-dihydroxybenzene,

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The author reports no actual or potential conflict of interest in relation to this article.

hydroquinone 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. Hydroquinone 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.¹ Hydroquinone is available in both the prescription and OTC US markets. The maximum concentration in OTC formulations is 2%, while most prescription formulations are 4%. It is possible to compound hydroquinone creams as high as 8%, but the formulations are unstable, with rapid oxidation represented by browning of the product. In all concentrations, hydroquinone is unstable, turning brown on contact with air. Upon oxidation, hydroquinone is no longer active, and the product should be discarded. Increasing the potency of prescription hydroquinone formulations has been attempted by adding penetration enhancers such as glycolic acid, sunscreens, and tretinoin as supplemental skin lighteners. Other prescription formulations have microsponges added to create timed delivery of hydroquinone to the skin; some have the hydroquinone placed in a special canister dispenser.

Mequinol

Mequinol is the most recent new skin-lightening agent to be approved for use in the United States. It has also received approval in Europe. It is chemically known as 4-hydroxyanisole. Other names include methoxyphenol, hydroquinone monomethyl ether, and *p*-hydroxyanisole. Mequinol is available in the United States as a 2% concentration; it is commercially marketed as a prescription skin lightener in combination with tretinoin 0.01% as a penetration enhancer and vitamin C, in the form of ascorbic acid and ascorbyl palmitate, to enhance skin lightening. These active agents are dissolved in an ethyl alcohol vehicle. The exact mechanism of action behind the skin-lightening properties of mequinol is unknown; however, it is a substrate for tyrosinase, thereby acting as a competitive inhibitor in the formation of melanin precursors. Unlike hydroquinone, it does not damage melanocytes.

COSMETIC CONSULTATION

Tretinoin

Topical tretinoin is used alone or in combination with hydroquinone as a prescription skin-lightening treatment. The effect of tretinoin on skin pigmentation is seen by a decrease in cutaneous freckling and lentiginosities.² It is the irregular grouping and activation of melanocytes that accounts for the dyspigmentation associated with photoaging,³ but normalization of this change has been histologically demonstrated with retinoids.⁴ While this effect is more dramatic with topical tretinoin, topical retinol has been thought to provide similar effects as a cosmeceutical.

Azelaic Acid

Azelaic acid is available as a gel formulation with a 15% concentration and is approved in the United States for the treatment of rosacea. It is a 9-carbon dicarboxylic acid obtained from cultures of *Pityrosporum ovale* that may be a treatment alternative for individuals allergic to hydroquinone. Although the skin-lightening effects of azelaic acid are mild, several large studies of populations of different ethnicities have compared its efficacy with that of hydroquinone.^{5,6} It, too, interferes with tyrosinase activity but may also interfere with DNA synthesis. Azelaic acid appears to have a specificity for abnormal melanocytes; for this reason, it has been used to suppress the progression of lentigo maligna to lentigo maligna melanoma.

Miscellaneous Skin-Lightening Agents

A number of skin-lightening agents have not reached the prescription market in the United States. 4-Isopropylcatechol is a potent tyrosinase inhibitor that was studied in the 1970s.⁷ *N*-acetyl-4-*S*-cysteaminylphenol is a phenolic thioether amine that affects tyrosinase. It is slightly less irritating than hydroquinone.⁸ A skin-lightening agent known as 4-*N*-butylresorcinol is approved in Japan, but not in the United States, for the treatment of melasma. It is commonly used to treat postinflammatory hyperpigmentation following laser treatment in patients with melasma.

OTC Hyperpigmentation Topical Agents

A variety of OTC hyperpigmentation topical agents is used in cosmeceuticals and cosmetics. None of these is as efficacious as hydroquinone; however, they are considered safe for use in US and worldwide markets.

Ascorbic Acid

Ascorbic acid, also known as vitamin C, is used in the treatment of hyperpigmentation. It interrupts the production of melanogenesis by interacting with copper ions to reduce dopaquinone and blocking dihydrochinindol-2-carboxyl acid oxidation.⁹ Ascorbic acid, an antioxidant,

is rapidly oxidized when exposed to air and is of limited stability. High concentrations of ascorbic acid must be used with caution, as the low pH can be irritating to the skin.

Licorice Extracts

Licorice extracts are used as topical anti-inflammatory agents to decrease skin redness and hyperpigmentation. The active agents are known as liquiritin and isoliquirtin, which are glycosides containing flavonoids.¹⁰ Liquiritin induces skin lightening by dispersing melanin. It is typically applied to the skin in a dose of 1 g/d for 4 weeks to see a clinical result. Irritation is not a side effect.

α -Lipoic Acid

α -Lipoic acid functions as an antioxidant in a variety of antiaging cosmeceuticals, but it may also have very limited skin-lightening properties. It is a disulfide derivative of octanoic acid that is able to inhibit tyrosinase. However, it is a large molecule, and cutaneous penetration to the level of the melanocyte is challenging.

Kojic Acid

Kojic acid, chemically known as 5-hydroxymethyl-4H-pyran-4-one, is among the most popular cosmeceutical skin-lightening agents found in cosmetic-counter skin-lightening creams distributed worldwide. It is a hydrophilic fungal derivative obtained from *Aspergillus* and *Penicillium* species. It is the most popular agent employed in the Orient for the treatment of melasma.¹¹ Some studies indicate that kojic acid is equivalent to hydroquinone in skin-lightening ability.¹² The activity of kojic acid is attributed to its ability to prevent tyrosinase activity by binding to copper.

Aloesin

Aloesin is a glycoprotein of low molecular weight obtained from the aloe vera plant. It is a natural hydroxymethylchromone functioning to inhibit tyrosinase by competitive inhibition at the DOPA oxidation site.^{13,14} In contrast to hydroquinone, it shows no cell cytotoxicity; however, its ability to penetrate the skin is limited by its hydrophilic nature. It is sometimes mixed with arbutin to enhance its skin-lightening ability.

Arbutin

Arbutin is obtained from the leaves of the *Vaccinium vitis-idaea* and related plants. It is a naturally occurring glucopyranoside that decreases tyrosinase activity without affecting messenger RNA expression.¹⁵ It also inhibits melanosome maturation. Arbutin is nontoxic to melanocytes and is used in a variety of skin-lightening agents in Japan at concentrations of 3%. Higher concentrations are

more efficacious than lower concentrations, but paradoxical skin darkening may occur.

Summary

Skin lightening for the treatment of lentiginos, melasma, and postinflammatory hyperpigmentation is a challenge for the dermatologist. Hydroquinone remains the gold standard in the United States despite concerns in Europe and Asia regarding its safety. Many cosmeceutical skin-lightening agents exist, but current formulations are of limited efficacy. Fortunately, research into more efficacious skin-lightening agents is ongoing, with new formulations expected within the next year.

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