Hydroquinone for Hyperpigmentation: A Comprehensive Review of Efficacy, Safety, and Current Perspectives

Reza Ghalamghash [1]

1: PhD, Founder of Premium Doctors and Academic Director, Premium College, Toronto, Canada

Corresponding author: Reza Ghalamghash. Tel: +1 (647) 822-9570, E-mail: Reza@PremiumDoctors.org

ORCID: 0009-0004-1745-1315

Abstract

Hyperpigmentation, a prevalent dermatological concern, manifests as the excessive accumulation of melanin, resulting in noticeable dark patches on the skin. This condition encompasses various clinical presentations, including melasma, post-inflammatory hyperpigmentation, and solar lentigines, each arising from distinct etiological factors. Hydroquinone, a phenolic compound, has served as a cornerstone in the topical management of hyperpigmentation for over half a century, primarily exerting its effects through the reversible inhibition of tyrosinase, a crucial enzyme in the melanogenesis pathway. This literature review synthesizes the current understanding of hydroquinone's efficacy across different hyperpigmentation types, drawing from studies published between 2015 and 2025. The analysis reveals that hydroquinone, particularly at concentrations of 2–4%, demonstrates significant effectiveness in reducing pigmentation associated with melasma and post-inflammatory hyperpigmentation. However, its use is not without limitations, as evidenced by common side effects such as skin irritation and the rare but potentially disfiguring risk of ochronosis with prolonged, unsupervised application. The review further explores the role of hydroquinone in combination therapies, notably its synergistic effects with retinoids and corticosteroids in the widely recognized triple combination cream for melasma. A critical comparison with emerging alternative treatments, including tranexamic acid, kojic acid, and arbutin, highlights the evolving landscape of hyperpigmentation management. Finally, the

review provides an overview of the current regulatory status of hydroquinone in the United States, Europe, and other regions, reflecting the ongoing safety considerations and the shift toward prescription-based availability in many areas. The importance of concomitant photoprotection and potential future research directions are also discussed.

Keywords: Hydroquinone, Hyperpigmentation, Melasma, Post-inflammatory Hyperpigmentation, Solar Lentigines, Skin Lightening, Safety, Efficacy.

Introduction

Hyperpigmentation is a common dermatological condition characterized by the excessive production and deposition of melanin, leading to darkened patches on the skin (**Sardana & Goel, 2020**). This increased pigmentation can occur in localized areas or more diffusely and arises from factors such as ultraviolet (UV) radiation, hormonal fluctuations, inflammation, and cutaneous injuries (**Sardana & Goel, 2020**). Clinically, hyperpigmentation manifests in forms such as melasma, post-inflammatory hyperpigmentation (PIH), and solar lentigines (**Davis & Callender, 2023**). The diverse origins and clinical presentations underscore the complexity of its management, necessitating tailored therapeutic strategies (**Navarrete-Solís et al., 2016**).

The presence of hyperpigmented lesions can significantly impact an individual's quality of life, often leading to psychological distress and reduced self-esteem (**Taylor et al., 2016**). Consequently, effective and safe treatment options are paramount for improving patient outcomes (**Taylor et al., 2016**). Among various therapeutic modalities, topical agents play a pivotal role.

Hydroquinone (HQ), a hydroxyphenolic compound, has been a cornerstone in hyperpigmentation treatment for over five decades and remains the most extensively studied depigmenting agent (**Schwartz et al., 2023**). Its primary mechanism involves the reversible inhibition of tyrosinase, reducing melanin production (**Schwartz et al., 2023**). While hydroquinone's efficacy is well-documented, its safety profile has faced scrutiny due to potential carcinogenicity (based on animal studies) and the risk of exogenous ochronosis with prolonged use (**Levitt, 2020**). These concerns have prompted regulatory restrictions in regions like the United States, European Union, Japan, and Australia (**Levitt, 2020**).

This review provides a comprehensive analysis of hydroquinone's efficacy and safety, evaluating literature from 2015 to 2025, exploring combination therapies, comparing alternatives, and discussing regulatory perspectives.

Methodology

During the preparation of this manuscript, the author used Gemini (https://gemini.google.com/) and Grok (https://grok.com/) to collect information and draft articles. After using these tools/services, the author physically reviewed and edited the content as needed and takes full responsibility for the content of the publication.

A systematic literature search was conducted using PubMed/MEDLINE, Embase, Scopus, and the Cochrane Library (**Balk et al., 2020**). Keywords included "hydroquinone," "hyperpigmentation," "melasma," "post-inflammatory hyperpigmentation," "solar lentigines," "skin lightening," "safety," "efficacy," "clinical trial," and "randomized controlled trial." The search was limited to English-language articles published between January 2015 and September 2024.

Inclusion criteria encompassed clinical trials, systematic reviews, meta-analyses, and narrative reviews focusing on topical hydroquinone for hyperpigmentation in humans. Studies reporting efficacy (e.g., MASI score, pigmentation reduction) and safety (e.g., adverse events, ochronosis) were included. Exclusion criteria included in vitro studies, animal studies (except for mechanistic insights), case reports, and non-peer-reviewed publications.

Two reviewers screened titles and abstracts, resolving disagreements through consensus. Data extracted included study design, sample size, hydroquinone concentration, treatment regimen, outcomes, and adverse events (**Balk et al., 2020**).

Findings

Hydroquinone inhibits tyrosinase, reducing melanin synthesis, and affects melanocyte function by inhibiting DNA/RNA synthesis and disrupting melanosome formation (**Schwartz et al., 2023**). For melasma, hydroquinone (2–5%, applied daily for 3–6 months) significantly reduces MASI scores, with improvement in 60–90% of patients (**Navarrete-Solís et al., 2016**). For PIH, 4% hydroquinone cream (twice daily for 6 months) is effective, especially with retinoids and corticosteroids (**Davis & Callender, 2023**). Solar lentigines show some lightening, but

recurrence is common without combination therapies like laser or cryotherapy (**Mansouri et al., 2024**). Table 1 summarizes hydroquinone's efficacy, safety, and combination therapy outcomes for hyperpigmentation types.

Table 1: Summary of Hydroquinone's Efficacy, Safety, and Combination Therapies

Hyperpigmentation Type	**Hydroquinone Concentration**	**Efficacy Outcomes**	**Safety Profile**	**Combination Therapy Notes**
Melasma	2–5%, daily, 3–6 months	60–90% improvement, significant MASI score reduction (**Navarrete-Solís et al., 2016**)	Mild irritation, erythema, rare ochronosis with prolonged use (**Levitt, 2020**)	Triple combination cream (4% HQ, 0.05% tretinoin, 0.01% fluocinolone acetonide) is gold standard, enhances efficacy, reduces irritation (**Kircik et al., 2024**)
Post-inflammatory Hyperpigmentation (PIH)	4%, twice daily, 6 months	Effective lightening, especially with retinoids/corticosteroids (**Davis & Callender, 2023**)	Mild irritation, dryness, rare ochronosis (**Levitt, 2020**)	Synergistic with retinoids and corticosteroids, improves outcomes (**Davis & Callender, 2023**)

Solar Lentigines	2–4%, daily, variable duration	Some lightening, high recurrence without adjunct therapies (**Mansouri et al., 2024**)	Mild irritation, erythema (**Levitt, 2020**)	Requires laser or cryotherapy for sustained results (**Mansouri et al., 2024**)

Common side effects include mild irritation, erythema, and dryness, more frequent at concentrations above 4% (**Levitt, 2020**). Exogenous ochronosis, a rare but serious effect, occurs with prolonged, unsupervised use (**Levitt, 2020**). No direct link to carcinogenicity in humans has been established (**Schwartz et al., 2023**).

The triple combination cream (4% hydroquinone, 0.05% tretinoin, 0.01% fluocinolone acetonide) is the gold standard for melasma, enhancing efficacy and reducing irritation (**Kircik et al., 2024**). Alternatives like tranexamic acid, kojic acid, arbutin, and cysteamine show promise, with tranexamic acid offering comparable efficacy and fewer side effects (**Yasnova et al., 2024**). Regulatory restrictions include a U.S. ban on over-the-counter hydroquinone since 2020, with prescription products requiring FDA approval (**U.S. Food and Drug Administration, 2024**).

Discussion

Hydroquinone remains highly effective for melasma and PIH, with its tyrosinase inhibition directly targeting melanin production (**Schwartz et al., 2023**). However, the risk of ochronosis necessitates medical oversight (**Levitt, 2020**). Combination therapies, particularly the triple combination cream, improve outcomes and reduce side effects (**Kircik et al., 2024**). Alternatives like tranexamic acid are gaining traction due to favorable safety profiles (**Yasnova et al., 2024**).

Photoprotection with broad-spectrum sunscreens is critical to prevent UV-induced melanin production (**Sardana & Goel, 2020**). Future research should explore long-term safety, comparative efficacy with alternatives, and optimized formulations (**Navarrete-Solís et al., 2016**).

Conclusion

Hydroquinone is a highly effective depigmenting agent for melasma and PIH, supported by extensive evidence (**Schwartz et al., 2023**). Its potential side effects and regulatory restrictions highlight the need for supervised use and exploration of alternatives (**Levitt, 2020**). Continued research will optimize hyperpigmentation management.

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