Review

Hurdles in Melasma Management: An AI-Assisted Review of Placebo- and Hydroquinone-Controlled Clinical Studies (2014–2024)

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Hurdles in Melasma Management: An AI-Assisted Review of Placebo- and Hydroquinone-Controlled Clinical Studies (2014–2024)

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Abstract

Melasma is a chronic hyperpigmentation disorder that significantly impacts quality of life. Given the persistent challenges in melasma management, there is a need to evaluate therapies that may offer long-term treatment. This review analyzes placebo- and hydroquinone (HQ)-controlled interventional studies of melasma published between January 1, 2014, and December 31, 2024. Screening, data extraction, and discussion synthesis were performed with artificial intelligence assistance under human oversight. Treatments were grouped into five categories: HQ-based Standard Treatments, Isolated Molecules as Depigmenting Therapies, Botanical and Antioxidant-Based Therapies, Regenerative and Microenvironment-Modulating Therapies, and Procedure-Assisted and Combination Treatments. HQ remained a key benchmark, although recurrence and tolerability limitations were frequently observed. Several non-HQ or adjunctive approaches demonstrated benefit when administered orally, topically, intradermally, or via iontophoresis. Botanical antioxidants, synbiotics, epidermal growth factor, and platelet-rich plasma also showed promising efficacy. Nevertheless, the evidence base was constrained by small sample sizes, heterogeneous comparators, inconsistent endpoints, mixed objective and subjective assessments, and variable follow-up durations, which prevented meta-analysis. Research on melasma treatment is growing worldwide, with several promising non-HQ and adjunctive strategies emerging. However, standardization of outcomes, comparator selection, and longer follow-up periods is needed to clarify efficacy, tolerability, and relapse prevention throughout diverse skin tones.

Keywords: melasma; hydroquinone; intervention; hyperpigmentation; AI

1. Introduction

Melasma remains a therapeutic challenge due to current treatments often resulting in incomplete clearance and requiring prolonged use, which are associated with frequent relapse [1–3]. Although hydroquinone (HQ) has traditionally been regarded as the gold standard depigmenting agent, its use is constrained by adverse effects, tolerability issues, and limitations on long-term use [1,4,5]. These challenges have increased research into developing alternative depigmenting agents that may provide similar or superior efficacy with improved safety profiles. Consequently, recent clinical research has focused on evaluating novel melasma treatments to determine their potential as safer, more effective therapies for long-term management.

2. Background

2.1. Melasma

Melasma is an acquired skin pigmentation disorder characterized by asymmetrical, hyperpigmented brown to gray-brown patches that develop on sun-exposed areas of the face and neck [6,7]. This disorder predominantly affects women of reproductive age (ages 20-40) with darker

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skin types (Fitzpatrick skin types III-V) [7–12]. Globally, melasma is among the most prevalent pigmentary disorders, with an estimated prevalence ranging from 1% to 50% across various countries [7]. Although melasma is typically asymptomatic and considered a benign condition, its cosmetic impact can significantly affect quality of life because it involves visible areas of the face [6–9,13–15]. Patients frequently report low self-esteem and dissatisfaction with their appearance, which may lead to social withdrawal [16]. In some cases, suicidal ideation has been documented [17,18].

Despite its significant psychosocial impact, the pathogenesis of melasma remains poorly understood. The prevailing theory states that ultraviolet (UV) light exposure stimulates melanocytes, resulting in increased melanin production [19,20]. However, recent research has revealed that melasma is a multifactorial disorder more complex than previously recognized [18]. Multiple factors can exacerbate melasma beyond UV exposure, for example, hyperestrogenic states such as pregnancy, exogenous hormones (such as oral contraceptives and hormone replacement therapy), certain medications (such as antiepileptic and phototoxic drugs), cosmetics, and underlying disorders, including autoimmune thyroid disease [8,18]. Recent cellular and molecular studies have demonstrated that an altered basal membrane, activated melanocytes, and secreted factors from keratinocytes, fibroblasts, and endothelial cells contribute to the pathophysiology of melasma [2,21]. Increased vascularity is a hallmark of melasma, as human melanocytes can respond to angiogenic factors by expressing functional vascular endothelial growth factor receptors, such as VEGF [19,22,23]. Furthermore, UV-induced oxidative stress is recognized as a key contributor [24–26]. Hypermelanosis caused by UV radiation likely results from increased melanocyte activity and peroxidation of cell membrane lipids, generating free radicals that stimulate excessive melanin synthesis [27]. Similarly, visible light induces melanocyte activation, particularly in individuals with darker Fitzpatrick skin types, even though it does not cause significant DNA damage or early aging [28–30]. Given the multifactorial pathogenesis of melasma, dermatologists face challenges in prescribing an effective therapy for its management [31].

Melasma treatment modalities include topical, oral, and procedural approaches (e.g., lasers and intradermal injections), with topicals favored due to their ease of application, cost-effectiveness, and higher patient compliance [7,32]. The main treatments are photoprotection and depigmenting agents. However, their efficacy and safety remain suboptimal, indicating that melasma is often resistant or refractory, with frequent relapses [9]. These relapses result from inadequate sun protection and prolonged use of high-concentration depigmenting agents, thereby increasing the risk of adverse effects, especially among patients with skin phototypes IV-V [18]. This emphasizes the need to develop safer, more effective treatments to manage melasma long-term.

2.2. Primary Outcomes of Melasma Research

Assessment of melasma severity and treatment efficacy involves both subjective and objective methods. Clinician-rated composite indices are commonly used in melasma research to quantify baseline severity and monitor treatment responses. The Melasma Area and Severity Index (MASI) is a popular semi-quantitative tool that measures melasma based on the area affected and pigmentation intensity. MASI evaluates four facial regions (forehead, right malar, left malar, chin) by involvement extent (0–6), pigment darkness (0–4), and homogeneity (0–4). It applies fixed regional weights (0.3, 0.3, 0.3, 0.1) to produce a total score from 0 to 48 [33–35]. To improve ease of use and reduce subjectivity, the modified MASI (mMASI) excludes homogeneity while summing darkness and area scores across the same regions, using the same weights, resulting in a score range of 0 to 24 [33,34]. Another melasma scoring system is the Mottled Pigmentation Area and Severity Index (MoPASI), which is based on MASI and assesses mottled facial pigmentation and photodamage by assigning weights to different regions: forehead (0.2), nose/upper lip/chin (0.2), and each cheek (0.3). It scores each region for extent (A), darkness (D), and pigment pattern (P) [36]. These are the primary indices used in clinical studies to assess melasma improvement in treatment groups compared with placebo or hydroquinone (HQ). Additionally, there are objective instrumental assessments of parameters such as Lightness (L*), Individual Typology Angle (ITA°), and Melanin Index (MI), where increases

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in L* and ITA° and decreases in MI indicate reduced pigmentation. The Relative Melanin Value (RMV), which compares melanin levels between lesions and surrounding skin, is measured by devices that measure specific wavelengths of light related separately to melanin or hemoglobin, such as the Mexameter and DermacatchVR. In summary, research studies use various methods to measure hyperpigmentation, and the process is not consistently streamlined.

Given the persistent challenges of relapse, tolerability, and long-term safety in melasma management, there is a need to evaluate therapies that may offer advantages over HQ. This review synthesizes global clinical studies published between 2014 and 2024 that investigated alternative treatments for melasma. In doing so, this review aims to help dermatologists navigate the various options and use it as a guide in prescribing effective therapies for patients with melasma.

3. Methods

3.1. Literature Search

Papers published between January 1st, 2014, and December 31st, 2024, were retrieved from the PubMed database covering a span of 11 years. Two authors independently screened abstracts for eligibility for inclusion in the review using the criteria below. AI resolved any disagreements.

3.2. Inclusion and Exclusion Criteria

The PubMed database was searched on Monday, May 19th, 2025, using the keywords “skin hyperpigmentation treatment”. The filters applied were Full text; Clinical Study; Clinical Trial; Clinical Trial, Phase I; Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Comparative Study; Controlled Clinical Trial; Letter; Multicenter Study; Randomized Controlled Trial; English; Humans; Adult: 19+ years; Exclude preprints; from 2014/1/1 - 2024/12/31. The randomized controlled trials (RCTs) had to be original and include patients with any type of skin hyperpigmentation. Studies in languages other than English were excluded. We manually excluded studies unrelated to melasma.

3.3. Data Extraction

When applicable, the following data were collected from each included published study: title, author, year of publication, country, study design, aim of study, randomization, number of participants, sex, mean age, participant withdrawals or exclusions, duration of participation, skin hyperpigmentation type, intervention, dosage, duration of treatment, outcomes, evaluation, and comparison to control. One author and AI extracted the data; a second author verified it.

3.4. Use of Artificial Intelligence

We incorporated OpenAI’s ChatGPT assistance in two pre-specified, human-supervised steps of the review, as listed in sequence. All final decisions and text are the responsibility of the authors.

(1) Title/abstract screening. ChatGPT (model: GPT-4o) assisted with initial screening against our inclusion/exclusion criteria. We used structured prompts plus out-of-scope psoriasis-specific few-shot exemplars (titles/abstracts with labeled rationales) to calibrate behavior by in-context learning only; no model fine-tuning was performed. The model returned “include/exclude/unclear” calls with short rationales that two human reviewers independently verified; all disagreements and every “unclear” record were adjudicated by a human reviewer.

(2) Discussion of research recommendations. After inclusion decisions were finalized, GPT-5.2 Thinking synthesized recommendations for future research priorities (e.g., trial design, comparators, outcome timing) solely from the included studies and our a priori question framework. Two authors independently edited, verified against the source studies, and approved the final Discussion.

Model provenance, timing, and blinding. GPT-4o screening runs occurred in July–August 2025; GPT-5.2 Thinking RoB2 and Discussion support occurred in January-April 2026. To reduce

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automation bias, human reviewers were initially blinded to AI rationales and unblinded only for discrepancy resolution.

Data provided to ChatGPT. We shared only bibliographic metadata and published titles/abstracts (and full texts where licensed); no patient-level or otherwise sensitive personal data were entered. The out-of-scope psoriasis-specific "training" consisted solely of few-shot exemplars within each session; we did not retrain the underlying OpenAI models.

Compliance with OpenAI policies and privacy. We disclose AI assistance and affirm that human authors reviewed, edited, and take responsibility for all content, per OpenAI's Sharing & Publication Policy [37]. We used only published material and followed our company's data governance rules. Readers can consult OpenAI's pages on data usage and enterprise privacy/retention controls for context (note that enterprise and zero-retention Application Programming Interface options differ from consumer settings).

3.5. Figure Generation

Data processing and visualization were performed in Google Colab (Python). Tabular wrangling with Pandas, and figures were created with Plotly; static, publication-quality images were exported as PNG/SVG/PDF using Kaleido to ensure consistent resolution and sizing.

4. Results and Discussion

We begin by summarizing the paper selection process and characteristics. Using the specified methods, we screened 635 records from PubMed based on their titles and abstracts. In the full-text review stage, we ultimately included 28 papers from 13 countries (Figure 1) that compared various therapies for melasma (Figure 2).

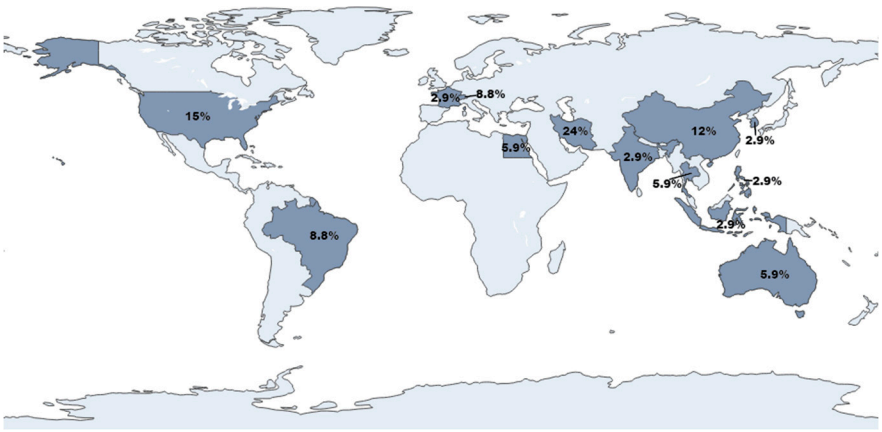

Figure 1. Geographic distribution of included melasma treatment studies (2014–2024). Choropleth world map indicating countries that published research studies following our inclusion/exclusion criteria. The percentages represent the proportion of studies contributed by each country. Countries with zero included trials are shown in neutral gray. Coastlines and borders are for visualization only. n= 28.

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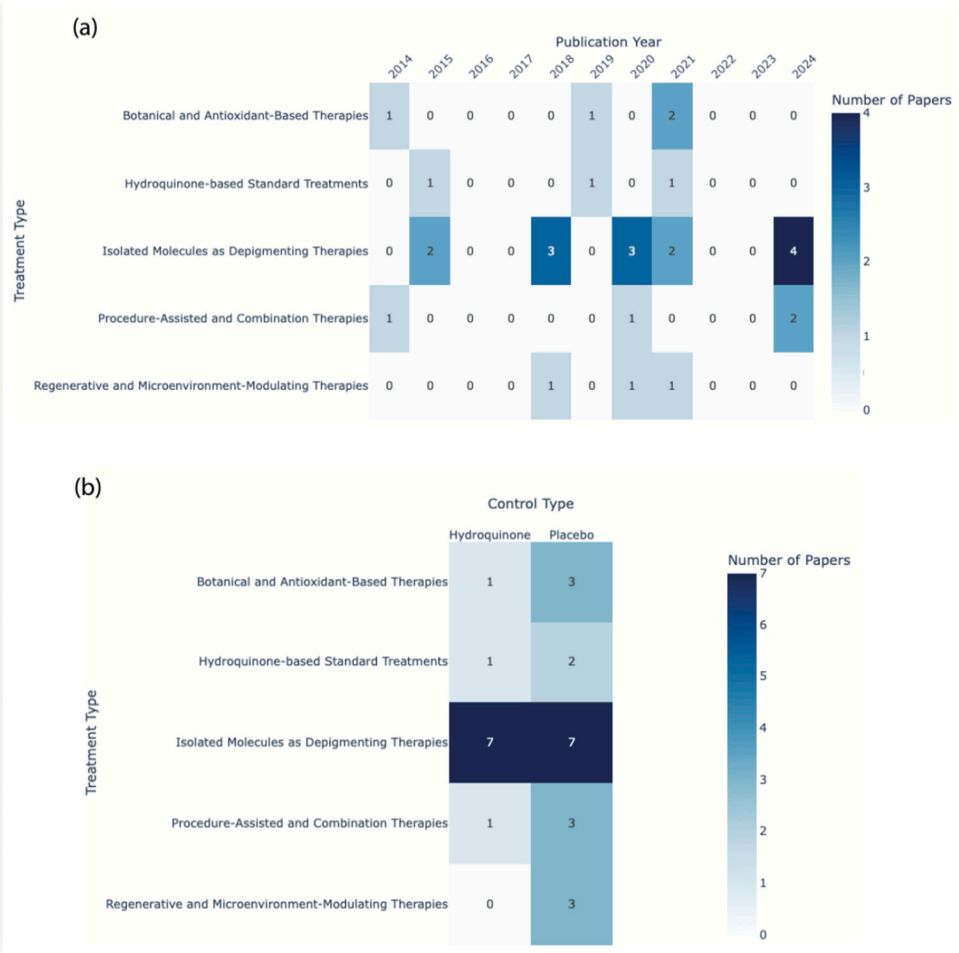

Figure 2. Temporal and methodological distribution of included melasma treatment studies (2014–2024). (a) Heatmap showing the number of published research studies by year and treatment type. (b) Heatmap showing the number of published research studies by treatment and control types. Only studies meeting our prespecified inclusion and exclusion criteria were included. Color intensity reflects the number of papers in each category.

4.1. Hydroquinone-Based Standard Treatments

Hydroquinone (1,4-dihydroxybenzene) has been widely used as a topical depigmenting agent for treating skin hyperpigmentation for the past 60 years [6,13,38]. Hydroquinone (HQ) has become the gold standard for treating melasma at commonly used concentrations ranging from 2–4% [19]. HQ suppresses melanogenesis by competitively inhibiting the tyrosinase enzyme and thereby preventing the conversion of 1-3,4-dihydroxyphenylalanine (DOPA) to melanin [39]. It also influences the formation, melanization, and degradation of melanosomes and alters the membranous structures of melanocytes, ultimately causing melanocyte necrosis by inhibiting RNA and DNA synthesis [27]. In the clinic, optimal improvement is typically observed after approximately two months of treatment, with high relapse rates [8].

Furthermore, a significant proportion of patients do not respond adequately to HQ treatment [18]. Although it is generally well tolerated, mild to moderate side effects, such as irritant and allergic contact dermatitis, have been reported [6,13,18]. Use of higher concentrations should not exceed three months to minimize the risk of severe side effects [6], including post-inflammatory hyperpigmentation, exogenous ochronosis, and "confetti" depigmentation due to melanocyte toxicity [7,9]. Concerns have also been raised regarding the cytotoxic and mutagenic properties of HQ, as it is oxidized by tyrosinase to 1,4-benzoquinone, a metabolite cytotoxic to melanocytes and keratinocytes [8]. Nevertheless, no cases of malignancy or skin cancer have been associated with topical HQ use in humans based on data available until 2021 [13]. Despite this lack of evidence of carcinogenicity, it still has adverse effects that are not compatible with the safety expected of a

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cosmetic product; therefore, several drug regulatory authorities globally have banned topical HQ as a cosmetic depigmenting agent, particularly in Europe [8,31].

A 2019 Iranian study with 20 volunteers aimed to improve the safety profile of HQ by encapsulating it in liposomes and delivering it in a topical formulation [40]. Liposomes are microscopic vesicles composed of phospholipid bilayers that contain aqueous spaces that can encapsulate both water-soluble and lipid-soluble medications, thereby enhancing the efficacy and specificity of these agents [41]. The present study compared the therapeutic effects of topical liposomal HQ with its conventional form in the treatment of melasma over a three-month period [40]. At the end of the study, the MASI score decreased significantly in both the liposomal and conventional HQ groups ($p < 0.001$); however, no significant difference between the groups was observed ($p > 0.05$). Results show that liposomal HQ provides a significant therapeutic effect for melasma but does not surpass conventional methods. The proposed benefit of this liposomal delivery system is reduced skin irritation, controlled cutaneous release, and prolonged moisturizing effects, which may result in fewer side effects. No adverse events were reported. These benefits are particularly relevant for HQ, which has been restricted in cosmetic products by the European Committee due to concerns about long-term side effects.

In 1975, Kligman and Willis introduced "Kligman's Formula" or "Kligman's Trio" [42], a hydrophilic cream formulation comprising 5% HQ, 0.1% dexamethasone acetate (a steroid to calm inflammation), and 0.1% tretinoin (a retinoid to induce epidermal thickening and keratolysis, thereby mitigating atrophoderma caused by topical corticosteroids), and intended for the external treatment of melasma over a three-month period. Due to irritation caused by Kligman's Trio, a new formulation was developed, termed FAHT, which lowers the HQ concentration from 5% to 4%, lowers the concentration of tretinoin to 0.05%, and substitutes dexamethasone acetate for 0.01% fluocinolone acetonide. Fluocinolone reduces melanosome production by decreasing cellular activity, thereby also alleviating the skin irritation and inflammation caused by HQ and minimizing adverse reactions. In 2002, the United States Food and Drug Administration approved Tri-Luma® for the treatment of moderate to severe cases of melasma. Furthermore, in 2015, the China Food and Drug Administration sought to evaluate the safety and clinical effectiveness of the FAHT cream in treating moderate to severe facial melasma in the Chinese population via a 233-volunteer, randomized, double-blind, placebo-controlled, multicenter clinical trial [43]. FAHT cream demonstrated superior efficacy compared to the placebo in managing moderate to severe melasma over an eight-week period, while also exhibiting a high safety profile and being well-tolerated within the Chinese population.

Despite an eight-week FAHT treatment period, recurrence of melasma is observed in some individuals. FAHT should not be used for more than eight weeks to minimize adverse effects such as telangiectasia and skin atrophy [44]. Ongoing research focuses on developing new formulations to complement FAHT for relapse prevention. For instance, a 2021 Indian study with 46 volunteers described a three-phase treatment protocol for melasma [44]. In Phase 1, both experimental and control groups applied FAHT once nightly for eight weeks, accompanied by daily sunscreen application (hybrid SPF 30 containing avobenzone, octocrylene, octyl methoxycinnamate, oxybenzone, and zinc oxide). In Phase 2, the experimental group received a proprietary sunscreen formulation containing phenylethyl resorcinol, nonapeptide-1, aminoethyl phosphinic acid, and antioxidants, applied twice daily for 16 weeks, while the control group used a placebo sunscreen. Phase 3 consisted of an approximately eight-week follow-up period without therapy. The proprietary formulation was more effective than sunscreen alone in maintaining remission, with minimal side effects, enabling longer maintenance therapy and improved relapse prevention, thereby providing better control of melasma with minimal patient inconvenience.

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4.2. Isolated Molecules as Depigmenting Therapies

Cysteamine hydrochloride, also known as beta-mercaptoethylamine hydrochloride, is the simplest stable aminothiol and a potent depigmenting agent recognized for over 50 years [45]. It is naturally produced in the human body as a degradation product of L-cysteine. Cysteamine slows melanogenesis through mechanisms involving the inhibition of tyrosinase and peroxidase, scavenging DOPA quinone, chelating Fe and Cu ions, and shifting eumelanin to pheomelanin production by increasing intracellular glutathione levels [46]. An Iranian and Swiss clinical study with 40 volunteers from 2018 showed significant differences in melasma patients who received 5% cysteamine in comparison to a placebo group at two- and four-months by using measuring tools such as Dermacatch and Mexameter [47]. Another 2015 Iranian and Swiss study, involving 50 volunteers, found that 5% cysteamine creams demonstrate high efficacy in treating melasma [48]. However, complete lesion clearance is not achieved if a patient has resistant melasma that is unresponsive to other therapies, such as HQ. Adverse effects were more common in the treatment group than in the placebo group in both studies, but were primarily transient and resolved within approximately one week of treatment initiation. The adverse effects reported were mainly mild erythema and acne exacerbation. Despite its safety and efficacy, the development of cysteamine as a topical depigmenting agent has been limited by its offensive odor.

A 2021 Australian study randomized 20 participants to receive either topical 5% cysteamine cream or 4% HQ cream for 16 weeks [13]. By week 16, 14 participants completed the study, with 5 in the cysteamine group and 9 in the HQ group. Intention-to-treat analysis revealed a 21.3% reduction in mMASI for the cysteamine group and a 32% reduction for the HQ group, with no statistically significant difference between groups ($p = 0.3$). Side effects were more frequently reported with cysteamine. Two participants experienced skin redness and irritation shortly after application, and one participant reduced application from week 9 onwards due to side effects, which resolved after this adjustment. Another participant withdrew before week 8 due to an acne breakout. The remaining participants in the cysteamine group reported mild to moderate irritation, burning, pruritus, or erythema shortly after application. One participant noted an unusual odor from the cream but was not significantly bothered and continued using it. In the HQ group, one participant reduced use due to moderate irritation, dryness, redness, itch, and a rosacea flare, subsequently withdrawing after 8 weeks. HQ cream was generally better tolerated than cysteamine cream. Despite being discovered decades ago, the pungent odor and side effects of cysteamine limit its use as a topical depigmenting agent.

A better alternative, due to having no odor, is methimazole. Methimazole is an oral antithyroid agent that has recently gained attention for its depigmenting effects when applied topically. Methimazole is reported to exert its depigmenting action through peroxidase inhibition, without the cytotoxicity and mutagenicity of HQ. Peroxidase is an enzyme involved in several stages of melanogenesis, including the oxidation of DOPA to dopaquinone, the oxidative polymerization of melanin monomers to form eumelanin, and the production of pheomelanin [49]. Melanocyte peroxidase plays a central role in this pathway, and its inhibition results in a depigmenting effect. As a peroxidase inhibitor, methimazole has shown potential benefits in melasma management, although few studies have assessed its efficacy. In one 2020 Iranian study, 50 volunteers with melasma were randomly assigned to apply either 5% methimazole or 4% HQ once daily for eight weeks, then volunteers continued using sunscreen only for another 4 weeks [8]. Both groups showed lower MASI scores at week 8, with a greater reduction in the HQ group. By week 12, MASI scores had decreased from baseline in both groups ($p < 0.001$ for methimazole; $p < 0.0001$ for HQ). Notably, the MASI score increased in the HQ group between weeks 8 and 12 ($p = 0.005$), while no significant change was observed in the methimazole group, meaning that a higher relapse rate was observed in the HQ group after discontinuation of treatment. Side effects were similar between the two treatment groups. At week 8, mild-to-moderate erythema was reported in four patients (20%) in the methimazole group and three patients (15%) in the HQ group. Burning was reported by one patient (5%) in each group, and mild-to-moderate dryness occurred in five patients (25%) in both groups. Since methimazole is

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an antithyroid pharmacologic, concerns exist regarding potential adverse effects of methimazole on the thyroid gland due to systemic absorption. However, several studies have confirmed the absence of systemic side effects, as indicated by stable serum TSH levels. Methimazole may represent an alternative treatment for melasma, either as monotherapy or in combination with other depigmenting agents, due to its noncytotoxic and nonmutagenic properties, odorlessness, ability to reduce ultraviolet-induced erythema, and resistance to auto-oxidation. All these factors make it a safe depigmenting agent and have prompted several clinical studies on its safety and efficacy in melasma treatment.

Thiamidol (isobutylamido-thiazolyl-resorcinol) is a recently developed, potent tyrosinase inhibitor specifically designed to inhibit human tyrosinase and has demonstrated efficacy as a cosmeceutical agent for melasma depigmentation [6]. In vitro studies indicate that thiamidol exhibits greater tyrosinase inhibition than HQ, kojic acid, and arbutin, without cytotoxic effects. In a 2021 Brazilian clinical study, 49 volunteers were randomly assigned to apply either a double layer of 0.2% thiamidol twice daily or 4% HQ cream at bedtime for 90 days [9]. Both groups also used tinted sunscreen (SPF 60, PPD 20) during the day. The primary outcome was the mean reduction in mMASI scores, which were 43% for thiamidol and 33% for HQ. No significant difference was observed between the groups in the reduction in mMASI score, indicating that the improvement in melasma with 0.2% thiamidol was comparable to that achieved with 4% hydroquinone cream.

Another cosmeceutical agent is salicylic acid (SA), recognized for its keratin-dissolving, antibacterial, anti-inflammatory, and photoprotective properties [50]. SA has been studied in various formulations, but limited evidence supports the combined use of commercial SA and niacinamide for melasma. A supramolecular form of SA (SSA) is under investigation for melasma treatment. SSA is a novel formulation based on reversible noncovalent bonds that form stable, water-soluble complexes, enabling slow SA release, increased efficacy at low pH, and fewer side effects without the need for an alkali neutralizer. However, direct evidence for SSA's effectiveness in melasma remains limited. A 2024 multicenter study in China involving 300 volunteers evaluated the safety and efficacy of a 30% SSA mask applied once every two weeks for eight cycles (16 weeks) [51]. The mask was applied evenly to the face for up to 20 minutes and paired with a 10% niacinamide essence, which participants used daily after cleansing. Results demonstrated greater and more rapid improvements in mMASI scores and lower Griffiths 10-point scores compared to placebo after 16 weeks, supporting the efficacy of SSA combined with niacinamide in melasma management. The combination of SSA and niacinamide theoretically reduces melanin accumulation and inflammation following UVA exposure, thereby minimizing skin damage and aging.

Although several cosmetic products have undergone clinical testing, few have been directly compared with 4% HQ. A 2020 French study involving 43 volunteers compared the efficacy and tolerability of a skin-lightening cosmetic combination of two products (CCP), a serum and a treatment sunscreen, with those of 4% HQ plus placebo sunscreen over 12 weeks [21]. The CCP routine contained five complementary active ingredients (licorice extract, niacinamide, diacetylboldine, a biomimetic peptide acting as DKK1, and a biomimetic active that downregulates the production of endothelin-1), said to synergistically restore cutaneous homeostasis and target key pathways involved in melasma, such as calcium flux regulation, tyrosinase function, the WNT pathway, melanosome transfer, and endothelin-1 production. In the CCP group, volunteers applied the serum once daily in the evening and SPF 50+ cream once daily in the morning. The HQ control group applied 4% HQ once daily in the evening and SPF 50+ cream once daily in the morning. The sunscreen provided to the HQ group was similar to that in the CCP group but did not contain the depigmenting compounds. By week 12, 90% of volunteers in the CCP group showed improvement in pigmentation, compared to 79% in the HQ group. Both treatments significantly reduced mMASI scores from baseline throughout the study. The CCP group experienced a 43% decrease in mean mMASI score ($p = 0.004$), while the HQ group saw a 37% reduction ($p = 0.0005$). No statistically significant difference was observed between the two groups during the study.

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In 2020, a USA study involving 16 volunteers compared a cosmetic topical brightener (CTB) with 4% HQ, applied to opposite sides of the face twice daily for 12 weeks [52]. The HQ-free CTB formulation contained tranexamic acid (TXA), phenylethyl resorcinol, niacinamide, and tetrapeptide-30, all of which target multiple melanogenesis pathways. After 12 weeks, both CTB and 4% HQ produced statistically significant improvements in half-face MASI ($p=0.004$) compared to baseline. No significant differences in half-face MASI scores or overall hyperpigmentation scores were observed between the two treatments at any point during the study. However, only 4% HQ was associated with significant reductions in the melanin index at weeks 4, 8, and 12 compared to baseline. Reported adverse events included a mild rash on the HQ-treated side and mild burning on the CTB-treated side. Overall, both products were well tolerated, with most volunteers experiencing no burning, irritation, itching, or rash. These findings indicate that a combination of cosmetic ingredients can be as effective as HQ in managing melasma and may serve as a safe alternative.

Isonicotinic acid hydrazide (isoniazid) is an oral antibiotic primarily used for tuberculosis treatment, acting by targeting the catalase-peroxidase enzyme in Mycobacterium tuberculosis, which leads to the formation of bactericidal radicals [53]. It has been repurposed as a depigmenting agent due to its promising ability to reduce hyperpigmentation since peroxidase also plays a key role in melanin synthesis by catalyzing the oxidation of tyrosine to dopaquinone. Studies suggest that isoniazid may be metabolized by melanocyte peroxidases, resulting in reduced melanin production and potential hypopigmentation. A 2024 Iranian and Swiss clinical trial with 20 volunteers evaluating topical 10% isoniazid for melasma demonstrated significant reductions in melanin index (MI) and mMASI when applied nightly for three months, with SPF 50 sunscreen used before sunlight exposure [54]. No adverse effects on hepatic enzymes or blood counts were observed, in contrast to the side effects sometimes associated with oral administration. The treatment was well tolerated, with only minor irritation reported in some patients. Overall, topical isoniazid appears to be an effective and safe agent for melasma treatment.

Metformin is an affordable, well-tolerated, and relatively safe medication widely prescribed for diabetes [55]. Metformin's mechanism for treating melasma involves reducing cAMP levels and inhibiting the Wnt signaling pathway, thereby inhibiting melanogenesis. Studies have also shown that metformin decreases the expression of key melanogenesis genes, including tyrosinase, TRP-1, TRP-2, MITF, often independently of the AMPK pathway. Notably, long-term improvements in melasma have been observed following various forms of therapy combined with metformin. The cellular effects of metformin vary depending on the route of administration. Two studies conducted in Egypt by separate research groups investigated different routes of metformin treatment for melasma. One 2024 study with 18 volunteers explored the potential of combining topical metformin with microneedling to treat melasma [56]. Microneedling is a minimally invasive method that facilitates targeted delivery of therapeutic agents through skin microchannels and is associated with a low risk of PIH. The study employed a split-face design to compare the effectiveness of combined microneedling and topical metformin (30% metformin in a vehicle comprising 70% alcohol and 30% propylene glycol) against microneedling and a placebo, with evaluations conducted at baseline, after four sessions, and one week post-treatment by dermatologists. Results demonstrated that the combination therapy significantly outperformed microneedling with placebo, reducing hyperpigmentation and hemi-mMASI scores. Microneedling pre-treatment appeared to enhance the absorption of topical metformin. Over six to eight weeks, pigmentation within patches diminished with a punctate pattern and patches' edges softened. The combined therapy offers a safe, painless, and side-effect-free approach to improve clinical and histopathological outcomes in recurrent cases.

The second Egyptian group investigated cosmetic facial masks in 2024, specifically peel-off masks that enhance the effects of active ingredients by forming an occlusive film as they dry. A split-face study was conducted to assess the effectiveness and safety of a weekly 30% topical metformin peel-off mask compared to placebo in 20 female patients with melasma [57]. Despite metformin being applied only once a week, patients achieved results comparable to those from previous studies using daily lotions and creams with the same concentration, likely due to the occlusive properties of the

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peel-off masks enhancing absorption. In both studies [56,57], no side effects were reported, supporting the favorable safety profile of topical metformin across various delivery methods.

Tranexamic acid (TXA), a well-known hyperpigmentation treatment, is a repurposed antifibrinolytic drug primarily approved for treating cyclic heavy menstrual bleeding and is also used to reduce bleeding during surgery, trauma, and in bleeding disorders [58]. TXA inhibits plasmin, thereby contributing to its anti-inflammatory and skin-brightening effects, making it a promising option for melasma treatment. One 2018 USA and Australian study in 39 volunteers demonstrated that 250mg of TXA taken orally twice daily, combined with sunscreen for three months, followed by three months of sunscreen alone, was effective and superior to placebo in treating moderate to severe melasma [59]. At three months, the TXA group experienced a 49% reduction in mMASI score, compared to an 18% reduction in the placebo group. Patients with severe melasma showed greater improvements than those with moderate melasma. Three months after discontinuing treatment, the TXA group maintained a 26% reduction from baseline, while the placebo group had a 19% reduction.

Topical TXA has also been evaluated at various concentrations and protocols. A liposomal delivery system, previously described for HQ, was evaluated in a 2015 Iranian study that encapsulated TXA. The study assessed the effectiveness of topical liposomal TXA [60]; 23 volunteers applied 5% liposomal TXA and 4% HQ cream to opposite sides of their faces twice daily, along with a designated daytime sunscreen. After 12 weeks, mean MASI scores decreased significantly on both sides ($p < 0.001$), with the 5% liposomal TXA group showing a greater reduction, although this difference was not statistically significant. Mild irritation was reported in three patients using HQ, while no adverse events occurred with TXA.

In addition to topical administration, alternative TXA delivery routes have been explored, including intradermal options. A 2018 comparative study in Iran evaluated the efficacy and safety of intradermal TXA injections versus topical HQ for melasma [61]. Thirty-seven volunteers received three monthly sessions of intradermal TXA injections on one side of the face, while topical HQ was applied nightly to the other side for three months. TXA injections were more effective than daily HQ in reducing melanin levels during the first four weeks ($p = 0.013$). However, after 20 weeks, the overall differences between the two treatments were not statistically significant ($p = 0.17$). These findings suggest that localized intradermal TXA injections may be effective for melasma and could offer advantages over topical HQ monotherapy. Further research is required to clarify the long-term efficacy and safety of this approach, as some volunteers discontinued participation due to acne development from TXA injections (two volunteers), discomfort during injections (one volunteer), and dissatisfaction with improvement (two volunteers). While intradermal injections are effective, they may cause discomfort and hematomas.

4.3. Botanical and Antioxidant-Based Therapies

Botanical depigmenting antioxidants are plant-derived actives that reduce hyperpigmentation by scavenging reactive oxygen species, down-regulating melanogenic signaling, and sometimes inhibiting tyrosinase.

Iranian traditional medicine offers natural remedies that research groups are validating. *Dorema ammoniacum* from the *Apiaceae* family is one of these notable plants being used as therapy. It is used in Iran for its significant skin-related effects, supported by recent studies demonstrating its antimicrobial, anti-inflammatory, immune-regulating, vasodilating, wound-healing, and skin-promoting properties. A cream in a 2021 clinical study with 39 volunteers in Iran containing 6% *D. ammoniacum* gum extract has shown a significant reduction in melasma-affected areas with no reported side effects against placebo [62]. These findings suggest it could be an effective, minimally adverse treatment to brighten skin and improve pigmentation in melasma patients.

In 2019, a Chinese and USA study involving 90 volunteers compared a new herbal mixture cream formulated to target the development of melasma against a placebo [63]. The herbal mixture is made up of 1% China camellia (with antioxidant properties that inhibit tyrosinase and reduce melanogenesis), 0.5% Sanchi (*Panax notoginseng*, which improves microcirculation, reduces

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inflammation, and provides antioxidant effects), 1% *Portulaca oleracea* (with anti-inflammatory and anti-allergy properties), and 0.5% *Prinsepia utilis* oil (said to strengthen the skin barrier by stimulating ceramide production). Results show significant melasma improvement, measured through MASI and MI, over the course of 12 weeks.

Another herb that inhibits tyrosinase activity to prevent melanin synthesis is *Rumex occidentalis*, a perennial herb native to Asia, North America, China, and Central Asia. A 2014 Filipino study in 45 volunteers evaluated the safety and efficacy of 3% *R. occidentalis* cream applied twice daily for eight weeks as a skin-lightening agent for melasma, comparing it to 4% HQ cream and a placebo [64]. Results showed that both *R. occidentalis* and HQ reduced melasma severity, with *R. occidentalis* demonstrating a greater mean decline against placebo in MASI and Mexameter readings by week 8, comparable to HQ in efficacy, but with minimal adverse effects. This is the first study to assess 3% *R. occidentalis* cream in Filipino patients, demonstrating its safety and effectiveness as an alternative to HQ. Further research is recommended to evaluate long-term safety.

Botanical depigmenters can also be taken orally. Pycnogenol® is the standardized extract obtained from the bark of the French maritime pine, *Pinus pinaster*, formerly known as *Pinus maritima*, that has demonstrated effectiveness in treating melasma due to its antioxidant, anti-inflammatory, and anti-tyrosinase properties. Studies have shown that it can reduce melanin density and improve depigmentation, with ex vivo research indicating that its antioxidant activity surpasses that of vitamins E and C [65]. Pycnogenol® also protects endothelial cells from oxidative injury while inhibiting VEGF expression, potentially reducing vascular components in melasma. Due to all of these properties, a 2021 Brazilian clinical trial in 44 volunteers compared a placebo to 75mg of Pycnogenol® taken twice daily, combined with FAHT cream and broad-spectrum sunscreen [38]. The treatment showed improved outcomes over 60 days. Overall, oral Pycnogenol® may be a beneficial adjunct for women with facial melasma, enhancing treatment efficacy when combined with topical therapies.

4.4. Regenerative and Microenvironment-Modulating Therapies

Regenerative and microenvironment-modulating biotherapeutics are bioactive therapies that restore skin homeostasis by supporting repair, rebalancing inflammatory/pigment signaling, and remodeling the extracellular matrix to lessen hyperpigmentation.

Apart from the broader advantages for skin health and well-being, probiotics may be beneficial for the treatment of skin disorders like melasma through anti-inflammatory effects, antioxidant, UV protection, and inhibition of tyrosinase activity. A 2021 Thai study with 57 volunteers researched a proprietary oral synbiotic (TS6), composed of 50 billion CFUs from six probiotic strains said to treat melasma: Lactococcus lactis, Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium longum, Bifidobacterium infantis, and Bifidobacterium bifidum [66]. The study used placebo powders similar in appearance but without synbiotics. Results showed significant improvement in melasma severity, measured by mMASI score, across weeks 4, 8, and 12, with greater improvement compared to placebo at week 12. MI, measured by the Mexameter MX 18, also decreased significantly only in areas around the eyes, with notable improvements starting from weeks 4 and 8.

Looking beyond probiotic modulation, regenerative treatments for skin care have gained attention. Epidermal growth factor (EGF) stimulates cell growth by binding to the EGF receptor on cell surfaces. It is used in cosmeceuticals as a skin lightening agent, moisturizer, and for wound healing. A randomized, double-blind, placebo-controlled, split-face 2018 study in the USA assessed the effectiveness of topical EGF serum for treating melasma [67]. Forty-four subjects applied EGF serum and placebo twice daily to the designated side of their face for eight weeks. The GAIS scores showed improvement in melasma in 73.4% of subjects, compared to 13% of subjects with improvement on the placebo side. The EGF used in the study is bioengineered from barley without E. coli bacteria, and retains its potency under UV exposure and at room temperature. This study suggests that topical EGF is a safe, non-invasive, and effective treatment for melasma.

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Another regenerative biotherapeutic is platelet-rich plasma (PRP). PRP is created by centrifuging the patient's own blood to concentrate platelets containing growth factors. This biologic has drawn attention due to its potential for skin rejuvenation, wound healing, and collagen synthesis. Although case studies suggest PRP is effective in reducing hyperpigmentation, there is a lack of controlled trials. Therefore, a 2020 Thai study using a randomized, split-face, single-blinded design evaluated the efficacy of intradermally injected PRP in 10 volunteers [68]. The results showed no significant difference in MI between PRP and control groups; however, there was a notable reduction in melasma severity, as measured by mMASI scores, indicating PRP's partial benefit. Overall, the study concludes that PRP shows promise as an effective, less invasive treatment for melasma, with improvements seen within six weeks.

4.5. Procedure-Assisted and Combination Treatments

A 2014 South Korean study with 52 patients evaluated a combination therapy for melasma involving low-fluence 1064-nm Q-switched Nd:YAG laser (QSNYL) and Jessner's chemical peel [69]. Recent trends favor laser toning with QSNYL, which reduces thermal damage but still requires multiple sessions for visible results and is associated with prolonged downtime [70]. Jessner's solution chemical peels, containing lactic acid, salicylic acid, resorcinol, and ethanol, effectively induce epidermal desquamation, facilitate melanin removal, and consequently improve skin brightness and hyperpigmentation, with re-epithelialization typically occurring within 3–5 days [71]. The study compared a group receiving QSNYL followed by Jessner's peel to a control group receiving QSNYL followed by placebo over 10 sessions at two-week intervals. Both groups demonstrated improvement after ten sessions; however, the Jessner's peel group experienced a significant reduction in MASI scores, with a 23% improvement after four sessions, though this effect was not sustained in subsequent weeks. These findings indicate that four to six treatment sessions of QSNYL followed by Jessner's peel may be optimal, as additional sessions provide limited incremental benefit.

In 2024, another research group in China examined the use of TXA in combination with iontophoresis to enhance transdermal delivery for melasma treatment in a study involving 30 volunteers [72]. This method aims to improve drug delivery precision and efficacy while reducing oral side effects. In a randomized, double-blind, placebo-controlled trial, participants received either placebo or 3% TXA via iontophoresis twice weekly for three months. The combination of TXA and iontophoresis resulted in significant improvements in MASI scores and L* values compared to placebo, confirming its therapeutic effectiveness. A separate Indonesian and USA study with 50 volunteers in 2020 assessed the efficacy of 250 mg oral TXA administered twice daily in combination with 4% HQ cream for melasma treatment, while the control group received a placebo capsule in combination with 4% HQ [18]. After 12 weeks, the TXA group exhibited a 55% reduction in mMASI scores, compared to a 10.9% reduction in the control group. Although some patients experienced relapse after discontinuing treatment, their severity remained below baseline levels after three months. The greater improvement in mMASI scores relative to similar studies may be attributed to a synergistic effect between TXA and hydroquinone, and the use of hydroquinone may have mitigated significant rebound following therapy. Notably, improvements were observed as early as two weeks, indicating a rapid onset of action. While changes in melanin index (MI) were less pronounced than mMASI score reductions, the most substantial MI improvement was observed in severe cases at 12 weeks.

Lastly, a 2024 Brazilian study with 50 volunteers assessed the tolerability and efficacy of 0.05% clobetasol followed by 4% HQ (CLOB-HQ) compared to 4% HQ alone [73]. Clobetasol is a potent topical glucocorticoid steroid used for inflammatory, pruritic dermatoses [74]. In this study, the CLOB-HQ group applied 0.05% clobetasol nightly for 14 days, followed by 4% HQ for 46 days, while the control group used 4% HQ for 60 days. Both groups also applied a broad-spectrum tinted sunscreen SPF 70. No significant differences in mMASI were observed at day 14 or day 60. At day 14, irritative adverse effects (burning, irritation, itching, or erythema) were more frequent in the HQ group ($p = 0.03$). In the CLOB-HQ group, 2 cases (8%) of acne (papule, pustule, and erythema), 4 cases

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(16%) of irritation or burning, and 1 case (1%) of dryness were reported at day 14. Patients with acne were advised to temporarily discontinue the protocol for 5 days, then resume application on alternate days. In the HQ group at day 14, eight cases (32%) of irritation or dryness, four cases (16%) of itching, and two cases (8%) of papule formation were observed. At day 60, no difference in irritative adverse effects was reported between groups ($p = 0.76$). The CLOB-HQ group had 3 cases (12%) with acne and 7 cases (28%) with burning, irritation, or erythema. In the HQ group, there were three cases (12%) of pruritus, one case (1%) of acne, three cases (12%) of dryness, and five cases (20%) involving burning, irritation, or erythema. Volunteers who experienced side effects other than acne were advised to increase facial hydration between applications, and all showed improvement without discontinuing treatment. Although this sequential CLOB-HQ regimen demonstrated safety and good tolerability, its efficacy and side effect profile did not differ from HQ alone at 14 or 60 days, indicating that initiating clobetasol 14 days before hydroquinone is not necessary for melasma management.

5. Conclusion

Melasma is a cosmetic disorder with multifactorial pathogenesis that can significantly affect psychological well-being, resulting in reduced self-confidence and social engagement. Treatment options are usually topical and/or oral skin-depigmenting agents and laser therapy, all used in conjunction with sunscreens. Hydroquinone (HQ) remains the gold standard for melasma therapy since it can achieve a resolution rate of up to 60%. Nevertheless, recurrence and refractory melasma cases are common after ending HQ treatment, and side effects such as contact dermatitis, post-inflammatory hyperpigmentation, and exogenous ochronosis may occur. Recent melasma clinical research has shifted from focusing on HQ monotherapy toward identifying alternatives with comparable efficacy and improved safety profiles. Evidence suggests that many topical herbal treatments utilized for skin diseases are associated with fewer side effects than prescription formulations. However, establishing the safety and efficacy of medicinal herbs is essential to ensure their appropriate integration into patient care [75]. The HQ-free skincare formulations represent a practical and well-tolerated alternative to HQ, suitable for use in combination with other topical products or as an adjuvant to procedural therapies such as chemical peels and lasers [52]. Lasers as melasma treatments, particularly in Fitzpatrick skin types IV-VI, are generally reserved for complicated cases due to the risk of post-inflammatory hyperpigmentation and melasma exacerbation. Despite these treatment options, managing melasma across diverse skin tones remains challenging due to durable remission being rare with frequent relapses. Therefore, researching an optimal depigmenting agent that provides rapid and selective lightening of hyperactive melanocytes, resulting in sustained pigment reduction without adverse effects, is still necessary.

The authors recommend that broad-spectrum photoprotection should anchor any hyperpigmentation regimen. Among repurposed active pharmaceutical ingredients, tranexamic acid (TXA) has the most substantial evidence, with topical metformin emerging, but many patients still experience incomplete clearance and relapse. For resistant melasma and other stubborn presentations, HQ and FAHT remain benchmarks. Combination therapy is often needed for induction and maintenance: pair well-tolerated topicals with selective procedures (e.g., superficial peels), using conservative parameters, especially in darker skin tones, to enhance outcomes and limit PIH; in several contexts, thoughtfully combined modalities can outperform single-agent approaches. Sustainable botanical depigmenting antioxidants are gaining demand as consumers seek “natural” actives that align with bioeconomy goals; early data suggest these are effective and safe treatments, but stronger standardization and controlled trials are needed. In parallel, biologic and microenvironment-modulating strategies aim to restore skin homeostasis by supporting re-epithelialization, tempering inflammation, and normalizing keratinocyte–melanocyte crosstalk, thereby reducing relapse when combined with pigment-directed topicals. Microbiome-directed adjuncts are promising but remain formulation- and indication-dependent pending more rigorous evidence.

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The AI recommends a stepwise approach anchored by strict daily photoprotection (broad-spectrum with visible-light tint). As starting treatment, use FAHT triple-combination cream, which delivers the most consistent results. If HQ is unsuitable, consider switching to short-contact cysteamine 5% with daily niacinamide 4% for maintenance. If response remains suboptimal, consider oral TXA 250mg twice daily after appropriate risk screening. Add procedures selectively (e.g., low-fluence 1064-nm QS Nd:YAG or superficial peels) and use conservative parameters in darker phototypes to minimize PIH. Utilize adjuncts (PRP, dissolving microneedle resorcinols, botanical/EGF serums) in a supportive role, with clear expectations set. For maintenance, continue tinted sunscreen daily, maintain niacinamide in combination with gentle actives, and use pulse FAHT or cysteamine 2–3 nights per week to prevent relapse.

The authors were unable to conduct metadata analysis due to studies mixing objective and subjective assessment methods and inconsistent timepoints and reporting. Some of the clinical studies included in this review reported results as percent change or in graphs without mean ± standard deviation (SD), others used non-comparable melasma scoring variants such as MASI, mMASI, or half-face/MoPASI, and handled split-face designs without paired-effect reporting. These different strategies for reporting results make it challenging to compare effects between treatments. This difference in reporting clinical results can also make it confusing for dermatologists attempting to recommend the best course of treatment for their patients. To streamline future research and enable robust meta-analyses, the authors, alongside the AI, recommend a standardized measurement and reporting framework to be incorporated into study design and manuscript preparation (Figure 3). This framework includes prespecification of core outcomes, such as an objective colorimetric value (e.g., Melanin Index), alongside a clinical metric (e.g., mMASI or MASI). For reporting results, primary endpoints with extractable statistics are needed, such as the number of volunteers [n] analyzed, baseline and follow-up means ± SD, and change-from-baseline ± SD for each study arm. For split-face trials, within-person volunteer mean ± SD or side-to-side correlations should be reported. Additionally, skin tone should be documented using both Fitzpatrick type and a device-based colorimetric baseline (e.g., L* or ITA°) to stratify results across diverse skin tones. Background photoprotection and co-interventions should also be standardized and documented. Although several high-quality randomized controlled trials utilized objective colorimetry and blinding, limitations such as small sample sizes, short follow-up periods, inconsistent outcomes, suboptimal registration or blinding, and selective reporting due to inaccessible analysis plans reduce the certainty of findings and should also be addressed in future studies.

This review summarizes different melasma treatments, acting as a guide created by both humans and AI to help dermatologists explore available options. No matter the treatment approach, strict photoprotection remains essential. Additionally, this review offers guidance for clinical researchers developing new melasma therapies, aiming to improve reporting consistency and facilitate direct comparison of benefits and side effects.

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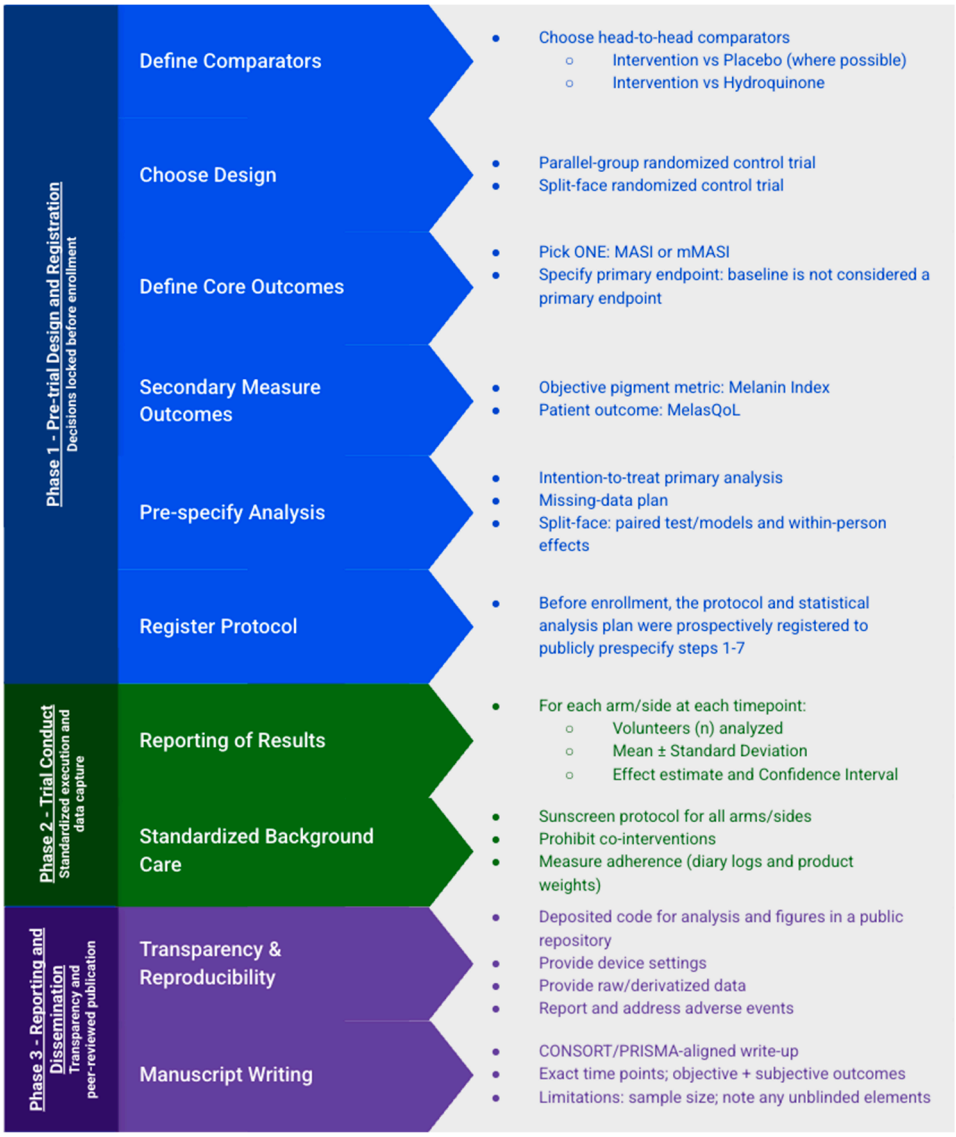

Figure 3. Proposed flowchart for standardized design and reporting framework for future "meta-analysis-ready" melasma treatment studies.

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