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Review Article

UPDATE ON ORAL AND TOPICAL THERAPY FOR MELASMA IN REPRODUCTIVE AGE: A LITERATURE REVIEW

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ABSTRACT

Melasma is a common pigmentation disorder often seen in women of reproductive age with Fitzpatrick skin types IV-VI, characterized by symmetrical hyperpigmented patches on the face. Major factors influencing melasma include UltraViolet (UV) exposure, genetic predisposition, and hormonal changes. This condition can significantly impact patients' quality of life, thus requiring effective and safe therapeutic approaches. This study aims to evaluate the effectiveness and safety of various melasma treatments, both topical and systemic, based on the latest literature review. This research uses a literature review design with a PICO (Patient, Intervention, Comparison, Outcome) approach to select articles from PubMed and ScienceDirect databases. Articles analyzed include studies published in the last 5 years, written in English, and involving patients with melasma.

Various treatments for melasma, such as hydroquinone, Triple Combination Cream (TCC), tranexamic acid, vitamin D, and natural-based treatments, show effectiveness in reducing the severity of melasma. Mild side effects were reported for some treatments, such as irritation with hydroquinone or mild gastrointestinal disturbances with oral tranexamic acid. Each treatment has advantages in specific contexts, depending on the patient's needs and characteristics. All therapies evaluated show positive results with varying degrees of effectiveness. Treatment selection should consider the severity of melasma, patient tolerance to the medication, and potential side effects. An individualized approach and combination therapy can be adapted to optimally meet patient needs.

Keywords: Melasma, Therapy, Hyperpigmentation

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INTRODUCTION

Melasma is a skin condition that causes hyperpigmentation or darkening of the skin, affecting millions of people worldwide. This condition typically appears on the face, especially in individuals with darker skin tones (Fitzpatrick skin types IV–VI) who are frequently exposed to UltraViolet (UV) rays. Melasma can have a significant emotional impact due to its effect on facial appearance [3].

Melasma is more commonly experienced by women, particularly during their reproductive years, typically between the ages of 20 and 50. This age group is often associated with hormonal changes due to pregnancy, contraceptive use, or other factors that may exacerbate melasma. The increasing prevalence of melasma can also be attributed to higher sun exposure and the use of certain cosmetics that may trigger or worsen pigmentation [20].

Melasma is characterized by dark or brown patches that appear symmetrically on the face, with varying shapes, ranging from uneven, irregular, curved, to circular patterns. Based on its location, melasma can appear in the centrofacial area (forehead, nose, cheeks, and chin), malar area (cheeks and nose), or mandibular area (around the jawline). Additionally, based on the pigment's depth in the skin, melasma is classified into three types: epidermal (brown patches with well-defined borders), dermal (grayish-brown patches with indistinct borders), and mixed (a combination of both) [3].

Melasma treatment includes both non-pharmacological and pharmacological approaches, which are typically combined and applied simultaneously, considering the long duration of treatment, effectiveness, and potential side effects of each medication. Non-pharmacological approaches include patient education, avoiding triggers, sun protection, and the use of cosmetic camouflage to conceal the pigmentation. Pharmacological treatment consists of topical and systemic therapies. Topical therapies involve the use of one or a combination of the following: hydroquinone, retinoic acid, azelaic acid, tranexamic acid, medium-potency topical corticosteroids, glycolic acid, kojic acid, imiquimod (not available in Indonesia), or other depigmenting agents such as arbutin, botanicals, niacinamide, cysteamine, licorice, and ascorbic acid. Systemic therapy is recommended for more widespread melasma or when it reaches the dermis. Systemic treatment options include low-dose tranexamic acid, antioxidants like glutathione and ascorbic acid (Vitamin C), and other agents such as pycnogenol and proanthocyanidin-rich compounds [19].

Based on the above explanation, we aim to evaluate the effectiveness of melasma therapies, both topical and oral, through a literature review using valid and relevant articles. This study is based on the differences in effectiveness results from previous studies and new findings related to melasma therapy. The goal of this review is to identify the latest evidence to provide more comprehensive therapeutic recommendations.

MATERIALS AND METHODS

Methods

This research adopts a literature review design, which involves summarizing, analyzing, and critiquing a specific topic or issue based on multiple sources. It serves as a foundation or theoretical framework for conducting further studies. The literature review is presented narratively to identify and interpret relevant previously published articles.

This article applies the PICO method as a strategy for searching clinical information, which is an acronym representing four components: P (patient, population, problem), I (intervention, prognostic factor, exposure), C (comparison, control), and O (outcome). By using PICO, we can ensure that the research we seek aligns with our clinical questions, allowing us to provide care based on evidence-based medicine.

The literature review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Articles obtained were synthesized and analyzed according to inclusion and exclusion criteria. Inclusion criteria included English-language articles that were not review articles, containing the predefined keywords, published within the last five years, involving patients of productive age (15–64 y) diagnosed with melasma (both males and females), accessible articles, and studies linking the three relevant variables. Exclusion criteria were studies that were not Randomized Controlled Trials (RCTs), prospective or retrospective studies, and those not involving oral and/or topical therapies.

Table 1: PICO

P (*patient, population, problem*)	Melasma in reproductive age
I (*intervention, prognostic factor, exposure*)	Oral and topical therapy
C (*comparison, control*)	-
O (*outcome*)	Clinical improvement

The systematic literature search was conducted using PubMed and ScienceDirect, guided by the PICO framework. Search terms included: "melasma", "treatment" OR "therapy", "hydroquinone", "tranexamic acid", "topical corticosteroids", and "randomized controlled trial" OR "RCT", combined using Boolean operators and and or. Filters applied were: English-language articles published between 2018 and 2023, focusing on clinical trials, cohort studies, or interventional studies. Grey literature and unpublished studies were not considered, which may contribute to publication bias and is acknowledged as a limitation.

Inclusion criteria were: (1) clinical studies evaluating melasma treatments, (2) adult populations with clinically diagnosed melasma, and (3) reporting of relevant clinical outcomes. The five-year publication window was chosen to reflect current therapeutic advancements and exclude outdated protocols. Exclusion criteria included animal studies, case reports, and narrative reviews.

The primary outcome was defined as clinical improvement, operationalized as reduction in MASI (Melasma Area and Severity Index) score, patient-reported outcomes, or clinician-assessed improvement. Due to variation across studies, outcome definitions are addressed in the synthesis.

RESULTS AND DISCUSSION

The PRISMA flowchart presented below outlines the process of data collection for this study, which was conducted using online databases from PubMed and ScienceDirect. The search was carried out using the keywords (melasma or chloasma) and (therapy or treatment or management) not (review).

The search was limited to studies published within the last 5 y, resulting in 1464 articles from PubMed and 249 articles from ScienceDirect. Next, 399 review articles were excluded. After removing the review articles, 1314 titles remained. Following that, 805 articles were excluded because they were either not in English or were published more than 5 y ago. An additional 326 articles were excluded due to the lack of free full-text access, and 171 articles were excluded because they were not Randomized Controlled Trials (RCTs), prospective, or retrospective studies.

Finally, a full-text screening was conducted, leading to the selection of 6 studies that metal the inclusion criteria. This process ensured that only the most relevant and appropriate studies were included in the literature review.

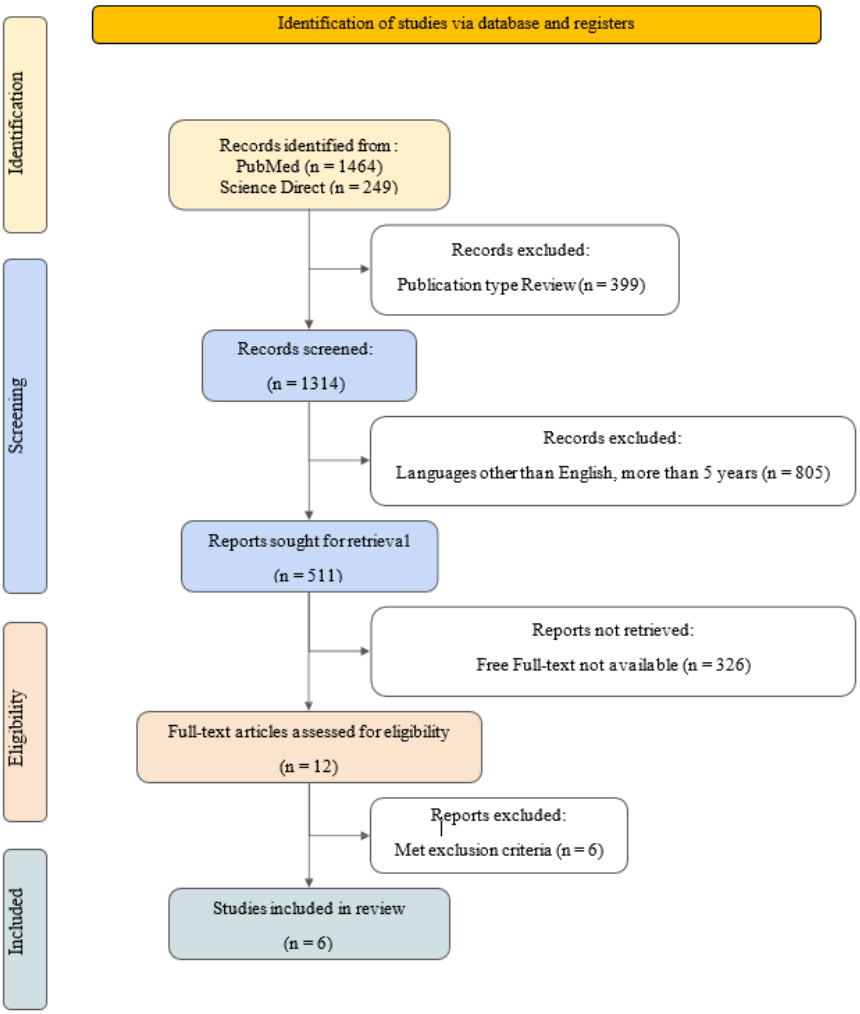

Fig. 1: Flowchart PRISMA

Table 2: Characteristics of articles

S. No.	Title	Author/Published year	Method	Research population	Therapy	Results
1	Histological changes in facial melasma after treatment with triple combination cream with or without oral tranexamic acid and/or microneedling: A randomised clinical trial	Daniel Pinho Cassiano *et al.*/2022	A factorial, randomised, controlled and evaluator-blinded clinical trial	64 women with melasma who are willing to undergo a biopsy.	- Triple Combination Cream (TCC). - TCC+Monthly Microneedling. - TCC+Oral Tranexamic Acid (250 mg twice a day). - Combination of TCC, Microneedling, and Tranexamic Acid. TCC: Triple Combination Cream (TCC): A combination of hydroquinone, tretinoin, and fluocinolone acetonide.	The combination of TCC, microneedling, and tranexamic acid yields more significant results for melasma compared to single or dual-component therapies. Microneedling enhances TCC penetration, while tranexamic acid reduces melanin production and vascular activity. This combination therapy provides optimal improvement, though histological outcomes vary among patients.
2	Vitamin D and wound healing: Assessing skin barrier function and implications for chloasma treatment	Qiong Chen *et al.*/2023	A double-blind, placebo-controlled clinical trial	Involving 480 individuals diagnosed with chloasma.	The intervention involved vitamin D supplementation to assess its potential in enhancing wound healing and reducing chloasma symptoms.	Vitamin D shows potential in regulating skin function and could be an effective adjunctive therapy for chloasma.
3	The effectiveness and safety of 3% tranexamic acid cream vs 4% hydroquinone cream for mixed-type melasma in skin of color: a double-blind, split-face, randomized controlled trial	Yasnova *et al.*/2024	A double-blind, randomized controlled trial was conducted using a split-face method	This study included 20 participants. The study involved female patients aged 18 to 60 y who were diagnosed with melasma and had Fitzpatrick skin types III to V.	Participants in this study received two types of topical therapies: 3% tranexamic acid cream and 4% hydroquinone cream. Both products were applied simultaneously on different sides of the face, allowing for a direct comparison of the effectiveness and safety of each therapy.	Topical 3% tranexamic acid cream effectively reduces mmolASI and MI scores in mixed-type melasma, comparable to 4% hydroquinone, but with fewer side effects. The cream is well-accepted by patients and presents a potential therapeutic alternative.
4	Oral Tranexemic Acid With Triple Combination Cream (Flucinolone+Hydroquinone+Tretinoin) Versus Triple Combination Cream Alone in Treatment of Melasma	Anam Basit *et al.*/2021	A randomized controlled trial	This study involved 63 patients aged 18 to 60 y with a diagnosis of melasma, with 60 patients completing the study. The inclusion criteria were individuals who had not received melasma treatment in the past six months, while patients with a history of thromboembolism, psychological disorders, or the use of photosensitive medications were excluded.	Patients in Group A took 250 mg of tranexamic acid twice daily and applied a triple combination cream (consisting of fluocinolone acetonide 0.01%, hydroquinone 4%, and tretinoin 0.05%) once daily at night. Meanwhile, Group B used only the triple combination cream in the same manner. Treatment continued for eight weeks, with effectiveness measurements taken at the end of the period.	Oral tranexamic acid does not significantly enhance the reduction in MASI scores compared to the use of triple combination cream alone (p=0.56). Tranexamic acid may serve as an adjunct, but it does not provide meaningful additional results.
5	A randomized, controlled, split-face, double-blind comparison of a multimodality pigment-correcting serum containing lotus sprout extract versus hydroquinone for moderate to severe facial hyperpigmentation, including melasma, in a diverse population	Priscilla Huang, BA *et al.*/2024	Split-face, double-blind, randomized, controlled	This study involved 113 subjects with moderate to severe facial hyperpigmentation, including melasma. The population included individuals from diverse racial/ethnic backgrounds: 22% Asian, 27% African American, 22% Hispanic, and 28% Caucasian.	Participants received ABT therapy (lotus bud extract-based serum) on one side of the face and 4% hydroquinone on the other side, applied twice daily for 12 w.	ABT (serum based on lotus bud extract) is effective, safe, and preferred over 4% hydroquinone for moderate to severe facial hyperpigmentation, including melasma, across various races and skin phototypes (FST I-VI). ABT is suitable for long-term treatment of chronic hyperpigmentation.
6	Efficacy of topical Raphanus sativus seed powder mixed with honey versus hydroquinone 4 % cream in the treatment of melasma – A randomized controlled trial	Horti *et al.*/2024	Randomized controlled trial	A total of 40 participants (20 per group), aged between 18 and 65 y and diagnosed with melasma, successfully completed the study.	Participants in the experimental group applied a topical formulation containing Raphanus sativus seed powder mixed with honey, while the control group used a 4% hydroquinone cream. Both treatments were applied for a specified duration, and adherence to the treatment was monitored throughout the study period. Effectiveness was evaluated based on clinical assessments and patient-reported outcomes.	Tukhm-i Turb (Raphanus sativus) seed powder with honey is as effective as 4% hydroquinone for melasma, with improvements in dermatological quality of life and a favorable safety profile, making it a promising alternative treatment.

TCC = Triple Combination Cream (Flucinolone+Hydroquinone+Tretinoin), MASI = Melasma Severity Scores, ABT = Advanced Brightening Treatment (ABT)

DISCUSSION

Melasma, also known as chloasma, is a chronic, acquired skin disorder characterized by hyperpigmented macules and patches on areas exposed to UltraViolet (UV) radiation, particularly the face. This condition predominantly affects women with darker skin tones (Fitzpatrick skin phototypes III–V) in their third and fourth decades of life, although men account for approximately 10% of cases. The exact pathogenesis of melasma remains unclear, but multiple factors, including UV exposure, hormonal changes (e. g., pregnancy or oral contraceptive use), genetic predisposition, and certain medications, are known to contribute. Historically, the term "melasma" derives from the Greek word *mélas*, meaning black, with the earliest descriptions attributed to Hippocrates, who linked pigmentation disorders to environmental triggers such as solar radiation and skin inflammation [11, 21].

Despite its prevalence, melasma is often dismissed as a cosmetic issue, leading to underdiagnosis and inadequate treatment. Its complex pathophysiology, variable clinical presentations, and high recurrence rates make it a challenging condition to manage. Patients frequently experience significant emotional and psychological distress, including frustration, low self-esteem, and social withdrawal, exacerbated by the often high cost and limited efficacy of available treatments. Clinically, melasma is categorized into epidermal, dermal, or mixed types, with diagnosis commonly aided by a Wood's lamp. Given its profound impact on health-related quality of life, effective diagnosis and management strategies are critical to improving outcomes for affected individuals [12].

The treatment of melasma is often challenging due to its recurrent nature and the limited therapies available that offer long-term resolution. Hydroquinone, recognized as the gold standard in melasma treatment due to its superior efficacy, is widely used both as monotherapy and as part of triple combination therapy that includes retinoids and steroids, although side effects such as skin irritation and peeling are frequently reported in some patients [11]. Despite the availability of various treatments, there are still limitations in the scientific evidence supporting melasma therapies, particularly in large sample sizes and consistent outcomes. This review aims to evaluate existing therapies for melasma and identify potential new treatments that may be more effective and safer.

Hydroquinone

In the study by Yasnova *et al.* (2024), a split-face design was used where the right and left sides of patients' faces were randomly treated with 3% tranexamic acid cream or 4% hydroquinone. Both treatments showed a significant reduction in mmolASI scores, but the hydroquinone group reported mild erythema in 25% of patients. This suggests that hydroquinone is as effective as tranexamic acid in reducing melasma severity, but hydroquinone causes side effects like erythema, making it less suitable for long-term use. Hydroquinone, widely regarded as the gold standard for treating melasma, works by inhibiting tyrosinase, an enzyme essential for melanin production. However, its long-term use can lead to serious adverse effects, such as paradoxical hyperpigmentation and exogenous ochronosis, due to the metabolites formed during tyrosinase oxidation [18, 26].

In the randomized, double-blind, controlled trial by de Amorim *et al.* (2024), two melasma treatment methods were compared: a combination of clobetasol 0.05% for 14 d followed by 4% hydroquinone for 46 d (CLOB-HQ) versus 60 d of 4% hydroquinone alone (HQ). Results showed no significant differences in mmolASI score reduction, quality of life improvement (MELASQoL), or skin luminosity between the groups. At day 60, the CLOB-HQ group had a 43.1% reduction in mmolASI, while the HQ-only group had a 44.8% reduction. Although both treatments were safe, the addition of clobetasol did not offer significant clinical benefits, making hydroquinone monotherapy an effective and safer choice for melasma avoiding the risks of corticosteroid side effects [9].

In a study by Lima *et al.* (2021) comparing the effectiveness and safety of 0.2% Thiamidol and 4% hydroquinone for melasma treatment, both treatments led to similar results. Both Thiamidol and hydroquinone caused a reduction in mmolASI scores, with a slightly greater reduction in the Thiamidol group. Both treatments also showed improvements in quality of life and melasma severity. Thiamidol was better tolerated, with mild side effects, while hydroquinone could cause allergic contact dermatitis in some patients. Thiamidol is thus an appropriate alternative, particularly for patients intolerant to or unresponsive to hydroquinone [16].

While hydroquinone is effective in treating hyperpigmentation such as melasma, it has several side effects, particularly with long-term use. Common side effects include allergic or irritant contact dermatitis, hypopigmentation, and post-inflammatory hyperpigmentation. More serious long-term side effects include exogenous ochronosis, which causes bluish-brown or gray pigmentation in sun-exposed skin and is often permanent, though treatable with procedures like dermabrasion or laser therapy. Chronic hydroquinone use can also lead to trimethylaminuria, or "fish odor syndrome," in which the body emits a foul fish-like odor. Other side effects include nail hyperpigmentation, reduced skin elasticity, and peripheral neuropathy [10].

Melasma treatment is often unsatisfactory due to the limited effectiveness of existing therapies and potential side effects. The depigmenting effect of HQ may be partly linked to its ability to compete with tyrosine oxidation in inactive melanocytes, acting as an alternative substrate for tyrosinase [23]. Hydroquinone is commonly used as a first-line therapy for melasma but may cause skin irritation and post-inflammatory hyperpigmentation. To address these issues, a multimodal approach is recommended, including combining treatments with tretinoin and fluocinolone acetonide, as well as using non-hydroquinone skin-lightening agents. UV protection with effective sunscreen is crucial to prevent melasma recurrence. Additional therapies like chemical peels and lasers can be used for difficult-to-treat cases, but caution is needed to avoid further side effects [17].

TCC (combination *hydroquinone, tretinoin, fluocinolone acetonide*)

In the study by Basit *et al.* (2021) a comparison between the use of Tranexamic Acid (TA) with Triple Combination Cream (TCC) and TCC alone showed interesting results regarding melasma treatment. The analysis revealed that the mean reduction in Melasma Area Severity Index (MASI) scores for the group using TA and TCC (Group A) was 6.4933±4.38358, while for the group using only TCC (Group B), it was 5.7833±5.04251. Although both groups showed significant reductions in MASI scores after 8 w of treatment, the difference between the two groups was not statistically significant, with a p-value of 0.56. This indicates that the addition of TA did not contribute meaningfully to the reduction in MASI scores compared to using TCC alone. The study concluded that although TA may function as an adjunct, its use does not significantly improve treatment outcomes compared to exclusive use of TCC [4].

TCC consists of three active components: hydroquinone (4%), tretinoin (0.05%), and fluocinolone acetonide (0.01%). This combination is designed to reduce hyperpigmentation through various mechanisms. Hydroquinone works by inhibiting the enzyme tyrosinase, which plays a key role in melanin synthesis. Tretinoin increases skin cell turnover and accelerates the shedding of dead skin cells, while fluocinolone acetonide has anti-inflammatory effects that help reduce skin inflammation [4].

Ahmad *et al.* (2019) evaluated the safety and efficacy of a combination cream containing hydroquinone (4%), tretinoin (0.05%), and fluocinolone (0.01%) in treating melasma in Middle Eastern skin. Twenty-two women with mild to severe melasma participated, with 17 completing the study. Participants applied the cream every night for 8 w and used sunscreen (SPF ≥30) during the day. Assessments were made using the mmolASI score, digital image analysis, and skin biophysical parameters. Results showed a significant reduction in the mmolASI score from 3.61 to 2.45 after 8 w ($p<0.001$), an improvement in skin luminosity (L-value), and a decrease in melanin index. Most side effects, such as dry skin or mild irritation, were manageable with moisturizers, and satisfaction surveys showed a positive response to treatment. The study concluded that the combination cream of hydroquinone (4%), tretinoin (0.05%), and fluocinolone (0.01%) is effective and safe for treating melasma in Middle Eastern skin [2].

While Basit *et al.* (2021) showed that TA did not provide significant benefits as an adjunct in Triple Combination Cream (TCC) therapy,

Cassiano *et al.* (2022) reported that combining TCC with TA and microneedling could yield better histological results [4, 6]. This difference may be related to the protocols used, where Basit *et al.* applied a low dose of TA (250 mg twice daily) for 8 w, whereas Cassiano *et al.* used an approach involving microneedling, which could potentially influence the results by offering a more comprehensive melasma treatment strategy.

Tranexamic acid

In the study published by Cassiano *et al.* (2022), the researchers compared histological changes in the skin of melasma patients following treatment with Triple Combination Cream (TCC) with or without the addition of Tranexamic Acid (TA) and/or microneedling. The results showed that the combination of TCC with TA and microneedling led to more significant improvements in reducing epidermal melanin density and increasing epidermal thickness compared to using TCC alone [6].

Tranexamic acid is a lysine derivative that functions as a plasminogen inhibitor, preventing its conversion into plasmin. In melasma treatment, TA works through several mechanisms, such as reducing the interaction between keratinocytes and melanocytes involved in melanin production, inhibiting the production of arachidonic acid and prostaglandins, thus decreasing melanin stimulation, and enhancing autophagy pathways that contribute to melanin reduction. Additionally, TA can lower the synthesis of Vascular Endothelial Growth Factor (VEGF), which affects angiogenesis and melanin production [6].

In the study by Yasnova *et al.* (2024) 3% tranexamic acid was found to be as effective as 4% hydroquinone in reducing melasma severity. However, TA has the advantage of a better safety profile with fewer side effects compared to hydroquinone, making it a safer option for long-term use [26].

Tranexamic acid is generally safe and effective for melasma treatment, whether used orally, topically, or intralesionally. However, oral TA can cause side effects such as gastrointestinal upset and menstrual disturbances in some patients. Moreover, the pro-thrombotic properties of this drug need to be considered before prescribing, especially for patients with a risk of blood clotting. Topical tranexamic acid, however, has a better side effect profile than hydroquinone [15].

A meta-analysis by Yuniandari and Wijayanti (2022) evaluated the effectiveness and safety of Tranexamic Acid (TA) as an adjunct in melasma treatment compared to Hydroquinone (HQ) and TCC. The analysis included data from randomized controlled trials involving melasma patients, where they were divided into groups receiving TA via various routes (oral, topical, intradermal) and a control group receiving only hydroquinone or TCC. The results indicated that oral TA improved the effectiveness of melasma treatment, with several studies showing a significant reduction in Melasma Severity Scores (MASI) in the TA group compared to the control group. Side effects of TA were generally mild, including symptoms like nausea and menstrual irregularities. The study concluded that combining TA with hydroquinone or TCC is more effective for treating melasma than using hydroquinone alone and recommended the inclusion of TA in clinical practice to improve treatment outcomes and prevent melasma recurrence [27].

Basit *et al.* (2021) used oral tranexamic acid at a dose of 250 mg twice a day (500 mg/day) for 8 w, while Yasnova *et al.* (2024) used 3% tranexamic acid cream topically [4, 26]. These differences reflect the focus of each study, with one exploring the systemic effects of oral TA, while the other evaluated the local effectiveness of topical cream. Based on the available evidence, topical tranexamic acid tends to be more effective in treating melasma because it provides a direct effect on the affected area, while oral forms may show less significant results in certain contexts. However, treatment effectiveness may vary depending on the individual and the type of melasma being treated. Therefore, a comprehensive treatment approach tailored to the patient's needs remains crucial in managing melasma.

Vitamin D

Vitamin D, which plays a role in the metabolism of calcium, magnesium, and phosphate, is primarily obtained through skin synthesis with the help of sunlight and to a lesser extent from food. However, daily requirements are often not fully met from these two sources alone [25].

In the study by Chen *et al.* (2023), a randomized, double-blind, placebo-controlled trial compared the effects of topical vitamin D3 cream (0.025%) applied twice daily and oral vitamin D3 supplementation at doses of 5000–10,000 IU per day with a placebo group. The trial involved 480 patients with chloasma over a period of 6 mo. Results showed a significant reduction in chloasma severity scores compared to placebo, with clear differences observed after 3 and 6 mo. Participants using vitamin D3 reported higher satisfaction with the treatment compared to the placebo group [8].

However, there were some reported side effects, with the most common being skin irritation (in 15 participants, about 6.25%), followed by mild gastrointestinal disturbances (reported by 10 participants, around 4.17%) and headaches (experienced by 20 participants, about 8.33%). Despite these mild side effects, the overall severity and tolerability of vitamin D3 therapy were low, making it a relatively safe long-term treatment option for patients with melasma. Further studies are needed to optimize the dosage and use of vitamin D3 in chloasma management [8].

Vitamin D, which is produced in the skin upon exposure to sunlight, plays a crucial role in various skin functions, such as regulating cell growth, supporting the immune system, and reducing inflammation. It is involved in regulating melanin production and improving skin barrier function, which helps address pigmentation issues like chloasma. Vitamin D has been proven to enhance melanogenesis while also regulating the activation, growth, and movement of melanocytes, making it beneficial for improving skin pigmentation [8].

While the author did not find other studies specifically examining the effectiveness of vitamin D supplementation or topical therapy for melasma, several studies, including those by Shope *et al.* (2023), Abdalla *et al.* (2019), and Platsidaki *et al.* (2024), have explored the relationship between vitamin D levels and melasma. Despite using different methodologies, these studies consistently found that patients with melasma tend to have lower serum vitamin D levels compared to control populations or other groups [1, 22, 24].

Platsidaki *et al.* (2024) reported that 22% of melasma patients had mild vitamin D deficiency, with higher average Modified Melasma Area Severity Index (MASI) scores compared to the study population [22]. This suggests a potential link between low vitamin D levels and melasma severity. Shope *et al.* (2023) further supported this finding, suggesting that melasma patients with lower serum vitamin D levels could benefit from vitamin D supplementation [24]. Based on these findings, all three studies recommend increasing vitamin D levels through supplementation as a beneficial approach for patients with melasma.

Advanced brightening treatment (ABT)

The study conducted by Huang *et al.* (2024) demonstrated that ABT serum, containing lotus bud extract, is effective, safe, and more preferred than 4% hydroquinone, which is the current standard treatment, for facial hyperpigmentation, including melasma, with significant improvement after 12 w. The study recommended using ABT serum as a long-term option for treating difficult-to-treat hyperpigmentation, particularly in populations with diverse skin types and ethnicities [14].

Advanced Brightening Treatment (ABT) is an innovative serum developed to treat skin pigmentation concerns without relying on hydroquinone. ABT employs multiple strategies to minimize hyperpigmentation, featuring a specialized formula enriched with a lotus bud extract complex. This extract interferes with the formation and activity of melanosomes, the cellular structures responsible for producing skin pigment, while also aiding in their breakdown. The serum also includes tranexamic acid, which targets the activation of melanocytes, and niacinamide, known for its anti-inflammatory

properties, its role in regulating melanocyte activity and melanin distribution, and its contribution to enhancing skin barrier function [14].

ABT is generally considered to have good tolerability, but, like other skin care products, it may cause some skin irritation, such as redness, itching, or a burning sensation, particularly on sensitive skin. Allergic reactions are rare but may result in rashes or swelling. Some ingredients in ABT may cause dry skin or skin discoloration, although this is more commonly observed with hydroquinone-containing products. The use of ABT can also increase sensitivity to sunlight, so it is advised to use sunscreen when applying it. Although these side effects may occur, the study indicates that ABT has better tolerability compared to 4% hydroquinone. However, as individual responses may vary, it is recommended to perform a patch test on a small area of skin before widespread use [14].

To date, there have been no other studies specifically addressing the efficacy of Advanced Brightening Treatment (ABT) serum-containing lotus bud extract for melasma. Therefore, the study by Huang *et al.* (2024) serves as the primary reference. The absence of comparative studies highlights the need for further exploration to strengthen the existing findings and provide a broader context regarding ABT's effectiveness. Further research should be conducted with more diverse study designs, including larger control groups and variations in the studied populations, as well as long-term evaluations of the effects and tolerability of this serum. Additional studies could also explore the mechanisms by which lotus bud extract works to address melasma and hyperpigmentation and compare it with other existing treatments [14].

Mixture of *Raphanus sativus* seed powder and honey

An RCT study by Horti *et al.* (2024) compared the effectiveness of a mixture of Raphanus sativus seed powder and honey with 4% hydroquinone cream in the treatment of melasma. This 8-week study with 40 participants showed that both treatments significantly reduced melasma severity, as measured using the Modified Melasma Area and Severity Index (mMASI), Visual Analog Scale (VAS), and Dermatology Life Quality Index (DLQI), with no significant difference between the two. In addition to demonstrating effectiveness equivalent to hydroquinone, the *Raphanus sativus* and honey-based therapy did not cause any side effects, making it considered safe. This study affirms the potential of traditional Unani medicine as an effective alternative for melasma treatment, although further research is needed to address limitations such as the small sample size and the less pleasant aroma of the formulation [13].

Raphanus sativus seed powder (radish) mixed with honey is known for its skin-cleansing (*jālī*), tyrosinase-inhibiting, and antioxidant properties [13]. *Raphanus sativus* L., a medicinal vegetable from the Brassicaceae family, is known for its abundance of biologically active compounds that offer various health benefits, including anticancer, antimicrobial, antioxidant, and anti-inflammatory properties. In traditional Persian medicine, this plant has been utilized for its wound-healing capabilities, attributed to its potent antioxidant, antimicrobial, anti-inflammatory, and free radical scavenging effects [28].

The author has not found other studies specifically addressing the effectiveness of *Raphanus sativus* seed powder mixed with honey for melasma. Therefore, no comparative data is available for the results of the study by Horti *et al.* (2024) Further research is essential to explore the potential of this combination, including its mechanism of action against hyperpigmentation, its effectiveness compared to standard therapies, and its long-term safety. It is recommended that clinical trials with larger populations be conducted to strengthen the validity of the findings and provide broader insights into its application in melasma management [13].

Most studies affirmed the efficacy of hydroquinone (HQ) as the gold standard for melasma treatment, with notable MASI score reductions. However, long-term use carries risks such as paradoxical hyperpigmentation and ochronosis. Discrepancies between studies (e. g., Yasnova *et al.* vs. Lima *et al.*) may stem from differences in dosage, treatment duration, or participant demographics.

Tranexamic acid (TA), particularly in topical form, showed a favorable safety profile and moderate efficacy. Nevertheless, potential thrombotic risks with oral formulations must be acknowledged. Topical TA may outperform oral administration due to improved local targeting and reduced systemic exposure. Novel agents such as Raphanus sativus and ABT demonstrated therapeutic potential but are limited by small sample sizes, short follow-up periods, and unclear mechanisms of action.

CONCLUSION

This review primarily reflects studies conducted in populations with Fitzpatrick skin types IV–VI. Thus, caution should be exercised when generalizing findings to other skin types. We propose a stepwise treatment algorithm: initial management with triple combination cream (TCC) and sunscreen as first-line therapy, followed by topical tranexamic acid for refractory cases. Emphasis should be placed on patient education regarding sun protection and realistic expectations for treatment outcomes.

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AUTHORS CONTRIBUTIONS

Meylia Arinda Candra Dewi, as the first author, was responsible for conceptualizing the study and designing the research framework. She also played a leading role in writing the introduction and discussion sections and coordinated the overall research process as the project administrator. Miranda Azahra, as the second author, contributed to data collection and analysis and was responsible for writing the methods and results sections. She also assisted in data visualization to support the interpretation of the research findings. Flora Ramona Sigit Prakoeswa played a key role in securing funding that enabled the implementation of this study. In addition, she provided technical support and the necessary resources for data analysis and result validation. Ratih Pramuningtyas, as the corresponding author, supervised the entire research process. She critically reviewed the manuscript, provided substantial input, and revised the manuscript to enhance its academic quality. All authors have read and approved the final version of the manuscript prior to submission for publication.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest in this study.

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