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REVIEW ARTICLE

Medical therapies for melasma

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Abstract

Melasma is a common malady affecting all races with a higher incidence in Hispanics, Middle Eastern, Asians, and African origin females (Fitzpatrick skin phototypes III–V). Women are affected much more often than men. Melasma remains a significant cause of cosmetic morbidity and psychosocial embarrassment affecting quality of life necessitating effective and reliable treatment. Unfortunately, treatment remains unsatisfactory due to limited efficacy, adverse effects, and relapses after stopping treatment. Although chemical peels, laser and light therapies and dermabrasion may have utility, the evidence available for their efficacy is limited and they often cause post-inflammatory hyperpigmentation, particularly in individuals with darker skin types. Medical therapies remain mainstay in the management of melasma. The triple combination, hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01% (Triluma, Galderma, Ft. Worth Texas, often modified incorporating different corticosteroids) remains the only US FDA-approved treatment for melasma and is the gold standard due its demonstrated efficacy across ethnicities. Oral tranexamic acid alone or in combination with other modalities has also shown significant efficacy. Several cosmeceuticals and botanical extracts used as skin lightening agents have been demonstrated to be useful. Physical sunscreens containing zinc oxide, iron oxide, titanium dioxide, and silicones provide photoprotective and camouflage effect. We propose that a multimodality approach to the treatment of melasma is the most effective treatment approach. This review is focused on the medical therapies for melasma.

KEYWORDS
chemical peels, cosmeceuticals, hydroquinone, natural ingredients, tranexamic acid

1 | INTRODUCTION

Melasma (Greek- Melas; Black) is a common acquired skin hyperpigmentation primarily affecting sun-exposed areas of forehead, cheeks, nose, upper lip, and chin, and occasionally the neck and forearms. Its exact prevalence in general population is understudied but accounts for 5–6 million people in US alone, 0.25%–4% of dermatology clinic attendees in Southeast Asia and it is one of the common pigmentary disorders among Indians.[1] Melasma affects all races but individuals of Hispanic, Latin American, Middle Eastern,

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Asia and African origin (Fitzpatrick skin phototypes III–V) predominate.[2] Women are affected much more often than men who comprise 10%–20% of cases mostly in their 3rd and 4th decade of life with mean age of 30 years at onset.[3–5] Variable presentations are reported based on clinical examination, histology, and intensification of pigment under long wave ultraviolet light (Wood's light) (Table 1). The diagnostic significance of "Fitzpatrick macule," a confetti-like macule of regularly pigmented skin observed in about 89% clinical photographs of large hyperpigmented patch of melasma cases compared with 1% cases of poikiloderma of Civatte and 6% of solar lentigenosis cases has been highlighted recently.[6]

Melasma remains a significant cause of cosmetic morbidity and psychosocial embarrassment affecting quality of life.[3,4] However, treatment remains unsatisfactory for most individuals due to limited efficacy and adverse effects of available therapies, and frequent relapses after stopping treatment. This paper presents an overview of hydroquinone, often used as first-line therapy and non-hydroquinone medical treatment options in patients with melasma.

2 | ETIOPATHOGENESIS

A high incidence of up to 70% in family members favors genetic predisposition to develop melasma. Other frequently implicated etiologic factors include pregnancy, oral contraceptives, endocrine dysfunction, hormone replacement treatments, thyroid disorders, drugs, cosmetic contact sensitivity, light exposure including both sun and artificial light and stress.[7,8] Pigmentation is usually confined to the epidermis, but dermal factors have been implicated for its recurrent and refractory nature. Ultraviolet (UV) irradiation induced increased proliferation on dermal vasculature proliferation and upregulation of dermal proangiogenic factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and interleukin (IL)-8) have been implicated in the pathogenesis of melasma.[9,10] Interaction between VEGF receptors on epidermal keratinocytes and dermal proangiogenic factors leads to release of mediators such as arachidonic acid metabolites and plasminogen from proliferated vessels, which enhance melanogenesis in melasma.[11,12] Plasmin also converts extracellular matrix-bound VEGF into freely diffusible forms and plays an important role in angiogenesis and melanogenesis.

Recently, the role of mast cells in the pathogenesis of melasma has been also highlighted. They are related to various histological changes and their increased number observed in melasma lesions is attributed to repetitive UV irradiation. The mast cell tryptase degrades type IV collagen that might be the cause of weak basement membrane observed in melasma. Solar elastosis is another histological feature of melasma, and elastin content in UV-exposed skin correlates with mast cell counts suggesting their role in this process. Interestingly, in experimental mast cell-deficient mouse models, solar elastosis was not observed even after repeated UV irradiation.[13] The mast cells can also induce vascular proliferation by secreting various dermal proangiogenic factors like VEGF, FGF-2, TGF-B enhancing melanogenesis in melasma.

Recently, the effect of visible light in inducing pigmentation and the role of UV radiation on keratinocyte–melanocyte interaction, dermal inflammation, and fibroblast activation through a complex interaction and interplay between increased melanocyte proliferation, fibroblast activation, stem cell factor, prostaglandin synthesis, inducible nitric oxide synthesis and melanogenesis has been elucidated.[11,12]

3 | CLINICAL EVALUATION OF MELASMA

Despite being a subjective assessment tool, the Melasma Area Severity Index (MASI) is commonly used to measure severity before and after treatment (Figure 1). Recently, a modified MASI (mMASI)

TABLE 1 Various patterns of melasma

Patterns	Description	Remarks
Clinical patterns		
Centrofacial	Involves forehead, cheeks, upper lip, nose, and chin	Commonest type, Reported in 55%–75%
Malar	Involves butterfly area over cheeks and nose	Reported in 43%–24%
Mandibular	Involves mandibular area	Reported in 1.5%–2%
Histological patterns		
Epidermal	Melanin increased in the epidermis	Has well-defined borders and brown tone, good response to treatment
Dermal	Many melanophages present in the dermis	Has ill-defined borders and responds poorly to conventional therapies
Patterns under Wood's light		
Epidermal	Pigmentation intensified	Reported in 8%–66%
Dermal	Pigmentation not intensified	Reported in 11%–12%
Mixed (Dermo-epidermal)	Mix of both epidermal and dermal patterns	Reported in 23%–80%
Indeterminate	Pigment is not discernible in dark skin	Seen in Fitzpatrick's skin phototype V-VI

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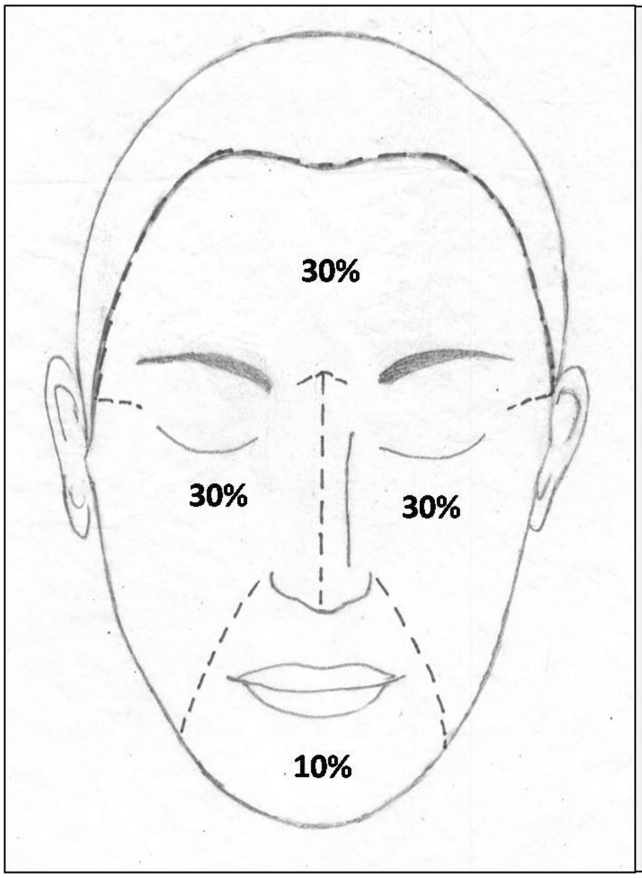
score has been introduced wherein homogeneity is excluded and only area (A) of involvement and darkness (D) of pigmentation are measured on similar pattern and the calculated range of score is 0–24.[14] The Physician's Global Assessment (PGA) is the most commonly used scoring system for assessing outcomes of treatment. Patient's satisfaction from treatment is usually measured on Likert's scale.[15] A Likert scale is a questionnaire-based psychometric ordinal scale used widely to assess level of a responder's agreement to a given question or level of satisfaction scored on five points: Strongly disagree/Not at all satisfied = 1; Disagree/Not really satisfied = 2; Neither agree nor disagree/Undecided = 3; Agree/Somewhat satisfied = 4; Strongly agree/Very much satisfied = 5. A five-point scale rather than a seven-point scale is preferred as it is easy to comprehend by respondents as well as the survey administrators and takes less time and effort to complete.

4 | TREATMENT OF MELASMA

The main objectives of treatment involve inhibiting the proliferation of melanocytes, formation of melanosomes and advancement in their degradation. These can be achieved by inhibiting melanin synthesis and melanocyte activity, removing melanin, and disrupting the melanin granules contained within melanosomes.[16]

Medical therapies remain preferred first-line modalities to treat, maintain remission, and prevent recurrences in melasma. However, non-medical therapies such as chemical peels, dermabrasion, and lasers (Q-switched Nd-YAG laser, Erbium:YAG laser, Q-switched ruby, Pulsed dye laser, Fractional lasers), intense pulsed light (IPL) and radiofrequency microneedeling therapies used alone or in combination with lasers, peels, or other therapies, have their utility in treatment-resistant or difficult-to-treat cases despite the risk of rebound hyperpigmentation, acneiform eruptions, physical urticaria, petechiae, reactivation of herpes simplex infection (Table 2).[17–31] Glycolic acid, salicylic acid, trichloracetic acid, Jessner's solution, and phytic acid are conventional chemical peels in use to treat melasma (Table 3). Although chemical peels improve hyperpigmentation by removing unwanted melanin, they can cause irritation and post-inflammatory hyperpigmentation particularly in patients with Fitzpatrick skin phototypes III-V necessitating extreme caution for their use. These agents are used mostly in combination with various other treatment options including oral, topical agents or lasers or intense pulsed light



1. **MASI score is calculated by dividing the face into four areas; and each area is weighted such that the forehead (F), right malar area (MR), and left malar area (ML) are 30% each, and the chin (C) is 10%.**
2. **Amount of pigmentation involved by melasma in these four areas (F, MR, ML, and C) is graded as a numerical value:**
   - **0 = no involvement**
   - **1 = less than 10% involvement**
   - **2 = 10–29% involvement**
   - **3 = 30–49% involvement**
   - **4 = 50–69% involvement**
   - **5 = 70–89% involvement**
   - **6 = 90–100% involvement**
3. **Severity of melasma is graded on two factors; darkness (D) of melasma compared to the normal skin and homogeneity (H) of hyperpigmentation on a scale from 0 to 4: The rating scale for both darkness and homogeneity of melasma is:**
   - **0 = absent**
   - **1 = slight**
   - **2 = mild**
   - **3 = marked**
   - **4 = maximum**

1. **MASI score is then obtained by adding the values of sum of severity ratings.**
2. **The final formula for MASI Score = 0.3 (DF + HF) AF + 0.3 (DMR + HMR) AMR + 0.3 (DML + HML) AML + 0.1 (DC + HC) AC.**
3. **The total MASI score is 0 to 48.**

FIGURE 1 The Melasma Area and Severity Index (MASI) score. The amount of pigmentation of melasma is evaluated in each of the four regions of face, forehead (30%), right malar region (30%), left malar region (30%), and chin (10%) based on percentage of the total area (A) involved and graded as a numerical value of 0 (no involvement) to 6 (90–100% involvement). The severity of pigmentation is graded on darkness (D) and homogeneity (H) on a scale of 0 (absent) to 4 (maximum). A MASI score of 0 to 48 is obtained by adding the values of sum of severity ratings.

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TABLE 2 Quality of evidence for commonly used therapies in melasma

Treatment			Quality of evidence
Topical	Phenol derivatives- Hydroquinone (HQ 2%–4%)		B–C
	Retinoids- Tretinoin (0.05%–0.1%), Adapalene, Isotretinoin (0.05%)		B–C
	Azelaic acid (10%–20%)		B
	Combinations	HQ2% + Tretinoin 0.05% + Fuocinolone acetonide (0.01%)	A–B
		HQ2% + Tretinoin 0.05% + Dexamethasone (0.01%) Modified Kligman's formula (KF)	C
		Modified KF + Glycolic Acid (GA 30%–40%)	B
		Kojic Acid (4%)+ Glycolic Acid (GA 5%)	B
		HQ 4% + GA 10%	B
		Azelaic acid (20%) + Retinoic acid 0.05%	C
Chemical peels	Alpha hydroxyl acids (GA 30%–70%)		A
	Phytic acid, Pyruvic acid		C
	Trichloroacetic acid, Lactic acid, Salicylic acid, Jessner's solution		B-C
	Dermabrasion		E
LASERS	LASER therapy alone or in combinations with chemical peels and/or topical therapies		C–D
	Pulsed CO2 laser followed by Q-switched alexandrite laser (for dermal melasma)		C

Note: Quality of evidence: description; A—there is good evidence to support the use of this procedure; B—there is fair evidence to support the use of this procedure. C—there is poor evidence to support the use of this procedure. D—there is fair evidence to reject the use of this procedure. E—there is good evidence to reject the use of this procedure.

for maximum benefit. Newer peels like phytic acid peels and amino fruit acid peel are developed to overcome the drawbacks of conventional peels. Phytic acid peels have low pH and do not need neutralization. They are applied on face overnight and used once every week and clinical effect is observed usually after 5–6 sessions.[17] Recently introduced 10% tretinoin peel mask has shown significant therapeutic benefit in 20 patients with melasma.[32] Ilknur et al.[33] in a single-blinded, randomized study found amino fruit acid peels were superior to glycolic acid peels in melasma treatment after 12 sessions. These carboxylated acidified amino acid peels have an alkaline pH, are better tolerated compared to conventional peels, and have been used effectively in combination with triple combination therapy in a patient with treatment-resistant melasma.[34] Obagi blue peels have fixed concentrations of trichloroacitic acid with nonionic base which ensures uniform distribution of trichloroacitic acid and even peeling. The newly described lipohydroxy acids are salicylic acid derivatives with additional fatty acid chains with improved lipophilicity and keratolytic efficacy.[35]

The use of laser and light therapy is based on observations that the melanin has a broad absorption spectrum and melanosomes having a shorter thermal relaxation time (50–500 nano sec) and longer wavelengths will penetrate deeper to target dermal melanin allowing use of a variety of devices. Several lasers and light-based devices have been used alone or in combination with other modalities to treat melasma mostly in Fitzpatrick skin phototypes II–IV but the benefit in other skin types remain debatable. Their cautious use is advocated as the damage to the surrounding tissue and resultant inflammation and pigmentary changes may be long-lasting. Q-switched ruby lasers and erbium:yttrium-aluminum-garnet (Er:YAG) lasers may worsen melasma and combination of carbon dioxide laser with Q-switched alexandrite laser when used in ablative settings is not beneficial with additional risk of worsening of melasma in patients with dark skin.[36–40] However, these lasers when used properly with adequate cooling and in a non-ablative setting may be useful, especially when combined with topical therapies including topical use of triamcinolone or other mid-potency topical corticosteroids.

5 | MEDICAL THERAPIES

Most medical treatment modalities in melasma are usually targeted to slow melanocyte proliferation, inhibit melanosome formation, and promote their degradation. Traditionally, hydroquinone, a tyrosinase inhibitor, has been used alone or as "triple combination" with retinoic acid and a corticosteroid worldwide. In recent years, the focus has shifted to non-hydroquinone-based medical therapies (Table 4).

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TABLE 3 Non-hydroquinone-based therapies for melasma

Mechanism of action		Common skin lightening agents
Tyrosinase inhibitors	Competitive	Arbutin (α or β Arbutin), Deoxyarbutin, Aleosin, Azelaic acid, Kojic acid, Gentisic acid, Mequinol, Flavonoids
	Non-Competitive	Glabridin, Liqourice extract, Mulberry extract, N-acetyl glucosamine (Chitin), Hydroxystilbenes (resveratrol, genitol),
Melanosome transfer Inhibitors		Niacinamide (Vit B3), Soy extract (Soyabean trypsin inhibitor), Retinoic acid
Melanosome maturation inhibition		Arbutin, Deoxyarbutin
Antioxidants		Vitamin E (α-Tocoferol acetate), Vitamin C (Sodium ascorbyl phosphate, Ascorbyl Palmitate, Ascorbyl Glucoside)
Epidermal turnover enhancers		Retinoic acid, α-hydroxy acids, Salicylic acid, Linoleic acid
Plasmin inhibitor		Tranexamic acid
α-MSH induced melanin reduction		β-carotene
Protease activator receptor-2 inhibitor		Soyabean trypsin inhibitor
By interaction with copper		Kojic acid, Ascorbic acid

5.1 | Hydroquinone and its derivatives in melasma

Hydroquinone (1,4 dihydroxybenzene), a hydroxyphenolic compound, has been used extensively as a standalone or in combination with other agents for topical treatment of melasma. It inhibits conversion of DOPA to melanin by inhibiting the activity of tyrosinase possibly interacting with copper at the active end of the enzyme.[41] It is also said to alter melanosome formation, increase their degradation, destroy melanocytes, and inhibit DNA and RNA synthesis. It is used topically as a 2% to 5% cream or alcohol-based solution and has been found effective even in monotherapy. The pigmentation decreases evidently in a dose-dependent manner by 5–7 weeks of treatment that needs to be continued at least for 3 months to a year.[8,42–45] Hydroquinone 4% has resulted in complete or partial clearance of melasma in 95% patients versus 67% patients in the placebo group at 12 weeks without significant adverse effects.[46] Although azelaic acid 20% produced a more favorable response than hydroquinone 2% resulting in excellent or good overall improvement (73.8% vs. 19.4%), hydroquinone 4% was as effective as azelaic acid 20% over 24 weeks without causing itching and burning noted with the latter.[47–49] It was equally effective as monotherapy in 4% concentration and in a combination with glycolic acid (20%–30%) peel leading to significant improvement in a split face study comprising 21 Hispanic women.[50] Hydroquinone 4% showed a 77% improvement over a 3-month period when compared with a 67% improvement from a skin whitening cream containing *uva ursi* extract, fermented *Aspergillus*, rice extract and grapefruit extract.[51] Pruritus was the major adverse effect from hydroquinone. A twice-daily application of 4% hydroquinone was superior to placebo and improved melasma in 38% and 77% patients versus 10% and 67% patients in placebo group in two separate studies.[46,51] Apparently, a 4% concentration is particularly useful when used as monotherapy. However, nearly 25% patients may experience a dose- and duration-dependent irritation from transient inflammatory reaction with higher concentrations, especially during initial 2 weeks of topical therapy.[43,44,52] Mild itching, burning sensation, erythema, irritant and allergic contact dermatitis, transient hypopigmentation, nail discoloration, and post-inflammatory hyperpigmentation are reported more often with 4% than 2% formulations. Prolonged use and higher concentration is also associated with exogenous ochronosis, a difficult-to-treat, gray-blue-black pigmentation over treated areas.[46,51] However, these adverse events may also be associated with other substances added to the hydroquinone formulation.[41,53] Another concern is its propensity for rapid oxidation resulting in unstable formulations, discoloration, decreased efficacy, and actual depigmentation from melanotoxic hydroxybenzoquinone and *p*-benzoquinone, the byproducts of its oxidation.[17] The risk of possible bone marrow toxicity, development of renal adenomas or carcinogenic effect of topical hydroquinone therapy in humans is considered insignificant since it bypasses its metabolism in liver.[41,54] There was also no significant risk for premature death or malignancy among workers exposed to the compound during industrial production than normal population.[41] Nevertheless, its use in over-the-counter cosmetics in USA, Australian, European, Japanese, and Indian markets is not allowed while Poland and West African country Ghana have totally banned it.

5.2 | Hydroquinone combination therapies

Currently, hydroquinone is often used in combination with other agents such as retinoids, topical corticosteroids, kojic acid, and/or glycolic acid for added effect. It is also used along with chemical peels.

5.2.1 | Triple combination treatments

The triple combination of hydroquinone with a retinoid and a corticosteroid remains the most studied modality to treat melasma because of improved tolerability and efficacy. The original triple combination developed by Kligman–Willis in 1975 consisted of hydroquinone 5%, tretinoin 0.1%, and dexamethasone 0.1%.[55] Overall, it has been noted that hydroquinone 10% is more effective but highly irritating, tretinoin 0.2% is irritating without being more effective while tretinoin 0.05% is less irritating but takes a long time

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TABLE 4 Classification of chemical peels

Classification		Examples	Depth of exfoliation
Very superficial peels		Glycolic acid 30%–50% Trichloroacetic acid (TCA)10% Jessner's solution (1–3 coats) Salicylic acid 20%–30% Lactic acid 50% Tretinoin 1%–5%	Stratum corneum
Superficial peels		Glycolic acid—50%–70% TCA 10%–30% Jessner's solution[a] (4–7 coats)	Epidermis extending to papillary dermis
Medium peels		Glycolic acid 70% TCA 35%–50% Phenol 88% Pyruvic acid	Upper reticular dermis
Deep peels		Baker Gordon phenol formula[b]	Mid reticular dermis
Classic peels	Mono peels	Glycolic acid Trichloroacetic acid Salicylic acid Retinoic acid Phenol	–
	Combination peels	Jessners peel Modified Jessners peel (lactic acid, salicylic acid and citric acid) Baker-Gordon peel (phenol, croton oil, septisol and water) Salicylic - mandelic acid	-
Newer peels	Mono peels	Mandelic acid Pyruvic acid Lactic acid Ferulic acid Jasmonic acid Tartaric acid Malic acid	-
	Combination peels	Salicylic-mandelic acid peel VI peel (TCA 10%–12%, salicylic acid 10%–12%, tretinoin 0.1%–0.4%, phenol 10%–12%, and vitamin C 4% in mineral blend) Phytic acid Lipohydroxy acid Polyhydroxy acid Black peel	-

[a]Jessner's solution: salicylic acid 14%, lactic acid 14%, resorcinol 14% in 95% ethanol.

[b]Baker Gordon phenol formula: 3 ml phenol, 2 ml water, 8 drops of hexachlorophene (septisol), and 3 drops of croton oil yielding 48.5% phenol and 2.2% croton oil.

to be effective, and dexamethasone can be increased up to 0.2% to enhance activity without significant difference in irritancy potential.[45,55] Several modifications using different corticosteroids (hydrocortisone 0.1%, mometasone 0.1%, fluticasone 0.1%, betamethasone valerate, flucinolone acetonide 0.01%) have been in use since then. The fluorinated corticosteroids are apparently more effective than non-fluorinated steroids. A formulation of hydroquinone 4%, tretinoin 0.05%, and flucinolone acetonide 0.01% (HTF, Triluma®) remains the only US FDA approved triple combination for melasma therapy. Studies across ethnicities have documented its superior efficacy even in moderate to severe melasma and improved quality of life compared with hydroquinone monotherapy or other combination therapies. This triple combination was more effective than hydroquinone 4% alone from 4 weeks onwards in a comparative study in 120 Brazilian patients with moderate-to-severe melasma.[45] A complete clearance of pigmentation in 35% and >75% improvement occurred in 73% at 8 weeks compared with 5% and 49% patients, respectively, in hydroquinone-only group without a significant difference in adverse effects in both the groups. Chan et al.[56] also demonstrated a superior effect of HTF triple combination compared with hydroquinone 4% cream alone in a multicenter randomized study of 206 Southeast Asian patients. Nearly 70% of 125 patients with moderate to severe melasma achieved complete clearance in triple combination group as compared to 44% of 129 patients in hydroquinone group. Similar observations on its efficacy and safety have been made in 1290 Latin American patients

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(including 23% Hispanics) in a phase IV community-based study (PIGMENT trial).[57] A statistically significant reduction in degree of melasma was observed and nearly 49% patients improved from moderate or severe (99%) at first visit to absent or mild melasma at 8 weeks. The adverse events were mild in 68%, moderate in 25%, and severe in 6.9% only. Sequential treatment with triple combination cream and IPL was more efficacious than sequential treatment with an inactive (control) cream and IPL in a 10-week split-face study by Goldman et al.[58] They treated 56 patients having moderate to severe melasma with triple combination cream on one side of the face and an inactive control cream on the other side of the face. Patients also had two IPL treatments 2 and 6 weeks after suspending topical treatment one day before IPL treatments. Melasma severity was significantly less with triple combination cream and IPL compared with control cream and IPL at 6 weeks and end of 10-week study period.

The triple combination therapy has also proven impact on improving quality of life in patients with melasma. A statistically significant reduction in MASI and MelasQoL scores observed after 4 and 8 weeks of treatment with HTF triple combination in 135 of 300 patients (mean age 42 years) with skin phototypes I through V in a Brazilian multicenter study.[59] Similarly, HTF triple combination was superior in improving quality of life in comparative clinical trial for efficacy and safety, and effect on MelasQoL when compared with hydroquinone 4% and tretinoin 0.05% in studies of melasma patients from Latin America, Mexico, and Hispanic women with a range of Fitzpatrick skin types I through VI.[60–62] Triple combination therapy was overall the best topical treatment for melasma in a recent Cochrane review.[63] Its efficacy has been attributed to synergistic effect of individual components and time taken for its beneficial effect with a twice-daily application is roughly three weeks. Tretinoin prevents oxidation of hydroquinone and improves epidermal penetration of other agents while topical corticosteroid decreases cellular metabolism, inhibits melanin synthesis, and reduces irritation from the other two components.[55] Nevertheless, adverse effects such as erythema, burning, pruritus and irritation, dryness and desquamation are not uncommon and other corticosteroid-induced cutaneous adverse effects may occur from its unsupervised prolonged use. Another problem is of post-inflammatory hyperpigmentation from irritant reaction noted in few patients with darker skin. A less frequent application may ameliorate irritation in such patients.

5.2.2 | Dual combination treatments

Dual combination treatments tested for melasma include hydroquinone plus retinoic acid or hydroquinone (4%) plus glycolic acid (5–10%) with moderate improvement and generally tolerable irritant effects.[13,64,65] A combination of hydroquinone 4%, glycolic acid 10%, antioxidants and sunscreen showed reduction in melasma pigmentation after 12 weeks of treatment that was more significant than seen with antioxidants/sunscreen alone in a comparative study.[66] A combination of hydroquinone and kojic acid or glycolic acid demonstrated a significant decrease in degree of melasma in a study of 39 patients.[67] However, addition of glycolic acid peel did not improve the efficacy of similar regimen of hydroquinone 4% and glycolic acid 10% over 7 months in a Brazilian study.[68]

5.3 | Mequinol

Mequinol (4-hydroxyanisole, monomethyl ether of hydroquinone), a derivative of hydroquinone with a similar mechanism of action is used as 2% concentration in combination with tretinoin (0.01%) for treating melasma. It was superior in efficacy to hydroquinone 3% and tolerated well in a randomized, parallel-group, double-blind study of 216 patients with solar lentigines/hyperpigmented lesions.[69] Keeling et al.[70] achieved moderate improvement in one and complete clearance with the combination in four males with melasma at 12 weeks with effect lasting up to 16 weeks. The combination is usually safe and well tolerated but caused mild erythema, irritation/burning, stinging/tingling, desquamation, pruritus, and hypopigmentation in another open-label study using twice-daily application of mequinol/tretinoin and sunscreen with SPF ≥25 for 24 weeks to treat solar lentigines and related hyperpigmented lesions.[71] Experimentally, mequinol was effective in treating melasma and showed less irritant potential than hydroquinone and adverse effects were less than those from monobenzyl ether of hydroquinone.[72,73] Although licensed for monotherapy in Europe and Brazil or in combination with tretinoin in United States and Canada, hydroquinone and not mequinol remains preferred first-line therapy for melasma world over.[74] Few large controlled clinical studies for mequinol in the management of melasma will perhaps resolve issues related to its efficacy and safety for a wider acceptance.

6 | NON-HYDROQUINONE-BASED THERAPIES

Topical corticosteroids, retinoids, and alpha hydroxy acids (glycolic acid, kojic acid, azelaic acid), several plant extract-based therapies have been used alone or in combinations with hydroquinone in dual or triple therapy. Other competitive tyrosinase inhibitors (arbutin, deoxyarbutin, aloesin, kojic acid, flavonoids, saponin, oregonin, and yohimbine) or non-competitive tyrosinase inhibitors (glabiridin, hydroxystilbenes) have been also used in place of hydroquinone. Studies have also reported usefulness of rucinol, tranexamc acid (TA), zinc sulfate, vitamins E and C compounds, and several plant extracts as newer therapies for melasma. New tyrosinase inhibitors diaryl propane, hydroxyphenolnaphthol, calycosin, and quinolines need further *in vivo* and *in vitro* evaluation.[75]

6.1 | Corticosteroids

Topical corticosteroids are rarely used alone for treating melasma due to their cutaneous adverse effects such as skin atrophy, facial

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hypertrichosis, acneiform eruptions, telangiectasias, rosacea, and perioral dermatitis.[16,76] Moreover, the short-lived beneficial effect prompts repeated and prolonged treatment without supervision causing marked skin atrophy and other adverse changes. The mechanism for their skin lightening effect remains poorly understood and is often attributed to their direct anti-metabolic effect on melanin synthesis, alteration of melanocyte function without being melanotoxic and/or inhibition of synthesis of inflammatory mediators such as leukotriene and prostaglandins.[76] Topical use of a potent or super potent corticosteroid alone has demonstrated good therapeutic effect.[77] Corticosteroids such as hydrocortisone, dexamethasone, mometasone furoate, fluocinolone acetonide, and fluticasone remain preferred in (triple) combination therapy of melasma. Once daily futicasone (0.05%) topical application was as effective as betamethasone (0.12%) twice daily or mometasone furoate without hypothalamic-pituitary-adrenal axis suppression and caused less skin atrophy than mometasone furoate and fluocinolone acetonide in the triple combination.[78,79] Topical corticosteroids as monotherapy for melasma are usually not preferred for their atrophogenic potential and other adverse effects, although fluticasone is less atrophogenic than others. However, they are beneficial when used with caution to reduce irritation from other topical agents or when pigmented cosmetic dermatitis is suspected.

6.2 | Retinoids

Tretinoin (0.05%–0.1%) remains a common retinoid used effectively to treat melasma even as monotherapy but needs at least 24 weeks for apparent clinical improvement.[80] It inhibits tyrosinase transcription and related proteins 1 and 2 (TRP-1 and TRP-2) to decrease post-transcriptional levels of tyrosinase and TRP-1and interrupts melanin synthesis after UVB exposure.[13,81–84] Additionally, it also decreases melanosome transfer by accelerating keratinocyte turnover and desquamation.[83] When used in combination, it improves penetration of other active ingredients like hydroquinone and antagonizes atrophogenic effect of corticosteroid.[13] Topical tretinoin lead to 68% improvement in 38 patents over a 40-week treatment period.[85] However, 88% patients experienced burning, itching, erythema, and scaling from continuous therapy. Tretinoin (10%) peeling mask was effective in a study of 20 women with Fitzpatrick skin type II-VI and tretinoin 1% peel was as effective as 70% glycolic acid peel.[32,86] Topical adapalene, isotretinoin and tazarotene are other retinoids used in melasma.[82,83,87] Adapalene is well tolerated and equally effective among retinoids in long-term melasma treatment. Retinol causes less irritation but its comparative efficacy is lower than tretinoin or tazarotene.[41]

6.3 | Kojic acid

Kojic acid (5-hydroxy-2-hydrxymethyl-4-pyrne), a metabolite of *Aspergillus orzae* and certain species of *Acetobacter* and *Penicillium*, inhibits free tyrosinase by chelating copper at the enzyme's active site and exhibits antioxidant effects. It is available in 1–4% concentration and has efficacy almost equal to other therapies. Addition of hydroquinone 2% or glycolic acid (5%–10%) has an augmenting effect. Its combination with hydroquinone 2% was superior in efficacy than kojic acid used alone or its combination with betamethasone valerate 0.1% or glycolic acid 5%, or a combination of betamethasone valerate 0.1% and hydroquinone 2%.[6,88] A combination of kojic acid 2%, glycolic acid 10%, and hydroquinone 2% was more effective in melasma than the same combination without kojic acid in a spilt-face study.[89] The combination of kojic acid 2% and glycolic acid 5% had efficacy equal to that of hydroquinone 2% and glycolic acid 5% in a split-face study to treat melasma.[49] It makes a useful option in patients responding poorly to hydroquinone and glycolic acid or who are intolerant to other first-line therapies. However, it is potentially an irritant and a contact sensitizer and known to cause paradoxical pigmented contact dermatitis.[90]

6.4 | Azelaic acid

Azelaic acid, a dicarboxylic acid, produced by *Pityrosporum* sp., is responsible for hypopigmentation in tinea versicolor. It has antiproliferative and selective cytotoxic effect on abnormally hyperactive melanocytes by its inhibitory effect on tyrosinase and mitochondrial oxidoreductase enzymes with minimal effects on normally pigmented skin. Azelaic acid (15%–20%) is effective in melasma and post-inflammatory hyperpigmentation as monotherapy and was equally effective as hydroquinone 4% but superior to hydroquinone 2% while its combination with tretinoin 0.05% and glycolic acid 15%–20% showed synergistic effect.[47,48,91,92] A combination of azelaic acid 20% and glycolic acid 15%–20% was as effective as hydroquinone 4% in moderate to severe melasma and other facial hypermelanoses in patients with skin of color.[91] It makes a safe choice in hydroquinone intolerant patients. However, mild and transient itching and burning may occur while acneiform eruptions and telangiectasias, hypertrichosis, vitiligo, and asthma are extremely rare occurrences.[92]

6.5 | Arbutin

Arbutin, a d-glucopyranoside derivative of hydroquinone, derived from bearberry leaves is widely used for its skin lightening and depigmenting effect. It hydrolyses to hydroquinone in vivo and competitively inhibits enzyme tyrosinase and 5,6-dihydroxyindole-2-carboxylic acid polymerase activity in vitro in a dose-dependent manner.[93] Deoxyarbutin and α-arbutin, the synthetic derivatives of arbutin, are more stable and show better efficacy than the natural one. The inhibitory effect of arbutin on tyrosinase activity equals to that of hydroquinone and deoxyarbutin in an in vitro study but is less effective than kojic acid.[41,49] However, deoxyarbutin also has inhibitory effect on melanosome maturation and is comparatively

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less toxic in vitro to melanocytes than hydroquinone. A significant skin lightening and improvement in solar lentigines was observed following topical deoxyarbutin treatment for 12 weeks in patients with either light or dark skin tones.[93] However, good clinical studies are lacking for its efficacy and safety in patients with melasma.

6.6 | Tranexamic acid

The efficacy of Tranexamic acid (TA) (Trans-4-Aminomethylcyclohexanecarboxylic acid) in treating melasma has immensely renewed interest for this mode of therapy in recent years. This synthetic derivative of the amino acid lysine is a plasmin inhibitor and antifibrinolytic agent used primarily to prevent and treat blood loss in menstrual disorders and surgeries with high risk of blood loss such as cardiac, liver, vascular, and orthopedic procedures.[94,95] It exerts its effect by reversibly blocking lysine binding sites on plasminogen molecules thus inhibiting plasminogen activator from converting plasminogen to plasmin. It has no effect on coagulation parameters in recommended antifibrinolytic doses of 0.5–1.5 g given three times daily or up to 2.0–4.5 g/day. It is given intravenously as 10 mg/kg immediately before surgery or in 6–8 hourly doses one day prior to surgery. The peak plasma concentrations are reached within 3 h after oral administration and its absorption is not hampered by food. Approximately 3% of the drug is bound weakly to plasma protein, the plasminogen. Almost 45% of the dose is recovered in the urine in first 3 hours and 90% of the intravenous administered drug is eliminated mostly in one day. The drug can cross the blood–brain barrier and the placenta but excretion into breast milk is minimal.

6.6.1 | Tranexamic acid in melasma

Sadako[96] incidentally observed that severity of melasma reduced significantly after 2–3 weeks of TA in a patient under treatment for urticaria. It has been reported effective when used alone or in combination with other modalities to treat melasma topically (liposome formulations), intradermally (by microinjection), transepidermally (by mesotherapy), orally, or intravenously with comparable efficacy.[15,97–104] Although intravenous TA has been advocated for the "whitening of skin" in Taiwan since 2007, the usual recommended intravenous dose (500 mg every 2–4 weeks administered directly or with normal saline infusion) is potentially risky and considered too low for skin whitening effect.[103] Further, there are no clinical studies to justify such use.

6.6.2 | Topical tranexamic acid

Topical TA 2% or 5% in liposomal formulations has been found effective with clinical effect observed in 2–3 months.[105–107] Although no significant difference was noted between 5% TA versus vehicle in a 12-week randomized controlled split-face study, topical 3% tranexamic acid was as effective as topical hydroquinone 3% and 0.01% dexamethasone combination cream in another similar trial.[105,106] It was also effective as topical emulsion in melasma and freckles applied for 5–18 weeks.[107]

6.6.3 | Intralesional tranexamic acid

TA is not commercially available for intralesional use but prepared as 4 mg/ml solution from 100 mg/ml commercial injectable solution for mesotherapy (transepidermally by microneedling or intradermal by localized microinjections) to treat melasma in both genders.[15,102] Lee et al.[99] reported significant decrease in MASI score in 8–12 weeks from baseline in 100 patients with melasma but injection site erythema and pain were major limiting factors. Although the results were not statistically significant, the improvement in baseline MASI score was better with drug administration by microneedling than microinjections (44.4% vs. 35.7%) in a comparative study comprising two groups of 30 patients each.[98] However, TA by microinjection was superior to topical TA in a small study comparing the two routes of administration.[108] Similarly, an overall efficacy with comparable reduction in MASI score was noted in patients receiving intradermal or oral TA in a recent study.[102] These results suggest that the efficacy of TA is perhaps independent of its route of administration. Nevertheless, direct injection to the affected sites is minimally invasive, offers the advantage of delivering adequate amount of medication directly at the affected skin, and allows use of lower than oral dose. However, pain and discomfort during injection procedure and turn around period of 2–3 days are real drawbacks. The use of TA by ionotophoresis chemical enhancer and constant electric current may have the advantage of being without pain and discomfort but requires further clinical evaluation.[109]

6.6.4 | Oral tranexamic acid

Oral TA in doses varying between 500 mg/day and 2.25 g/day for up to 6 months have been used alone or as adjuvant with almost equal efficacy (Table 5). Hajime et al.[110] in a study showed 33 of 40 patients aged 24–60 had their melasma reduced in severity with 1–1.5 g daily oral TA in 10 weeks. Zhu et al.[111] compared oral 250 mg TA, vitamin C (0.2 g) and vitamin E (0.02 g), all given thrice daily to treat 128 patients with melasma and vitamins C and E only in 30 controls for a period of 6–8 weeks. They observed statically significant reduction in melasma in the treatment group. Similar results were obtained by Liu et al.[112] in a study comprising 176 patients and 70 controls. The treatment group who received oral TA 250mg three times daily, and vitamin C (0.3 g/d), and vitamin E (0.1 g/d) in controls given for 2 months showed more improvement with about 24% patients showing 90% improvement and 40% patients having 60% improvement compared with the control group. Thirty-three percent of the 256 melasma patients of Wu et al.[113] showed improvement in the first month from oral TA 250 mg given twice daily and 33% improved further after

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TABLE 5 Clinical studies using oral tranexamic acid in the treatment of melasma

Reference number	No. of patients/ Control	Age in years	Dose of oral Tranexamic acid	Controls	Duration	Results	Adverse effects of TXA	Remarks
[15]	66/66	18-52	250 mg once daily (Group-A) Topical sunscreen	500 mg twice daily (Group-B) Topical sunscreen	4 months	MASI ↓60.1% (Group-A) versus 78.09% (Group-B)	Mild gastrointestinal upset in both groups; oligomenorrhoea in 3 cases in Group-B (self-limiting)	Although, 500 mg twice daily showed early clinical response and overall better efficacy both in per-protocol and intention-to-treat analysis, 250 mg once daily was also effective and can be a choice to maintain remission.
[99]	12/0	30–69	1.5 g/day + Vitamin B, C, E	No control	5 months	11/12 patients had obvious result	Not mentioned	Effect onset mostly in 4 weeks
[102]	130/130	17–55	500 mg/day+ topical hydroquinone and sunscreen	Topical hydroquinone and sunscreen	3 months	mMASI ↓ 82.3% versus 40.8% $p < 0.05$	Oligomenorrhea 14.7% Belching 9.2% Abdominal cramp 6.9%	–
[104]	39/41	18–55	250 mg twice daily	Intradermal TXA	3 months	64%>75%↓ 36% 50%–75%↓	Mild gastrointestinal upset in 2 cases; oligomenorrhoea in 6 cases (self-limiting)	Both were equally effective
[106]	24/27	32–50	500 mg/day + IPL-Nd:Yag	IPL- Nd:Yag	6 months	mMASI ↓ 43.8% versus 23.6% $p < 0.005$	No significant adverse effect	–
[112]	40/0	24–60	1–1.5 g/day	No control	10 weeks	33/40 patients had decrease severity	Not mentioned	–
[113]	128/30	30–49	750 mg/day + Vitamin C, E	Vitamin C, E	6–8 weeks	20% >95% ↓ 30% >60% ↓33% 20–60%↓ $p < 0.001$	Gastrointestinal upset in few cases	Observed increase duration of TXA more effective than increased dose. No change in clotting profile
[114]	176/70	25–57	750 mg/day + Vitamin C, E	Vitamin C, E	2 months	24% >90% ↓ 40% >60% ↓ $p < 0.01$	5% gastrointestinal upset in both group	No change in clotting profile
[115]	256/0	21–65	500 mg/day	No control	6 months	10.5% >90% ↓ 18.8% >60% ↓ 51.6% 30%↓	Gastrointestinal upset in 4.3%, oligo- menorrhea in 3.5%	33% response in 1st month, 33% in 2nd month. No change in clotting profile
[116]	99/100	>15	2.25 g/day	Placebo	8 weeks	76.8% improved versus 27% placebo ($p < 0.001$)	Transient chest discomfort in one case	–

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the second month. Nearly 77% of the TA group (oral 750mg three times daily) showed improvement compared with 27% in the placebo group in another 8 weeks placebo-controlled trial without significant adverse effects except for transient chest discomfort in one case.[114] The results as good to very good response were also comparable with oral TA 250 mg twice daily (in 80% patients) versus triple combination (hydroquinone, fluocinolone acetonide, and tretinoin) therapy (in 70% patients) at 16 weeks in another comparative study.[115] TA 500 mg twice daily showed significant early reduction in mean MASI score at 8 weeks onwards compared with 250 mg given once daily with comparable safety and therapeutic efficacy at 16 weeks in a recent open-label cross-sectional study.[15] However, TA 500 mg twice daily showed early clinical response and overall better efficacy both in per-protocol and intention-to-treat analysis.

6.6.5 | Tranexamic acid as an adjuvant

TA also enhanced effects of hydroquinone and laser therapy when used as an adjuvant.[100,103,104,116] Karan et al.[100] used oral TA (250 mg twice daily) with topical measures (hydroquinone and sunscreen) given for 3 months and compared the results with topical measures alone. Statistically significant decrease in the mean MASI score was observed from baseline at 8 and 12 weeks with addition of oral TA. Cho et al.[104] used oral TA (500mg/day) as an adjuvant therapy with intense pulse light of Nd:YAG laser for treating melasma in 24 patients and observed statistically significant decrease in MASI score as compared with results in 27 patients treated with laser treatment alone. They also found it useful as prophylaxis for post-inflammatory hyperpigmentation after IPL therapy in melasma.

6.6.6 | Mechanism of action of tranexamic acid in melasma

The exact mechanism of action of oral or topical TA in reducing melasma remains conjectural at the moment. Few studies have demonstrated that inhibition of plasminogen/plasmin system plays an important role in TA-induced reduction of melasma pigmentation. Maeda and Naganuma[9] demonstrated that it decreased melanocyte tyrosinase activity by preventing the binding of plasminogen to the keratinocytes in UV-induced pigmentation in guinea pigs. Maeda and Tomitab[9] also suggested that TA inhibits melanin synthesis in melanocytes by interfering with the interaction of melanocytes and keratinocytes through inhibition of the plasminogen/plasmin system. Zhang et al.[117] opined that TA can inhibit melanogenesis by interfering with the catalytic reaction of tyrosinase. TA also prevents activation of melanocytes by sunlight or hormonal influence, and injured keratinocytes (after UV exposure, peeling, IPL, laser) through the inhibition of the plasminogen activator system.

Although it remains unknown which dermal factors are primarily causal in melasma, it is possible that melasma-related dermal changes such as vessel proliferation and number of mast cells decrease after TA treatment suggesting that its efficacy may partly be due to its inhibitory effects on mast cells which may affect vascularization and dermopathy and this might explain the differential effects of tranexamic acid on lesional skin.[100,118,119] Furthermore, it reduces epidermal pigmentation and erythema of melasma perhaps through its inhibitory effect on plasmin or by decreasing UV-induced plasmin activity in keratinocytes resulting in decreased prostaglandin synthesis that in turn decreases tyrosinase activity in melanocytes providing a rapid and better lightening in melasma and prevent recurrences when used as an adjuvant.[99,117] TA also suppresses angiogenesis and inhibits neovascularization induced by bFGF.[117,118] This anti-angiogenesis activity due to TA perhaps also results in reduced erythema and vessel counts leading to decreased mast cell activation and reperfusion injury is almost completely abolished post-treatment.[119]

6.6.7 | Adverse effects of tranexamic acid

The commonly reported side effects of oral TA are nausea or diarrhea and abdominal pain in 5.4% of treated subjects.[102] These can be alleviated when TA is administered after a meal. Oligomenorrhea perhaps is frequent occurring in 3%–15% of patients on oral TA, it is not mutagenic and it does not have harmful effects on the fetus.[102,103] Disturbances in color vision, anaphylactic shock, skin rash, orthostatic hypotension, and acute renal cortical necrosis are extremely rare but adverse effects of concern. Thromboembolism, myocardial infarction, and pulmonary embolism have been reported in some cases when higher doses are used for hemostasis, but risk remains minimal and not statistically significant.[103] However, it remains contraindicated for patients with acquired color vision abnormalities, active coagulopathies, and known hypersensitivity to TA. It also needs careful use in patients with cardiovascular or cerebrovascular diseases and who are on anticoagulants. Topical tranexamic acid formulations are usually safe and can be a good option for maintenance therapy to prevent relapse. However, higher concentration may cause some degree of irritation and stinging.

7 | MISCELLANEOUS THERAPIES

In spite of these well-studied therapies, the quest for more effective and safe treatment for melasma continues with the introduction of several new molecules. The efficacy and safety of these treatment options needs to be evaluated in larger studies.

7.1 | Glutathione

Glutathione (γ-l-glutamyl-l-cysteinylglycine), a low-molecular-weight thiol-containing tripeptide having amino acids glutamate, cysteine, and glycine, is present in almost all living bacterial and mammalian cells. Glutathione in its reduced form

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is a key antioxidant and significantly decreased levels of plasma glutathione have been reported in patients with melasma as compared to controls.[120–122] Its efficacy in treating melasma is attributed to inhibition of tyrosinase enzyme by chelation of copper ions, transfer of tyrosinase to premelanosomes for melanin synthesis, shifting of the process of melanogenesis from eumelanin to pheomelanin, and inherent antioxidant effect in free radicals and peroxides quenching, preventing tyrosinase activation and melanin formation.[123]

7.1.1 | Glutathione in melasma

Glutathione has been used topically (cream, face wash, soap, lotion, and glutathione-based chemical peels), intradermally as mesotherapy solution, and orally alone or in combination with alpha lipoic acid, pyruvic acid, N-acetyl cysteine, vitamin C, vitamin E, grape seed extract and other antioxidants, or intravenously as skin lightening agent in patients with melasma. While loading glutathione into the hyaluronic acid microneedles for transdermal delivery enhanced efficacy, its use for mesotherapy remains under reported.[124,125] Its topical use is also limited because of its foul odor, poor permeability, and absorption.

Most of the orally administered glutathione is absorbed within the gut luminal cells and there is only a transient increase in blood levels, finally gets eliminated via renal excretion. Sublingual administration has better bioavailability than orally administration drug and is considered safe by US FDA. However, sulfurous taste remains a major drawback for its acceptability in general. The usual recommended oral dose is 20–40 mg/kg/d (maximum 1–2 g/d) given in two divided doses with a maintenance dose of 500 mg/d and significant response occurs within 3–6 months in dark brown skin, in 6–12 months in very dark skin and in 2 years or more in black skin.[126]

The intravenous administered glutathione (600–1200 mg, given once or twice in a week) has a half-life of 10 min and gets oxidized immediately into its three constituent amino acids (glutamate, glycine, and cysteine).[127] Intravenously, it is usually given in a dose of 900 mg weekly or can be repeated 2–3 times a week. The skin whitening effect usually occurs as early as 2–3 weeks.[128] However, intravenous use of glutathione as skin whitening agent remains under-evaluated and is banned by US FDA because of commonly reported adverse effects such as skin rashes, abdominal pain that may be severe, thyroid, and renal function derangement, Stevens–Johnson syndrome, and toxic epidermal necrolysis.

The results of its efficacy to treat melasma remain variable.[128–131] Wahab et al.[128] in a double-blind randomized controlled study involving 46 subjects found glutathione an effective skin-lightening agent and a combination of topical and oral glutathione was superior than either route used alone. Another randomized, double-blind, placebo-controlled clinical trial comprising 124 Asian females demonstrated significant skin-lightening and reduction in size of facial pigmentation after oral supplementation with combination of l-cystine and l-glutathione.[129] While benefits of skin lightening with 500 mg/d orally administered glutathione given for 4 weeks were limited to certain age groups and body areas in 60 healthy Asian subjects, no significant improvement occurred in 16 patients receiving glutathione and any improvement seen in two separate randomized controlled trials was short lasting.[130–132]

7.2 | Cosmeceuticals and botanicals

Table 6[43,133–170] lists some naturally occurring depigmenting agents and flavonoids such as vitamin C, vitamin E, rucinol, glucosamine, niacinamide, extracts of soybean (soy), safflower (linoleic acid), licorice, mulberry and grapes (hydroxylstilbene compound resveratrol), coffee berry, orchid, green tea leaves (epigallocatechin-3-gallate), eucalyptus and strawberry (ellagic acid), *Silybum marianum* (sylimarin), *Pinus pinaster* (pycnogenol) *Boswellia serrata* (boswellic acids), citrus fruits (bioflavonoid hesperidin), grape seed, aloe (aloesin), sunflower seed (octadecenedioic acid), ginseng, and plants of Apiaceae family such as carrot and coriander (umbelliferone). They are said to be useful in the sequential treatment of melasma albeit, only a few of them have been added to cosmetics or cosmeceuticals for want of adequate information on their efficacy and potential adverse effects. Few of them with some clinical evidence of their efficacy are reviewed here.

7.2.1 | Ascorbic acid

Ascorbic acid (Vitamin C), used in many skin-whitening formulations is a water-soluble vitamin occurring naturally in green leafy vegetables and citrus fruits and in human skin. It has low permeability and limited stability because of rapid oxidation as compared to its esterified forms; magnesium ascorbyl-2-phosphate (MAP), ascorbyl-6-palmitate, and tetrahexyldecyl ascorbate. Ascorbic acid in MAP cream form is more effective than in natural form.[43,133] It reduces dopaquinone to DOPA and acts as an antioxidant in addition to its photoprotective effect as it prevents absorption of ultraviolet radiation and promotes collagen synthesis.[134] It also inhibits melanogenesis by inhibiting tyrosinase activity via interacting with copper. A split-face randomized controlled trial compared ascorbic acid 5% and hydroquinone 4% used on either side of the face for 16 weeks by sixteen patients with melasma.[136] The study found about 62% and 93% improvement with ascorbic acid and hydroquinone, respectively. Although, response to hydroquinone was significantly better but adverse effects were less frequent with ascorbic acid. It has been demonstrated experimentally that ascorbic acid 25% formulated with a penetration enhancer significantly improves melasma.[136] It is more effective when used in combination with licorice extracts, vitamin E (α-tocopherol acetate), iontophoresis, mesotherapy, Q-Switched Nd:YAG laser or fractional Q-Switched Ruby Laser than when used alone in the treatment of melasma.[134,137–141] Side effects such as allergic or irritant reactions are rare and occur because of poor permeability of ascorbic acid in natural form.[138]

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TABLE 6 Clinical studies for cosmeceuticals and botanicals in the treatment of melasma

Ref. no.	Intervention	Type of study	Outcome measurement	Number of study subjects	Results	Mechanism of action, adverse effects and other Remarks
[155]	Oral proanthocyanidin (grape seed extract) x 6 months	Efficacy study	Colorimetry Focal macule size	12 women	Maximum improvement occurred after 6 months and none thereafter	Antioxidant properties, reduces melanin biosynthesis, reduces UV-induced hyperpigmentation
[156]	Oral procyanidin with vitamins A, C, E x 8weeks	Efficacy study	–	–	Effective	–
[166]	Oral ginseng (3 g)	Open-label, prospective clinical study	Reduction in MASI, Improved MELAS QoL scores, PGA	25 women	MASI decreased and MELAS QoL improved in 74% patients	Inhibition of key enzymes of melanogenesis. Nausea, mild gastrointestinal discomfort.
[151]	Topical *N*-acetyl glucosamine, applied twice daily x 8weeks	Randomized, double-blinded, placebo-controlled split-face clinical trial.	Reduction in MASI score	50 women	improves facial hyperpigmentation	–
[154]	Topical Niacinamide 4% versus hydroquinone 4%	Spilt-face randomized trial	Reduction in MASI score	27 subjects	Both sides responded equally to treatment with progressive reduction in pigmentation	–
[157]	Topical dioic acid 1% versus HQ 2% crème applied twice daily x 12 weeks	Open label comparative study	Reduction in MASI score	96 women	Equal therapeutic efficacy	Reduces tyrosinase mRNA expression
[158]	Topical Cysteamine 5% Cream versus placebo cream	Open label comparative study	Reduction in MASI score	25 subjects	Significant reduction in cysteamine treated groups as compared to placebo group	–
[159]	Topical 75% mulberry (*Morus alba*) extract oil versus placebo versus placebo, applied for 8 weeks	Randomized, single-blind, placebo-controlled trial	Reduction in MASI, Improved MELAS QoL scores	50 subjects	MASI and MELASQoL scores improved significantly in the mulberry group	Tyrosinase inhibition, superoxide scavenging properties. Mild itching.
[160]	Topical Lignin Peroxidase cream applied for 8 weeks	Efficacy study	Reduction in MASI score	31 women	significant reduction in MASI scores	–
[161]	Topical Zinc sulfate versus HQ 4% cream	Randomized controlled trial	Reduction in MASI score	–	Better reduction in MASI scores from Zinc sulfate versus HQ	–
[162]	Topical Flutamide1% cream versus HQ 4% cream	Randomized controlled trial	Reduction in MASI score	74 women	Flutamide showed higher reduction in MASI score versus HQ	–
[163]	Topical methimazole applied for 8 weeks	Case report	Reduction in MASI score	2 HQ resistant cases	Significant improvement noted in both cases	–
[164]	Total soy (*Glycine soja*) extract applied for 3months	Efficacy study	Reduction in hyperpigmentation	16 women	12% reduction in 14 of 16 treated women	–

(Continues)

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TABLE 6 (Continued)

Ref. no.	Intervention	Type of study	Outcome measurement	Number of study subjects	Results	Mechanism of action, adverse effects and other Remarks
[165]	Topical soy containing moisturizer with sunscreen (SPF 30) x 12 weeks	Randomized, double-blind, placebo-controlled clinical trial	Reduction in hyperpigmentation	68 subjects	Significant reduction noted in mottled hyperpigmentation and blotchiness	–
[140,167]	Topical soyabean and soya milk paste applied daily ×8–9 weeks	In vivo and in vitro study	Decreased pigment deposition in histology	–	–	Have antioxidant photoprotective properties. Inhibits melanosome transfer to keratinocytes. No evidence of visual/histological irritation.
[169]	Topical liquiritin 2% versus Vehicle cream	Split face clinical trial, 4 weeks	Photographs and clinical evaluation	20 women	Reduction in lesion size in 60% patients, reduction in pigment intensity in 70%–75% patients	Melanin dispersibility via the amelanodermic and epidermal stain removing property Mild skin irritation in the form of erythema and burning sensation
[169]	Topical licorice ×12 weeks	Efficacy study	Reduction in MASI score, PGA	34 women	Significant improvement	Tyrosinase enzyme inhibitor, anti- inflammatory. No adverse effects
[170]	Topical licorice 4% 12 weeks	Randomized, double-blind, placebo-controlled clinical trial	Reduction in mMASI score	40 women	Notable improvement	Solid lipid nanoparticles technology. Minimal side effects
[171]	Topical 4% *N*-acetyl glucosamine + 2% nicotinamide cream versus 4% HQ cream, applied twice daily ×12 weeks	Randomized, double-blinded, split-face clinical trial	Reduction in mMASI score, Digital photography, Patient's satisfaction rating	30 women	Efficacy of *N*-acetyl glucosamine + nicotinamide was slightly better than HQ	Prevents tyrosinase glycosylation and reduces melanin production, decreases melanosome transport within the cell. Erythema, pruritus, and burning were reported less than HQ cream
[172]	Topical Hesperidin	in vitro	–	–	Hesperidin decreased tyrosinase activity	Inhibits melanogenesis through scavenging and interacting with melanogenic intermediates
[173]	Topical silymarin 0.7% and 1.4% applied twice daily versus HQ 4% once daily ×3 months	Open label comparative study	Reduction in mMASI, Digital photography, Patient's satisfaction rating	42 women (3 groups of 14 subjects each)	Significant decrease in MASI scores in all groups but was slightly higher in hydroquinone group. No significant difference in patient satisfaction scores	Antioxidant and photoprotective effects. It decreases the expression of tyrosinase protein. No adverse effects from topical slymarin as compared to erythema, burning, and scaling in HQ group

Note: The list is by no means complete as new formulations discovered and become available routinely.

Abbreviations: HQ, Hydroquinone; MASI, Melasma Area and Severity Index; MELASQoL, Melasma Quality of Life Scale; mMASI, Modified Melasma Area and Severity Index.

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7.2.2 | Vitamin E

Vitamin E (Alpha-tocopherol), a major lipophilic antioxidant in the tissues, membranes, and plasma, includes four molecules each of tocopherols and tocotrienols occurring naturally. Alpha-tocopherol is the most abundant vitamin E derivative in humans.[142] It has photoprotective effects and cause depigmentation by tyrosinase inhibition, increased intracellular glutathione content and interfering with lipid peroxidation of melanocyte membranes.[143] Alpha-tocopheryl ferulate, a compound of α-tocopherol and ferulic acid, can absorb ultraviolet radiation and reportedly showed significant effect in retardation of melanogenesis.[144] Topical α-tocopherol 5% or less is mostly used in cosmeceuticals in combination with vitamin C for lightening effect. A significant improvement in melasma and pigmented contact dermatitis lesions was observed with topical vitamins E and C in a double-blind study and results were better with combination compared with either vitamin used alone.[145] Allergic or irritant reactions from topical use are infrequent.

7.2.3 | Polypodium leucotomos

Extract of *Polypodium leucotomos*, a tropical fern with anti-inflammatory, antioxidant, and photoprotective properties, has been tried in the oral treatment of melasma with variable results. Nestor et al.[146] in their randomized placebo control study reported significant reduction in MASI scores and melasma quality of life (MelasQoL) scale with oral *P. leucotomos* compared with placebo given twice daily for 12 weeks. However, Ahmed et al.[147] in a double-blind controlled study reported no significant reduction in MASI score or improvement in MelasQoL scale from its combination with a sunscreen versus sunscreen alone in 40 Hispanic women with moderate to severe melasma randomized to get *P. leucotomos* 240 mg or placebo three timed daily.

7.2.4 | Topical rucinol

Rucinol (4-n-butylresorcinol), a phenolic derivative, inhibits tyrosinase and tyrosinase-related protein (TRP-1). A significant improvement in melasma was seen on treated side in a double-blind randomized split-face study on 23 Korean women after 8 weeks of treatment with twice-daily application of rucinol 0.1% cream as compared to vehicle-treated side.[148] Huh et al.[149] in a double-blind split-face randomized controlled trial conducted on 32 women with melasma also reported significant improvement in melasma with rucinol 0.3% serum applied twice daily for 12 weeks on treated side as compared to vehicle-treated side. The adverse effects of stinging, burning, erythema, dryness, peeling, and desquamation were mild.

7.2.5 | Cysteamine

Cysteamine, a natural aminothiol biological compound found in mammalian tissues and human milk, provides powerful synergistic effects for skin depigmentation *without the concerns for adverse effects associated with triple combination therapy*.[171] It is part of the vitamin B3 family and works as antioxidant and inhibits melanosomal transfer. Available as Cyspera® (cysteamine + isobionic-amide complex) 5% cream for topical use and has been found very safe with very low risk of adverse effects. Initial results are visible after 6 weeks of daily use of Cyspera/cysteamine cream applied for 15 min to the affected skin. Rarely, mild skin irritation (warm sensation, mild redness on immediate application and dryness) may occur temporarily. Its three-product system includes: (1) *Cyspera® Intensive™* comprises a dual chamber technology that keeps the cysteamine+isobionic-amide complex and alpha hydroxyl acid (AHA) separate until use. The immediate antioxidant effect of isobionic-amide with AHA after application causes instant pigment reduction effect. (2) *Cyspera® Neutralize™* has AHA and L-Arginine - Lactobionic Acid complex to neutralize the odor of cysteamine and re-balance the epidermis before application of Cyspera® Boost™. The L-Arginine complex stops the Isobionic-Amid Complex™ - AHA reaction and the mild-surfactant gently removes any residue, helps soothe skin, and promote healthy skin barrier. The Lactobionic Acid complex neutralizes and balances the skin pH. (3) *Cyspera® Boost™* features Isobionic-Amide Complex™ and retinol which works synergistically with Cyspera® Intensive™ to even skin tone, improve complexion and provide natural skin glow. The retinol has an anti-inflammatory effect and leads to a visual pigment reduction by increased skin shedding and non-pigmented skin layers after application of Cyspera® Intensive™.

Although cysteamine formulations have shown significant decrease in MASI score after 4 months of application compared with placebo and even in a case resistant to Kligman's triple combination therapy, it was not found superior to 4% hydroquinonein or tranexamic acid mesotherapy in comparative trials.[155,172–174] However, a recent systematic review suggests that insufficient sample size, lack of long-term follow-up, and efficacy in cases with epidermal melasma only remain major limitations of clinical studies to draw a meaningful conclusion for the cysteamine's role in treating melasma that often remains unsatisfactorily treated.[175]

7.2.6 | Sunscreens and camouflage makeup

It is well established now that both UV radiation and visible light play a significant role in the pathogenesis of melasma. Several studies have demonstrated the benefit of concomitant photoprotection and sunscreens of at least SPF 15 should be prescribed to all patients with melasma (Table 7). The sunscreens effectively reduce pigmentation following sun exposure, significantly increase the efficacy of topical therapy, and prevent relapses of melasma.[176–178] Physical sunscreens containing zinc oxide, iron oxide, titanium dioxide, and silicones (dimethicone, cyclomethicone) are not only photoprotective for the whole spectrum but also provide immediate whitening camouflage effect and are preferred. However, a blend of physical and organic sunscreens can be used for persons who do not find inorganic salts cosmetically elegant because of their high

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TABLE 7 Commonly used sunscreens

Usage	Chemical nature	UV spectrum	Compound (Conc. used)
Topical Sunscreens	Organic	UVA	• Avobenzone (3%) (butyl-methoxy-dibenzoyl methane)
		UVB	PABA & PABA esters • *p*-aminobenzoic acid (5%–15%) • Ethyl-dihydroxy-propyl-PABA (1%–5%) • Padimate-O (octyl dimethyl PABA) (1.4%–8%) • Glyceryl PABA (2%–3%) Cinnamates • Cinox (1%–3%) • Ethyhexyl *p*-methoxy-cinnamate (2%–7.5%) • Octocrylene (7%–10%) • Octinoxate (7.5%) Salicylates • Ethyhexyl salicylate (3%–5%) • Homosalate (4%–15%) • Octyl salicylate (3%–5%) Others • Methyl anthranilate (3.5%–5%) • Digalloyl triolate (2%–5%) • Methylene-bis-benzotriazole tetra-methylbutylphenol (Tinsorb M) • Bis-ethylhexyloxyphenol methoxy-phenol triazine (Tinsorb S)
		UVA & UVB	Benzophenones • Oxybenzone(2%–6%) • Dioxybenzone (3%)
	Inorganic[a]	UVA, UVB & Visible light	• Zinc oxide, Titanium oxide, Iron oxide • Calamine, Kaoline, Icthamol • Red veterinary petrolatum
Systemic Sunscreens			Antimalarials, β-carotene, Ascorbic acid, α-tocopherol, Retinol, Selenium, Corticosteroids, PABA

Note: The list is by no means complete as new formulation discovered with time and made available routinely.

Abbreviations: PABA, para-amino benzoic acid; UVA, ultraviolet-A; UVB, ultraviolet-B.

[a]Can be used alone or in combinations, or can be combined with organic sunscreens, has good camouflage effect, non-allergenic but can be messy, visible, and comedogenic.

concentrations. As UVA can penetrate through clouds and window panes, the chosen sunscreen needs to be applied daily irrespective of time/season.

As prescribed treatment takes time to make a visible difference, a cosmetic camouflage should be prescribed in the meantime. A cosmetic camouflage is basically a makeup available in several shades and hues to match with the skin tone and color to conceal skin discoloration and improve appearance. The presence of 25% more pigment and fillers with optical properties differentiate them from foundations. They should be easy-to-blend, non-irritating, and provide smooth coverage.

8 | PATIENT EDUCATION

Patient education about melasma, identification and avoidance of precipitating factors, long-term prognosis, treatment strategies including preventative measures such as adequate sun protection are imperative for a successful treatment and prolonged remission. Additionally, the patient must be counseled for treatment adherence, use of broad-brimmed hats and avoidance of sun exposure during peak radiation times, frequent use of soaps, astringents, toners or other products with irritant potential, over-the-counter products, and to maintain adequate skin hydration by use of emollients and moisturizing creams.

9 | CONCLUSION

The management of melasma remains challenging and needs long-term treatment and constant counseling for treatment adherence. Topical agents remain the mainstay of treatment despite unsatisfactory therapeutic outcome and some of them may be associated with significant adverse reactions. Although hydroquinone, alone or in triple combination, remains the gold standard of topical treatment despite concerns for its adverse effects, several new agents with a potential to inhibit melanogenesis have been developed and can be opted in sequential therapy in the management of melasma despite poor evidence for their efficacy for lack of controlled clinical trials. The evidence for observed efficacy of platelet-rich

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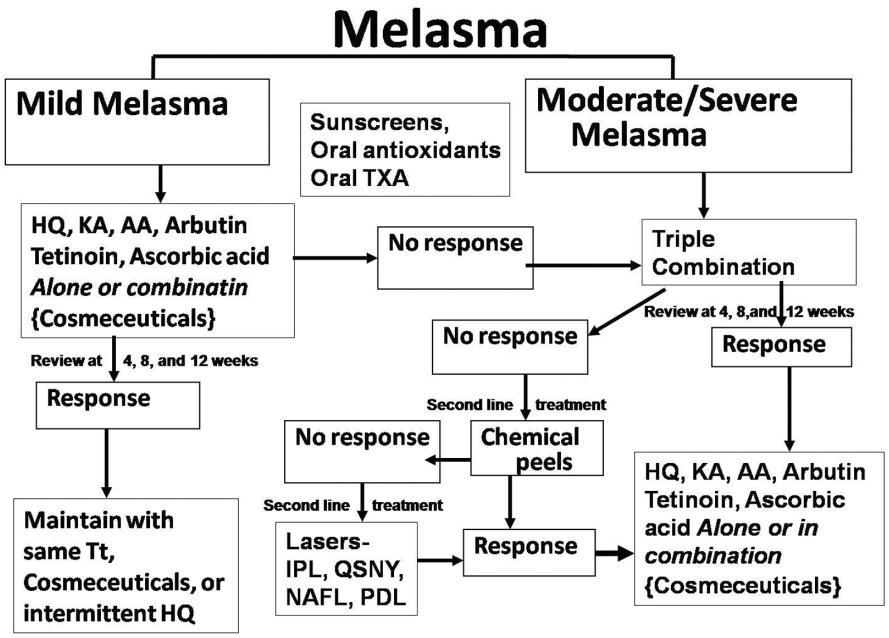

FIGURE 2 Treatment algorithm for melasma. Before actual treatment, other causes of facial pigmentation such as post-inflammatory hyperpigmentation, lichen planus pigmentosus, lichen planus actinicus, pigmented cosmetic dermatitis, facial acanthosis nigricans, nevus of Ota, Hori nevus, frictional melanosis, drug-induced pigmentation, photosensitivity disorders, and secondary ochronosis must be excluded. If possible, assessment for melasma should be made both clinically and with Wood's lamp. Advise photoprotection to all patients by physical barriers and prescribe a broad-spectrum sunscreen specially containing titanium oxide/zinc oxide. Consider chemical peels and lasers for resistant cases only. Abbreviations: AA, Azelaic acid; HQ, hydroquinone; IPL, Intense pulse light; KA, Kojic acid; NAFL, Non-ablative fractional laser; PDL, Pulsed dye laser; QSNY, Q-switched Nd:YAG laser; TXA, tranexamic acid.

plasma (PRP) therapy alone or in combination with topical TA or IPL in small studies or that of needling (microneedling, mesoneedling, radiofrequency microneedling) to increase the delivery of topical medications or to induce epidermal thickness for protection against UV radiation remains limited for lack of controlled clinical trials.[179,180]

Pregnancy remains the most common trigger for melasma (mask of pregnancy) and it is mostly treatment-resistant. However, melasma in pregnancy may be transient lasting until parturition and improve significantly thereafter. The treatment during pregnancy is thus usually deferred until delivery/lactation. Nevertheless, physical sunscreen can be prescribed for regular use in the meantime.

Since relapses are common after discontinuation of the treatment, it is imperative to maintain remission and prevent relapse with continuous use of medical therapy that is safe and effective along with adequate sun protection. Relapses are usually treated on similar lines. A recent study has suggested that TA 500 mg twice daily can be used as initial therapy to achieve early clearance of melasma and follow-up treatment with TA 250 mg or a lesser dose once daily can be used safely to maintain prolonged remission.[15] Several treatment algorithms have been proposed for mild as well as moderate to severe melasma.[74,181] The suggested treatment algorithm (Figure 2) is simple, easy to follow and can be a quick reference guide in routine office practice. Nevertheless, a multimodality approach such as using a topical formulation, sunscreen, oral TA, and *Polypodium leucotomos* in combination or in a sequential manner with IPL and/or PDL to treat the vascular component then a low fluence 1927 nm laser will perhaps provide an effective treatment approach.

AUTHOR CONTRIBUTIONS

Vikram K Mahajan involved in conception, writing and revising the manuscript. Anant Patil, Martin Kassir, Nellie Konnikov, Michael H. Gold, Mitchel P Goldman, Hassan Galadari, and Leszek Blicharz involved in review and revising the manuscript. Mohamad Goldust involved in conception, writing, review, and revising the manuscript. We confirm that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met and that each author believes that the manuscript represents honest work.

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CONFLICT OF INTEREST

None.

ETHICAL APPROVAL

No ethical approval was required as this research did not involve human subjects or animals.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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