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SYSTEMATIC REVIEW

Melasma Treatment: An Evidence-Based Review

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Abstract

Background Melasma is an acquired, chronic pigmentary disorder predominantly affecting women. It may significantly affect quality of life and self-esteem due to its disfiguring appearance. Multiple treatments for melasma are available, with mixed results.

Objective The aim of this article was to conduct an evidence-based review of all available interventions for melasma.

Methods A systematic literature search of the PubMed electronic database was performed using the keywords 'melasma' and/or 'chloasma' in the title, through October 2018. The search was then limited to 'randomized controlled trial' and 'controlled clinical trial' in English-language journals. The Cochrane database was also searched for systematic reviews.

Results The electronic search yielded a total of 212 citations. Overall, 113 studies met the inclusion criteria and were included in this review, with a total of 6897 participants. Interventions included topical agents, chemical peels, laser- and light-based devices, and oral agents. Triple combination cream (hydroquinone, tretinoin, and corticosteroid) remains the most effective treatment for melasma, as well as hydroquinone alone. Chemical peels and laser- and light-based devices have mixed results. Oral tranexamic acid is a promising new treatment for moderate and severe recurrent melasma. Adverse events from all treatments tend to be mild, and mainly consist of skin irritation, dryness, burning, erythema, and post-inflammatory hyperpigmentation.

Conclusions Hydroquinone monotherapy and triple combination cream are the most effective and well-studied treatments for melasma, whereas chemical peels and laser- and light-based therapies are equal or inferior to topicals, but offer a higher risk of adverse effects. Oral tranexamic acid may be a safe, systemic adjunctive treatment for melasma, but more studies are needed to determine its long-term safety and efficacy. Limitations of the current evidence are heterogeneity of study design, small sample size, and lack of long-term follow-up, highlighting the need for larger, more rigorous studies in the treatment of this recalcitrant disorder.

Key Points

Melasma has a significant effect on quality of life due to its disfiguring appearance, chronic course, and recalcitrance to treatment

Topical hydroquinone alone or combined with a retinoid and a corticosteroid has the greatest evidence of efficacy in the treatment of melasma

Oral tranexamic acid offers a promising systemic option for recalcitrant melasma

1 Background

1.1 Etiology

Melasma is a common, acquired disorder of hyperpigmentation that mainly affects women during childbearing years and has a significant impact on quality of life [1, 2]. Although the pathogenesis of this disease remains unclear, several etiologic factors have been identified, including exposure to ultraviolet (UV) radiation and visible light, familial predisposition, pregnancy, and exogenous hormone use [3–6].

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1.2 Clinical Features

Melasma presents as bilateral, brown macules or patches on the malar cheeks, forehead, upper lip, and/or mandible, most commonly in a centrofacial pattern [7]. Histologically, melasma is characterized by increased melanin in the epidermis and/or dermis. Clinical examination using Wood's lamp may aid in diagnosis [5]. Unfortunately, the clinical course of melasma is often protracted and resistant to treatment, and melasma often returns after discontinuation of treatment or with increased sun exposure [7].

1.3 Interventions

Current treatments include topical and systemic agents, as well as chemical peels and laser- and light-based therapies. Improvement of existing lesions and prevention of recurrence should be goals of treatment. Topical therapies include depigmenting agents, retinoids, corticosteroids, visible and UV light protection, tranexamic acid (TXA), and combination creams. Commonly used chemical peels include glycolic acid (GA), salicylic acid (SA), and trichloroacetic acid (TCA). Laser- and light-based therapies include intense pulsed light (IPL), Q-switched neodymium-doped yttrium aluminum garnet (QS-Nd:YAG) laser, pulsed-dye laser (PDL), fractionated laser, and others. New systemic medications include TXA and plant-based supplements. There are also myriad topical plant-based agents and commercially available skin-brightening therapies that lack scientific evidence of efficacy with rigorous study design.

2 Objective

The objectives of this systematic review were to define the available treatments for melasma and determine their efficacy, identify limitations of current research, and suggest areas for future research.

3 Methods

A systematic review of the literature was conducted through PubMed (National Library of Medicine) using the keywords 'melasma' and 'chloasma' in the title/abstract (Fig. 1). Filters for 'randomized controlled trial', and 'controlled clinical trial' were applied to the search. The Cochrane database was also searched for systematic reviews. Studies were limited to prospective, randomized, controlled clinical trials evaluating treatment for melasma that were available in English through October 2018. Studies including pregnant subjects were excluded. Outcome measures reviewed included subjective physician- and participant-assessed response to treatment, objective measures of treatment response, time elapsed before clinical improvement, and adverse events.

4 Results

4.1 General

The electronic search resulted in 212 citations (Fig. 1), of which 113 met the inclusion criteria and were included in this review. The total sample size was 6897 subjects, with

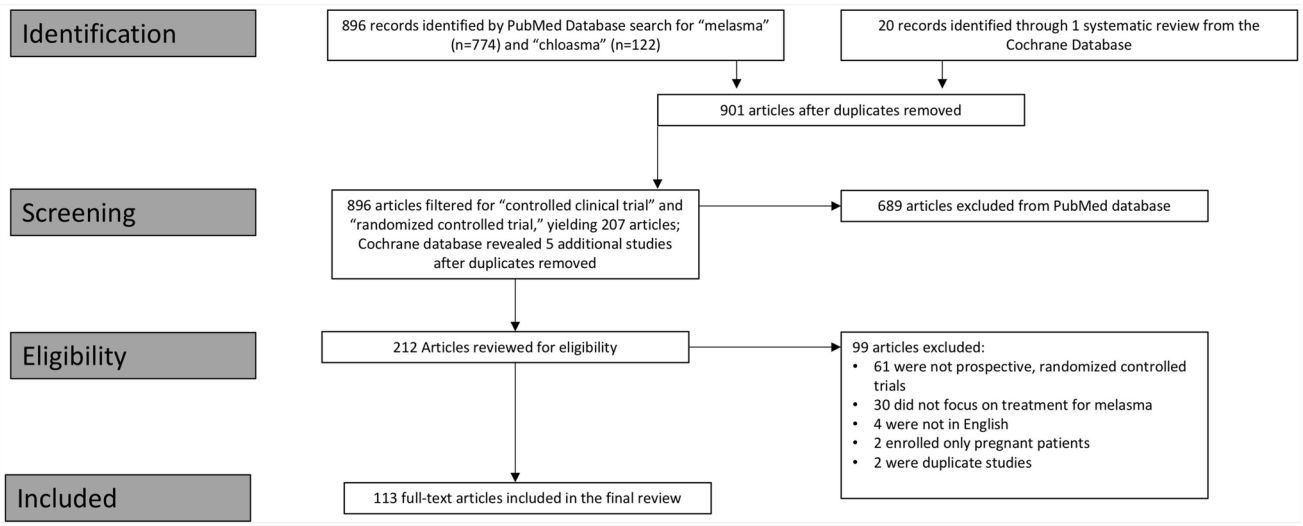

Fig. 1 Article selection flow diagram

each study including between 6 and 641 subjects. The length of time for each study ranged from 4 weeks to 12 months. Thirty-seven studies were placebo-controlled, 41 were comparative, and 35 were split-face (Tables 1, 2, 3, 4, 5, 6). There was one systematic review from the Cochrane database [8]. Given the variable objective and subjective outcomes identified between studies, we could not pool the data for grouped statistical analysis.

4.2 Topical Agents

4.2.1 Depigmenting Agents

Depigmenting agents are classically regarded as the gold-standard treatment for melasma (Table 1). Hydroquinone (HQ), a tyrosinase inhibitor, is one of the most frequently used and well-studied lightening products in the world, with mild to moderate risk of local adverse effects [9–11].

Ennes et al. compared 4% HQ cream twice daily + sunscreen versus sunscreen alone for 12 weeks [12]. Thirty-eight percent of subjects in the HQ group showed complete resolution compared with 8% in the placebo group. Improvement in melasma was seen as early as 3 weeks, with no difference in adverse effects. Vázquez et al. showed 96% improvement with 3% HQ twice daily + sunscreen versus 81% with HQ alone [13]. These studies highlighted the importance of concomitant use of sunscreen with topical agents.

Another depigmenting agent, azelaic acid (AA), is a competitive inhibitor of tyrosinase. It has similar efficacy to that of 4% HQ but may have greater risk of irritant adverse effects. Verallo-Rowel et al. conducted a randomized, controlled trial comparing 20% AA with 2% HQ over a 24-week period [14]. Seventy-three percent of subjects demonstrated good to excellent results compared with only 19% in subjects treated with HQ. Sivayathorn et al. also compared 2% HQ with 20% AA in a 24-week trial of 340 subjects [15]. Good to excellent response was observed in 69% of subjects compared with 44% in the HQ group. Baliña and Graupe performed a clinical trial comparing 4% HQ with 20% AA twice daily in 243 melasma subjects, demonstrating no difference in response between groups, suggesting that AA was not superior to this higher concentration of HQ [16]. Farshi conducted a similar trial comparing 4% HQ with 20% AA for 2 months, showing no significant difference in Melasma Area and Severity Index (MASI) reduction between groups [17]. Sarkar et al. performed a split-face trial, testing the efficacy of sequential therapy consisting of clobetasol 0.05% cream for 8 weeks followed by 20% AA twice daily for 16 weeks, compared with 20% AA cream alone [18]. Both groups had a good to excellent response but a more robust improvement was seen with sequential therapy. In the abovementioned studies, adverse effects tended to be more frequent with AA compared with HQ, and were most notable for local irritation.

Topical vitamin C or ascorbic acid has also been studied as a treatment for melasma due to its ability to chelate copper ions, which serve as enzymatic cofactors for melanogenesis. Huh et al. failed to show significant clinical improvement in a split-face study comparing vitamin C iontophoresis with distilled water iontophoresis [19]. Espinal-Perez et al. studied 5% L-ascorbic acid compared with 4% HQ once daily in 16 subjects over 16 weeks, however superior results were seen in the HQ-treated group (93% vs. 63%, with good to excellent improvement) [20]. Adverse effects were higher in the HQ group (69% vs. 6%).

Rucinol serum, a tyrosinase inhibitor, was studied by Khemis et al. and Huh et al. [21, 22] Compared with vehicle, both studies showed a decrease in melanin index by week 8. Adverse effects included stinging, burning, and pruritus, however these improved after using a liposomal encapsulated cream.

4.2.2 Retinoids

Retinoids target multiple pathways in the synthesis and dispersion of melanin in the skin, including reduction of tyrosinase transcription and melanin synthesis, and have been used in multiple studies on melasma [23] (Table 1). They also enhance epidermal keratinocyte metabolism and turnover, stimulating a decrease in melanosome transfer and loss of melanin, as well as facilitating trans-epidermal penetration of other topical therapies [24].

Griffiths et al. compared 0.1% tretinoin cream with vehicle over a 40-week period [25]. Sixty-eight percent of the treatment group showed improvement, confirmed by colorimetry and histological evaluation. Of note, the effects of therapy were not seen for 24 weeks and 88% of the treatment group experienced adverse effects from this high concentration of tretinoin. Kimbrough-Green et al. performed a similar trial in African American subjects, with comparable results [26]. Leenutaphong et al. failed to show a significant improvement using a lower concentration of 0.05% tretinoin cream twice daily compared with vehicle + sunscreen [27].

Interestingly, adapalene may be less irritating than tretinoin, as suggested in a trial performed by Dogra et al. comparing adapalene 0.1% gel with tretinoin 0.05% cream once daily + sunscreen. There were more adverse effects in the tretinoin group but similar efficacy in both groups [28].

Recently, Truchuelo et al. performed a split-face trial using a proprietary product containing two different retinoids in the treatment of melasma: Neoretin® Discrom control gel cream and Neoretin® Discrom control serum booster (IFC Pharmaceuticals) [29]. After 3 months, a 74% reduction in MASI score was seen, with 3/28 subjects experiencing burning, pruritus, or erythema.

Table 1 Studies evaluating topical agents as monotherapy for the treatment of melasma

First author, year	Study design	Treatment	Duration	N	Outcome(s) [subjective]: physician- and participant-assessed	Outcome(s) [objective]: objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Depigmenting agents									
Ennes [12], 2000	DB, PC	4% HQ and two sunscreens (SPF15) bid vs. sunscreen alone. Both groups applied SPF30 sunscreen daily	12 wk	48	Complete resolution: 38.1% HQ vs. 8.3% placebo Partial improvement: 57.2% HQ vs. 58.2% placebo Treatment failures: 0% HQ vs. 16.7% placebo	None	3 wk	No SS difference between groups. Five cases of erythema in treatment group and one with contact dermatitis	Outcome based on clinical and photographic observations only, using non-validated scale of 'total improvement' vs. 'partial improvement' vs. 'failure'
Vázquez [13], 1983	R, DB, PC	3% HQ bid and placebo cream vs. 3% HQ bid and BS sunscreen	12 wk	53	96.2% vs. 80.7% improved with HQ + sunscreen vs. HQ alone	None	NA	Mild and transient local irritant effects	Subjective evaluation by investigators and participants only
Verallo-Rowell [14], 1989	R, DB, C	AA 20% bid vs. HQ cream 2% bid. All subjects applied BS sunscreen	24 wk	155	NA	73% of AA patients vs. 19% of HQ patients had good to excellent results based on melasma pigmentary intensity and lesion size	NA	Both groups had mild to moderate skin irritation	Patients were of Indo-Malay-Hispanic origin
Sivayathorn [15], 1995	R, DB, C, MC	2% HQ bid vs. 20% AA bid. Both groups used sunscreen	24 wk	340	68.9% in AA group had 'good' or 'excellent' results vs. 43.7% in HQ group (SS)	None	NA	Mild itching and burning (both groups). 36.5% of AA group had AEs vs. 12.7% in HQ group	
Baliña [16], 1991	R, DB, MC	4% HQ cream bid vs. 20% AA cream bid. All subjects applied sunscreen daily	24 wk	243	Good or excellent results in 65% of AA subjects vs. 72% of the HQ group (not SS)	Based on planimetric mapping of melasma lesion size, 60% of AA group and 66% of HQ group achieved 50% reduction in lesion size (not SS)	4 wk	Mild, transient local irritation in both groups Pronounced irritation in 1 HQ subject vs. 18 AA subjects	SPF or frequency of sunscreen use not specified

Table 1 (continued)

First author, year	Study design	Treatment	Duration	N	Outcome(s) [subjective]: physician- and participant-assessed	Outcome(s) [objective]: objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Farshi [17], 2011	Open-label, R, C	AA 20% bid vs. HQ 4% bid. Both groups applied BS sunscreen every 3 h	2 mo	29	MASI scores decreased from 7.6 ± 3.5 to 3.8 ± 2.8 in the AA group, vs. 7.2 ± 3.2 to 6.2 ± 3.6 (p = 0.05) No SS difference between groups after only 1 mo of treatment	None	1 mo	SS more erythema in the HQ group vs. AA in the first month (7.3% vs. 46.6%) No SS difference in erythema, pruritus, irritation in the second month	Studied patients with mild melasma
Sarkar [18], 2002	R, SF, comp	20% AA bid (24 wk) to half of the face vs. clobetasol 0.05% cream qd for 8 wk, followed by 20% AA only bid for 16 wk to the other half of the face. BS sunscreen applied qd	24 wk	30	Melasma lightening was more significant on the side of the face receiving sequential therapy (clobetasol for 8 wk followed by AA for 16 wk) [p < 0.001] Both groups had > 90% of cases with good to excellent responses to treatment	None	4 wk	Mild and transient local irritant effects	Enrolled dark-skinned patients. Outcomes were subjective, based on clinical evaluation, photography, and assessment of 'overall response'
Huh [19], 2003	R, DB, PC, SF	Vitamin C iontophoresis vs. distilled water iontophoresis for 8 min twice weekly. Both groups applied sunscreen qd	12 wk	29	Subjects reported the same improvement in both treatment and vehicle-treated skin	Colorimetry showed a significant decrease in luminance value, from 4.60 to 2.78 in the vitamin C-treated side vs. 4.45 to 3.87 in the control side (p < 0.01)	NA	21% with mild sense of electric shock, 7% with itching, 7% with erythema, 3% with burning, 3% with dryness	
Espinal-Perez [20], 2004	R, DB, SF	5% L-ascorbic acid daily vs. 4% HQ daily. Daily sunscreen was also applied to both sides of the face	16 wk	16	Participants rated improvement as 'good' or 'excellent' in 93% of the HQ group vs. 62.5% in the ascorbic acid group	No SS difference based on colorimetry	1 mo for HQ, 3 mo for ascorbic acid	68.75% of cases had irritation in HQ-treated skin vs. 6.25% in skin treated with ascorbic acid	

Table 1 (continued)

First author, year	Study design	Treatment	Duration	N	Outcome(s) [subjective]: physician- and participant-assessed	Outcome(s) [objective]: objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Khemis [21], 2007	R, DB, PC, SF	Phase 1: rucinol serum 0.3% vs. vehicle bid Phase 2: subjects treated with an additional 3 mo of full-face rucinol serum. All groups applied SPF60 sunscreen	12 wk + 24 wk	28	Good or fair efficacy in 78% of subjects in the treatment group. SS improvement in clinical pigmentation score in the treated skin compared with vehicle based on physician assessment	Colorimetric measurements showed skin was significantly less yellow and lighter, and trended toward significantly reduced redness with rucinol therapy	4 wk	In both groups, few patients reported stinging, burning, and pruritus. One patient had blepharoplasty. There were less AEs on the treated side compared with placebo	The clinically apparent depigmenting effects of rucinol seemed to plateau after 16 wk of treatment. This coincided with the summer months so may have been mitigated by increased UV exposure. However, the colorimetric measurements continued to improve
Huh [22], 2010	R, DB, PC, SF	Liposome encapsulated 4-n-butylresorcinol 0.1% cream vs. vehicle bid	8 wk	23	Subjectively, 4-n-butylresorcinol therapy achieved excellent or good response in 65.2% of patients	MI decreased 7.51% in the treatment group vs. 3.26% in the vehicle group ($p = 0.043$)	4 wk	No AEs reported	
Retinoids									
Griffiths [25], 1993	R, DB, PC	0.1% tretinoin vs. vehicle qd. Both groups applied SPF15 sunscreen	40 wk	38	68% of tretinoin group showed improvement vs. 5% in vehicle group, based on subjective physician evaluation	Epidermal pigment was *decreased* by 36% in the tretinoin group vs. a 50% *increase* in the vehicle group Colorimetry and histological evaluation correlated with clinical assessment	24 wk	Erythema and desquamation in 88% of the treatment group vs. 29% of the vehicle group	Took an average of 24 wk to get significant clinical improvement. All subjects were Caucasian. No subjective assessment completed by subjects
Kimbrough-Green [26], 1994	R, PC	Tretinoin 0.1% vs. vehicle qd. All subjects applied SPF15 sunscreen	10 mo	28	MASI score improved 32% in treatment group vs. 10% in vehicle group	Histologic evaluation showed a significant decrease in epidermal pigmentation in the treatment group	24 wk	67% of the treatment group had skin irritation vs. 7% in the vehicle group	African American subjects Took an average of 24 wk to get significant clinical improvement

Table 1 (continued)

First author, year	Study design	Treatment	Duration	N	Outcome(s) [subjective]: physician- and participant-assessed	Outcome(s) [objective]: objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Leenutaphong [27] 1999	R, DB, PC	0.05% isotretinoin gel vs. vehicle cream bid. Both groups applied SPF28 qd	40 wk	23	MASI score decreased 68.2% in the isotretinoin group vs. 60% in the vehicle group (not SS)	Melasma Area and MI scores improved by 47% in the treatment group vs. 34% in the control group (no SS difference). It took 12 wk to see a SS reduction in colorimetric measurement	4 wk	Mild, transient dermatitis in 27% of the treatment group vs. 0% in the vehicle group	Thai patients
Dogra [28], 2002	R, comp (preliminary report only)	Adapalene 0.1% gel vs. tretinoin 0.05% cream. All subjects applied SPF15 sunscreen qd	14 wk	30	37% reduction in MASI score in tretinoin group vs. 41% in adapalene group (not SS)	None	NA	63% in tretinoin group had pruritus, burning, dryness, erythema, and scaling vs. 21% in adapalene group (mild erythema and dryness)	Adapalene may be less irritating than tretinoin
Truchuelo [29] 2014	R, DB, PC, SF	Neoretin® Discrom control gel cream daily + Neoretin® Discrom control serum booster fluid nightly vs. vehicle. All subjects applied SPF50 sunscreen daily	3 mo	28	Treatment group had 74% ± 31% reduction in MASI score vs. 55% ± 36% in vehicle-treated side of the face (p =0.009) 70% of subjects reported satisfaction with treatment	None	1.5 mo	2 patients with pruritus, 1 with burning, and 1 with erythema	Product tested retinol encapsulated glycospheres plus hydroxypinacolone retinoate (retinoic acid ester) in addition to other depigmenting agents: *N*-acetylglucosamine, kojic acid, Cromabright® and Natriquest®, Albatin®, Alistin®, and niacinamide. It also contained hydrating, anti-irritant, and anti-inflammatory ingredients

Table 1 (continued)

First author, year	Study design	Treatment	Duration	N	Outcome(s) [subjective]: physician- and participant-assessed	Outcome(s) [objective]: objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Visible light protection									
Castaneda-Cazares [32], 2014	R, C, sunblock alone as control	UV + VL protection with iron oxide vs. UV protection alone (UV only). All groups received 4% hydroquinone	8 wk	68	MASI improved 77.8 ± 11% in UV-VL group vs. 61.9 ± 16% in UV-only group (p <0.001). Based on physician global assessment, 75% of UV-VL group achieved good or excellent results vs. 47% of UV-only group (p =0.03)	SS relative lightening of pigmented lesions in UV-VL group vs. UV-only group based on colorimetry UV-VL group also had significantly superior reduction in melanin and mast cells	NA	Two patients in the UV-VL group and three in the UV-only group reported mild/transient facial irritation from hydroquinone	UV-VL sunscreen enhances depigmentation efficacy of HQ. Applied UV protective creams every 2–3 h between 8:00 am and 5:00 pm
Yousefi [33], 2014	R, DB, C	Zinc sulfate 10% or HQ 4% qd. Each cream was applied for 2 mo, followed by 3 mo of follow-up using sunscreen only	2 mo + 3 mo' follow-up	82	HQ group had superior results, with MASI score improvement of 43.5 ± 15.5% vs. 18.6 ± 20.8% in zinc group (p <0.001). Both groups showed significant improvement in MASI score by 5 mo	None	2 mo	Post-inflammatory hyperpigmentation in 5.2% of the zinc group (two cases) and 30.9% had skin irritation in HQ group	Did not compare with the sunscreen-only arm to demonstrate the potential UV protective benefits of topical zinc. More patients dropped out in the zinc group due to unsatisfactory treatment, unwillingness to be followed, distance from the treatment center
Topical tranexamic acid									
Ebrahimi [34], 2014	R, DB, C, SF	3% topical TXA bid vs. 3% HQ and 0.01% dexamethasone bid	12 wk	39	No SS difference between groups. MASI in the TXA group improved 74.1% vs. 64.5% in the HQ + dexa group On physician grading, both groups had 24–27% of patients with excellent improvement, 42–48% with good improvement, and 3–30% with fair improvement (3% of the HQ group vs. 30.3% of the TXA group)	None	4 wk	23.1% of TXA group experienced adverse effects vs. 51.3% in the HQ + dexamethasone group (p =0.01). Adverse effects of both groups included erythema, irritation, xerosis, and scaling	Although similar efficacy, more adverse effects were experienced in HQ + dexamethasone group over topical TXA group

Table 1 (continued)

First author, year	Study design	Treatment	Duration	N	Outcome(s) [subjective]: physician- and participant-assessed	Outcome(s) [objective]: objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Banihashemi [35], 2015	R, DB, C, SF	5% liposomal TXA versus 4% HQ cream bid	12 wk	23	Both sides showed SS improvement (trend toward greater improvement with liposomal TXA). TXA group mMASI decreased from 14.72 ± 2.2 to 6.78 ± 2.9 (54% improvement) vs. 14.60 ± 2.3 to 7.60 ± 2.2 (48% improvement) in the HQ group	None	1 mo	Irritation in three patients treated with 4% HQ cream. None in the topical TXA group	
Atefi [36], 2017	R, DB, C	Topical 5% TXA bid vs. 2% HQ bid. All subjects applied SPF30 sunscreen	12 wk	60	No SS difference in MASI score between groups (treatment group: 4.80 ± 1.06 reduced to 2.33 ± 0.71 vs. 4.37 ± 0.93 to 2.39 ± 0.65 in the HQ group) Treatment group expressed 33.3% satisfaction vs. 6.7% in the control group (p = 0.015)	None	NA	No AEs reported in the TXA group, but 10% of the HQ group experienced erythema and skin irritation	No SS difference between groups based on Wood's lamp examination
Laothaworn [37], 2018	R, C, SF	3% topical TXA for 8 wk and QS-Nd:YAG 1064 nm (0 and 4 wk) vs. laser alone	8 wk	25	48% of subjects with remarkable improvement vs. 20% in the laser-only group SS reduction in mMASI in the combination group vs. no SS change in laser-only	Significant reduction in MI in the combination group by the fourth week of treatment.Negligible decrease in the laser-only group	4 wk	Mild erythema after laser treatment (2/25 patients)	
Xu [38], 2017	R, C, SF	Functional microarray of microneedles + 5% TXA solution vs. 5% TXA solution alone	12 wk	30	96.15% in the combined treatment group had > 25% improvement vs. 38.46% in TXA-only group based on physician evaluation Satisfaction scores increased significantly in both groups	More significant reduction of brown spot scores by Visia in the treatment vs. control groups (only seen after 12 wk) MI decreased significantly in both groups without a SS difference between groups	8 wk	No AEs reported	

Table 1 (continued)

First author, year	Study design	Treatment	Duration	N	Outcome(s) [subjective]: physician- and participant-assessed	Outcome(s) [objective]: objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Saki [39], 2017	R, C, SF	TXA intradermal injection 20 mg/mL (monthly for 3 mo) vs. 2% HQ cream qhs	20 wk	37		No SS difference in melanin value between groups although both showed SS reduction by the end of the follow-up period	4 wk	TXA injection: two patients with burning after injection; two who developed acne More patients had erythema in the HQ group	Measured melanin value using Dermacatch® colorimeter
Tehranchinia [40], 2018	R, SB, SF	TXA intradermal injection (1 mL of 100 mg/mL solution every 4 wk for 12 wk) and 4% HQ cream nightly vs. 4% HQ cream alone	16 wk	55	MASI in the combination group decreased from 5.165 ± 1.875 to 1.769 ± 0.981 compared with 5.204 ± 1.935 to 2.926 ± 1.219 in the the control group ($p = 0.001$) Patient satisfaction was significantly higher in the combined therapy group	None	NA	Erythema (47.3%) and pruritus (10.9%) at the site of injection. In the HQ-alone group, 50.9% had erythema and 12.7% had pruritus, with no SS difference in adverse effects between groups	
Steiner [41], 2009	R, open-label, comp	Group A: 3% TXA bid (topical) vs. Group B: intradermal TXA 4 mg/mL weekly for 12 wk SPF30 every 4 h	12 wk	17	Investigator assessment of photographs revealed (Group A vs. B): Improvement: 12.5% vs. 66.7% Worsening: 50% vs. 11.1% No change: 37.5% vs. 22.2% mMASI improved in both groups (22% vs. 36% improvement); no SS difference between groups	Colorimetry showed SS improvement in both groups, but no SS difference between the two	NA	Mild erythema, local bruising, and burning	INR and CBC showed no change before and after treatment

Table 1 (continued)

First author, year	Study design	Treatment	Duration	N	Outcome(s) [subjective]: physician- and participant-assessed	Outcome(s) [objective]: objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Budamakuntia [42], 2013	R, open-label	4 mg/mL TXA injections vs. 4 mg/mL TXA applied after microneedling Therapy performed at weeks 0, 4, and 8	8 wk + 3 mo follow-up	60	mMASI improved 35.7% (microinjection) vs. 44.4% (microneedling). 26% vs. 41% showed > 50% improvement based on PGA No SS difference between groups	None	NA	Mild discomfort, burning, erythema	Authors suggested microneedling may be preferable due to more uniform and deeper delivery of medication 26% of participants dropped out, most from the injection group

Neotone®: 4% DAB, licorice extract, ascorbic acid, glycolic acid, salicylic acid, and α-arbutin

Neotone Radiance®: 4% DAB, 0.05% TGF-β1 biomimetic oligopeptide-68, ascorbic acid, UVA and UVB filters, and spread spectrum SPF50 sunscreen (skin-whitening complex: extract of uva-ursi, biofermented *Aspergillus*, grapefruit extract, rice extract) [Thiospot intensive: ethyl linoleate, thioctic acid, octadecenedioic acid, lactic acid, ethylhexyl methoxycinnamate]

Manufacturer information: GigaWhite® (Pentapharm/DSM, Basel, Switzerland); Thiospot® (Synchroline, Salo, Italy); Melaplex™ (Monheit 2013; Neocutis Inc., San Francisco, CA, USA); Neoretin® Discrom control gel cream daily/Neoretin® Discrom control serum booster fluid nightly (IFC Pharmaceuticals); Neotone® and Neotone Radiance® (ISIS PHARMA, Lyon, France); Tri-luma® (Galderma Laboratories, Fort Worth, TX, USA)

AA azelaic acid, *AEs* adverse events, *bid* twice daily, *BS* broad spectrum, *C* controlled, *CBC* complete blood count, *comp* comparative, *DAB* diacetyl boldine, *DB* double-blind, *dexa* dexamethasone, *HQ* hydroquinone, *INR* international normalized ratio, *MASI* Melasma Area and Severity Index, *MC* multicenter, *MI* melanin index, *mMASI* modified MASI, *mo* months, *N* number of subjects, *NA* not available, *PGA* Patient Global Assessment, *PC* placebo-controlled, *qd* once daily, *qhs* nightly, *QS-Nd:YAG* Q-switched neodymium-doped yttrium aluminum garnet, *R* randomized, *SB* single-blind, *SF* split-face, *SPF* sun protection factor, *SS* statistically significant, *TGF* transforming growth factor, *TXA* tranexamic acid, *UV* ultraviolet, *VL* visible light, *wk* weeks

Table 2 Studies evaluating combinations of topical agents for the treatment of melasma

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: physician- and participant-assessed	Outcome(s) [objective]: objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Triple combination cream									
Taylor [43], 2003	R, MB, multi	TC cream: HQ 4%, tretinoin 0.05% (RA), fluocinolone acetonide 0.01% (FA) qd vs. dual combinations of the above ingredients qd	8 wk	641	26.1% using TC achieved complete clearing, vs. each of the dual therapy groups (vs. maximum of 9.5% achieving clearance in HQ + tretinoin group). 77% in TC group had complete/near-complete clearing (vs. maximum 46.8% in HQ + tretinoin group)	None	NA	All groups experienced erythema, desquamation, burning, dryness, and pruritus. Less adverse effects in the HQ + FA group than TC, RA + HQ, and RA + FA	Improvement based on subjective physician evaluation. More adverse effects in creams containing RA
Torok [44], 2005	R, MB, multi	TC cream (extension of the Taylor et al., 2003 study)	12 mo	569	Physician's static global assessment showed 80% of subjects were clear/nearly clear by 12 mo	None	1 mo	61% experienced mild/transient AEs. The most common were erythema and desquamation. Atrophy < 1%, telangiectasia 4% 2.5% discontinued due to AEs	When subjects reached resolution or melasma, or had lack of response, subjects were transitioned to sunblock only
Cestari [45], 2007	R, C, open-label	TC cream qd vs. HQ 4% bid. Both groups applied SPF30 sunscreen qd	8 wk	120	MASI scores were SS lower in the TC group vs. the HQ group ($p < 0.003$) at wk 4, 6, and 9. Clearance of melasma in 35% vs. 5.1% (TC vs. HQ); > 75% improvement in 73% vs. 49% (TC vs. HQ). Subjects reported 'excellent' results in 50% using TC cream vs. 34% using HQ-only cream	None	4 wk	Mild erythema, burning, and desquamation (no difference between groups). Telangiectasias in 15% TC vs. 9% HQ-only. Systemic AEs in 33% vs. 35% (TC vs. HQ); headache most common	Brazilian patients There were no cases of skin atrophy

Table 2 (continued)

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: physician- and participant-assessed	Outcome(s) [objective]: objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Chan [46], 2008	R, C, MB, multi, parallel comparison study	TC cream qhs vs. HQ 4% bid	8 wk	260	Melasma global severity score showed mild or no melasma in 64.2% of TC patients vs. 39.4% in HQ group ($p<0.001$). TC was statistically superior as early as week 4. Subjects showed 70.8% satisfaction in the TC group vs. 49.6% in the HQ group	None	4 wk	More AEs in the TC vs. HQ group (48.8% vs. 13.7%) Adverse effects included erythema, irritation, skin exfoliation, and skin discomfort No cases of telangiectasia or skin atrophy	East and South-East Asian patients with moderate to severe melasma
Gong [47], 2015	R, DB, PC, multi	TC cream vs. placebo qhs	8 wk	233	Based on clinical assessment (total target score), TC group was superior to placebo at all time points. 69.91% vs. 0.88% improvement	Integral therapeutic efficacy (based on clinical and instrumental measure) 68.57% in the TC group vs. 0.94% controls ($p<0.001$) On mexametry, 71.3% improvement vs. 6.6% in placebo	2 wk	30.1% in the TC group with mild AEs, including erythema, pain, peeling, telangiectasia, burning, swelling, xerosis, pruritus, and darker pigmentation. 2.6% of the placebo group reported burning, itching, and skin tightening	Chinese patients

Table 2 (continued)

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: physician- and participant-assessed	Outcome(s) [objective]: objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Arellano [48], 2012	R, MB, multi	Maintenance therapy TC cream. All groups initially treated with 8 wk of TC qd, then randomized to either twice-weekly TC or tapering regimen of thrice weekly for 1 mo followed by twice weekly for 1 mo then once weekly for 1 mo	6 mo	242	84% reduction in MASI. All subjects rated their melasma as completely clear or minor by end of the study	Twice-weekly group trended toward a lower relapse rate than the tapering regimen group, most notably in subjects with more severe melasma. 53% of patients remained relapse-free after the 6-mo trial in both groups. Both groups had a mean time to relapse of 190 days	NA	11.6% of subjects in the twice-weekly group experienced AEs, mostly erythema and skin irritation. One subject with skin atrophy. 1.88% of subjects had mild telangiectasia during the first 8 wk. AEs were similar in both groups during maintenance therapy (10.92% in the twice-weekly group vs. 12.2% in the tapering regimen)	Study included 16 centers in Brazil and Mexico. The relapse rate was related to melasma severity at baseline, but not related to melasma severity at the time of transition to the maintenance/tapering regimen. Even in the relapsed group, final MASI scores were still 42% lower than baseline
Other combination topical agents									
Guevara [50], 2003	R, DB, PC	4% HQ, 10% buffered glycolic acid, vitamin C and E, sunscreen cream bid vs. sunscreen alone	12 wk	35	70% of the TC group had moderate or greater improvement based on physician global evaluation vs. 20% in vehicle group	75% of the treatment group showed improvement compared with 13% in the sunscreen-only group SS based on mexametry	4 wk	85% mild or moderate erythema; 65% scaling, and 40% edema, 35% with burning sensation, 10% itching, 60% redness, 60% dryness, and 30% peeling 67% of patients in the vehicle group had mild erythema	SPF of study cream unknown

Table 2 (continued)

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: physician- and participant-assessed	Outcome(s) [objective]: objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Lim [51], 1999	R, DB, C, SF	2% kojic acid + 10% glycolic acid + 2% HQ gel vs. 10% glycolic acid and 2% HQ only. Applied bid. SPF15 sunscreen qd	12 wk	40	> 50% improvement in 60% hemifaces applying kojic acid, compared with 47.5% of hemifaces using gel without kojic acid	None	4 wk	All subjects experienced redness, stinging, and mild exfoliation on both sides of the face. Effects were transient and resolved by 3 wk	

AEs adverse events, *bid* twice daily, *C* controlled, *DAB* diacetyl boldine, *DB* double-blind, *FA* fluocinolone acetonide 0.01%, *HQ* hydroquinone, *MASI* Melasma Area and Severity Index, *MB* monoblinded, *mo* months, *multi* multicenter, *N* number of subjects, *PC* placebo-controlled, *qd* once daily, *qhs* nightly, *R* randomized, *RA* tretinoin 0.05%, *SF* split-face, *SPF* sun protection factor, *SS* statistically significant, *TC* triple combination cream: 4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide unless otherwise specified, *TGF* transforming growth factor, *wk* weeks

4.2.3 Visible Light Protection

Visible light can induce sustained hyperpigmentation in the skin through mechanisms similar to that of UV radiation, including the generation of reactive oxygen species [30, 31]. Therefore, agents that act as physical blockers may enhance the efficacy of broad-spectrum sunscreens. This concept was proven by Castanedo-Cazares et al. comparing UV and visible-light protective sunscreen with UV-only sunscreen in subjects routinely applying 4% HQ cream [32]. After 8 weeks, the combination group showed a higher improvement in MASI score, colorimetry, and histopathology.

Zinc sulfate has been tested as both a physical blocker of visible light and antioxidant, however it is not superior to 4% HQ [33]. More subjects dropped out of the zinc sulfate group, which may have been partially attributed to unsatisfactory results.

4.2.4 Topical Tranexamic Acid (TXA)

Treatment with topical TXA, an antifibrinolytic agent, has recently been explored in the treatment of melasma but has shown mixed results (Table 1). Topical formulations include 2–5% creams or solutions and intradermal injections (4–100 mg/mL). Ebrahimi et al. performed a randomized, split-face trial with 3% topical TXA versus 3% HQ + 0.01% dexamethasone twice daily for 12 weeks [34]. The improvement in MASI was higher in the topical TXA group (74% vs. 65% for HQ + dexamethasone) but this was not statistically significant. Banihashemi et al. performed a study comparing 5% liposomal TXA versus 4% HQ cream, again failing to show a statistically significant difference between groups (54% vs. 48%) [35]. Atefi et al. compared 5% topical TXA twice daily with 2% HQ, with no significant difference in MASI score between groups, despite a higher patient satisfaction rate in the TXA group [36].

Topical TXA has also been studied as an adjuvant treatment. Laothaworn et al. compared QS-Nd:YAG laser with and without 3% topical TXA [37]. Forty-eight percent of subjects reported a remarkable improvement in the combination group versus 20% in the laser-only group. Xu et al. successfully showed that microneedling combined with 5% topical TXA can improve pigmentation after 12 weeks [38].

TXA has also been tested as an intradermal injection, using different concentrations (4–100 mg/mL) and treatment protocols, with mixed results when compared with topical HQ or topical TXA [39–41]. Microneedling and intradermal injections of TXA were compared by Budamakuntla et al. in a 12-week trial [42]. No significant difference was seen in mean MASI scores, however more subjects in the microneedling group experienced > 50% improvement, suggesting that microneedling may be superior to intradermal injections.

Table 3 Studies evaluating skin-brightening creams and plant-based extracts as topical agents for the treatment of melasma

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: Physician- and participant-assessed	Outcome(s) [objective]: Objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Haddad [52], 2003	R, DB, PC, SF	Group 1: HQ 4% on hemiface vs. vehicle qhs Group 2: SWC 5% on hemiface vs. vehicle qhs All subjects applied SPF25 sunblock qd	3 wk	25	Group 1: 76.9% improvement, 25% adverse effects Group 2: 66.7% improvement, 0% adverse effects (not SS) Patient satisfaction level 66.7% in the HQ group and 69.2% in the SWC group	None	NA	Skin irritation in 25% of the HQ group. No AEs in the SWC group	Included patients from Brazil with Fitzpatrick skin types III, IV, and V
Francisco-Diaz [53], 2004	R, DB, PC, SF	Gigawhite® 5% solution bid vs. placebo solution bid. Both groups applied SPF60 sunscreen qd	12 wk	26	MASI decreased by 18.5% on the Gigawhite side of the face vs. 13.5% on the placebo side. There was no SS difference between groups based on subjective measurement	Colorimetry showed 6.9% improvement of luminance value on the Gigawhite side of the face vs. 1.03% on placebo side, which was SS	NA	No AEs reported	
Thirion [54], 2006	R, DB, PC SF	Thiospot® intensive cream vs. moisturizing cream bid to the forehead	3 mo	27	36% improvement after 3 mo vs. no significant change in placebo	SS improvement seen in the treatment group based on Mexameter, video-recorded UV light reflection, corneomelametry, and physician assessment. No SS change in the control group	2 mo	No AEs reported	Treatment was limited to forehead melasma
Makino [55], 2013	R, DB, SF	Skin-brightening formulation containing SMA-432, a prostaglandin E2 inhibitor, vs. 4% HQ bid	12 wk	68	No difference between groups in overall hyperpigmentation, global improvement. Subjects tended to favor the cream containing SMA-432 regarding improvement of skin tone, skin appearance, and dark spots A dose-dependent reduction in hyperpigmentation was seen with SMA-432 based on physician evaluation	Chroma meter measurements found a SS improvement in luminance (L*) values in the treatment groups by week 8	4 wk	No SS difference in erythema between groups. Treatment group experienced mild burning and transient skin tightness	This was a split-face study with four groups: the first three groups all had slightly different formulations of SMA-432, and the fourth group was the control group applying HQ

Table 3 (continued)

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: Physician- and participant-assessed	Outcome(s) [objective]: Objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Monheit [56], 2013	R, SB, C, SF	SLC (Melaplex®) + 4% HQ cream vs. TC	12 wk	20	Comparable efficacy of SLC vs. TC cream. After 4 wk of treatment, MASI score decreased 57% for both the SLC and TC groups, which further improved to 77% reduction and 79% reduction, respectively, by 12 wk	None	4 wk	35% of subjects had skin irritation with either cream	SLC contained disodium glycerophosphate, L-leucine, undecylenoyl phenylalanine, and phenylethyl-resorcinol
Wanner [57], 2015	R, SB, C	Four treatment groups: 1. Proprietary LP 2. Proprietary LP with iontophoresis 3. Tretinoin 0.05% cream 4. Vehicle	16 wk	74	Improvement was 22% with LP alone; 17% LP + iontophoresis; 14% tretinoin; and 9% on placebo, based on investigator assessment. Under Wood's light, LP + iontophoresis produced the greatest results, with a 28% reduction in hyperpigmentation (vs. 9.9% in the 'LP only' group and 16% in the tretinoin group)	None	NA	56% of subjects in the tretinoin group had AE vs. 15% with LP only and 21% with iontophoresis and 11% with placebo	Caucasian patients
Pratchyapurit [58], 2016	R, C	DAB 4% cream qhs (Neotone®) + TGF-β1 biomimetic oligopeptide-68 + sunscreen (Neotone Radiance®) bid vs. control	12 wk	38	2.6% of subjects graded themselves as markedly improved, 76.3% as moderately improved, and 21.1% as slightly improved. 47.4% improvement in MASI by 12 wk	Pigment reduction was most significantly reduced with the combination of DAB (Neotone®) and TGF-β1 and sunscreen (Neotone Radiance®) vs. either ingredient or HQ (4% and 2%) alone	6 wk	2.5% with erythema, 20% with pruritus, 7.5% with skin exfoliation, and 2.5% with skin dryness	The comparison of treatment creams with HQ was performed on unaffected skin. When applying treatment cream to skin affected by melasma, no control was used DAB stabilizes tyrosinase in its inactive form and TGF-β1 inhibits tyrosinase activity

Table 3 (continued)

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: Physician- and participant-assessed	Outcome(s) [objective]: Objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Amer [59], 2000	SF, C	Topical liquiritin 1 g/day vs. vehicle bid	4 wk	20	Treatment group: 80% of patients with an excellent response, 10% had a good response, and 10% had a fair response. One patient in the vehicle group achieved a fair response	None	4 wk	Two patients in the treatment group experienced skin erythema and burning	Tested liver enzymes, serum creatinine, blood urea, and complete blood count, all of which remained normal throughout the study
Costa [60], 2010	R, SB, C	Belides, Emblica, and Licorice 7% bid vs. hydroquinone 2% qhs	60 days	50	Both groups had improved skin depigmentation based on medical and subject evaluation (not SS)	Visea-based pattern of melasma showed improvement in number, size, and tone of UV stains in both groups, but no difference between groups	15 days	Fewer adverse effects in the treatment group then the control group	Belides is an antioxidant from the *Bellis perennis* flower that inhibits melanin synthesis, transfer of melanosomes to epidermal cells, and endothelin-1 Licorice contains glabridine, a flavonoid from the plant *Glycyrrhiza glabra*. It acts to inhibit tyrosinase and has anti-inflammatory properties Embilica is derived from the fruit *Phyllanthus emblica*, which has antioxidant activity

Table 3 (continued)

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: Physician- and participant-assessed	Outcome(s) [objective]: Objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Morag [61], 2015	R, DB, PC	2.5% arbutin cream bid vs. placebo	8 wk	102	75.86% of melasma patients had improved skin lightening and evening skin tone	Melanin level decreased in the treatment group and increased in the placebo group	4 wk	No AEs reported	This product contained a β-anomer of arbutin
Alvin [62], 2011	R, SB, PC	75% mulberry extract oil vs. placebo qd	8 wk	50	MASI score improved from 4.076 ± 0.24 to 2.884 ± 0.25 in the treatment group. MelasQoL improved most significantly in the treatment group	Mexameter scores improved from 356 ± 60 to 313 ± 57 at week 8 in the treatment group compared with 368.24 ± 46.62, worsening to 372.12 ± 44.47, in the placebo group	4 wk	Erythema and pruritus in both the treatment (n = 4) and placebo (n = 12) groups	
Draelos [63], 2015	R, C, SF, paired	Cohort 1: lignin peroxidase vs. control Cohort 2: lignin peroxidase vs. 4% HQ	12 wk	60	Cohort 1: SS improvement with lignin peroxidase in dark spots, roughness, skin discoloration and overall appearance by week 8, and continuing to week 12 Cohort 2: No SS difference in skin appearance or MASI score between lignin peroxidase and HQ	Cohort 1: Improvement in spot size, texture, roughness, lack of clarity, overall appearance, and MASI score. SS reduction in target spot pigment based on spectrophotometer at wk 4, 8, and 12 Cohort 2: No difference between lignin peroxidase and HQ	4 wk	No AEs reported	Lignin peroxidase is an enzyme derived from the tree fungus *Phanerochaete chrysosporium*. This product breaks down melanin in the outer epidermis
Khosravan [64], 2017	R, C	Parsley (*Petroselinum crispum*) vs. 4% HQ daily. Both groups applied SPF30 sunscreen qd	8 wk	54	No SS difference between groups. MASI score in parsley group improved 6.66 ± 4.39 to 4.92 ± 3.07 vs. 6.68 ± 3.24 to 5.06 ± 2.66 in the HQ group	HQ group had 10.5 times the expense as those in the parsley group	NA	Two members in each group with redness and irritation	The parsley was brewed and applied with cotton. The article did not elaborate on 'expenses' incurred by either group

Table 3 (continued)

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: Physician- and participant-assessed	Outcome(s) [objective]: Objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Mendoza [65], 2014	R, DB, PC	3% *Rumex occidentalis* cream vs. 4% HQ cream vs. placebo bid	8 wk	45	Greater decline in MASI score in the HQ group from wk 2 to 6, but *R. occidentalis* had a slightly greater improvement by week 8 (mean decline in MASI 0.60 ± 0.8 compared with 0.55 ± 0.62 in the HQ group). Investigator assessments showed a slightly more noticeable improvement in the HQ group Subjects reported equal efficacy	Greater decline in melanin content based on mexametry in the treatment group compared with the HQ group	2 wk	One subject in the *R. occidentalis* group with mild facial peeling	
Altaei [66], 2012	R, DB, PC	Group 1, silymarin cream 7 mg/mL bid vs. Group 2, silymarin cream 14 mg/mL bid vs. Group 3, placebo cream. All subjects applied SPF15 sunscreen qd	4 wk	96	Group 1 MASI improved from 17.1 ± 3.12 to 0 at the end of treatment, and Group 2 MASI improved from 16.5 ± 2.8 to 0 at the end of treatment ($p = 0.0001$). No significant improvement in MASI in the control group. Patient satisfaction was 100% in the treatment groups	None	1 wk	No AEs reported	Iraqi patients MASI score reduction was seen in all treatment groups as early as week 1 (SS)
Lee [67], 2002	R, DB	Vehicle (Group A) vs. 2% lincomycin + 0.05% BV (Group B) vs. 2% lincomycin + 0.05% BV + 2% linoleic acid (Group C) qhs. Applied SPF15 sunblock qd	6 wk	47	MASI score decreased by 31.1% in Group C, 14.6% in Group B, and 2% in Group A (vehicle) [$p < 0.05$]. There was no SS difference between Groups A and B	43.7% of patients in Group C had more than moderate improvement, vs. 12.5% in Group B and 0% in Group A	2 wk	No AEs reported	Korean patients. Subjects with a negative family history of melasma and malar involvement of melasma showed better improvement after 6 wk of treatment

Table 3 (continued)

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: Physician- and participant-assessed	Outcome(s) [objective]: Objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Katoulis [68], 2014	R, DB, PC	Topical treatment undecylenoyl phenylalanine 2% vs. vehicle. All subjects applied sunscreen qd	12 wk	37	80% of subjects in the treatment group were 'extremely satisfied' or 'satisfied' Based on physician assessment, 85% of the treatment group had partial response and 0% had complete response. The vehicle group had 23.5% of patients with partial improvement and 76.4% who remained stable or worsened	None	4 wk	Minor erythema, itching, and burning in 30% of the treatment group and 11.7% of the control group	SPF of sunscreen not reported
Mansouri [69], 2015	R, DB, PC	Cysteamine cream 5% vs. placebo qd	4 mo	50	MASI score decreased from 13 ± 8.1 to 7.2 ± 5.5 in the treatment group vs. 17.2 ± 8.1 to 11.6 ± 7.9 in the placebo group. Investigator's global assessment and patient questionnaires indicated superiority of cysteamine	In the treatment group, there was a SS improvement in melanin content based on Mexameter	2 mo	46% erythema, 29% dryness, 42% itching, 43% burning, 32% irritation	One subject experienced hyperpigmentation with cysteamine cream
Farshi [70], 2018	R, DB, PC	Cysteamine cream 5% vs. placebo qd	4 mo	40	MASI score decreased from 18.1 ± 8.1 to 8.03 ± 5.2 in treatment group vs. 13.2 ± 7.4 to 12.1 ± 7.4 in the placebo group ($p = 0.04$)	Superior results were seen based on Mexameter and Dermacatch measurements of pigment content ($p = 0.0001$) There was good correlation between the Dermacatch and Mexameter readings	2 mo	35% erythema, 20% dryness, 25% itching, 25% burning, 20% irritation There was no SS difference in AEs between groups	Used the Dermacatch, a portable visible-spectrum reflectance skin colorimeter (Colorix, Neuchatel, Switzerland) to measure erythema and melanin content in the skin and compared with Mexameter

Table 3 (continued)

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: Physician- and participant-assessed	Outcome(s) [objective]: Objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Adalatkhah [71], 2015	R, C	1% flutamide cream qhs vs. 4% HQ cream qhs. All subjects applied SPF30 sunscreen three times daily	4 mo	74	Patients were more satisfied in the flutamide group based on improvement of melasma, satisfaction with adverse effects, skin succulence, and skin darkness. More SS improvement in MASI score in the flutamide group	Mexameter melanin assay did not show any difference between the two groups	2 mo	None reported	Overall comparative outcomes between groups, but higher patient satisfaction with flutamide. Flutamide is an anti-androgenic agent
Eshghi [72], 2016	R, C	Intralesional TAC (4 mg/cc at 5 mm intervals) vs. TC controls	8 wk	42	MASI score decreased from 11.57 ± 4.22 to 8.01 ± 3.1 in the intralesional TAC group vs. 10.46 ± 5.61 to 8.96 ± 4.96 in the control group. The intralesional group had superior results ($p < 0.001$)	None	4 wk	Atrophy and telangiectasias observed in the treatment group	TC, Kligman's formula: HQ 5%, tretinoin 0.1%, dexamethasone 0.1%

Neotone®: 4% DAB, licorice extract, ascorbic acid, glycolic acid, salicylic acid, and α-arbutin

Neotone Radiance®: 4% DAB, 0.05% TGF-β1 biomimetic oligopeptide-68, ascorbic acid, UVA and UVB filters, and spread spectrum SPF50 sunscreen (skin-whitening complex: extract of uva-ursi, biofermented *Aspergillus*, grapefruit extract, rice extract) [Thiospot intensive: ethyl linoleate, thioctic acid, octadecenedioic acid, lactic acid, ethylhexyl methoxycinnamate]

Manufacturer information: GigaWhite® (Pentapharm/DSM, Basel, Switzerland); Thiospot® (Synchroline, Salo, Italy); Lignin Peroxidase Study Lotion (Elure, Syneron Medical Ltd, Yokneam, Israel); Melaplex™ (Monheit 2013; Neocutis Inc., San Francisco, CA, USA); Neoretin® Discrom control gel cream daily/Neoretin® Discrom control serum booster fluid nightly (IFC Pharmaceuticals); Neotone® and Neotone Radiance® (ISIS PHARMA, Lyon, France); Tri-luma® (Galderma Laboratories, Fort Worth, TX, USA)

AEs adverse events, *bid* twice daily, *BV* betamethasone valerate, *C* controlled, *DAB* diacetyl boldine, *DB* double-blind, *HQ* hydroquinone, *LP* lightening product, *MASI* Melasma Area and Severity Index, *MelasQoL* Melasma Quality of Life Score, *mo* months, *NA* not available, *PC* placebo-controlled, *qd* once daily, *qhs* nightly, *R* randomized, *SB* single-blind, *SF* split-face, *SPF* sun protection factor, *SS* statistically significant, *SLC* skin-lightening cream, *SWC* skin-whitening complex, *TAC* triamcinolone, *TC* triple combination cream: 4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide unless otherwise specified, *TGF* transforming growth factor, *UV* ultraviolet, *wk* weeks

Table 4 Studies evaluating chemical peels for the treatment of melasma

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: Physician- and participant-assessed	Outcome(s) [objective]: Objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Glycolic acid peels									
Lim [73], 1997	R, MB, SF	2% HQ, 10% GA gel bid, followed by 20–70% GA peel (every 3 wk for 24 wk) vs. pretreatment with 8% GA cream bid for 2 wk then 2% HQ, 10% GA gel bid for 24 wk. Daily SPF15 sunscreen	26 wk	10	Melasma and fine wrinkles improved on both sides. No SS difference between sides of the face	None	7 wk	Erythema and stinging, 10% PIH	Small sample size. Sunscreen frequency unclear
Hurley [74], 2002	R, MB, SF	4% HQ bid for 8 wk vs. 4% HQ cream bid + 20% GA peel (every 2 wk for 4 wk) followed by 30% GA peel (every 2 wk for 4 wk). SPF25 sunscreen was used	12 wk	18	Significant decrease in MASI score from baseline to follow-up visit. No SS difference between groups	Significant improvement based on mexametry. No SS difference between groups	8 wk	Erythema, dryness, and scaling	Small sample size
Ilknur [75], 2010	R, MB, SF	GA 20%, 35%, 50%, 70% (12 sessions, every 2 wk) vs. amino fruit acid 20%, 30%, 40%, 50%, 60% (12 sessions, every 2 wk). SPF30 sunscreen was used	24 wk	24	MASI scores decreased in both groups at 3 and 6 mo. No SS difference between groups	None	12 wk	Erythema, edema, and frosting	Amino fruit acid peel found to be more tolerable
Kumari [76], 2010	R, MB	Group A: 20–35% GA peel (7 sessions, every 2 wk) Group B: 10–20% TCA (7 sessions, every 2 wk) Daily SPF15 was used in all subjects	24 wk	40	79% reduction in MASI score at 12 wk in the GA group vs. 73% in the TCA group. No SS difference between groups	None	8 wk	95% mild burning in the GA group. 75% moderate to severe burning in the TCA group	Quicker initial improvement in the TCA group, but response was comparable at the end of the study. Most patients were skin type IV–VI. The relapse rate was low
Faghihi [77], 2011	R, SF	GA 70% on one side of the face vs. tretinoin 1% on the opposite side (4 sessions, every 2 wk)	12 wk	63	No SS difference observed between MASI scores on both sides of the face	None	8 wk	Erythema, stinging, and scaling	Tretinoin 1% peel was more tolerable than GA peel. Use of sunscreen unclear

Table 4 (continued)

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: Physician- and participant-assessed	Outcome(s) [objective]: Objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Sarkar [78], 2002	R, PC	Group A: Serial 30–40% GA peel (6 sessions, every 3 wk) + TC cream (2% HQ, 0.05% tretinoin, 1% hydrocortisone) Group B: TC cream alone SPF15 + used in all subjects	21 wk	40	SS decrease in MASI by 46% at week 12 and 80% at week 21 in Group A, and 33% (week 12) and 63% (week 21) in Group B (both SS). Group A SS was superior. Subjective improvement by patients was higher in Group A	None	12 wk	Mild erythema, desquamation in both groups 10% PIH in Group A	All patients were skin type IV–V
Erbil [79], 2007	R, PC	Group A: GA peel + 20% AA bid + 0.1% adapalene gel qhs Group B: 20% AA bid + 0.1% adapalene qhs	20 wk	28	Decrease in MASI in both groups. SS superior results in Group A	None	8 wk	PIH in the GA group	Use of sunscreen is unclear
Dayal [80], 2017	R, MB	Group A: GA peel (8 sessions, every 3 wk) + 20% AA bid Group B: 20% AA bid alone SPF50 was applied by all subjects	24 wk	60	Significant decrease in MASI and MelasQoL at 12 wk compared with controls	None	12 wk	Post-peel erythema, pruritus, burning sensation, and PIH	Adverse effects were higher in Group A
Sarkar [81], 2016	R, MB	Group A: 35% GA peel Group B: 20% salicylic and 10% mandelic acid Group C: 50% phytic acid combination 6 sessions, every 2 wk	20 wk	90	Decrease in MASI score in all three groups. More significant reduction in Group A vs. Group C and Group B vs. Group C, but no difference between Groups A and B	None	4 wk	Group A: 19% mild erythema and desquamation, 15% PIH Group B: 25% burning sensation Group C: 32% burning sensation	All patients were skin type IV–V SPF sunscreen not clear

Table 4 (continued)

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: Physician- and participant-assessed	Outcome(s) [objective]: Objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Salicylic acid peels									
Ejaz [82], 2008	R, DB	Jessner's solution (14% SA, 14% lactic acid, 14% resorcinol) peel for 5 min, every 2 wk for 12 wk vs. 30% SA peel for 5 min, every 2 wk for 12 wk. Daily SPF60 sunscreen used	24 wk	60	Both groups had a decrease in MASI scores. No SS difference found between groups	None	4 wk	Erythema and scaling	Subjects underwent 2 wk of priming with 0.05% tretinoin before treatment
Kodali [83], 2010	R, SF	20–30% SA peel (every 2 wk) on one side of the face, and concomitant use of 4% HQ to both sides of the face bid. SPF30 sunscreen was used	8 wk	18	mMASI scores decreased on both sides of the face. No SS difference between sides in mMASI and Global Assessment	Narrowband reflectance spectrophotometry showed SS reduction in pigment on both sides. No SS difference between the sides	2 wk	20% erythema, burning, peeling	Small sample size
Balevi [84], 2017	R, MB	Group A: 30% SA peel (every 2 wk for 2 mo) Group B: 30% SA peel (every 2 wk for 2 mo) + vitamin C mesotherapy SPF15 + was used two to three times a day	24 wk	50	MelasQoL and MASI score decreased in both groups. No SS difference between groups	None	8 wk	Burning sensation	Quality of life was slightly higher in Group A
Azzam [85], 2009	R, PC	Group A: 2 wk priming with 0.05% retinoic acid qd and Jessner's solution (6 weekly sessions) Group B: 2 wk priming with 0.05% retinoic acid qd and TCA 20% (6 weekly sessions) Group C: Topical 2% HQ qhs for 8 wk Group D: Topical 2% kojic acid qhs for 8 wk	16 wk	45	Group B with SS reduction in MASI score compared with the other groups. There was a SS difference between Groups A vs. B and Groups B vs. C	None	6 wk	20–30% erythema PIH was more common in the TCA group vs. Jessner's group	Sunscreen use not mentioned

Table 4 (continued)

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: Physician- and participant-assessed	Outcome(s) [objective]: Objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Trichloroacetic acid peels									
Murtaza [86], 2016	R, MB	Group A: 20% TCA peel (6 sessions, weekly) + magnesium ascorbyl phosphate cream qd Group B: 20% TCA (6 sessions, weekly)	6 wk	148	Significant MASI score decrease in Group A (80%) vs. Group B (66%)	None	6 wk	Erythema, burning sensation, desquamation	Short-term follow-up. Use of sunscreen unclear
Abdel-Meguid [87], 2017	R, MB, SF	TCA 20–25% plus Jessner's solution on one side of the face vs. TCA 20–25% alone on the opposite side (6 sessions, 2-week interval)	12 wk	24	MASI score reduction on both sides of the face, significantly lower on the side treated with combined treatment	None	12 wk	10% PIH on the combined side Transient erythema, burning, discomfort, itching, and crusting	Significant negative correlation between improvement and age of the patients and duration of melasma. Only patients with skin types III–IV were included

AA azelaic acid, *bid* twice daily, *DB* double-blind, *GA* glycolic acid, *HQ* hydroquinone, *MASI* Melasma Area and Severity Index, *MB* monoblinded, *mMASI* modified MASI, *MelasQoL* Melasma Quality of Life Score, *mo* months, *PC* placebo-controlled, *PIH* post-inflammatory hyperpigmentation, *qd* once daily, *qhs* nightly, *R* randomized, *SA* salicylic acid, *SF* split-face, *SPF* sun protection factor, *SS* statistically significant, *TC* triple combination cream: 4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide unless otherwise specified, *TCA* trichloroacetic acid, *wk* weeks

In the above trials, the adverse effects of topical TXA tended to be less common than HQ.

4.2.5 Combined Topical Agents

Triple combination cream (TCC) consists of HQ, a retinoid, and a fluorinated corticosteroid, and has become widely regarded as a safe and effective treatment for melasma. In a large, multicenter, randomized controlled trial conducted by Taylor et al., TCC (4% HQ, 0.05% tretinoin, and 0.01% fluocinolone acetonide) was found to be more effective than any dual combination of the three active ingredients [43]. Seventy-seven percent of subjects achieved complete or near complete clearing versus a maximum of 47% in the dual-combination groups. Twenty-six percent of subjects using TCC achieved complete clearance by 8 weeks. All groups experienced erythema, desquamation, burning, dryness and pruritus, particularly in the groups using tretinoin. The same authors performed a 12-month extension study on 569 subjects to determine the safety and efficacy of TCC, with only 2.5% discontinuing treatment due to adverse events [44]. Later, Ferreira Cestari et al. confirmed the higher efficacy of TCC compared with 4% HQ once daily in a controlled, open-label, 8-week trial [45]. Clearance of melasma was seen in 35% of subjects using TCC versus 5% using HQ alone. Adverse events were similar in both groups. Chan et al. also reported higher efficacy using TCC when compared with 4% HQ twice daily [46]. There were higher adverse effects in the TCC group (49% vs. 14%). Gong et al. confirmed the efficacy of TCC compared with placebo using a Mexameter to measure pigmentation, showing 71% improvement, with early response at 2 weeks [47].

Arellano et al. performed a large, multicenter, randomized, investigator-blinded trial testing the efficacy of maintenance therapy using TCC [48]. After an initial 8-week daily use period, subjects were randomized to either receive twice-weekly TCC for the duration of the 6 months or a tapering regimen, consisting of TCC three times weekly for 1 month followed by twice weekly for 1 month, then once weekly for 1 month. The group treated twice weekly had a lower relapse rate than the tapering regimen group. Relapse rate was highest in those with more severe baseline melasma. At follow-up, 55% of all subjects remained relapse-free and the final MASI score was 42% lower than baseline. Grimes et al. also tested the efficacy of maintenance TCC therapy in an open-label, 24-week trial [49]. After 12 weeks of daily TCC therapy, subjects were either transitioned to twice-weekly therapy if they were clear or almost clear, or continued on daily therapy if not clear. Unfortunately, most subjects who transitioned to maintenance therapy relapsed.

Other combination topical therapies have been considered in the treatment of melasma, such as solutions containing GA and kojic acid (KA). KA and GA may be effective adjuvant topicals, however they can cause increased adverse effects when combined with HQ (Table 2) [50, 51].

4.2.6 Miscellaneous Treatments

Other miscellaneous depigmented topicals are found in Table 3 [52–72].

4.3 Chemical Peels

Chemical peels are commonly used in daily practice for the management of skin rejuvenation, solar lentigines, acne, and hyperpigmentation. Most of the current studies on melasma lack an objective assessment tool and results continue to be controversial (Table 4). Known potential adverse effects include skin irritation and post-inflammatory hyperpigmentation (PIH).

4.3.1 Glycolic Acid Peels

GA peels have been used in several studies but most have not shown superior efficacy to topical agents. Results may be superior when combining GA peels with TCC. It is important to note that the risk of adverse effects, notably PIH, is more pronounced when GA peels are included in the treatment regimen.

A split-face study by Lim and Tham compared 2% HQ + 10% GA gel twice daily, followed by 20–70% GA peels versus pretreatment with 8% GA cream, followed by 2% HQ and 10% GA gel [73]. No significant difference was seen between sides. Hurley et al. failed to show a significant difference when comparing 4% HQ twice daily to the entire face and 20–30% GA peels on one side of the face [74]. Later, Ilknur et al. performed a split-face trial using 20–70% GA peel versus 20–60% amino fruit acid peels [75]. Both sides improved equally by week 24, with slightly higher adverse effects in the GA group. Kumari and Thappa compared the use of 20–35% GA peel with 10–20% TCA peels [76]. A quicker initial response was seen in the TCA group, however, by week 12, response was comparable between groups. Another split-face study performed by Faghihi et al. compared the use of 1% tretinoin versus 70% GA peel, showing no significant difference between sides [77].

Sarkar et al. performed a randomized, placebo-controlled study using 30–40% GA peels + TCC versus TCC alone. A significant decrease of 46% was seen as early as 12 weeks in the combination group versus 33% in the monotherapy group [78]. Of note, 10% of subjects in the GA peel group experienced PIH. Another randomized, placebo-controlled study performed by Erbil et al. compared 20–30% GA peels + 20% AA twice daily + 0.1% adapalene gel once daily versus 20% AA + 0.1% adapalene [79]. A decrease in MASI score was seen in both groups, with significantly greater improvement

in the intervention group; however, the incidence of PIH was higher. A similar study performed by Dayal et al. used 20% AA twice-daily alone versus 20% AA plus GA peels (eight sessions) in 60 subjects [80]. A significant decrease in MASI and Melasma Quality of Life Score (MelasQoL) was seen at week 12 when compared with controls. Adverse effects, such as erythema, burning sensation, and PIH were higher in the combination group.

A recent study compared the use of three different chemical peels: 35% GA peel, 30% SA + 10% mandelic acid (SMA) and 50% phytic acid (PA). Results were significantly greater in the GA peel group compared with the PA peel group, however the efficacy of GA was similar to that of SMA [81].

4.3.2 Salicylic Acid Peels

SA peels have also been used for treating melasma and other forms of hyperpigmentation, however they have consistently failed to show significant improvement when compared with controls. Of note, salicylic-mandelic acid, a combination of α- and β-hydroxy acids, may be a safer option for those with sensitive skin and dark-skinned phenotypes [81]. Mandelic acid has a high molecular weight, allowing for greater and more sustained and uniform penetration of the epidermis, and also with lower propensity to cause stinging and burning [81].

Ejaz et al. performed a randomized assessor-blinded study, which failed to show a significant difference between Jessner's solution and 30% SA peels [82]. Another study performed by Kodali et al. failed to show a significant difference between 20 and 30% SA peels and 4% HQ [83]. The addition of vitamin C mesotherapy to 30% SA peel did not show any significant difference [84].

Azzam et al. performed a randomized, placebo-controlled study comparing Jessner's solution, 20% TCA peel, 2% HQ, and 2% KA [85]. No significant difference was seen between the chemical peel groups, however a significant decrease was seen in the TCA group versus the 2% HQ alone group. PIH was more common in the TCA group.

4.3.3 Trichloroacetic Acid Peels

TCA peels are commonly used in dark-skinned subjects with melasma, however there is a lack of randomized controlled studies with this agent. A recent large, randomized, assessor-blinded study compared 20% TCA peel + magnesium ascorbyl phosphate cream once daily versus TCA peels alone [86]. A significant decrease in MASI scores was seen by week 6 in the combination group compared with the chemical peel group. Another randomized, assessor-blinded, split-face study compared the use of 20–25% TCA acid peels plus Jessner's solution on one side of the face versus 20–25% TCA peels alone on the opposite side [87]. A decrease in MASI scores was seen on both sides of the face but it was significantly lower on the side treated with combined peels.

4.4 Laser and Light Therapies

Laser- and light-based therapies continue to be popular in the management of hyperpigmentation and skin rejuvenation; however, an increased risk of adverse effects may be seen, including paradoxical increase in pigmentation because of direct damage to the skin. These adverse effects tend to be more common in subjects with skin of color, therefore they should be avoided or performed using conservative parameters in these cases. Despite the risks, some studies have shown promising results in randomized trials (Table 5).

4.4.1 Intense Pulsed Light

IPL has shown contradictory results in the treatment of melasma. Wang et al. showed significant improvement in a randomized controlled trial comparing 4% HQ cream versus 4% HQ cream + IPL (four sessions) [88]. Thirty-five percent of subjects in the IPL group had over 50% improvement versus 14% in the control group; improvement was also shown by relative melanin index (MI; 40% vs. 12%). Thirteen percent of subjects in the IPL group had PIH. Later, Goldman et al. demonstrated that two sessions of IPL plus TCC was superior to IPL alone (57% vs. 23% clear/almost clear at 10 weeks) [89]. A trial by Figueiredo Souza et al. showed a 49% improvement in modified MASI (mMASI) using IPL + TCC at week 24. Surprisingly, no subject using the TCC had marked improvement [90]. Chung et al. failed to show significant improvement in MI and MASI with IPL in a randomized split-face, vehicle-controlled study. The study compared IPL to the whole face plus topical 2% TXA to half of the face [91]. Improvement was only significant on the TXA-treated side of the face. Furthermore, the authors suggested TXA was helpful in preventing rebound pigmentation after IPL sessions.

The most recent randomized, placebo-controlled study performed by Shakeeb et al. evaluated the use of TCC + IPL, comparing it with either therapy alone [92]. Improvement was more notable in the combined therapy group compared with either treatment alone.

Recently, the use of fractionated IPL (F-IPL) has also been used for treating hyperpigmentation, possibly having higher efficacy than conventional IPL. Yun et al. performed a study comparing the use of F-IPL + low-fluence QS-Nd:YAG laser versus F-IPL alone [93]. MASI scores improved 47% and 15%, respectively, with a comparable reduction in MI (20% vs. 15%); however, the combined group had more adverse effects, including first-degree burns. Later, Yun et al. performed a split-face study comparing the

Table 5 Studies evaluating laser- and light-based therapies for the treatment of melasma

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: Physician- and participant-assessed	Outcome(s) [objective]: Objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Intense pulsed light									
Wang [88], 2004	R, C	Group A: 4% HQ cream Group B: 4% HQ cream + IPL treatments (4 sessions, every 4 wk) for 16 wk. Daily sunscreen use in both groups	24 wk	32	35% of patients in Group B had > 50% improvement vs. only 14% in the control group	IPL group had 40% improvement in relative MI vs. 12% in the HQ-alone group	16 wk	IPL group: 13% had transient PIH	Frequency of HQ not mentioned. SPF of sunscreen, and frequency, unclear
Goldman [89], 2011	R, MB, SF	One side: TC qd + IPL (2 sessions, at wk 4 and 6) CL side: vehicle + IPL (2 sessions, at wk 4 and 6)	10 wk	56	IGA showed 57% vs. 23% of subjects were clear or almost clear at week 10 (TC + IPL vs. vehicle + IPL, respectively) [41% vs. 15% clear/almost clear at 6 wk]. Patients preferred TC	None	6 wk	Skin erosions, cutaneous irritation	None
Figueiredo Souza [90], 2012	R, MB, open-label	Group 1: IPL (single session) + TC cream Group 2: TC cream alone	48 wk	62	mMASI showed a 49% reduction at 24 wk and a 45% reduction at 48 wk. 32% of patients in the IPL group showed marked improvement versus 0% in the TC cream-alone group	None	24 wk	Mild erythema, crusting, and PIH	Investigators used a non-validated scale. Frequency of TC cream was not established

Table 5 (continued)

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: Physician- and participant-assessed	Outcome(s) [objective]: Objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Chung [91] 2015	R, PC, SF	One side: Topical 2% TXA + IPL (4 monthly sessions) Contralateral side: IPL alone (4 monthly sessions)	24 wk	15	mMASI decreased on the TXA side ($p<0.03$) compared with the vehicle side ($p=0.306$). The TXA-treated side had a continuous and SS decrease at 24 wk ($p=0.049$)	SS decrease in MI at 12 wk on the TXA side ($p<0.001$) vs. the vehicle side. At 24 wk, the TXA-treated side had a greater decrease in MI ($p=0.025$) vs. the vehicle side	12 wk	None	IPL was effective at decreasing melasma, however 4 sessions were not enough to be statistically significant. TXA was helpful as adjuvant treatment and to prevent rebound after IPL sessions
Shakeeb [92], 2018	R, PC	Group A: TC cream qd at pm Group B: IPL (4 sessions, every 2 wk) Group C: IPL (4 sessions, every 2 wk) + TC cream qd at pm	8 wk	96	Decrease in MASI was higher in Group C vs. Groups A and B	None	8 wk	NA	Short-term follow-up. Adverse effects were not mentioned. Use of sunscreen is unclear
Yun [93], 2014	Prospective, MB, comp	Group A: F-IPL and low-fluence QS-Nd:YAG, 6 sessions (every 2 wk) Group B: F-IPL alone, 6 sessions (every 2 wk)	20 wk	12	Decrease in MASI of 47% in Group A vs. 15% in Group B at 16 wk. Patient's self-assessment was better in Group A vs. Group B	Decrease in MI of 20% at week 16 in Group A vs. 15% in Group B	16 wk	Group A: first-degree burn	Use of sunscreen not mentioned. No recurrence observed in either group. Small sample size
Yun [94], 2015	Prospective, SF, comp	Fractionated IPL (6 sessions, weekly) vs. conventional IPL (3 sessions, biweekly)	14 wk	30	Decrease in mMASI of 30% in the conventional IPL group vs. 34% in the F-IPL. Rebound was observed in the conventional IPL group after 2 sessions	Decrease in melanin pigment was noted in the F-IPL group by H&E	14 wk	Conventional IPL: erythema and PIH Fractionated IPL: PIH	Use of sunscreen not mentioned

Table 5 (continued)

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: Physician- and participant-assessed	Outcome(s) [objective]: Objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
QS-Nd:YAG laser									
Park [95], 2011	R, MB, SF	1064 nm QS-Nd:YAG (6 sessions, 1- to 2-week intervals) to the entire face + 30% GA peel (3 sessions, at 2-week intervals) to one side of the face	26 wk	16	38% improvement in mMASI on the combined side vs. 17% on the laser-only side. Patient- and physician-assessment were better on the combined side of the face	33% improvement in Mexameter on the combined side vs. 22% on the laser-only side	6 wk	Transient burning and mild edema	Sunscreen use was unclear
Lee [96], 2014	R, PC	Group A: QS-Nd:YAG (10 sessions) + placebo (2-week interval) Group B: QS-Nd:YAG + chemical peel with Jessner's solution (2-week interval)	20 wk	52	Significant decrease in MASI at 8 wk in Group B vs. Group A. At 20 wk, there was no SS difference in MASI, PGA, and self-assessment	None	8 wk	Jessner's group: 15% had burning sensation on the laser side; mild pain and erythema	Sunscreen use was unclear
Ustuner [97], 2017	R, MB, SF	QS-Nd:YAG to the entire face (4 sessions, 4-week intervals) and additional microneedling with vitamin C to one side. SPF15 + used two to three times daily	24 wk	34	MASI SS lower on the combined side vs. the laser-only side at 1 mo and final follow-up visit. SS improvement in quality of life in the combined treatment group	None	12 wk	Erythema, hyperpigmentation, and hypopigmentation	Both groups presented with recurrence of melasma

Table 5 (continued)

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: Physician- and participant-assessed	Outcome(s) [objective]: Objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Kaminaka [98], 2017	R, PC, SF	Low-fluence QS-Nd:YAG 10 weekly sessions (1 mo rest period after the fifth treatment)	9 mo	22	Patient subjective assessment showed 50% of patients had good to excellent improvement	Decrease in MI on lesional skin at the fifth and tenth sessions ($p < 0.0001$). Decrease in epidermal and dermal melanophages by histopathological assessment. Decrease in number of vessels and mast cells since the fifth treatment session	5 wk	5% PIH, 15% xerosis, 5% pruritus	Clinical assessment was not properly performed due to the lack of MASI scores
Jeong [99], 2010	R, MB, SF	Group A: TC cream qd for 8 wk, followed by 8 sessions (weekly) of low-fluence QS-Nd:YAG Group B: 8 sessions (weekly) of low-fluence QS-Nd:YAG, followed by TC cream qd for 8 wk	16 wk	13	MASI showed a greater decrease in Group A. Greater relapse at 16 wk in Group B	Spectrophotometer showed a lighter skin tone in Group A only after 8 laser sessions	8 wk	TC cream: 30% erythema Laser: mild pain and erythema	All patients had mild melasma at baseline. Laser treatment was effective only after initial 8 wk of TC cream
Wattanakrai [100], 2010	R, SF	Low-fluence QS-Nd:YAG (5 weekly sessions) vs. HQ 2% qd on the other side	17 wk	22	The laser side achieved a 76% improvement by mMASI vs. 24% on HQ side	The laser side achieved a 93% improvement in relative lightness index vs. 20% on HQ side	5 wk	Laser side: 14% mottled hypopigmentation	SPF60 + was applied. All patients had recurrence of melasma.

Table 5 (continued)

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: Physician- and participant-assessed	Outcome(s) [objective]: Objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Kar [101], 2012	R, MB	Group A: low-fluence QS-Nd:YAG (10 weekly sessions) Group B: 35–75% GA peel 6 sessions, every 2 wk) Group C: high-fluence QS-Nd:YAG (6 sessions, every 2 wk)	12 wk	70	MASI showed significant improvement in all three groups at 12 wk. Great improvement in Group A, followed by Groups B and C	None	12 wk	Group A: 5% mottled hypopigmentation Group B: 5% PIH Group C: 24% mottled hypopigmentation, 29% PIH	All groups showed a rise in MASI at 12 wk. The high fluence group had the greatest adverse effects
Kim [102], 2013	R, MB, SF	Low-fluence QS-Nd:YAG (10 sessions, at 2-week intervals) to the entire face, followed by 5 sessions, at 4-week intervals of 1550 nm erbium dope fractional photothermolysis (NFP) to the hemiface	36 wk	26	MASI showed a decrease at 4 and 12 wk follow-up in both groups. No SS difference between groups. Slightly greater improvement in the QS-Nd:YAG-alone group. PGA was similar in both groups	None	24 wk	Mild erythema, mild pain	Recurrence was observed in both groups, slightly higher in the combination group
Shin [103], 2013	R, PC	Group A: Oral TXA (750 mg PO qd for 8 wk) + low-fluence QS-Nd:YAG (2 sessions, 4-week interval) Group B: Only low-fluence QS-Nd:YAG (2 sessions, 4-week intervals)	12 wk	48	At 8 wk, decrease in mMASI was higher in the combination group. Clinical improvement was slightly higher in the combination group: 22% with > 50% improvement and 9% with > 75% improvement vs. 11% and 0% in the laser-only group	None	8 wk	Oral group: 8% with heartburn, 4% (1 case) with nausea All cases had transient erythema after laser treatment	Sunscreen frequency was unclear Oral TXA pill also contained 318 mg ascorbic acid + 240 mg L-cysteine + 24 mg calcium pantothenate + 6 mg pyridoxine hydrochloric acid

Table 5 (continued)

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: Physician- and participant-assessed	Outcome(s) [objective]: Objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Jalaly [104], 2014	R, MB, SF	5 sessions (every 3 wk) of low-fluence QS-Nd:YAG 1064 nm to the hemiface vs. low-power fractional CO_2 laser to the contralateral side	23 wk	40	mMASI showed a greater improvement on the CO_2 side at 4 wk. Both sides had a SS decrease in mMASI at 23 wk. Patient's self-evaluation was better on the CO_2-treated side	MI showed a significant decrease only at 23 wk on both sides ($p < 0.001$). Greater improvement on the CO_2-treated side	4 wk	Erythema, edema, burning	Short follow-up time could not assess the recurrence rate
Vachiramon [105], 2015	R, MB, SF	Low-fluence QS-Nd:YAG 1064 nm to the entire face (5 weekly sessions) vs. additional IPL (3 sessions, at 2-week intervals) to one side	12 wk	20	MASI improved 55% on the combination side vs. 37% on the laser-only side. Patients' satisfaction was higher on the combined side	55% improvement in mean relative lightness index on the combined side at 2 wk vs. 37% improvement on the laser monotherapy side at 3 wk	2 wk	Combined side: 70% had microcrusts Both sides had erythema and burning	Recurrence of melasma was higher on the combined side, however it was still lower compared with baseline
Vachiramon [106], 2015	R, MB, SF	Low-fluence QS-Nd:YAG 1064 nm to the entire face vs. an additional 30% GA peel to one side (5 weekly sessions). SPF50 + qd	16 wk	15	No SS difference in MASI. Patients' satisfaction was slightly higher in the combined side	No significant difference in relative lightness index between sides	3 wk	Both sides: burning and stinging, guttate hypopigmentation	At final follow-up, patients still had severe melasma
Pulsed-dye laser									
Passeron [107], 2011	R, MB, SF	TC cream qd vs. TC qd + PDL (3 sessions, every 3 wk). SPF50 + sunscreen was used	21 wk	18	Decrease in MASI score in the combined side at 13 and 21 wk. Patient's satisfaction was higher in the combined treatment group	None	13 wk	PDL side: PIH	Sunscreen frequency unclear. All patients in the study had mild melasma

Table 5 (continued)

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: Physician- and participant-assessed	Outcome(s) [objective]: Objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Fractional laser therapy									
Wind [108], 2010	R, MB, SF	Four to five non-ablative FLT vs. TC cream (HQ 5% + tretinoin 0.05% + triamcinolone acetonide 0.1%) to both sides	24 wk	29	Worsening hyperpigmentation on the FLT side by mean PGA and PhGA. No SS change on the TC side. Patients preferred TC	Increase in MI on the FLT side	3 wk	FLT: Erythema, burning, crusting, facial edema, blistering, PIH TC cream: erythema, burning, scaling	80% of patients included were skin type III–V. Frequency of FLT sessions is not mentioned
Kroon [109], 2011	R, MB	Four serial non-ablative 1550 nm NFP sessions at 2-week intervals vs. TC (hydroquinone 5%, tretinoin 0.05%, triamcinolone acetonide 0.1%) qd for 8 wk	24 wk	22	PGA showed improvement at 3 wk but no difference between groups. At 6 mo, melasma recurred in 5 patients in both groups. Patient satisfaction was higher in the laser group	None	3 wk	Erythema, burning sensation, edema, mild pain	Small sample size
Nouri [110], 1999	R, PC	Group A: Pulsed CO_2 laser (one pass, 300 mJ/cm^2) + Q-switched Alexandrite (one pass, 6 J/cm^2) Group B: Pulsed CO_2 laser only. TC cream was used 14 days before the laser procedures	24 wk	8	Investigator subjective assessment established slightly better response in Group A vs. Group B	None	4 wk	Combined group: Hypopigmentation CO_2 only: Peripheral hyperpigmentation	Assessment was performed subjectively. Only a 1 cm^2 spot of the melasma was treated

Table 5 (continued)

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: Physician- and participant-assessed	Outcome(s) [objective]: Objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Angsuwarangsee [111], 2003	R, PC, SF	One side: CO_2 + Q-switched Alexandrite 1 session Contralateral side: Q-switched Alexandrite alone 1 session	24 wk	6	No SS difference between groups. 83% of patients in Group 1 had SS decreased mMASI. Group 2 had non-SS decrease in mMASI. Patient satisfaction score: 50% preferred combination treatment	Physician assessment performed by MI (Mexameter), with only a SS improvement seen in the combined group	NR	16% had temporary hypopigmentation, 50% had PIH, 16% showed no improvement	2/6 were administered HQ 4% at 3 mo to treat PIH
Trelles [112], 2010	R, MB	Group A: TC cream only Group B: CO_2 fractionated laser (high power, fixed pulsed width, low frequency) Group C: CO_2 fractionated laser + TC cream	48 wk	30	Significant decrease in MASI in group C compared with Groups A and B. Overall efficacy and satisfaction index was similar between groups at mo 1, but decreased through follow-up in Groups A and B	None	4 wk	NA	Use of sunscreen is unclear Recurrence occurred in all groups

Table 5 (continued)

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: Physician- and participant-assessed	Outcome(s) [objective]: Objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Other laser therapies									
Hong [113], 2012	R, MB, SF	One session of 1550 nm (erbium fiber laser) to hemiface vs. 15% TCA (Obagi Blue Peel) to the contralateral side	12 wk	18	MASI showed SS improvement at 4 wk. At 12 wk, all patients showed relapse, some worse than baseline MASI. Patient assessment showed 43% improvement on the laser treated side vs. 39% on the TCA side. At 12 wk, improvement decreased to 25% in both groups	None	4 wk	50% erythema and PIH, which decreased at 12 wk	All patients included had mild melasma at baseline. Use of sunscreen was not mentioned. Patient assessment was performed by visual analog scale
Hammami [114], 2015	R, MB, SF	TC cream (HQ 5% + dexamethasone 0.1% + retinoic acid 0.1%) qhs for 4 wk followed by Bromide Copper laser to the hemiface (wk 4, 6, 9, 12) vs. TC cream to the contralateral hemiface	24 wk	20	No SS difference in MASI by 6-mo follow-up. No SS difference between the two groups ($p = 0.33$)	Laser confocal microscopy (VivaScope) did not show a decrease in vascularization on melasma lesional skin	12 wk	No scarring, no PIH	Copper bromide laser was not effective at reducing the vascular component

Table 5 (continued)

First author	Study design	Treatment	Duration	N	Outcome(s) [subjective]: Physician- and participant-assessed	Outcome(s) [objective]: Objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Choi [115], 2017	R, PC, SF	One side: Picosecond (1064 and 595 nm), 5 weekly sessions + 2% HQ qd Contralateral side: 2% HQ qd	18 wk	39	mMASI showed decrease at wk 7 on the laser treated side vs. HQ alone. No SS difference between sides at week 10, 14 and 18.	Physician assessment performed by relative skin lightness (RL*I performed by colorimeter). Significant decrease in RL*I at 7, 10, 14, and 18 wk compared with the HQ-alone side	7 wk	5% mild dermatitis and mild pain	Despite improvement, patients still had severe melasma at 18 wk suggesting recurrence after cessation of laser treatment
Chalermchai [116], 2018	R, MB, PC, SF	One side: Fractional picosecond (1064 nm) laser (wk 0, 4, 8) + 4% HQ qd Contralateral side: 4% HQ alone qd	12 wk	30	Group 1 with 62% decrease in mMASI at 12 wk versus 55% in Group 2 (SS; $p=0.035$). No difference based on patient satisfaction scale (DLQI) at 4, 8, and 12 wk	Mexametry showed no SS difference between the treated and untreated side	8 wk	6.7% mild erythema, 6.7% mild skin desquamation, 3.3% mild burning sensation	Despite significant improvement at 8 wk on the treated group, at 12 wk mMASI was similar on both treated sides. Mean mMASI at baseline was 9.47, which represents patients with severe melasma

C controlled, *comp* comparative, *DLQI* Dermatology Life Quality Index, *F-IPL* fractionated IPL, *FLT* fractional laser therapy, *GA* glycolic acid, *H&E* hematoxylin and eosin, *HQ* hydroquinone, *IGA* Investigator's Global Assessment, *IPL* intense pulsed light, *MASI* Melasma Area and Severity Index, *MB* monoblinded, *MI* melanin index, *mMASI* modified MASI, *mo* months, *NA* not available, *NR* not reported, *PDL* pulsed dye laser, *PGA* Patient Global Assessment, *PhGA* Physician's Global Assessment, *PC* placebo-controlled, *PIH* post-inflammatory hyperpigmentation, *qd* once daily, *qhs* nightly, *QS-Nd:YAG* Q-switched neodymium-doped yttrium aluminum garnet, *R* randomized, *RL*I* relative skin lightness, *SF* split-face, *SPF* sun protection factor, *SS* statistically significant, *TC* triple combination cream: 4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide unless otherwise specified, *TCA* trichloroacetic acid, *TXA* tranexamic acid, *wk* weeks

Table 6 Studies evaluating systemic agents for the treatment of melasma

First author, year	Study design	Treatment	Duration	N	Outcome(s) [subjective]: physician- and participant-assessed	Outcome(s) [objective]: objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Oral tranexamic acid									
Zhu [121], 2001	PC, prospective	TXA oral 250 mg tid plus vitamins C and E vs. placebo (30 controls)	6–8 wk	158	Of the treatment group, 20% had > 95% improvement, 30% had > 60% improvement, and 33% had 20–60% improvement Improvement was SS superior to controls	None	NA	Mild GI upset	
Karn [122], 2012	R, C	250 mg TXA bid vs. HQ (unknown percentage) + sunscreen	12 wk	260	mMASI decreased from 11.08 ± 2.91 to 7.84 ± 2.44 in the treatment group (70% improvement) vs. 11.60 ± 3.40 to 9.26 ± 3.0 in the control group (29.3% improvement) 45.5% of the treatment group reported 'excellent' satisfaction vs. 8.5% in the control group	None	8 wk	Oligomenorrhea (14.7%), belching (9.2%), abdominal cramps (6.9%), palpitation (1 patient), urticarial rash with angioedema (1 patient)	Compared with improvement at 8 vs. 12 wk, the treatment group continued to show SS improvement from 8 to 12 wk, whereas the control group no longer showed significantly different improvement
Wu [123], 2012	Prospective, interventional	Oral TXA 250 mg bid	6 mo	74	After 6 mo of treatment, excellent results in 10.8% of patients; 54% with good results, 31.1% with fair results, and 4.1% with poor results. Total improvement rate of 95.9%	Monthly testing of PT, aPTT, and clotting parameters showed no significant changes over the course of oral TXA treatment	1 mo	5.4% with mild GI discomfort, 8.1% with hypomenorrhea; 'rare': rash, dizziness, alopecia, drowsiness, hyposexuality	9.5% recurrence after 6-mo follow-up Grading of results: Excellent: 90% reduction in size, vanishing of hyperpigmentation Good: 60% decrease in size or significant diminishment of hyperpigmentation Fair: size decrease 30% or visible diminishment of hyperpigmentation Poor: < 30% decrease in size or no visible diminishment of hyperpigmentation

Table 6 (continued)

First author, year	Study design	Treatment	Duration	N	Outcome(s) [subjective]: physician- and participant-assessed	Outcome(s) [objective]: objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Li [124], 2013	Prospective, open-label	Compounded oral TXA 250 mg tid	16 wk	32	On physician assessment, 75% of subjects showed marked improvement, and 25% showed moderate improvement. 100% of subjects were satisfied	85% of patients improved in 4 wk, 97% by 12 wk, and 100% in 16 wk. Evaluation was performed using the Skin Tone Color Scale	4 wk	Elevation of ALT (3%), GI upset (12.5%), changes in menstruation (6%), drowsiness (3%)	Enrolled subjects with mild to moderate melasma
Lajevardi [125], 2017	R, C, MB	TXA 250 mg tid + 4% HQ cream qhs vs. 4% HQ qhs	3 mo treatment + 3 mo follow-up	88	After 3 mo of therapy, the MASI reduced by 51% vs. 33% in the treatment vs. control groups ($p < 0.001$). The treatment group expressed moderate-to-complete satisfaction in 82.2% versus 34.9% in the control group ($p < 0.001$)	None	4 wk	Mild abdominal pain and spotting (1 patient each)	The relapse rate after 3 mo was 30% in the treatment group vs. 26% in the control group (not SS)
Padhi [126], 2015	Open-label, R, C	TXA 250 mg bid + TC cream (fluocinolone acetonide 0.01%, tretinoin 0.05%, and hydroquinone 25%) vs. TC alone	8 wk	40	88% reduction in MASI score at 8 wk in the TXA + TC group vs. 54.65% in the control group ($p < 0.05$)	None	4 wk	10% erythema, 10% burning, 10% hypopigmentation, 5% oligomenorrhea. The frequency of AEs was not SS from the control group (15% erythema, 10% burning, 0% hypopigmentation, 0% oligomenorrhea)	No recurrence after 6-mo follow-up

Table 6 (continued)

First author, year	Study design	Treatment	Duration	N	Outcome(s) [subjective]: physician- and participant-assessed	Outcome(s) [objective]: objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Tan [127], 2017	Retrospective analysis	TXA 250 mg bid + TC cream	3.7 ± 0.33 mo plus 6 mo follow-up	25	MASI score improved 69%	None	1.7 ± 0.3 mo	None reported	72% of patients relapsed within 2 mo of stopping oral TXA despite continuing TC
Sharma [128], 2017	Open-label, R, comp	TXA 250 mg bid vs. intradermal microinjections of TXA 4 mg/mL q4w. All subjects applied SPF19 sunscreen qd	12 wk	80	77.96 ± 9.39% reduction in MASI in the oral TXA group vs. 79 ± 9.64% reduction in the intradermal injection group (equally as effective)	None	4 wk	15.4% of oral TXA had hypomenorrhea. Two patients with epigastric discomfort 26% of the injection group had injection site pain and transient edema	Two (5%) patients in the oral group had relapse at 24 wk. No relapses were seen in the intradermal injection group
Colferai [129], 2018	R, DB, PC	TXA 250 mg bid vs. placebo	12 wk	37	80% in the treatment group reported melasma lightening vs. 58.82% in the placebo group	50% in the treatment group improved vs. 5.9% in the placebo group The treatment group improved in MASI, MelasQoL, and colorimetry measurements, but the placebo group improved in the MelasQoL only	NA	The treatment group had GI upset (33%), headache (14%), and altered menstruation (10%)	

Table 6 (continued)

First author, year	Study design	Treatment	Duration	N	Outcome(s) [subjective]: physician- and participant-assessed	Outcome(s) [objective]: objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Del Rosario [130], 2018	R, DB, PC	TXA 250 mg bid vs. placebo. All subjects applied sunscreen qd	3 mo treatment + 3 mo follow-up	39	After 3 mo, the treatment group had a 49% reduction in mMASI score vs. 18% in the placebo group After drug discontinuation, mMASI worsened in the treatment group, but remained 26% improved from study baseline	Reduction in MI was similar to the mMASI results	4 wk	GI upset (22.7%), menstrual changes (18.2%), headache (13.6%), myalgias (9.1%), somnolence (9.1%), arthralgias (4.5%), blurry vision (4.5%) Adverse effects were mild and transient. One subject withdrew due to mild myalgias	Studied Hispanic women with moderate to severe melasma After 3 mo of drug discontinuation, mMASI and MI worsened, but remained improved from baseline
Oral polypodium leucotomos extract									
Martin [135], 2012	R, DB, PC	Oral PLE vs. placebo bid + SPF45 sunscreen qd	12 wk	21	SS improvement in MASI score and MelasQoL for the treatment vs. placebo groups. Mean MASI score improved from 5.7 to 3.3. Plain and UV-lamp photographs revealed 43% of subjects vs. 17% in the placebo group had mild improvement, and 14% vs. 0% had marked improvement. In the treatment group, 38% reported no change and no patients reported worsening of melasma (vs. 67% and 17% in the placebo group)	None	NA	There was no difference in AEs between groups	Patients with epidermal melasma were included. The dose of PLE was not reported

Table 6 (continued)

First author, year	Study design	Treatment	Duration	N	Outcome(s) [subjective]: physician- and participant-assessed	Outcome(s) [objective]: objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Ahmed [136], 2013	R, DB, PC	Oral PLE 240 mg tid vs. placebo. All subjects applied SPF55 sunscreen qd	12 wk	33	No SS difference in MASI scores There was minimal change in MelasQoL scores	Both groups showed SS improvement in MI (28.8% in the PLE group vs. 13.8% in the placebo group) and MASI score, however there was no difference between groups	NA	No AEs reported	Hispanic women. There was only a 5.1-point difference in MI between groups. The improvement in MASI and MI may be attributed to daily sunblock application
Goh [137], 2018	R, DB, PC	Oral PLE 240 mg vs. placebo bid. Both groups were treated with 4% HQ cream qhs + SPF50 + sunscreen	12 wk	40	mMASI score improved 54.9% in the treatment group vs. 44.4% in the placebo group (SS) 31.3% of the PLE group had > 75% improvement in mMASI score vs. 6.3% in the placebo group ($p=0.070$) MelasQol improved in both groups, with a greater improvement seen in the treatment group There was no difference in investigator evaluation based on photographs	The erythema index was reduced in both groups There was no SS difference in MI between groups, however there was a 28.8% reduction in MI from baseline in the treatment group vs. 13.8% in the placebo group ($p=0.140$)	28 days. Trend toward improved mMASI vs. placebo at this time	Two subjects from the PLE group and one from the placebo group had mild pruritus and stinging with the use of HQ	The authors suggest that PLE may accelerate pigment clearance as the improvement over placebo was seen as early as 28 days

Table 6 (continued)

First author, year	Study design	Treatment	Duration	N	Outcome(s) [subjective]: physician- and participant-assessed	Outcome(s) [objective]: objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Other systemic agents									
Handog [138], 2018	R, DB, PC	Procyanidin (24 mg) + vitamin A (6 mg β-carotene), vitamin C (60 mg), vitamin E (15 IU) bid. All patients applied SPF24 sunscreen qd	8 wk	56	MASI score improved significantly in both groups, however was more significant in the treatment group. Patients in the treatment group stated that they were slightly improved (10%), moderately improved (60%), or obviously improved (30%) compared with the placebo group, who mostly noted no improvement/slight improvement	Mexametry demonstrated a SS decrease in average MI on bilateral malar cheeks after 8 wk of treatment	4 wk	No AEs reported	Filipino women
Teo [139], 2015	R, DB, PC	Crystal Tomato® dietary supplement (800 mg caplet) and L-cysteine (50 mg caplet). All subjects applied daily sunblock and reapplied every 2 h	84 days	44		There was no SS difference between the treatment and placebo groups based on mexametry and MASI scores. The Mexameter erythema score showed significant improvement in both groups, with a greater improvement in the treatment group at 56 days of treatment	NA	Two patients from the active arm reported burning/redness and pruritus. One patient from the placebo group reported skin tone darkening	

Table 6 (continued)

First author, year	Study design	Treatment	Duration	N	Outcome(s) [subjective]: physician- and participant-assessed	Outcome(s) [objective]: objective measurements of melasma	Time elapsed before clinical improvement	Adverse events	Comments
Hamadi [141], 2009	R, DB, PC	Group A: Topical melatonin 5% cream bid Group B: Topical melatonin 5% cream bid + SPF50 sunscreen qd Group C: Topical melatonin 5% cream bid + oral melatonin (3 mg qd) Group D: 4% HQ cream bid Control group: Placebo	120 days (90 days treatment + 30 days placebo)	46	Group D (HQ) had superior results compared with all other groups, and there was no SS difference between Groups B and C All groups had a SS reduction in MASI score after 90 days of treatment; however, after the 30-day follow-up, Group A (topical melatonin) had a non-significant reduction in MASI compared with baseline	Plasma MDA and GSH were also measured, showing a decrease in MDA and an increase in GSH in the groups treated with melatonin Decreased MASI generally correlated with decreased plasma MDA and increased plasma GSH, but was not SS in any cases	NA	No AEs reported	Topical melatonin cream had the least effect on the treatment groups The HQ group had the lowest rate of relapse

Manufacturer information: Crystal Tomato® (Gromark Consumers Enterprise Pte Ltd, Singapore)

AEs adverse events, *ALT* alanine aminotransferase, *APTT* activated partial thromboplastin time, *bid* twice daily, *C* controlled, *comp* comparative, *DB* double-blind, *GI* gastrointestinal, *GSH* glutathione, *HQ* hydroquinone, *MASI* Melasma Area and Severity Index, *MB* monoblinded, *MDA* malondialdehyde, *MelasQoL* Melasma Quality of Life Score, *MI* melanin index, *mMASI* modified MASI, *mo* months, *NA* not available, *PC* placebo-controlled, *PLE* polypodium leucotomos extract, *PT* prothrombin time, *qd* once daily, *qhs* nightly, *q4w* every 4 weeks, *R* randomized, *SPF* sun protection factor, *SS* statistically significant, *TC* triple combination cream: 4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide unless otherwise specified, *tid* three times daily, *TXA* tranexamic acid, *UV* ultraviolet, *wk* weeks

use of F-IPL in six weekly sessions, with conventional IPL in three biweekly sessions [94]. Results were slightly better in the F-IPL group, however this was not significant.

4.4.2 Q-Switched Neodynium-Doped Yttrium Aluminum Garnet (QS-Nd:YAG) Laser

Park et al. performed a study evaluating the effectiveness of the 1064 nm QS-Nd:YAG laser to the entire face + 30% GA peels to one side of the face [95]. A 38% and 33% decrease in mMASI and MI, respectively, was reported on the combination side versus 17% and 22% on the laser-only side. Lee et al. evaluated the effectiveness of QS-Nd:YAG laser combined with Jessner's solution [96]. Despite an initial superior response with combined therapy, there was no difference between groups at the end of the 22-week trial. Ustuner et al. performed a randomized, assessor-blinded, split-face study comparing the effectiveness of QS-Nd:YAG to the entire face + microneedling, with vitamin C to one side of the face [97]. MASI score was significantly lower on the combined side at 1 and 6 months.

Recently, low-fluence QS-Nd:YAG laser, also called laser toning, has been commonly used for the treatment of melasma. Kaminaka et al. showed a decrease in MI in lesional skin after 5 and 10 sessions of low-fluence QS-Nd:YAG [98]. A decrease in epidermal and dermal melanophages was also noted by histopathological assessment, as well as a decrease in the number of vessels and mast cells. Jeong et al. performed a randomized, assessor-blinded, split-face study in which half of the face was exposed to TCC for 8 weeks followed by low-fluence QS-Nd:YAG, and the other hemiface was exposed to laser first, then TCC (Triluma®; Galderma Laboratories, Fort Worth, TX, USA) [99]. Greater improvement was seen on the hemiface treated with TCC followed by laser, which also had a lower relapse rate. Wattanakrai et al. performed a randomized split-face study, showing that additional use of low-fluence QS-Nd:YAG laser was more effective than 2% HQ monotherapy (76% vs. 24% improvement) [100]. Fourteen percent had mottled hypopigmentation on the laser-treated side. Kar et al. performed a randomized study comparing low-fluence QS-Nd:YAG, 35–75% GA peels, and high-fluence QS-Nd:YAG [101]. Greater improvement was seen in the low-fluence QS-Nd:YAG group, followed by the GA peel group, and lastly the high-fluence QS-Nd:YAG group. Greater risk of mottled hypopigmentation was seen in the high-fluence laser group. Kim et al. failed to show any additional efficacy of adding five sessions of erbium-doped laser to low-fluence QS-Nd:YAG laser, although slightly higher improvement and lower recurrence was seen in the QS-Nd-YAG-only group [102]. The combination of oral TXA + low-fluence QS-Nd:YAG laser has shown to be more effective than laser alone [103].

Few comparative studies using different laser modalities have been reported. Jalaly et al. performed a split-face study using low-fluence QS-Nd:YAG laser versus low-power fractionated CO_2 laser to the contralateral side [104]. Despite an initial superior response on the CO_2-treated side, both groups had significant improvement overall. Vachiramon et al. showed significant improvement when additional IPL sessions were added to conventional low-fluence QS-Nd:YAG laser therapy to the entire face [105]. A 55% decrease in MASI was reported in the combination group, versus 37% in the laser-only side, which was also confirmed by spectrophotometer evaluation. Of note, adverse effects and recurrence were higher in the combination group. Vachiramon et al. later failed to show improvement with the addition of 30% GA peels to conventional low-fluence QS-Nd:YAG treatments [106].

4.4.3 Pulsed-Dye Laser

PDL targets the vascular component of melasma. Passeron et al. performed a randomized, single-blinded, split-face study comparing the use of TCC (HQ 4%, tretinoin 0.05%, fluocinolone acetonide 0.01%) once daily + PDL (three sessions, 3-week intervals) [107]. A decrease in MASI was reported on the combined side at weeks 13 and 21. Of note, subjects had continued improvement of melasma following the PDL treatments and fewer relapses over the next few months.

4.4.4 Fractional Laser Therapy

Fractional laser monotherapy has not shown significant efficacy in treating melasma, especially in dark-skin subjects due to the risk of hyperpigmentation and recurrence [108, 109]. Nouri et al. showed slightly higher efficacy of CO_2 laser + QS alexandrite (QSAL) laser compared with CO_2 alone [110]. This was later confirmed by Angsuwarangsee et al., who treated six females with CO_2 + QSAL versus QSAL alone. Only those in the combination group showed statistically significant improvement in MASI and MI [111]. Use of TCC + CO_2 laser has shown higher efficacy compared with either treatment alone [112].

4.4.5 Other Laser Therapies

Trials utilizing other laser therapies are reviewed in Table 5 [113–116].

4.5 Systemic Agents

In recent years, systemic therapy has emerged as a potential treatment for melasma (Table 6). Proposed oral therapies include TXA, plant-based medications such as polypodium

leucotomos extract (PLE), procyanidin, carotenoids, and melatonin. Oral glutathione has also been studied as a skin-lightening agent, however our literature search did not find any randomized controlled trials specific to melasma with this agent.

4.5.1 Oral TXA

TXA is an antifibrinolytic agent directed at melanocyte–keratinocyte interaction and angiogenesis. It prevents the conversion of plasminogen to its active form, plasmin, by inhibition of the plasminogen activator enzyme. Studies thus far have indicated that oral TXA is most effective in subjects with melasma that is refractory to standard topical therapy.

The administration of TXA ranges from 500 to 1500 mg daily, with the most common dose being 250 mg twice daily. The most common adverse effects include gastrointestinal upset, oligomenorrhea, headache, and myalgias, occurring in up to 37% of subjects. TXA also carries the risk of deep venous thrombosis due to its antifibrinolytic properties, thus patients should be carefully screened for risk factors of thromboembolic disease. There has only been one case of deep venous thrombosis reported, whom, it was later discovered, had protein S deficiency that was not disclosed to investigators [117].

The earliest studies of oral TXA, treated subjects with 0.75–1.5 g daily for 2–4 months, showing improvement in 80–100% of subjects, but there was often a relapse after cessation of therapy [118–120]. Recent studies have supported these initial findings (Table 6) [121–133].

Karn et al. showed a 70% improvement in mMASI in subjects treated with 250 mg of TXA twice daily, compared with 30% in the control group receiving HQ and sunscreen only [122]. Similar findings were reported by Wu et al. [123]. Li et al. demonstrated similar findings with TXA 250 mg three times daily (compounded; Dai-ichi Sankyo Healthcare, Tokyo, Japan), reporting 85% of subjects improving by week 4 and 100% improving by week 16 [124]. Lajevardi et al. compared oral TXA 250 mg three times daily plus 4% HQ with 4% HQ alone, with superior results in the combination group, although the relapse rates in both groups was as high as 30% [125]. Padhi and Pradhan et al. performed a randomized study using TXA 250 mg twice daily + TCC versus TCC alone [126]. The combined therapy group had an 88% improvement versus 55% with TCC alone, with improvement seen as early as 4 weeks. Later, Tan et al. supported these findings, showing a 69% decrease in MASI using TXA 250 mg twice daily + TCC, however this was a retrospective analysis [127]. Lee et al. showed an improvement of 90% using the same dose of TXA [117]. Lastly, Sharma, et al. compared oral TXA with intradermal injections of TXA, with both treatments equally effective, averaging 78% improvement [128]. Notably, there were differential adverse effects of GI upset and hypomenorrhea in those taking oral TXA and edema/erythema in the injection group.

There have also been recent studies comparing oral TXA with placebo in efforts to more carefully define the efficacy of this medication. Colferai et al. compared TXA 250 mg twice daily with placebo, similar to another study by Del Rosario et al. [129, 130]. A mean improvement of 49% in MASI was reported compared with 18% in the placebo group in the latter study.

Histological and immunohistochemical analysis by Nagaraju et al. and Na et al. have supported the above findings, showing a reduction in MI, mast cells, epidermal pigmentation, and vessel number, as well as a decrease in melanin-A staining and melanin incontinence in subjects treated with oral TXA [131, 132].

A recent meta-analysis by Kim et al. compared vehicles of TXA in the treatment of melasma. Oral TXA demonstrated superior efficacy, followed by intradermal injection and topical cream [133]. When TXA was added as an adjuvant to routine treatment with HQ, TCC, IPL, or IPL plus QS-Nd:YAG laser, MASI reduction was greater in the TXA adjuvant group.

4.5.2 Oral Polypodium Leucotomos Extract

PLE is an antioxidant derived from the Calaguala fern that acts as a systemic photoprotective agent [134]. Controlled, randomized trials have failed to show significant benefit (Table 6) [135–137].

4.5.3 Other Systemic Agents

Other oral systemic agents have been studied, showing mild to moderate improvement. In a randomized, controlled trial by Handog et al., subjects were treated with an oral capsule containing 24 mg of procyanidin, 6 mg of β-carotene (vitamin A), 60 mg ascorbic acid (vitamin C), and 15 IU of D-α-tocopherol acetate (vitamin E) twice daily + sunscreen [138]. There was improvement in MASI in both groups, with slightly higher improvement in MASI and Mexameter in the treatment group. Teo et al. failed to show any difference in a randomized, double-blind, placebo-controlled trial of oral carotenoids [139]. Hamadi et al. conducted a trial using topical melatonin, oral melatonin, or HQ cream [140]. All groups had a significant reduction in MASI by 90 days, however HQ was superior to topical and/oral melatonin.

5 Discussion

Although there have been many studies in subjects with melasma, the majority have used subjective outcome measures; only a small number of studies included objective outcomes.

The most common outcome measures were based on clinical examination, photographic evaluation, and/or Wood's lamp examination. The most common scoring system used was the MASI score, followed by mMASI. The latter includes the analysis of the percentage of area affected by melasma in four different areas of the face, and darkness. Another scoring system utilized was the melasma severity scale, however this is a non-validated outcome measure. Comparison across studies was difficult as many articles included a variation on non-specific ratings, such as 'poor', 'excellent', or 'moderate'. Objective outcomes were used in some studies, including reflectance spectrophotometry. A few studies also included histopathological analysis of melanin content and blood vessels in the dermis. Several split-face studies used a mMASI score that included only the analysis of the malar surface involved instead of the entire face, as used in traditional methods. Better studies using validated and objective outcome measures, large sample size, and longer follow-up are needed.

5.1 Recommendations

Topical HQ continues to be the most extensively studied treatment for melasma. Despite theoretical risk of adverse effects, multiples studies have demonstrated its excellent safety profile. TCC continues to be the most effective treatment for melasma, and safety has been established in studies of daily use up to 12 months. Furthermore, a tapering regimen of TCC seems to be slightly less effective than a twice-weekly protocol for maintenance therapy of TCC, although a twice-weekly regimen may still result in relapse. Relapse rates seem to be most closely tied to severity of melasma at baseline. Multiple variations of the original formulation of TCC have been made to decrease adverse effects, particularly the tretinoin component, which is the most irritating component. The use of sunscreen with SPF $\geq$ 30 is mandatory in the management of melasma, and, recently, the use of iron oxide-containing sunscreen to provide additional protection from visible light has been advocated [141].

Other depigmenting agents, such as topical TXA, have not shown higher efficacy when compared with HQ. However, microneedling using TXA has shown promising initial results. Furthermore, microneedling may be a valuable tool for assisting drug delivery to the skin in lieu of laser therapy or chemical peels, which may induce PIH [142]. AA was found to be more effective than 2% HQ, but equivalent to 4% HQ cream, although it garnered more adverse effects. Vitamin C has been shown to decrease skin pigmentation and could be used as an alternative treatment when HQ is not an option. Topical tretinoin 0.05–0.1% has shown mixed results, with most studies showing efficacy; however, long-term use is necessary for clinical improvement.

The chemical peels reviewed did not show consistent results. GA peels and SA peels were not found to be more effective than HQ. TCA peels combined with Jessner's solution could be a promising alternative in recalcitrant melasma, but larger, controlled studies are needed. A major problem with chemical peels is the risk of erythema, burning, and PIH. Therefore, use of peels should only be considered as a second-line treatment and they must be used cautiously in dark-skinned subjects.

Laser- and light-based devices have yielded mixed results. IPL has been shown to improve melasma, however concomitant use of HQ or TCC is recommended to decrease the risk of rebound. QS-Nd:YAG has not been found to be more effective than HQ, and risk of mottled hypopigmentation is present. Low-fluence QS-Nd:YAG has shown higher efficacy than 2% HQ, but, again, carries the risk of mottled hypopigmentation. PDL laser is the only treatment that has shown decrease in the relapse of melasma, mainly targeting the vascular component of melasma. Fractional photothermolysis has a high risk of PIH and melasma recurrence. Laser- and light-based devices should be considered as a third-line treatment for melasma, and should be used judiciously in dark-skinned subjects.

Oral TXA has been shown to be a safe and effective treatment for recalcitrant moderate to severe melasma.

5.2 Limitations

Even with multiple treatment modalities, there is no topical, oral, or light-based monotherapy treatment that guarantees improvement of melasma. The lack of well-designed, placebo-controlled studies makes it difficult to compare treatments and assess statistical significance. Furthermore, this review did not include the myriad of studies reported as case series, reports, and retrospective reviews. Future studies should adhere to validated subjective and objective outcome measures so that comparison across studies can be made. Subjective validated outcome measures include MASI and mMASI scores. Objective assessment can be made by reflectance spectrophotometer, colorimeter, and/or skin biopsies from lesional and non-lesional skin. Quality-of-life measures should also be assessed using validated measures such as the MelasQoL questionnaire.

6 Conclusions

Melasma is an acquired chronic condition associated with negative social and psychological effects. Despite multiple treatment modalities being available, topical HQ alone or associated with a retinoid and a corticosteroid is the most studied agent and continues to be the most effective treatment modality. Importantly, sunscreens are essential in the

treatment of melasma. Recently, the use of oral TXA has been reported to be a useful adjuvant treatment in subjects with moderate to severe or recalcitrant melasma, and is associated with few adverse effects. Chemical peels and laser- and light-based therapies have mixed results and physicians should be aware of the risk of adverse effects, mainly in dark-skinned subjects. A broader understanding of melasma through further research will potentially give us new and improved therapies in the future.

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