Review Article

Topical and Systemic Therapies in Melasma: A Systematic Review

Abstract

Introduction: Melasma is an acquired disorder, which presents with well-demarcated, brown-colored hyperpigmented macules, commonly involving the sun-exposed areas such as the face. It is a chronic and distressing condition, affecting the patients' quality of life, and has been conventionally treated with "first-line" agents including hydroquinone (HQ) alone or as a part of a triple combination cream (TCC), while "second-line" options include chemical peels, and third line options include laser therapy. **Materials and Methods:** A systematic search was performed for all topical and systemic treatments for melasma up till May 4, 2021, using the PubMed and EMBASE databases, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol. The search terms "melasma" and "treatment" were used to search for the relevant articles on both these databases, and a total of 4020 articles were identified. After removing the duplicate entries and screening the titles, abstracts, and full-text articles, we identified 174 randomized controlled trials (RCTs) or controlled clinical trials. **Results:** Based on our review, HQ, TCCs, sunscreens, kojic acid (KA), and azelaic acid receive grade A recommendation. Further large-scale studies are required to clearly establish the efficacy of topical vitamin C, resorcinol, and topical tranexamic acid (TXA).Several newer topical agents may play a role only as an add-on or second-line drugs or as maintenance therapy. Oral TXA has a strong recommendation, provided there are no contraindications. Procyanidins, Polypodium leucotomos (PL), and even synbiotics may be taken as adjuncts. **Discussion:** Several newer topical and systemic agents with multimodal mechanisms of action have now become available, and the balance seems to be tipping in favor of these innovative modalities. However, it is worth mentioning that the choice of agent should be individualized and subject to availability in a particular country.

Keywords: *Melasma, review, systemic, topical, treatment*

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Introduction

Melasma is an acquired disorder which presents with symmetrical hyperpigmentation, commonly involving the face. Conventionally, melasma has been treated with first-line agents including hydroquinone (HQ) alone or as part of a triple combination cream (TCC), while second-line options include oral drugs and chemical peels, and third-line options include laser therapy.[1-3] Several newer topical and systemic agents with multimodal mechanisms of action have now become available, and the balance seems to be tipping in favor of these innovative modalities.[4]

We performed this review in an attempt to study the safety and efficacy profile of the presently available topical and systemic therapeutic agents for melasma and provide clinical recommendations based on the current evidence to guide the treatment protocol for melasma.

Materials and Methods

We performed a systematic search for topical and systemic treatments for melasma on May 4, 2021, using the PubMed and EMBASE databases, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol. The search terms "melasma" and "treatment" were used to search both these databases [Figure 1]. We included studies with a sample size of ten or more, had a controlled arm, and had utilized clinically measurable parameters (melasma area

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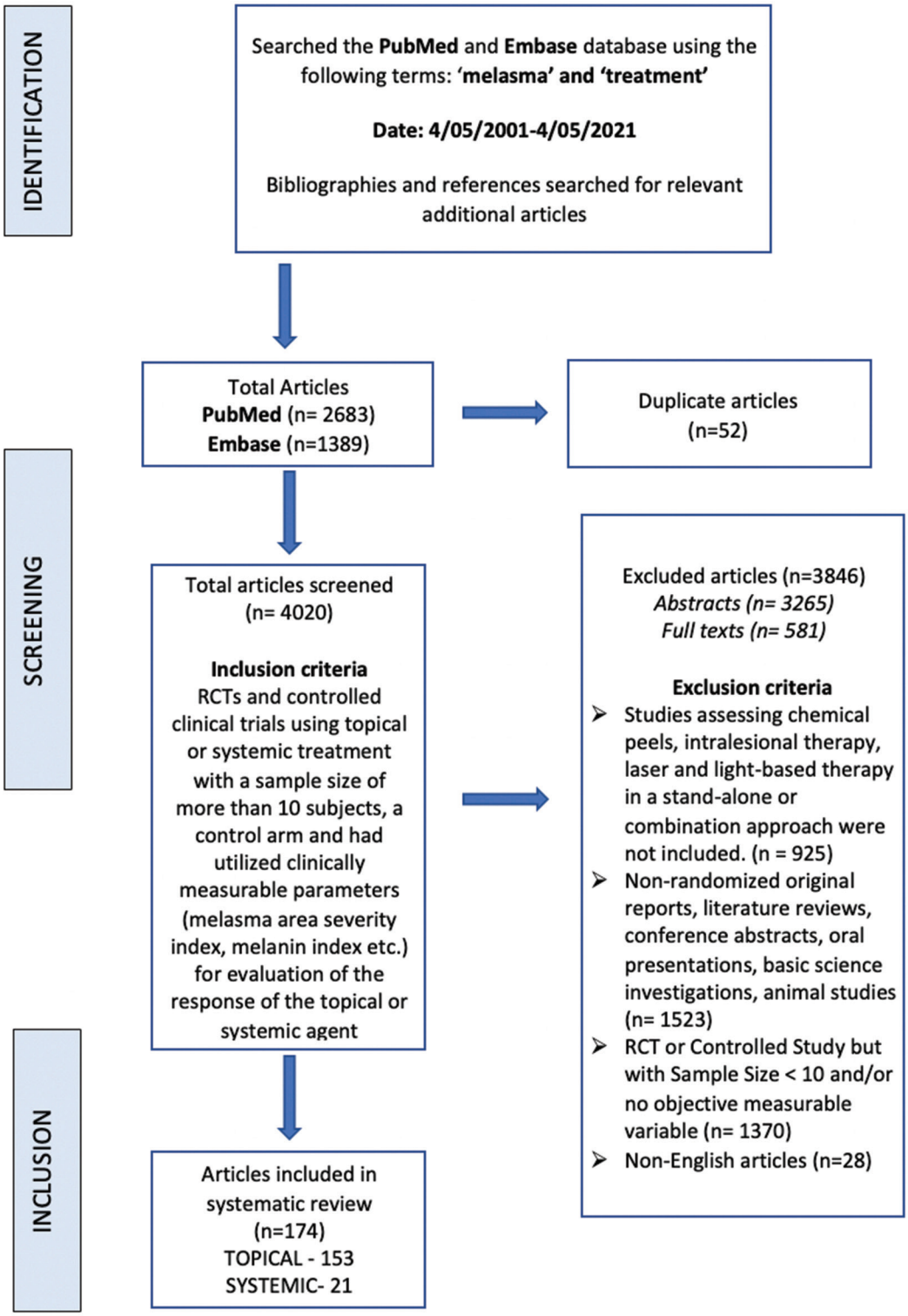

Figure 1: We performed a systematic search for novel and currently used topical and systemic treatments for melasma on May 4, 2021, using the PubMed and EMBASE databases, according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) protocol. The search terms "melasma" and "treatment" were used to search for the relevant articles on both these databases

severity index (MASI), modified MASI, Patient Global Assessment (PGA), erythema index (EI), and melanin index (MI)) for evaluation of the response. Only articles published within the last 20 years (since May 4, 2001) were included in the study.

In phase 1, two reviewers independently read the titles and abstracts of all identified electronic database citations. Any studies that did not fulfill the inclusion criteria were discarded. In phase 2, the same selection criteria were applied to the full articles to confirm their eligibility. Seven

reviewers participated independently in phase 2, and any disagreements were resolved by consensus. If it was not possible to reach consensus, the coordinator made the final decision and the final selection was based on the full text of the publication and subsequent assessment.

The references and bibliographies of the included studies and literature reviews were checked to confirm that all relevant articles were included in the systematic search. Grading of recommendation was carried out as per Oxford Centre for Evidence-Based Medicine (OCEBM)–level of evidence (LOE) (March 2009).

Results

We identified a total of 4020 articles from the PubMed and EMBASE databases, using the search terms mentioned above. After removing the duplicate entries and screening the titles, abstracts, and full-text articles, we identified 174 randomized controlled trials (RCTs) or controlled clinical trials.

A wide variation in patient inclusion was observed in the studies evaluated, in terms of severity of melasma, type of melasma, skin phototypes, duration of follow-up, and recurrence rates. Furthermore, heterogeneity was noted regarding the analysis of therapeutic outcomes according to phototype, melasma subtype, or the usage of previous melasma treatments. Outcome measures utilized by various studies included different scoring systems: MASI, mMASI, PGA, MI, and EI. A summary of the study design, treatment groups, primary and secondary outcomes, results, and side effects of the topical and systemic agents has been outlined in supplementary Tables 1 and 2, respectively.

Discussion

Sunscreen

A broad-spectrum sunscreen with a sun protection factor (SPF) of at least 30, which covers ultraviolet A (UVA) (minimum protection grade of UVA [PA]+++), UVB, and visible light (VL)—strength of recommendation A, LOE 1.

In multiple trials, sunscreens have been found to be a promising modality of therapy in melasma. It should be remembered that UV and VL both should be targeted to provide wholesome protection. In a double-blind randomized trial, UV-VL sunscreen was found to enhance the depigmenting efficacy of HQ compared with UV-only sunscreen in the treatment of melasma. Developing more effective filters against the wavelengths of VL could provide even better protection in the future.[5,6]

Triple combination

Triple combination of 4% HQ + 0.05% retinoic acid + 0.01% fluocinolone acetonide cream—strength of recommendation A, LOE 1.

Triple combination creams (TCC) remain the gold standard therapy for melasma and is more effective than dual combination therapy and HQ or kojic acid (KA) alone.[7-16] Improvement in pigmentation reaches a nadir at around 6 weeks, necessitating the need for an effective maintenance therapy.[8] A twice-weekly maintenance regimen has been found to be comparable or more effective in postponing relapse in severe melasma as compared to the tapering regimen.[9,10]

The long-term use of TCC as maintenance therapy is not recommended (strength of recommendation D), and if used as maintenance therapy, it is given twice weekly, very carefully up to 6 months to 1 year (strength of recommendation A) beyond which there is a risk of atrophy, telangiectasias, and other cutaneous side effects with daily usage.

Topical corticosteroids as monotherapy for melasma are usually not preferred for their atrophogenic potential and other adverse effects, although fluticasone is less atrophogenic than others.

Multiple RCTs have been conducted comparing TCCs with placebo, monotherapy with HQ, formulations consisting of 4% HQ and 0.02% triamcinolone acetonide in hydrophilic cream, tretinoin plus HQ (RA + HQ), tretinoin plus fluocinolone acetonide (RA + FA), and HQ plus fluocinolone acetonide (HQ + FA), and the combination containing 2% KA plus octinoxate and allantoin. Treatment with TCC is found to be superior to the rest.[11-16]

TCC in combination with chemical peels yields better results than either therapy alone.[17-20]

TCC is found to be comparable in efficacy to intralesional tranexamic acid (TXA) and intralesional triamcinolone acetonide[21-,23] TCC in combination with laser therapy yields better results than either therapy alone.[24-32]

HQ cream

HQ 4% cream—strength of recommendation B, LOE 1.

Multiple RCTs have been conducted, comparing HQ creams (of different percentages) with several topical agents, and variable results have been reported.[33-44] HQ is one of the most effective therapies for melasma, when compared with other agents. However, TCCs and 3% *Rumex occidentalis* (RO) cream score higher when a head-to-head comparison is performed.[12-14,34]

It is worth mentioning that liposomal HQ cream was not found to be better than the conventional HQ cream, in terms of effectiveness in an Iranian RCT published in 2019.[41]

An Asian study evaluated the role of Q-switched Nd: YAG laser as an add-on therapy, apart from HQ 2% cream, and the combination group was found to show significantly better results. Another trial reported that patients receiving Er: YAG (erbium: yttrium–aluminum–garnet) laser plus HQ 4% cream showed a higher reduction in MASI score,

in comparison with the group who received HQ 4% cream alone. A French study reported that 90% of the subjects who received the combination products (vs 79% in HQ-only group) had better results.[45]

The results of other comparative trials of HQ with miscellaneous molecules have been detailed in the supplementary file 1.[46-59]

KA

KA 2% cream—strength of recommendation A, LOE 2.

KA is one of the nonsteroidal and non-HQ alternatives for the treatment of melasma. KA 0.75% cream was inferior to HQ 4% cream and KA 2% cream was inferior to modified Kligman's formula (MKF), and the combination of KA 1% cream and HQ 2% cream was superior to either formulation.[16,60,61] Combination of 4% KA with 5% methimazole did not yield better results.[62] Therefore, the clinical improvement in melasma patients is more with MKF and topical HQ 4% compared with KA, and the combination of KA and HQ provides superior improvement compared to KA alone.

Azelaic acid

Azelaic acid 20% cream—strength of recommendation A, LOE 1.

The available evidence suggests that azelaic acid is a good depigmenting agent in melasma as a stand-alone therapy. Its efficacy is comparable to HQ 4% and TXA 10%. However, its efficacy is improved when used in combination with a Q-switched Nd: YAG laser and sequential glycolic acid peels.[58,63-69]

A recent study by Akl *et al.* has demonstrated the superior efficacy of liposomal 20% azelaic acid cream, compared with HQ 4% cream, when used as an adjuvant along with oral TXA to treat melasma.[57] Another interesting pilot study has demonstrated the effectiveness and safety of a novel combination containing tazarotene 0.075%, azelaic acid 20%, tacrolimus 0.1%, and (microfine) zinc oxide 10% in treating moderate-to-severe melasma (once daily application for 20 weeks).[70]

Arbutin

Arbutin cream—strength of recommendation D, LOE 2.

In a double-blind RCT, Morag *et al.* compared 2.51% arbutin with a placebo in 50 melasma patients of Polish origin. Clinical improvement was observed in 22 melasma patients, representing 75.86% of the study group.[71] Another randomized, open-label study compared the skin lightening effect of arbutin 1% gel, ellagic acid 1% gel, and ellagic acid plus plant extracts (1% gel) in mixed melasma, twice daily application for 6 months. They found arbutin gel to be more effective, which reduced the MI to 71% of baseline, compared with 79% and 76% with ellagic acid and ellagic acid–plant extract combinations, respectively. The only limitation of this study was the absence of a control group.[72] Additionally, several studies have highlighted the skin- depigmenting property of arbutin, when used in combination with other similar topical products such as nicotinamide, bisabolol, retinaldehyde, vitamin C, and TXA.[73] Besides, 7% arbutin cream has also demonstrated efficacy when used in combination with a Q-switched Nd-YAG laser to reduce the severity of melasma.[74]

Retinoids

Tretinoin 0.05% or 0.025% cream—strength of recommendation B, LOE 1.

As per the literature review, topical retinoids are better than placebo in a reduction in MASI score in melasma patients. Topical adapalene is better tolerated than topical retinoic acid. There is no advantage of combining microneedling (MN) with topical retinoids to treat melasma. HQ is a better priming agent for trichloroacetic acid (TCA) peel compared with topical tretinoin.[75-78]

Vitamin C

Insufficient evidence to recommend it as monotherapy or as adjuvant therapy.

Vitamin C is one of the novel therapeutic options for the management of melasma. Iontophoresis with vitamin C has been found to be superior to mineral water iontophoresis.[79] Besides, a combination of 1064 nm Q-switched Nd: YAG laser toning along with topical vitamin C, TXA, and glutathione has been shown to deliver better results when compared to laser toning alone.[80] In another study by Menon *et al*. which compared MN with TXA and MN with 20% vitamin C solution on either side of the face, improvement in MASI was mild with vitamin C and moderate with TXA.[81] Currently, there is insufficient evidence to recommend it as monotherapy or as adjuvant therapy.

Cysteamine (CA)

5% CA cream—strength of recommendation B, LOE 2.

5% CA cream has been compared with placebo cream applied daily, in two well-designed double-blind RCTs, among 50 and 40 patients of melasma over 4 months with a significant reduction in MASI scores reported in both the studies as compared with placebo.[82,83] CA cream has also been compared with 4% HQ cream, placebo cream, MKF, and TXA mesotherapy. It is inferior to HQ, but superior to a placebo preparation.[82-85] In a double-blind RCT, Karrabi *et al.* compared CA cream with MKF, and CA treatment was able to decrease the mMASI score to a greater degree.[80] Reduction in MASI was also found comparable to TXA mesotherapy with less complications observed with the CA group.[86] CA cream with a good efficacy and safety profile may be considered an alternative treatment option for melasma.

Resorcinol

0.1% liposome-encapsulated rucinol and 0.3% rucinol cream—LOE 2.

Resorcinol 0.3% serum is superior to vehicle, as concluded in a double-blind, randomized, vehicle-controlled split-face comparative trial (*LOE 2*).[87] In another double-blind split-face RCT, 4-n-butylresorcinol (4-n-BLR) 0.1% cream was better than vehicle.[88] Similar results have been documented when a preparation of liposome-encapsulated 4-n-BLR 0.1% cream was compared with vehicle.[89]

Tranexamic acid

Efficacious alternative to HQ products, with comparable results. LOE 2

TXA has been widely studied, in the management of melasma. Formulations such as 6.5% TXA and 5% TXA have been found to be superior to vehicle alone and comparable in efficacy to HQ.[90] TXA 5% cream has been found to deliver better results than HQ cream (both 2% and 4%).[91-93] However, in a split-face double-blind study, 5% liposomal TXA had similar efficacy in reducing patient score compared with 4% HQ.[88] TXA has also been compared with other agents besides HQ.[94-96] In a split-face double-blind study of twice daily 3% TXA vs 3% HQ and 0.01% dexamethasone, both treatments significantly reduced pigmentation.[94] In an interventional comparative study, a combination of oral and topical 3% TXA showed significantly better results than oral TXA with 20% azelaic acid for the treatment of melasma.[97] TXA can also be given as microinjections (MI) and with MN. In an open-label comparative study, 4 mg/ml TA with MN monthly showed more improvement in MASI score in comparison with 4 mg/ml TA MI monthly at end of 3-month follow-up.[98] Several other studies have compared TA MI with conventional melasma treatments with variable efficacy with injection-related side effects being a limiting factor.[99-103] MN with TXA has not shown promising results in most of the studies.[104-108] A combination of TXA with lasers has shown better results than lasers alone in treating melasma. No serious adverse events were reported.[109-113] Current evidence suggests that 5% TXA may be an efficacious alternative to HQ products, with comparable results, in patients without predispositions to thrombotic events.

Miscellaneous topical agents

Insufficient evidence to recommend it as monotherapy. May be used in combination therapy or as maintenance agent.

A variety of miscellaneous topical agents have been used either singly, or in conjunction with other established topical therapeutic options such as sunscreen, 4% HQ cream, and 20% TCA peel. Among the newer agents, 3% RO cream, undecylenoyl phenylalanine (UP) 2% cream, 30% metformin lotion, cream containing 0.05% tomato lycopene, and 3.45% wheat bran extract, 2% lincomycin +2% linoleic acid, 5% topical magnesium ascorbyl phosphate cream, 5% lignin peroxidase, *Petroselinum crispum* solution, 4% diacetyl boldine (DAB) serum, topical olive extract, 4% liquiritin cream, 10% zinc sulfate solution, 1% flutamide, and 0.2% thiamidol cream have high-to-moderate efficacy (grades A-B) and seem to be an efficacious alternative to HQ products, with comparable results. Topical epidermal growth factor (EGF) serum, topical mometasone fractional Er: YAG laser, 5% picolinamide cream, and 5% methimazole cream have low-to-very low or insufficient evidence (grades C-D).[34,62,114-125]

The details of these agents are summarized in the supplementary Table 2. In a study evaluating dioic acid (DA), which interferes with melanosome transfer, it was found to be as efficient and safe as 2% HQ; however, further large-scale-controlled, multicenter studies are required to support these results.[125] A novel topical hypopigmenting product containing ethyl linoleate, thioctic acid, octadecenedioic acid, lactic acid, and ethylhexyl methoxycinnamate was observed to have a significant skin lightening effect as compared to the control group.[126]

10% solution of zinc sulfate when compared to 4% HQ solution was not found to be as effective as the latter, although the frequency of irritation was significantly higher with HQ.[120]

Magnesium-L-ascorbyl-2-phosphate (MAP) is a stable derivative of ascorbic acid, known to inhibit melanin synthesis. Murtaza *et al.* reported that the combination of TCA peel and 5% topical MAP cream was significantly more effective than TCA peel alone.[118]

Hormonal influence is shown to exist in the pathogenesis of melasma, and flutamide, an antiandrogenic agent as a 1% topical cream was found to be as effective as 4% topical HQ with a better MASI improvement and higher patient satisfaction with the former.[127]

DAB stabilizes tyrosinase in its inactive form, while TGF-b1 biomimetic oligopeptide-68 inhibits tyrosinase activity. A combination of DAB serum at night and DAB/TGF-b1 biomimetic oligopeptide-68/sunscreen cream in the morning and at noon was observed to be as efficacious and safe for facial melasma.[128]

Mulberry is a novel whitening agent with antioxidant properties, and the efficacy of 75% mulberry extract oil (MEO) was assessed by Alvin *et al.* who reported a superior reduction in MASI, mexameter reading, and melasma quality of life score (MELASQoL) with MEO as compared to placebo with fewer adverse effects.[129] Individual studies have evaluated the efficacy of novel agents such as trifecting night cream, combination cream containing KA, phytic acid, and butyl methoxydibenzoylmethane, and trans-4-(aminomethyl) cyclohexanecarboxylic acid/

potassium azeloyl diglycinate/niacinamide have shown superior results, but further large-scale studies are required to establish their efficacy.[129-132]

Recommendation for topical agents

Topical agents are recommended as first-line therapy for melasma.

- Start with fixed TCC (4% HQ + 0.05% RA + 0.01% FA) cream—daily, once at night application for a maximum period of 8 weeks is recommended (grade A recommendation).
- HQ alone (2-4%) may be used as monotherapy (more effective than KA, 20% azelaic acid), and it can be continued for 3 months (up to 1 year).
- Maintain with any of the following topicals:
  - KA 2% cream, azelaic acid 20% cream, arbutin cream, ascorbic acid, or newer agents.
  - Fixed TCC: twice weekly for up to 6 months (or 1 year) (grade of recommendation A).

Systemic Agents

TXA

Oral TXA 500–750 mg/day in a divided dose, for a maximum period of 6 months (strength of recommendation A, LOE 2–4).

The efficacy and safety of oral TXA for melasma were first recognized by Nijor in 1979.[133] In general, the sixteen RCTs included in this review had an LOE of 1b based on Individual RCT (with narrow confidence intervals).[134] Subjects were mostly females with skin phototypes between II and VI. TXA was given at a dosage of 250 mg twice a day at a varying duration of 8–20 weeks. Only one study used 250 mg once a day[135] and another used a TXA-based medication at a higher dose of 750 mg/day.[136]

The intervention arm either used oral TXA alone[137-141] or in combination with sunscreen,[133,135,142-148] triple combination lightening cream,[142,149] HQ cream,[133,144] or QS Nd: YAG laser.[136] Supplementary Table 1 summarizes the interesting results from the different studies as the comparator arms were varied. Early onset of action was seen in 4th week in different studies.[142,149]

Adverse reactions were seen, albeit not sufficiently serious for the participants to discontinue the trial. Effects on the gastrointestinal system like nausea, vomiting, and diarrhea (5%–19%) were the most commonly encountered side effect.[133,135,137-143,145,148] Oligomenorrhea and hypomenorrhea (0.3%–14.7%) were experienced by some subjects.[133,135,138-140,142,144,145] No thrombotic event was reported. Overall, no serious side effects were noted among the subjects in the studies conducted by Shin, Del Rosario, and Padhi.[136,146,149]

Oral TXA leads to a mild-to-moderate improvement in melasma when used at a dose of 500–750 mg/day in a divided dose, for a maximum period of 6 months (strength of recommendation A). Current evidence suggests that oral TXA may be used alone or as an adjuvant to conventional topical drugs or in cases recalcitrant to conventional topical therapy.

Procyanidin (Pinus pinaster)

Insufficient evidence to recommend it as monotherapy. May be used in combination therapy or as maintenance agents.

Saliou *et al.* confirmed that procyanidin administered at a dose of 1.10 mg/kg for 4–8 weeks significantly prevented UV radiation-induced erythema in humans.[150]

The extract of French maritime pine bark (*Pinus pinaster*) contains flavonoids such as procyanidin. Kohama *et al.* showed that procyanidin possesses antioxidant and anti-inflammatory actions.[151,152] Procyanidin's capacity to decrease melasma pigmentation has been documented in multiple studies. The studies conducted by Handog *et al.*[153] and Lima *et al*.[154] are included in this review.

Polypodium leucotomos (PL)

Insufficient evidence to recommend it as monotherapy.

PL is a tropical species of fern that possesses antioxidant and photoprotective properties, apart from its antimutagenic and immunoregulatory properties.[155]

Previously published studies by Martin *et al.* and Ahmed *et al.* had conflicting results, and the number of subjects was low.[156,157] In the study by Goh *et al.*, no significant differences were observed between the two groups.[158]

Synbiotics

Insufficient evidence to recommend it as monotherapy.

Synbiotics are health products defined as a mixture of probiotics and prebiotics intended to increase the survival and activity of the beneficial microorganisms in the digestive system to as high as sevenfold.[159] Probiotics may help improve skin disorders, possibly including melasma, because of their anti-inflammatory, antioxidative, anti-tyrosinase, and ultraviolet protection capacities. The evaluation of synbiotic supplementation in the treatment of melasma was conducted by Piyavantin *et al.* in a 12-week RCT, wherein the mMASI score, MI, and EI between the two groups were significantly different ($P \leq 0.001$), in favor of the synbiotic treatment group. No untoward reactions were noted [Supplementary Table 2].[160]

Finasteride

Insufficient evidence to recommend it as monotherapy.

Finasteride is a synthetic 4-azasteroid compound whose antiandrogenic effect stems from its capacity to inhibit 5-alpha reductase, which is accountable for the conversion of testosterone to dihydrotestosterone (DHT).

In the RCT by Rassai and Mehrjui, it is interesting to note that among the patients included in the study,

Table 1: Strength of recommendation and level of evidence

Drug/therapy	Strength of recommendation/level of evidence (LOE)
A broad-spectrum sunscreen with a sun protection factor (SPF) of at least 30, which covers ultraviolet A (UVA) (minimum protection grade of UVA [PA]+++), UVB, and visible light	Strength of recommendation A, LOE 1
Triple combination of 4% HQ+0.05% retinoic acid+0.01% fluocinolone acetonide cream	Strength of recommendation A, LOE 1
Hydroquinone (HQ) 4% cream	Strength of recommendation B, LOE 1
Kojic acid 2% cream	Strength of recommendation A, LOE 2
Azelaic acid 20% cream	Strength of recommendation A, LOE 1
Tretinoin 0.05% or 0.025% cream	Strength of recommendation B, LOE 1
Arbutin cream	Strength of recommendation D, LOE 2
Vitamin C (ascorbic acid)	Insufficient evidence to recommend it as monotherapy or as adjuvant therapy
5% cysteamine cream	Strength of recommendation B, LOE 2
Resorcinol	Insufficient evidence to recommend it as monotherapy. May be used in combination therapy or as maintenance agents
0.1% liposome-encapsulated rucinol and 0.3% rucinol cream	*LOE 2*
Tranexamic acid (topical)	Efficacious alternative to HQ products, with comparable results
Miscellaneous topical agents	Insufficient evidence to recommend it as monotherapy. May be used in combination therapy or as maintenance agents.
Oral tranexamic acid leads to a mild-to-moderate improvement in melasma when used at a dose of 500–750 mg/day in a divided dose, for a maximum period of 6 months	Strength of recommendation A, LOE 2–4
Other oral agents	*Insufficient evidence to recommend it as monotherapy. May be used in combination therapy or as maintenance agents*

Grading of recommendation as per OCEBM – levels of evidence (March 2009). Level of evidence as per OCEBM 2011 – 1: systematic review of randomized trials, 2: randomized trial, 3: nonrandomized controlled cohort/follow-up study, 4: case series; case–control; or historically controlled studies. OCEBM: Oxford Centre for Evidence-Based Medicine 134

androgenetic features concurred with their melasma: 63.3% had androgenetic alopecia, 13.3% had acne, and hirsutism was noted in 20%. The thirty females with melasma were divided into two groups. For 12 weeks, all applied sunscreen with SPF 60 every morning, and 4% HQ cream on pigmented spots every night. Subjects in group A were given 5 mg finasteride tablet at night, while those in group B, a placebo tablet. At the end of the treatment period, although a higher number of patients in group A attained more than 50% reduction in MASI score compared with that of group B, there was no significant statistical difference observed between the two groups. Intake of finasteride by the female subjects did not produce any untoward reaction.[161]

Recommendation for systemic agents

- Oral TXA—leads to a mild-to-moderate improvement in melasma when used at a dose of 500–750 mg/day in divided doses, for a maximum period of 6 months (grade of recommendation A).
- Oral procyanidin/pycnogenol—available RCTs have reported a good-to-moderate LEV for oral procyanidin or pycnogenol use in melasma. Currently, there is insufficient evidence to recommend oral procyanidin or pycnogenol as monotherapy in melasma.
- Oral PL extract—previously published reports showed conflicting results, and the number of subjects evaluated is low. There is insufficient evidence to recommend it as monotherapy in melasma.

Conclusion

HQ, TCC (4% HQ + 0.05% retinoic acid + 0.01% fluocinolone acetonide), sunscreens, KA, and azelaic acid receive a grade A recommendation, and TCC is preferable to all other topical therapies when the potency of the therapy is the priority, such as for the initiation of therapy for a short period (strength of recommendation A).

However, it is worth mentioning that the choice of agent should be individualized and subject to availability in a particular country. Also, combinations work better with TCC making treatment durations shorter. Among the newer agents, 3% RO cream, UP 2% cream, 30% metformin lotion, cream containing 0.05% tomato lycopene, and 3.45% wheat bran extract, 2% lincomycin + 2% linoleic acid, 5% topical MAP cream, 5% lignin peroxidase, *Petroselinum crispum* solution, 4% DAB serum, topical olive extract, 4% liquiritin cream, 10% zinc sulfate solution, 1% flutamide, and 0.2% thiamidol cream have high-to-moderate efficacy (grades A–B) and seem to be efficacious alternatives to HQ products, with comparable results.

Few studies that did not fulfill our inclusion criteria have reported the usefulness of mequinol 2%, topical and oral glutathione, topical and oral tocopherol, and several plant extracts as effective therapies for melasma, and large controlled trials are needed to establish efficacy and safety for wider acceptance of these agents.

Oral TXA leads to a mild-to-moderate improvement in melasma when used at a dose of 500–750 mg/day in a divided dose, for a maximum period of 6 months (strength of recommendation A) and may be used alone or as an adjuvant to conventional topical drugs or in cases recalcitrant to conventional topical therapy. Procyanidins, PL, and even synbiotics may be taken as adjuncts. Finasteride, however, may work in melasma accompanied by androgenic concerns. The strength of recommendation and LOE of the various topical and systemic agents has been summarized in [Table 1].

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Conflicts of interest

There are no conflicts of interest.

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Supplementary File

Supplementary Table 1: Summary of the studies included : Topical agents

Authors, year	Study design	Sample size, Gender	Skin phototype/ Ethnicity	Intervention arm	Comparison arm	Follow-up duration	Scoring system	Primary end point	Secondary end point	Adverse Drug Reactions	Level of Evidence as per OCEBM 2011^
Sunscreen											
Castanedo Cazares et al 2014 [9]	DB, RCT	61	III, IV, V	UV-VL sunscreen and 4% HQ every 2-3 hour between 8am-5pm	UV-only sunscreen 4% HQ every 2-3 hour between 8am-5pm	8 weeks	MASI, colorimetry (L*) and histological analysis of melanin	UV-VL group showed 15%, 28% and 4% greater improvements than the UV-only group in MASI scores, colorimetric values and melanin assessments, respectively	-	No adverse events	1b
Bokari Feriel et al , 2015 [6]	RCT	39: 2 Male 37 Females	III, IV, V	Formula A Sunscreen (UV + Ferrous oxide) Apply 1 dose of the product BD, additional dose every 2 hours, 30 minutes before exposure to daylight	Formula B Sunscreen (UV) Apply 1 dose of the allocated product BD, additional dose every 2 hours, 30 minutes before exposure to daylight	6 months sunscreen use	MASI score	The median increase of the MASI score from baseline to month 6 was more important with Formula B (2.43 interquartile range; 0.45 to 3.68) than with Formula A (0.45 interquartile range; 0.0 to 1.65) ($P = .027$)	8 patients in the Formula B group used makeup during the trial. This subgroup of patients who combined the use of un-tinted sunscreen and makeup did not have fewer relapses than those using only un-tinted sunscreen	No adverse events	2b
Triple Combination Cream											
Gong et al 2015 [7]	RCT DB	211 (FAHT group- 105: 2 males, 103 females) Placebo group 106; females)	Chinese	0.4% HQ+ 0.05% RA and 0.01% FA OD	Placebo OD	8 weeks	Decreased Index of Total Target Score (DITTS)	DITTS FAHT -0.48 ± 0.21 Placebo- 0.10 ± 0.14	• Instrumental measured efficacy: Improvement rate of target skin melanin (IRTSM) (Spectrophotometer), FAHT : 56.14 ± 66.56 Placebo: 16.20 ± 32.89 • Integral therapeutic efficacy rate FAHT :0.69 ± 0.22 Placebo :0.31 ± 0.10	**FAHT** A/E rate : 30.1 % :erythema, stabbing pain, peeling, telangiectasia, burning, swelling, dry skin, itching, and darker pigmentation, **Placebo:** Burning, tautening, itching, dry skin	1b
Pratchyapruit et al2011 [8]	RCT Split Face Study	34 Females	Thai	Ready-made (RM) cream group : 4% HQ 0.05% tretinoin and 0.01% FA OD	Hospital made (HM) cream group : 4% HQ and 0.02% triamcinolone acetonide in hydrophilic cream and an adjunct 0.05% tretinoin cream OD	Treatment duration: 8 weeks Follow-up: 40 weeks	Pigmentation and Erythema evaluated with a Mexameter every 2 weeks Transepidermal water loss (TEWL) and skin surface hydration	Both HM and RM: Initial rapid; subsequent gradual decrease in pigmentation v/s pretreatment values. Reached nadir after 6 weeks; stable till 8 weeks. No objective difference between groups.	• 100% subjects in RM group and 97% in HM group expressed satisfaction • Increase in TEWL values, skin surface hydration and decrease in redness was more in the HM group. • HM-treated side :more rapid decrease in pigmentation, but more prominent rebound increase than with RM group.	Mild skin irritation, scaling with a burning and stinging and skin peeling	1b
Arellano et al 2011 [9]	RCT SB	242 Twice weekly (n=119; males :7, females: 112) Tapering Regimen (n=123; males =4, females:119)	II-V	4% HQ 0.05% tretinoin and 0.01% FA in a twice weekly regimen *Broad spectrum sunscreen (SPF 60) was used every morning.	4% HQ 0.05% tretinoin and 0.01% FA in a tapering regimen : 3 / week (1st month) 2 / week (2nd month) 1 / week (4th month) *Broad spectrum sunscreen (SPF 60) was used every morning.	6 months	Median time to relapse during the maintenance phase, based on Global; Severity Score (GSS)	The median time to relapse (50% of subjects with a first relapse) in both groups was comparable: 192 days for the twice weekly regimen vs. 190 days for the tapering regimen (P = 0.74). The relapse rate (relapse defined as GSS ‡ 2, meaning moderate or severe melasma) during the maintenance phase was similar between groups	• At 6 months, relapse free rate was 53.8% in the twice weekly and 53.0% subjects in the tapering regimen,(P = 0.901). • GSS and MASI scores remained low for both groups. • Regardless of the regimen, all relapse-free subjects rated their melasma as completely clear or minor. • In the population who relapsed, there was no worsening of the severity scores (GSS, MASI compared to baseline.	Reported by 11.6% of subjects, and erythema and skin irritation were the most frequently noted. No severe adverse events related to the use of TC were reported.	1b
Taylor et al 2003 [11]	RCT SB	641 Males and females	I-IV	RA 0.05%, HQ 4.0%, and FA 0.01% (N=161) OD	Dual combination products 1.0.05 % RA +4 % HQ OD (N=158) 2. 0/05% RA + 0.01% FA OD (N=161) 3. 4% HQ+ 0.01% FA OD (N=161)	8 weeks	Investigator's assessment of global improvement from baseline using an 8-point scale	Significantly more of the patients treated with RA+HQ+FA (26.1%) experienced complete clearing 9.5% 1..9% 2.5%	• Portion of patients with complete or near complete clearance: 28.6% • 10.1% • 1.9% • 3.1%	Erythema, Desquamation. Burning, Dryness, Pruritus	1b
Astaneh et al 2005 [12]	RCT DB	64 2 groups of 32 females	III to V	4% HQ+ 0.05% tretinoin + 0.05% dexamethasone OD (Group A) *Broad spectrum sunscreen (SPF 15) was used every morning.	4% HQ OD (Group B) *Broad spectrum sunscreen(SPF 15) was used every morning.	12 weeks	Improvement was determined subjectively compared with baseline, on a three-point scale as follows: worse, same and improved (excellent, good, moderate, slight).	81.2% of group B, compared with 31.3% of group A, had good to excellent results, as measured by reduction of melasma pigmentation intensity and lesion size. Group A showed significantly better results than the group B.	None	Erythema and scaling in the area of application. Experienced by 87.5% of patients in group B and in 43.7% of patients in group A. Significant difference between groups.	1b
Cestari et al 2007 [13]	RCT Open Label	119 patients: 2 groups (60: TC group; 59: HQ group)	II-IV	HQ 4%, RA 0.05%, and FA 0.01% OD *Broad spectrum sunscreen (SPF 30) was used every morning.	4% HQ cream BD *Broad spectrum sunscreen (SPF 30) was used every morning.	8 weeks	Investigator's static evaluation of melasma severity.	Proportion of patients with complete clearance 35% in TC group vs 5.1 %in HQ group	• Investigator's evaluation of overall improvement: significantly superior with TC cream than HQ cream. • "Secondary success," defined as > 75% improvement, achieved by 73% in the TC cream group;49% in the HQ cream group • Subjects who considered that treatment was "excellent": greater for TC cream (50%) v/s HQ cream (34%).	The incidence of adverse events (erythema, burning sensation, and desquamation) was similar in both groups.	1b
Chan et al 2008 [14]	RCT SB	247 Males and Females 121- TC group 126- HQ group	III-IV	4% HQ+ 0.05% tretinoin + 0.01% FA OD *Broad spectrum sunscreen (SPF 60) was used every morning.	4% HQ BD *Broad spectrum sunscreen (SPF 60) was used every morning.	8 weeks	Global severity Score (GSS)	TCC: 64.2 % patients with GSS of none or mild HQ: 39.4% patients with GSS of none or mild	• MASI reduction was statistically superior with TC ($P < 0.001$). • Investigator's assessment of global improvement, 49% in TC group had melasma 'completely clear', 'almost clear' or 'significant improvement' vs.18% in HQ group. • Patient's static global assessment, 69% in TC group had 'no evidence of hyperpigmentation' or 'minor evidence of hyperpigmentation' vs. 44.2% in HQ group • Patient satisfaction: overall satisfaction was significantly in favor of TC cream ($P = 0.005$).	Treatment-related adverse events were reported in 63/129 patients in the TC group and 18/131 patients in the HQ group Erythema, Exfoliation, Irritation, Discomfort	1b
Monheit et al 2013 [15]	RCT SB Split face	20 Females	I-III	4% HQ, 0.05% RA 0.01% FA OD *Broad spectrum sunscreen (SPF 30) was used every morning.	Novel skin-lightening cream (SLC) with 4% HQ which additionally contains 4 skin-brightening actives OD *Broad spectrum sunscreen (SPF 30) was used every morning.	12 weeks	Investigator's Global Assessment (IGA) MASI Investigator's Tolerability Assessment (ITA)	IGA for melasma severity reduced rom 2.45+/-0.51 before treatment to 1.35+/-0.75 for SLE And from 2.50+/-0.51 to 1.20 +/-0.52 for TCC after 12 weeks with significant difference. MASI reduction : 77% for SLC & 79% for TCC cream	• ITA showed that both creams were well tolerated, although the SLC appeared to be slightly better tolerated than TCC, although this difference was not significant.	Erythema, dryness, or peeling. At least 1 one of these was experienced by 35% of the subjects.	1b
Bhagwat et al 2016 [16]	RCT No blinding mentioned#	60: 2 groups 53 males, 7 females	III-V	Group A: 2%HQ, 0.025%RA, 0.01%FA OD	Group B: 2% kojic acid +octinoxate plus allantoin OD	12 weeks	MASI	Mean reduction in MASI score was 26.22% in group A and 66.5% in group B, and was statistically significant in both groups.	In comparison between the two groups, at the end of first month, second month and third month, group A showed better effect (P <0.0001 once at night) compared to group B •	No complications in Group B. Erythema, burning, irritation in 10% cases of Group A.	1b
Sarkar et al 2002 [17]	RCT OL	40 :2 groups 22 Females and 18 Males	III-IV	Serial GA peel combined with: 5% HQ+ 0.05% RA + 1% HA in a cream base OD. *Broad spectrum sunscreen (SPF 15) was used every morning.	HQ 5%, RA 0.05%, HA 1% in a cream base OD *Broad spectrum sunscreen (SPF 15) was used every morning.	12 weeks	MASI reduction evaluated by a clinical investigator	MASI reduction at 21 weeks: 79.9% in the Peel group v/s 63.14% in the control group. The difference was significant.	In the peel group, 80% of the patients graded their improvement as excellent, 10% as good, and 10% as fair. • In the control group, 60% of the patients gra improvement in their melasma as excellent, as good, and 20% as fair.	Nearly all patients in the peel group and eight patients in the control (MKF) group experienced mild cutaneous erythema and superficial desquamation,	1b
Chaudhary et al 2013 [18]	RCT OL	40 :2 groups 38 females, 2 males	III-IV	Serial GAcacid peel combined with: 2% HQ+ 0.05% RA + 1% HA in a cream base OD. *Broad spectrum sunscreen (SPF 15) was used every morning.	HQ 2%, RA 0.05%, HA 1% in a cream base OD *Broad spectrum sunscreen (SPF 15) was used every morning.	24 weeks	MASI	Percentage decrease in MASI at 24 weeks : 73.69% in peel group v/s 42.33% in control group. Difference between groups was significant. (P value<0.05)	• Peel group showed earlier and greater improvement than the control group.	Peel Group: Post peel erythema, post-inflammatory hyperpigmentation, hypertrichosis, burning and stinging. Control group: Burning and stinging sensation	1b
Mahajan et al2015 [19]	RCT SB	38: 2 groups	Indian	Group A (N=20) 2% HQ+ 0.05% RA + 0.01% FA once a day *Broad spectrum sunscreen (SPF 30) was used every morning.	Group B (N=18) GA peels(at 2 week intervals) plus AA 20% cream combination OD *Broad spectrum sunscreen (SPF 30) was used every morning.	12 weeks	MASI	Group A Decreased from 9.14 ± 6.25 to 4.3 ± 3.83 at 12 weeks [$P < 0.001$] Group B Decreased from 9.08 ± 4.0 to 4.67 ± 2.59 at 12 weeks; $P < 0.001$ No significant difference in mean MASI scores between the two groups.	The mean VAS decreased from 6.11 ± 1.52 at week 0 to 2.58 ± 1.61 at week 12 in group A ($P = 0.001$) and from 5.9 ± 0.98 at week 0 to 2.85 ± 1.09 at week 12 in group B ($P = 0.001$) • No significant difference in the mean VAS scores between the two groups at 12 weeks.	Irritation, dryness, photosensitivity Four patients in group A and 3 in group B experienced adverse effects.	1b
Patil et al 2019 [21]	RCT OL	180 patients in 3 groups Group A (65) Group B (76)	Indian	Group C 2% HQ+ 0.025% RA + 0.01% FA once a day	Group A Intradermal TXA Group B Topical 3% TXA	6 months	MASI	Group A MASI decreased from 15.4 (baseline) to 2.2 at 6 months *(Statistically significant)*	Proportionally greater decrease in MASI score in Group A and Group C than Group B. P value >0.05 was not significant.	Mild discomfort, burning sensation, and erythema were observed when TXA was used intradermally.	1b

		Group C (39)						Group B MASI decreased from 15.4 (baseline) to 6.4 at 6 months Group C MASI decreased from 15.3 (baseline) to 5.4 at 6 months		Groups A and B showing lesser side effects than Group C.	
Eshghi et al 2014 [22]	RCT OL	42 women: 2 groups	II-III	Group A: Subepidermal triamcinolone injections with a dose of 4mg per cc and 5mm intervals, repeated after 1month *Broad spectrum sunscreen was used every morning.	Group B 5% HQ + 0.1% RA and dexamethasone 0.1% OD *Broad spectrum sunscreen was used every morning.	8 weeks	MASI	Group A: Decrease in MASI from 11.57 ± 4.33 vs 8.01 ± 3.1 at 8th week, *P*-value < 0.001 Group B: 10.46 ± 5.61 vs 8.96 ± 4.96 at 8th week, *P*-value< 0.001 Significant differences between two groups: group A (case) had a much better response than group B (*P*< 0.001)	None	Painful injection, minimal skin atrophy, mild telangiectasia	1b
Nassar et al 2020 [23]	RCT OL	44: 2 groups	*Egypt	Group 1 Intralesional injection of triamcinolone acetonide at a concentration of 4 mg/mL,1 cm apart between injected points with a maximum dose of 20 mg per session, once monthly for four sessions.	Control group 5% HQ + 0.1% RA and dexamethasone 0.1% OD	12 weeks	Percentage of decrease in MASI scores at the end of treatment (No response no decrease in MASI, poor: MASI decreased by 25% or less, moderate: MASI decreased from 25% to 50%, good: MASI decreased from 50% to 75%, and excellent: MASI decreased by more than 75%).	Therapeutic response: • Good in 50% of both groups • Medium in 31.8% of group 1 v/s 36.4% of control group • Poor in 18.2% of group 1 vs 13.6% of control group. The difference between both groups regarding the therapeutic response was not statistically significant.	22.7% of group 1 were completely satisfied versus 36.4% of control group. 36.4% of both groups were greatly satisfied 36.4% of group1were moderately satisfied versus 18.2% of control group. Only 4.6% of group1 was not satisfied versus 9.1% of control group. The difference between both groups was not statistically significant. •	Group1 :Mild pain during injection Control group : Dermatitis, irritation, and *burning sensation.	1b
Wind et al 2010 [24]	RCT SB Split Face	29	II-IV	FLT group 4 – 5 sessions of non-ablative 1550 nm FLT (15mJ/microbeam, 14–20% coverage) for 15 weeks *Broad spectrum sunscreen (SPF 50) was used every morning. *After the last session treatment, patients asked to apply TTT twice weekly on both sides of the face during follow-up.	TTT group HQ 5% + 0.05% RA + triamcinolone acetonide 0.1% cream OD for 15 weeks *Broad spectrum sunscreen (SPF 50) was used every morning. *After the last session treatment, patients asked to apply TTT twice weekly on both sides of the face during follow-up.	6 months	• Patient's global assessment (PGA • Patient's satisfaction • Physician's global assessment (PHGA) • Melanin index • Lightness (L-value) At 3 weeks, and at 3 and 6 months after the last treatment.	Mean PGA and satisfaction were significantly lower at the FLT side (P<0.001).	• PhGA, melanin index, and L-value showed a significant worsening of hyperpigmentation at the FLT side. • At the TTT side, no significant change was observed. • At 6 months follow-up, most patients preferred TTT.	FLT group: erythema, burning sensation, edema, and pain, 31%) developed PIH after two or more laser sessions. TTT group: erythema, burning sensation, and scaling.	1b
Kroon et al 2011 [25]	RCT SB	29 females	II-IV	Nonablative fractional laser therapy performed every 2 weeks for a total of 4 times.	5% HQ+ 0.05% RA+0.01% TA OD	6 months	Physician Global Assessment(PGA) at 3 weeks, 3 months, and 6 months	PGA improved (P< .001) in both groups at 3 weeks. No difference in PGA between the two groups.	• Mean treatment satisfaction and recommendation were significantly higher in laser group at 3 weeks (P < 0.05).	Laser group-Erythema, burning sensation, facial edema, and pain; TCC-Erythema, burning, and scaling.	1b
Jeong et al 2010 [26]	RCT Split Face Cross-over	13 12 females, 1 male	III-IV	Group B (LASER followed by TCC) Collimated, 5- to 7-ns pulse width, 1.064-nm Q-switched Nd:YAG laser, 7-mm spot size, 1.6 to 2.0 J/cm2, two passes per session, weekly for 8 weeks. *Switched to Group A treatment with TCC after 8 weeks)	Group A (TCC followed by LASER) 4% HQ+ 0.05% RA+0.01% FA OD for 8 weeks *Broad spectru^{m} sunscreen (SPF 50) was used every morning. *Switched to Group B treatment (Qs Nd YAG laser treatment) after 8 weeks	16 weeks	MASI Spectrophotometry measurements Subjective self-assessment method.	MASI Group A reduced from 3.42+/-3.46 to 3.0 +/- 4.14 after 8 weeks of TC and then to 2.09+/-3.92 after an additional 8 weeks of laser treatment. Group B, reduced from 3.20 +/- 3.49 to 1.74+/- 3.93 after 8 weeks of laser and increased to 2.22 +/- 3.82 after an additional 8 weeks of TC treatment Comparison showed that laser treatment was more effective although the difference in overall improvement between the two groups was statistically nonsignificant.	Comparison of the two modalities during each period showed that the laser treatment was more effective than TC cream in the additional 8 weeks Although the difference in over- all improvement between the two groups was statistically nonsignificant • Collectively, laser treatment with a pre-treatment of TC cream was significantly mo effective than post-treatment use of TC crea	TCC Aggravation of the melasma, irritation Laser treatment Mild pain and erythema	1b
Dev et al 2020 [27]	RCT SB Split Face Study	38 females	IV-V	Group A QSNYL (fluence 1.5 J/cm2, spot size 6 mm, frequency 10 Hz, 10 passes or until clinical end points of immediate pigment lightening and whitening of fine hair.) *Broad spectrum sunscreen was used every morning.	Group B 4% HQ+ 0.05% RA+0.01% FA OD *Broad spectrum sunscreen was used every morning.	24 weeks	Melanin index (MI), modified Melasma Area Severity Index (mMASI),	• The mean baseline MI in groups A and B was 50.6+/-5.9 and 49.9+/-6.1, respectively, that significantly decreased to 48.3+/-5.9 and 47.8+/-5.4 • Baseline mMASI in group A and group B was 3.3+/-1.9 and 3.3+/-2.0 that decreased to 2.7+/-1.5 and 2.3+/-1.6, respectively, after 12 weeks of treatment. No statistically significant differences between the groups.	Photographic assessment showed an overall significant improvement of 17.3% in group A and 20.9% in group B at the end of 12 weeks of intervention. • All patients graded their baseline severity score and after 12 weeks of intervention, the scores decreased to 3.5+/- 0.9 (P<0.001) and 3.3 +/-1.1 (P<0.001) in groups A and B, respectively.	Group A Acute urticarial reaction Group B Erythema and telangiectasia The number of adverse events was more in group B as compared to group A (P < 0.001)	1b
Wang et al 2019 [28]	RCT SB	29 patients Group A1-9; Group A2-11; Group B-6 patients.	IV	Picosecond alexandrite laser using a diffractive lens array (DLA) Group A1 3 laser sessions at 4-week intervals Group A2 5 laser sessions at 4-week intervals	Group B 4% HQ+ 0.05% RA+0.01% FA OD for at least 8 weeks *Broad spectrum sunscreen (SPF 50) was used every morning.	Follow-up periods for groups A1 and A2 were 3 months and 1 month, respectively.	MASI	MASI significantly improved in all 3 groups at week 20. In groups A1, A2 and B, the improvement rates at week 20 were 53%, 38% and 50%, respectively although the improvement rates in each group were not significantly different.	• Visia complexion assessment :significant improvement in spots, porphyria, pores and brown spots after 3 laser sessions (P < 0.05). Group A2 :greater improvements than group A1 however, only red areas were significantly different (P < 0.001)	Group B Dryness, erythema and itching. Group A1 Erythema had focal desquamation. Group A2 Erythema, PIH, and focal desquamation	1b
Passerson et al 2011 [29]	RCT SB Split Face Study	18 patients	II-IV	4% HQ+ 0.05% RA+0.01% FA OD for 4 months PDL : started after 1 month of TCC application. Three sessions (compressio handpiece of 10 mm; pulse duration, 1.5 milliseconds; fluency, 7 J/cm^{2}). performed at 3-week intervals on the half face.	4% HQ+ 0.05% RA+0.01% FA OD for 4 months *Broad spectrum sunscreen (SPF 50) was used every morning.	2 months after the last treatment	MASI	Reduction in MASI was more with combination of PDL and TCC than TCC alone and the difference was found to be statistically significant.	• Patient satisfaction was significantly greater for the combination treatment in patients with skin phototypes II and III (*P* < .01), while no significant differences between the 2 treatment groups were reported for phototype IV	Transient and mild irritation due to the cream was reported by half of the patients. Post inflammatory hyperpigmentation was observed in 3 patients, all phototype IV, treated with PDL.	1b
Goldman et al 2011 [30]	RCT Split Face Study	56 Females	I-IV	Inactive control cream OD for 2 weeks Series of two IPL treatments (week 2 and 6) (560-nm cut-off filter, a double-pulse technique with pulses of 3.0 to 3.5 ms, fluence varied from 14 to 18 J/cm2) *Broad spectrum sunscreen (SPF 45) was used every morning.	4% HQ+ 0.05% RA+0.01% FA OD for 2 weeks Series of two IPL treatments (week 2 and 6) *Broad spectrum sunscreen (SPF 45) was used every morning. # After the second IPL treatment at week 6, patients resumed and continued applications of the creams until the last visit at week 10.	10 weeks	IGA based on a 5-point scale (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe)	The investigator determined that 30% at week 10 had excellent improvement with IPL plus TC cream. No patient demonstrated excellent improvement with IPL plus inactive cream at either time point.	The distribution of responses for the patients' evaluation of improvement significantly favoured IPL plus TC cream over IPL plus inactive cream at both time points	Cutaneous irritation, small skin erosion, allergic reaction to intravenous pyelography dye	1b
Souza et al FL 2012 [31]	RCT SB OL	62 patients (2 groups) (58 women, 4 men) totally or partially resistant to 6 months o treatment with combined bleaching agents	II-V	IPL group IPL (with a cooling device, real-time calibration, and automatic pulse in a single session with a filter of 560nm and fluencies ranging from 12 to 22 J) Stable fixed-dose triple combination treatment : 4% HQ+ 0.05% RA+0.01% FA OD (that had previously been totally or partially refractory) was restarted. *Broad spectrum sunscreen	Control group 4% HQ+ 0.05% RA+0.01% FA OD *Broad spectrum sunscreen	12 months	MASI IGA based on a 7-point scale 1 (worst) to 7 (clear).	IPL group • 49.4% reduction in MASI (from 17.6 to 8.9; p < 0.001) after six months • 44.9% reduction after 12 months (from 17.6 to 9.7; p < 0.001). Control group reduction in MASI (from 16.5 to 16.1 (p>0.001) Difference between the intense pulsed light and control group was significant (*p* = 0.002)	The IGA showed that difference in the improvement rate between the IPL group and control group was significant (p = 0.002), with a better response in the IPL group.	IPL group: Mild to moderate pain, burning sensation. Immediately after treatment, mild, transient erythema was present. Followed by slight darkening of the pigmented lesions.	1b
Hydroquinone											
Grimes et. al. 2007 [37]	RCT SB OL	??	II-IV	Microencapsulated HQ 4% and retinol 0.15% with antioxidants (A)	HQ 4% and retinol 0.3% with antioxidants) (B) and FA 0.05% (C)	12 weeks	Overall disease severity, pigmentation intensity and Melasma Area and Severity Index (MASI) score	Reduction in pigmentation intensity and MASI score	• Improvement in disease severity	All three treatment were well tolerated	1b
Mendoza et. al. 2014 [34]	RCT DB	45 15 Rumex occidentalis vs 15 HQ vs 15 placebo	III-V	3% Rumex occidentalis cream	4% HQ cream	8 weeks	MASI score, mexameter readings, physician global assessment scale (5 point ordinal scale)	Reduction in MASI score and mexameter reading	• Improvement in subject assessment scale	Tolerability of the R. occidentalis cream was considered to be good; one subject reported mild peeling in the second week	2
Tehranchinia et. al. 2018 [35]	RCT SB Split face study	55	II-IV	HQ 4% cream	HQ 4% cream plus 1 ml tranexamic acid intradermal injection	12 weeks	MASI score, patient's global assessment scale	Reduction in MASI score	• Improvement in subject assessment scale	TA+ HQ : erythema (47.3%) and pruritus at the site of injection (10.9%). HQ : erythema in 50.9% o cases and pruritus in 12.7%	2
Gheisari et. al. 2020 [36]	RCT DB	40, 20/20	II-IV	5% methimazole	4% hydroquinone	12 weeks	MASI score, patient satisfaction and	Reduction in MASI score	• Physician and patient global evaluation of melasma improvement	Mild- to- moderate erythema in 4 patients of methimazole and 3	1b

							physician score			patients of HQ group. One patient in each group had burning. Mild- to-moderate dry- ness in five patients of methimazole and mild dryness in five patients of HQ group.	
Janney et. al. 2019 [37]	RCT SB	100, 50/50	IV-V	Topical 5% TA solution	3% HQ cream	12 weeks	MASI score, patient satisfaction score	Reduction in MASI score	• Improvement in patient satisfaction score	10 patients and 9 patients of HQ group complained of erythema and irritation respectively. However, only 3 patients of TA group reported irritation	1b
Abadchi et. al. 2019 [38]	RCT SB Split face	40	II-V	Topical HQ 4%	Topical HQ 4% and fractional CO_2 laser	3 months	Darkness [D] and homogeneity [H] of hyperpigmentation, physician's global assessment (PGA) and patient satisfaction (visual analog scale [VAS] score).	Reduction in darkness [D] and homogeneity [H] of hyperpigmentation	• Improvement in physician's global assessme (PGA) and patient satisfaction (visual analog scale [VAS] score	In the combination therapy side, 2 patients experienced erythema, 3 had burning, and in the HQside, 1 patient experienced burning.	1b
Pazyar et. al. 2019 [39]	RCT SB Split face	49, 24/25	II-IV	R: TA intradermal injections every 2 weeks on the right side of the face with a concentration of 4 mg/ mL L: 4% HQ cream BD	R : TA intradermal injections every 2 weeks on the right side of the face with a concentration of 10 mg/ mL L : 4% HQ cream BD	12 weeks	MASI score, Dynamic Physician Global Assessment scale	Reduction in MASI	• Improvement in Dynamic Physician Global Assessment score	All patients experienced injection site burning pain,; one patient reported urticaria. No adverse effect was seen in the HQ group.	1b
Nofal et. al. 2019 [40]	RCT OL	42, 14 /14/14	III-V	Group 1 received silymarin 0.7% cream, group 2 received silymarin 1.4% cream	Group 3 received hydroquinone 4% cream.	3 months	MASI score, patient satisfaction scale	Reduction in MASI	• Improvement in patient satisfaction	HQ was associated with erythema in 10 patients (71.4%), burning in 10 patients (71.4%), scaling in 10 patients (71.4%), while no side effects were detected in both groups of silymarin	2b
Taghavi et. al. 2019 [41]	RCT DB Split face study	20	III-IV	Topical liposomal HQ cream	Conventional HQ cream	3 months	MASI	Reduction in MASI score	• --	--	1b
Kaufman et. akl. 2020 [42]	RCT DB Split face study	18	III-IV	HQ-free, retinol-free cosmetic topical brightener	HQ 4%	12 weeks	Melasma Area Severity Index (MASI), Overall Hyperpigmentation scale, and Melasma Severity Rating Scale (MSRS), Melasma Quality of Life (MelasQoL) questionnaire	Reduction in MASI, MSRS	• Improvement in MelasQoL score	Erythema and burning in HQ side of the face	1b
Namazi et. al. 2020 [43]	RCT Split face	29	II-IV	Er: YAG laser plus HQ 4%	HQ 4%	28 weeks	MASI score	Reduction in MASI	None	Five patients in this study developed post-inflammatory hyperpigmentation	2bb
Bronzina et. al. 2020 [44]	RCT DB	43	II-IV	Combination of cosmetic products (CCP): Neotone® serum once daily in the evening and Neotone® Radiance SPF 50+ (ISISPHARMA, Lyon, France)	4% HQ	12 weeks	mMASI score, Individual Typological Angle (ITA°) and patient satisfaction score	Reduction in mMASI score	• Improvement in patient satisfaction score	CCP group: one subject reported mild burning sensation on the bilateral cheeks. In the HQ group, only one subject reported mild acneiform lesions on the cheeks	1b
Wattanakrai et. al. 2010 [45]	RCT Split face	22	III-V	QS-Nd:YAG laser and 2% HQ	2% HQ	12 weeks	mMASI score, colorimetric measurement (absolute lightness index and relative lightness index), patient satisfaction score	Reduction in mMASI score, improvement in lightness indices	• Improvement in patient satisfaction score	After completing the five laser treatments, three patients (13.6%) developed mottled hypopigmentation; and eight of 22 cases developing ''confetti-like'' hypopigmented macules	2b
Azzam et. al. 2009 [46]	RCT OL	45, 15/15/15	III-IV	Group A received Jessner's solution peel, group B received trichloroacetic acid peel 20%	Group C received topical HQ 2% and kojic acid	16 weeks	MASI score	Reduction in MASI score	• None	Post peel erythema developed in 30% of patients in group (A) and 20% of patients in group (B) and it was transient	2b
Espinal-Perez et, al. 2004 [47]	RCT DB	16	IV-V	5% ascorbic acid cream on one side of the face	4% hydroquinone cream on the other side	16 weeks	Colorimetric scale and patient assessment scale	Improvement in colorimetric scale	• Improvement in patient assessment scale	irritation in one patient with l-ascorbic acid (6.25%) vs. 11 with hydroquinone (68.75%)	1b
Haddad et. al. 2003 [48]	RCT DB	30, 15/15	III-V	Group 1, one tube containing HQ 4% cream and one tube containing placebo to be applied to opposite sides of the face at night, and standardized sunscreen (SPF) 25] for daily use	Group 2, one tube containing skin whitening complex 5% cream and one tube containing placebo to be applied to opposite sides of the face at night, and standardized sunscreen (SPF 25)	3 months	Photographic assessment, patient satisfaction score	Improvement on photographic evaluation	• Improvement in patient satisfaction score	Group 1, with 25% of patients reporting an itchy eruption	1b
Hurley et. al. 2002 [49]	RCT DB Split face study	21	IV-V	20-30% GAcpeels plus 4% HQ on one side of face	4% HQ on other side of face	8 weeks	MASI score, physician global assessment scale	Reduction in MASI score	• Improvement in physician global assessment score	4 patients developed significant erythema with higher concentrations of peels	2b
Guevara et. al. 2003 [50]	RCT DB	39	III-IV	4% hydroquinone, 10% buffered GA vitamins C and E, and sunscreen (Glyquin, ICN Pharmaceuticals, Costa Mesa, USA)	Sunscreen alone	12 weeks	melasma area and severity index (MASI), mexameter, global evaluation by the patient and blind investigator	Reduction in MASI score and mexameter readings	• Improvement in global assessment	Irritation was more common in the active group, with 17 of the 20 patients (85%) developing mild to moderate erythema at week 12	1b
Banihashemi et. al. 2015 [51]	RCT DB Split face	30	III-V	5% topical liposomal tranexamic acid cream	4% HQ cream	12 weeks	MASI score	Reduction in MASI score	• None	Irritation occurred in three patients with hydroquinone	1b
Ibrahim et. al. 2015 [52]	RCT SB	100, 20/20/20/20/20	Egyptians	Group I (twenty patients were treated with cream formula containing 4% HQ), group II (twenty patients were treated with cream formula containing 4% HQ + 10% GA), group III (twenty patients were treated with cream formula containing 4% HQ + 0.01% hyaluronic acid), group IV (twenty patients were treated with cream formula containing 4% HQ + 10% GA + 0.01% hyaluronic acid)	Group V (twenty patients were treated with placebo cream).	6 months	mMASI score, dermoscopy, physician's global assessment scale	Reduction in mMASI score, improvement on dermoscopy	• Improvement in PGA scale	Group II showed the highest rate of side effects (pruritus, erythema, scaling, crusting, erosion) as all the patients reported side effects, followed by group IV (70%) of patients, followed by group I (60%) of patients, followed by group III (20%) of patients, while in group V, no side effects were reported	1b
Iraji et. al. 2012 [53]	RCT SB	72, 36/36	II-IV	10% zinc sulfate solution	4% HQ cream	6 months	MASI scale, Patient Global Assessment scale	Reduction in MASI score	• Improvement in PGA scale	some reports of mild burning and erythema	1b
Farshi et. al. 2011 [54]	RCT OL	29, 14/15	Iranians	20% AZA cream	4% HQ cream	2 months	MASI scale, Patient assessment scale	Reduction in MASI score	• Improvement in patient assessment scale	Erythema, induration and pruritus in 2, 7, 1 patient at the end of study in HQ group	2b
Navarrete-Solis et. al. 2011 [55]	RCT DB Split face	27	IV-V	4% niacinamide cream on one side of the face	4% HQ cream on the other	8 weeks	Chromameter, MASI, histology, physician global assessment (PGA), conventional photography, and infrared thermography	Reduction in MASI score	• Improvement on PGA scale and colorimetric assessment	On the niacinamide side, erythema, pruritus, or burning was present in 2 (7%) patients, and on the HQ side they were present in 5 (18%) patients.	1b
Costa et. al. 2010 [56]	RCT SB	50, 23/27	I-IV	Belides, Emblica and Licorice 7%	HQ 2%	2 months	Medical evaluation, self evaluation and Visia® (multi-spectral imaging system)	Improvement in medical evaluation and Visia	• Improvement in self evaluation	Side effects less noticed in Group A (association of Emblica, Licorice and Belides 7%), in which two events were reported (burning and increase of the number of previous acne lesions). Group B (HQ 2%) described seven adverse reactions (erythema, burning, erythematous papules on the periorial region)	1b
Akl et. al. 2021 [57]	RCT OL	50, 25/25	III-V	Liposomal form of AZA 20% + Oral tranexamic acid 250 mg	HQ 4% + Oral TXA 250 mg		MASI score and patient's quality of life	Reduction in MASI	• Improvement in patient's quality of life	Erythema, burning and irritation in HQ group	2b
Maryam Emad 2013 [58]	Split face Open clinical trial	33	Iranians	HQ 4% cream	AZA 20% cream	20 weeks	MASI and mMASI	Reduction in scores	• Subjective improvement	6 patients (2 in the HQ group, 3 in the AZA group, and 1 in both groups) showed some degrees of adverse effects as erythema, burning, and itching	2b
Khosravan 2017 [59]	RCT	50 (25/25)	Iranians	4% HQ cream	Topical Petroselinum Crispum (Parsley)	8 weeks	Wood's lamp and MASI score	Improvement in MASI score	• Subjective improvement	2 patients in the group receiving HQand 2 patients in the group receiving parsley showed irritation as redness and itching	1b
Kojic Acid											
Deo et al*	RCT SB	80 (20 in each arm)	Indians	KA 1% cream once daily	KA 1% +HQ 2% cream once daily	12 weeks	MASI	58.72% improvement in MASI in intervention arm compared to 71.87% improvement in the comparison arm.	• >75% reduction in MASI was achieved by 2 in intervention group compared to 60% in comparison group	One patient in intervention arm had burning compared to two patients in comparison arm	1b

2013 [60]		67 females and 13 males			KA 1% and betamethasone valerate 0.1% cream once daily	12 weeks	MASI	58.72% improvement in MASI in intervention arm compared to 36.46% improvement in the comparison arm.	• >75% reduction in MASI was achieved by 2 in intervention group compared to 10% in comparison group		
					KA 1%, HQ 2%, and betamethasone valerate 0.1% cream once daily	12 weeks	MASI	58.72% improvement in MASI in intervention arm compared to 54.23% improvement in the comparison arm	• >75% reduction in MASI was achieved by 2 in intervention group compared to 25% in comparison group	One patient in comparison arm had acneiform eruption	
Monteiro et al*2013 [61]	Prospective comparative trial	60 44 females and 16 males (30 in each arm)	Indians	KA 0.75% cream once daily	HQ 4% cream once daily	12 weeks	MASI and Wood light examination	Hydroquinone 4% showed better reduction in MASI compared to kojic acid 4% at 12 weeks	• None	Erythema was noted in one patient receiving 0.75% KA and two patients receiving 4% hydroquinone cream	2b
Yenny et al, 2018* [62]	RCT, SB, split face	45	Indonesi-ans	KA 4%	5% methimazole	12 weeks	Melasma Area and Severity Index (MASI), mexameter score, patient satisfaction	There was no statistically significant difference in reduction in MASI/ mexameter between the two groups at week 12.	Patient satisfaction was not significantly different in both groups.	Application site reaction was found in 20% patients in methimazole group and 11% in kojic acid group	1b
Azelaic Acid											
Sarkar 2002* [63]	SB Split face Observer blinded	30 (25 females and 5 males)	Indians	Twice daily application of20% AZA cream to one half of the face	0.05% clobetasol propionate cream, to be applied for 8 weeks only and then to be followed by 20% azelaic acid cream only for the next 16 weeks on the other half.	24 weeks	Physician global assessment	At 24 weeks, 29 (96.7%) and 27 (90%) on the side treated with the sequential therapy and that given only 20% azelaic acid cream, respectively, had a good to excellent responses	None	Itching and burning were experienced by 6 patients with 20% AZA cream. Acneiform eruptions were observed in 5 patients	1b
Bansal et al* 2012 [64]	RCT OL	60 (20 each in three arm) 59 females and 1 male	III-V	Twice daily application of20% AZA cream	Low-fluence Q-switched Nd: YAG laser	12 weeks	MASI	No statistically significant difference in reduction of MASI between the two groups at 12 weeks	There was a statistically significant reduction in MASI in each group compared to baseline values	One patient treated with topical 20% AZA cream experienced slight burning sensation	2b
					Low-fluence Q-switched Nd: YAG laser + 20% AZA cream BD	12 weeks	MASI	The reduction in MASI was significantly higher in the comparator arm compared to interventional arm	There was a statistically significant reduction in MASI in each group compared to baseline values	In combination group, 1 patient developed erythema and 1 suffered slight burning sensation	
Dayal et al 2016 [65]	RCT OL	60 M:F 1:14 in treatment arm 1: 9 in comparator arm	IV, V	AZA 20% cream twice daily	GA peel every three weeks * 8 + AZA 20% cream BD	24 weeks	MASI MELASQOL	There was a statistically significant higher reduction in MASI/MELASQOL in comparator arm compared to treatment arm	There was a statistically significant reduction in MASI in both groups compared to baseline values	Four patients in comparator arm and one in treatment arm developed post-peel erythema. Pruritus was experienced by four patients in comparator arm while two in treatment arm. Burning sensation was observed in two patients in comparator arm and five in treatment arm. Post-inflammatory hyperpigmentation was observed in two patients in comparator arm and one patient in treatment arm	2b
Erbil et al 2007 [66]	RCT OL	28 Females: 27, male: 1 (12 patients in treatment arm, 16 in comparator arm)	Turkish	AZA 20% cream BD + adapalene 0.1% gel (HS).	Serial GA peels + AZA 20% cream (b.i.d.) + adapalene 0.1% gel (HS).	20 weeks	MASI	Prominent decrease in MASI scores at the end of the treatment in both groups, although the results were better in the comparison arm	None	Three patients in the comparator arm developed a mild-degree of post-inflammatory hyperpigmentation with total clearance at the end of the treatment period.	2b
Mazurek et al 2016 [68]	RCT OL	60 females (20 in each arm)	I-III	AZA: 10% d-panthenol: 10% BD	AZA: 5% pyruvic acid: 5% BD	24 weeks	Mexameter	The reduction in pigmentation in the treatment and comparator arm was comparable	Maximum reduction in pigment was noticed in the initial 12 weeks	None	2b
Akl EM, 2021 [69]	Open label, 2-group	50 females (25 in each group)	Egypt	Liposomal 20AZA cream OD plus oral tranexamic acid (250 mg OD)	HQ 4% cream (OD) plus oral tranexamic acid (250 mg OD)	12 weeks	MASI	Reduction in the MASI score from baseline	-	Patients using adjuvant liposomal 20% AZA showed significantly more improvement than 4% Hydroquinone. No ADR reported.	3
Kirsch et al, 2019 [70]	Pilot study	16 patients	USA	Novel combination cream containing tazarotene 0.075%, AZA 20%, tacrolimus 0.1%, and (microfine) zinc oxide 10%	-	20 weeks	MASI	Change in the MASI score by 8 points from baseline	-	25% patients reported MASI reduction by less than 8 points. Improvement started 4-weeks onwards. No ADR was noted	4
Arbutin											
Morag et al 2014 [71]	RCT DB	50 melasma 52 lentigo solaris all women	Polish	2.51% of arbutinin cream twice daily (obtained from leaf of five-leaf serratula) n=54	Placebo N=48	8 weeks	Mexameter	Reduction of melanin was observed in 22 melasma patients, representing 75.86% of the study group.	• None	None	1b
Ertam et al, 2008 [72]	Randomized, prospective, 3-arm open-label study	30 patients (10 in each group)	Turkey	Arbutin (1%), ellagic acid (1%), and ellagic acid plus plant extract (each 1%)- 3 groups	-	6 months	Melanin index	Maximal reduction of melanin index noted with arbutin gel (29%), compared to elagic acid (21%) and elagic acid-plant extract combination.	• None	None	IIb
Retinoids											
Truchuelo et al 2014 [75]	RCT DB Split face	28 (27 females and 1 male)	II- IV	Combination of retinoids and depigmenting agents twice daily	Placebo	12 weeks	Hemificial MASI	The side treated with active agent achieved a MASI reduction of 74% vs. a reduction of 55% on the side that received the vehicle with SPF.	• 60% of the sides treated with active agent achieved moderate to intense improvement a per PGA compared to 42% of placebo treate sites	Minimal and comparable on both sides	1b
Nanda et al 2004 [77]	RCT DB	50 (40 females and 10 males)	III- V	2% HQ once daily for 2 weeks as priming agent prior to Trichloroacetetic Acid (TCA) peel	0.025% tretinoin once daily for 2 weeks as priming agent prior to TCA peel	24 weeks (12 weeks treatment phase + 12 weeks follow-up phase)	Hyperpigmentation Area Severity Index scoring	In 2% HQ group continued improvement was seen in 24%, maintained results in 48% and worsening in 28% of patients. In 0.025% tretinoin group continued improvement was seen in only 16%, maintained results in 44%, and worsening in 40%	• None	Erythema and irritation were mild and equally present in both groups	1b
Da Silva Bergmann et al. [78]	RCT SB	42 women	I–IV	Microneedling and 5% retinoic acid for 6hours : 2 sessions at a gap of 2 weeks.	5% retinoic acid alone for 6 hours : 2 sessions at a gap of 2 weeks.	60 days	MASI	Reduction in MASI score was observed at 60 days for both treatments, with no differences between treatment	None	None	2b
Vitamin C (Ascorbic Acid)											
Huh et al' 2003 [79]	RCT, DB, placebo controlled	29, females	Korean II-IV	Vit C iontophoresis, 29-one half face. Iontophoresis was performed for 8 min. In particular, 6 min was specifically allowed to treat the melasma lesion on each visit. The patients were treated twice a week, for 12 weeks	Mineral water iontophoresis, 29 other half face . Iontophoresis was performed for 8 min. In particular, 6 min was specifically allowed to treat the melasma lesion on each visit. The patients were treated twice a week, for 12 weeks	12 weeks	Change in luminance (by colorimeter)	A significant decrease in the L (luminance)value (from 4.60 to 2.78, p = 0.002), compared to that of the control site (from 4.45 to 3.87, p = 0.142)- at 12 weeks	None	Mild sense of electric shock 6 (21%) Itching 2 (7%) Erythema 2 (7%) Burning sensation 1 (3%) Dryness of face 1 (3%)	1b
Chen et al 2019 [80]	Retrospective, Comparative study	30, females in each group. Total 60	IV	Five sessions of Q-switched NdYAG laser therapy monthly followed by transdermal delivery of vitamin C via sonophoresis	Q switched Nd YAG Laser alone at monthly intervals	6 weeks	mMASI	After treatment, the mMASI scores in the combination treatment group was significantly lower than the laser only group (P < 0.001)	Chloasma area and colour scores reduced significantly more in the combination group	Xerosis, pigmentation, recurrence	3b
Menon et al 2020 [81]	Split face, Comparative study	30 females	IV-VI	30 patients, left side of face- microneedling with 20 % vit C at 0, 4 weeks	30 patients, right side of face- microneedling with TXA at 0, 4 weeks	4 weeks	MASI, PGA, PtGA	The total MASI reduced from 268 at baseline to 246 with TXA and 258 with Vitamin C at the end of 4 weeks. At the end of 8 weeks, it further reduced to 213 with TXA and 235 with Vitamin C. P value >0.05	None	10 (33.3%) complained of mild itching and burning sensation, which resolved spontaneously	1b
Cysteamine cream											
Mansouri et al 2015 [82]	DB, RT	53 pts. Female and male, 18-50 years	III-IV	28: 5% cysteamine cream once daily	25 : placebo cream once daily	2 and 4 months	Mexameter scores, MASI, IGA	After 2 and 4 months application of cysteamine and placebo cream, the mean differences in mexameter scores between pigmented and normal skin were 39.7 ± 16.6 and 26.2 ± 16 in cysteamine group, and 63.8 ± 28.6 and 60.7 ± 27.3 in placebo group, respectively	At the end of the treatment, the MASI scores were significantly lower in the cysteamine group vs. placebo (7.2 ± 5.5 vs. 11.6 ± 7.9, p = 0.02). The Investigator Global Assessments and patients' viewpoints indicated significant efficacy of cysteamine cream in contrast to placebo.	13 patients in the cysteamine group reported some degrees of adverse effects. The degree of adverse effects was rather mild in these patients, except for two of them who showed higher degrees of erythema and had to be treated with a topical corticosteroid for a few days	1b

Farshi eta al 201[83]	DB, Prospective Comparative	40 males and females	III-IV	Cysteamine cream once daily, 20	Placebo cream once daily, 20	2 and 4 months	MASI Photography, Mexameter, IGA, New instrument- Dermacatch	At 2 months, the mean differences were 38.1 ± 15.3 (Dermacatch®) and 49.9 ± 19 (Mexameter®) in the cysteamine group and 64.9 ± 25.3 (Dermacatch®) and 68 ± 26.2 (Mexameter®) in the placebo group. At 4 months, the mean differences were 23.8 ± 12.9 (Dermacatch®) and 35.5 ± 16.1 (Mexameter®) in the cysteamine group, and 50 ± 18 (Dermacatch®) and 51.2 ± 16.8 (Mexameter®) in the placebo group. Statistically significant differences were found between the cysteamine and placebo group outcomes at both time points (p = .01, p = .02).	At the end of the treatment period, MASI scores were significantly lower in the cysteamine group versus placebo (8.03 ± 5.2 vs. 12.2 ± 7.4, p = .04). IGA scores and patient viewpoints indicated significant efficacy of cysteamine cream versus placebo.	Seven patients in the cysteamine group reported some adverse effects. The degree of these effects was rather mild and tolerable in these patients and was resolved by continuing the treatment. In the placebo group, no patient complained of any adverse events No significant differences in erythema, dryness, itching, burning sensation, and irritation.	2b
Lima et al 2020[84]	Quasi-RCT DB	40 patients, females	II-IV	20 topical 5% cysteamine OD	20 4% hHQe OD	60 and 120 days	m MASI, Melasqol, colorimetric luminosity assessment, global aesthetic improvement scale(photograph)	HQ-group showed early (T60) improvement in mMASI scores (41%) than cysteamine(24%) and a final (T120) superior MELASQoL reduction.	Colorimetric assessment disclosed progressive depigmenting in both groups without any difference between them (P > 0.160).	Sulfur like odour; one patient developed headache due to odour with cysteamine- ; 20 % in cysteamine- erythema and burning sensin	1b
Karrabi et al 2021[85]	DB RCT	50	-	25 each 5% Cysteamine cream OD (15 min exposure)	25 Modified Kligman Formula (MKF) : daily at night	2 months, 4 months	mMASI	After 2 months: mean mMASI score decreased to 9.25 (2.78) in the MKF group and to 8.46 (2.61) in the cysteamine group, with no significant difference being found at this point (P = .320). At the end of month 4: the mean mMASI score was 7.04 (2.23) in the MKF group and 6.09 (2.01) in the cysteamine group (P = .122). The cysteamine treatment was able to decrease the mMASI score to a greater degree (32.3%, 51.3%) compared to MKF (23.7%, 42.3%) at 2 and 4 months, respectively, and these differences were strongly statistically significant (P = .005 and .001 in turn).	None	Overall, a minority of subjects in the cysteamine group reported adverse effects, with the degree being mostly reported as mild by these subjects. In fact, cysteamine cream did not induce any severe skin irritation and was significantly better tolerated than MKF. However, few in cysteamine group complained of bad odour which did not necessitate discontinuation.	1b
Karrabi et al*, 2020[86]	SB, RT	54 5 males 49 females	III, IV	TA mesotherapy (4mg per ml) every 4 weeks	Cysteamine 5% cream 30 min before bedtime OD	4 months treatment 8 weeks follow up	mMASI, Dermatech Device	mMASI scores were substantially improved in both groups at the and) as compared to Baseline (cysteamine vs TA: 11.68 ± 2.70 and 10.43 ± 2.69) Second visit (cysteamine vs TA 8.48 ± 2.34 and 7.03 ± 3.19; P = 0.359) Third visit (cysteamine vs TA 6.32 ± 2.11 and 5.52 ± 2.55; P = 0.952	Dermacatch® values were significantly declined, although the improvement rates between two groups were not significantly different Baseline (cysteamine vs TA 45.76 ± 13.41 and 42.41 ± 10.48) • Second and Third visits (cysteamine vs TA 42.54 ± 12.84 and 38.75 ± 9.80, P = 0.365; 40.74 ± 12.61 and 36.17 ± 10.3, P = 0.123, respectively)	Complications are less in the cysteamine than the TA mesotherapy group Erythema, itching, burning, and irritation ($P < 0.001$) Dryness ($P = 0.844$)	1b
Rucinol cream											
Khemis et al 2007[87]	DB, RCT, bilateral (split-face) comparative trial	32 women	-	32 split face- rucinol 0.3% serum BD	32 split face vehicle BD	4, 8, 12 weeks- phase 1 Phase 2- optional open full face rucinol reatment. Reviews at 16,20,24 weeks	clinical evaluations by a dermatologist, chromametry, ultraviolet and standard photography, and assessments of skin acceptability and tolerability	After 12 weeks, the clinical pigmentation score for rucinol-treated skin was significantly lower than for vehicle-treated skin (P ¼ 0.E027). Phase 2, rucinol induced a significant reduction in mean pigmentation score on the half of the face previously treated with vehicle. Chromametry measurements showed that skin was significantly lighter, with a strong trend towards reduced redness, following rucinol therapy compared with vehicle	• Rucinol serum showed good tolerability and acceptability and was considered to have go or fair efficacy by 78% of the patient popula	Very few instances of stinging, burning or pruritus were reported by patients for either study product, all were mild in intensity. Investigators observed a very low frequency of erythema, dryness, peeling and desquamation, and no effects with a greater than mild intensity	1b
Huh et al 2010[88]	RCT DB Split face	20 females	Korean	4-n-butylresorcinol 0.1% cream each side of face BD	Vehicle each side of face	8 weeks.	Mexameter measurements were performed along with photography at baseline, 4 weeks and 8 weeks	Mexameter measurements demonstrated that the melanin index of the treated side showed a significant decrease when compared with that of the vehicle-treated side after 4 weeks (p=0.006) and after 8 weeks (p<0.0005).	None	Adverse effects mild and transient Mild erythema and itching in 10 %- self limiting	1b
Huh et al 2010[89]	Randomized, DB, vehicle-controlled and split-face comparison study	23 females	Korean	Liposome encapsulated 4-n-Butylresorcinol 0.1% cream each side of face BD	Vehicle each side of face	8 weeks	Mexameter measurements were performed along with photography at baseline, 4 weeks and 8 weeks	Melanin index of the 4-n-butylresorcinol-treated side showed a significant decrease when compared with the vehicle-treated side after 8 weeks (P = 0.043).	• All patients completed the questionnaire and assessed their improvement subjectively. After 4 weeks, 4.3% and 43.5% of patients graded their improvement on the 4-n-butylresorcinol-treated skin as excellent or good, respectively. After 8 weeks, 65.2% of patients rated their response as excellent (13.0%) or good (52.2%)	No adverse reactions were observed throughout the study	1b
Tranexamic Acid (topical, injectable)											
Atefi et al*, 2017[91]	RT, DB	60 F	-	TA%5 BD	HQ 2% BD	BD for 12 weeks	MASI	Mean MASI scores Baseline Group A 4.80 ± 1.06 Group B 4.37 ± 0.93, (p = 0.098) At end of treatment Group A 2.33 ± 0.71 Group B 2.30 ± 0.65, (p = 0.850)	Patient Satisfaction level Group A 33.3% Group B 6.7% • (p = 0.015)	TX 5% - No side effects HQ 2% - erythema and skin irritation in 10% patients (p = 0.131)	1b
Banihashemi et al*, 2015[92]	DB, Split Face, comparative trial	23, female	III, IV, V	5% liposomal TA twice daily	4% HQ twice daily	12 weeks treatment One month follow up	MASI	MASI scores 5% TA Group (P < P = 0.001) Baseline - 14.72 ± 2.2 12 weeks -7.69 ± 2.4 4% HQ Group (P < P = 0.001) Baseline 14.60 ± 2.3 12 weeks 7.86± 3.5 A greater decrease was observed with 5% liposomal TA, although this difference was not statistically significant		Irritation occurred in three patients with HQ	1b
Husseiny et al*2020[93]	Split Face, Comparative	100 female	II, III, IV	TA 5% cream (liposomal) on right-sided facial lesions two times	HQ 4% cream on left-sided lesions at night	12 weeks treatment	Hemi MASI, MELASQOL, area% of melanin through histopathological examination	No significant difference in treatment response regarding Hemi MASI, MELASQOL scores and Antera average level of melanin (P > .05)	Significant reduction in area % of melanin was recorded with TA 5% than HQ 4% creams (P = .000) TA 5% - 8.21 ± 4.48 • HQ 4% - 12.46 ± 4.48	TA 5% - No side effects HQ 4% cream - Skin irritation, erythema, and burning sensation (21.21%) and post inflammatory hyperpigmentation (2%)	2b
Ebrahimi et al, 2014[94]	DB, Split Face, RCT	50	-	Topical solution of 3% TA on one side of the face, two times a day	Topical solution of 3% HQ+ 0.01% dexamethasone on other side two times a day	12 weeks treatment	MASI	Mean MASI score Group A (P < .00) Baseline (31.68 ± 10.32 End 10.76 ± 9.43 Group B (P < .00) baseline (29.52 ± 11.72 End 10.48 ± 7.84 No significant difference between them during the study (P < 0.05)	• No differences were seen in patients' and investigator's satisfaction of melasma improvement between two groups (P < 0.05	Side effects of hQ + dexamethasone were significantly prominent compared with TA (P = 0.01)	1b
Fioranelli et al*, 2020[95]	RCT, DB, Polycentric	60 F	IV	Group A – multiple ingredients cream BD	Group B multiple ingredients cream plus TA BD Group C – Placebo cream BD	Twice daily for 10 weeks	MASI, MI	MASI scores declined significantly in groups A and B compared to group C (P < .05).	Cream B, containing tranexamic acid, resulted superior to cream A in subjects with hypervascular melasma		1b
Hassan A et al, 2018[96]	Split Face, Comparative	30 Female patients	III, IV, V 6 IV 20 V 4	1% flutamide gel right side at night	5% tranexamic acid gel left side at night	12 weeks	mMASI score	mMASI score Group A Baseline - 3.34 ±1.88 At 12 weeks - 2.94 ± 1.83 P = 0.007 Group B Baseline - 3.72 ± 1.7 At 12 weeks - 1.63 ± 1.34 P = 0.002 Intergroup P = 0.001	• There was significant difference between the studied groups, as regards the patient satisfaction (P =0.017), with the better results on side B	No side effects	1b
Malik et al, 2019[97]	RCT	100	-	Oral TA 250 mg BD with topical 3% TA BD	Oral TA 250 mg BD with topical 20% azelaic acid BD	6 months treatment 6month follow up	MASI	mean MASI score was significantly less in group A (6.06 ±5.06 vs. 10.62 ±7.43) in group B (p<0.001)	• In group A, 14 (28%) had excellent response whereas in group B, 11 (22%) had excellent results	No major adverse events	1b
Budamakuntlae t al, 2013[98]	OL, Randomised comparative	60 6 M 54 F	IV V	TA microinjections monthly	MN + TA monthly	3 sessions 3 months follow up	mMASI, patient global assessment and physician global assessment	mMASI microinjection group, Baseline -6.93 ± 2.16 End of follow up 4.45 ± 1.69 $P < 0.01$ Microneedling group Baseline 9.11 ± 4.09 end of follow-up 5.06 ± 2.14 $P < 0.001$ Both Groups - $P = 0.299$	Six patients (26.09%) in the microinjections group, as compared to 12 patients (41.38%) in the microneedling group, showed more than 50% improvement	No major adverse events observed in both the groups apart from mild discomfort, burning sensation and erythema	2b

Saki et al*, 2018 [99]	RCT, Split Face	31 F	II, III, IV	TA microinjections monthly for 3 sessions on one side of face	HQ at night for 3 months for other side of face	3 months	Melanin value, Erythema value	Melanin value TA group Baseline – 614.8 ± 51.3 3 months follow up 575.2 ± 49.7 HQ group Baseline – 611.9 ± 51.5 3 months follow up 583.4 ± 52.3 Intragroup (p value <.001) Intergroup (p value =.17)	No difference was observed for erythema during the treatment (p values of .085 for TA side and 0.5 for HQ side) VAS statistically supported TA (5.9 ± 1.8 vs. 3.9 ± 2.5, p values <.001	One had burning pain during injection and the other two developed acne in TA group	1b
Pazyar et al*, 2019 [100]	Split Face, RCT	41F	II, III, IV, V 4 III 19 IV 16 V 2	TA microinjections 2weekly 4mg/ml (right) 4% HQ BD (left)	TA microinjections 2weekly 10mg/ml (right) 4% HQ BD (left)	12 weeks treatment , 12 weeks follow up	MASI	No statistically significant difference was observed between the MASI score in groups A 4mg/ml and B 10mg/ml, comparison of TA at the concentration of 4 mg/ mL compared to the 4% HQ cream showed that the MASI scores in the eighth week (P=0.02) and the 12th week (P=0.02) were significantly less in the HQ group. However, no significant difference was observed between the MASI score changes in Group B (10 mg/mL) and the 4% HQ group.	Patients in group A had higher satisfaction than patients in group B (P=0.001)	TA group - injection site burning pain HQ group - No adverse effect was seen in the	1b
Kaleem et al*, 2020[101]	Split Face, CT	60 54 F 6 M	III, IV, V	TA microinjections 2weekly 4mg/ml	Normal Saline (NS) two weekly	12 weeks treatment	H-mMASI	Group A Baseline 3.19 ±2.57 End 1.52 ± 1.2 (P < 0.05) Group B Baseline 3.46 ± 2.7 End 3.45 ± 2.6 (P > 0.05)	Total of 90% patients showed good to excellent satisfaction level at the end of study on TA side	Erythema, swelling, and burning on both sides	2b
Tehranchinia et al*, 2018 [102]	DB, Split Face, RCT	55 49 F 6 M	II, III, IV	TA microinjections monthly+ 4% HQ daily night	4% HQ daily night	16 weeks treatment 4 weeks follow up	MASI, patient's satisfaction score	MASI score TA + HQ group Baseline – 5.16±1.8716 weeks 1.76±0.98 HQ group Baseline – 5.20±1.93 16 weeks 2.92±1.21 Intragroup (p value <.01) Intergroup (p=0.001)	Patient satisfaction with treatment was significantly higher in the TA + HQ group (P < 0.001)	The difference between the two groups regarding side effect occurrence was not statistically significant (P = 0.43)	1b
Sharma et al*, 2017 [103]	Comparative	80	IV	TA 250 mg BD	TA microinjections monthly 4mg/ml	12 weeks treatment	MASI	MASI percentage reduction at 12 weeks Group A77.96 ± 9.39 Group B 79.00 ± 9.64	Two patients in group A had relapses at 24 weeks	Group a - Mild epigastric discomfort, hypomenorrhea, headache and injection site pain	2b
Meymandi et al*, 2020 [104]	SB, RT	60 F	II, III, IV, V	MN+TA 4% monthly	4% HQ night	12 weeks treatment	MASI, patient and physician assessments at 4th, 8th and12th weeks	Mean MASI score Group A (P < .01) Baseline (12.89 ± 5.16) End 6.84 ± 4.31 Group B (P < .01) baseline (13.56 ± 4.88 End 7.16 ± 4.38) No statistical difference between 2 groups (p = .77)	No statistical difference between 2 groups Physician and patient assessment (p = .529) (p = .721)	Erythema %; $\chi 2$ = 21.7, P < .01), Group A (83.3%) Group B (23.3%) but it was usually disappeared after 3-5 days of the treatment. PIH (P = .33) Group B (13.3%) Group A (6.7%),	1b
Ibrahim Tahoun et al, 2021 [105]	Split Face, SB	30, F	-	4 weeks modified kligman at night Then MN+TA (R)	4 weeks modified kligman at night Then MN+ Vit C (L)	5 biweekly sessions	MASI, $MASI_{dit}$ and $MASI_{rd}$, VAS, DLQI t weeks 0, 4, 12, and 16	MASI decreased significantly (p < .001) in both groups	• Significant diminution in dark fine granules value < .001), homogeneous pigmentation (p value = .005) and pseudoreticular brown network (p-value = .028). However, telangiectasia significantly improved only o TXA treated side (p = .002). DLQI improve significantly on both sides (p < .001)		1b
Xing et al, 2020 [106]	RCT	50	III, IV	Group A 1.8% liposomal TA BD	Group B MN+TXA 5% weekly Group C – 2% HQ at night	12weeks treatment	MI, EI, Dermatoscopy and reflectance confocal microscopy	Improvement of MI in MN +TA group and HQ is higher than liposomal TA group. EI was significantly diminished in liposomal TA group and MN +TA group.	Dermatoscopy and reflectance confocal microscopy revealed decreased brown granules in all groups and reduced telangiectasia in liposomal TA group and MN + TA group	Transient erythema 1 patient (Group B) Aggravated pigmentation 4 patients (Group A)	1b
Yang Xu et al, 2017 [107]	Split Face, RCT	28, Female	III, IV	MNs, followed by topical 0.5% TA solution weekly	sham device plus topical 0.5% TA solution weekly	12 weeks	MI, parameters determined by Visia, Patient satisfaction scores and the biophysical parameters measured by Mexameter	MI was significantly less on the combined side at week 12 (P=.002) EI value no statistical difference between sides at both the beginning and the end of the entire follow-up period (MNs plus TA: P=.05; TA: P=.08)	Transepidermal water loss, roughness, skin hydration, skin elasticity, and erythema index showed no significant differences between 2 sides	No obvious adverse reactions	1b
Chung et al*, 2016 [108]	RCT, Split Face	13 female	-	4 IPL monthly session Topical TA during and after treatment	4 IPL monthly session Topical vehicle during and after treatment	12 weeks follow up	MASI, MI	mMASI score Topical TNA side (14.77±4.55 to 9.38±5.49, p=.003) Vehicle side (10.62±6.67 to 9.15±6.30, p=.306)	Mean MI score Topical TNA side (39.55±29.76 to 9.72±32.60, p<.001) Vehicle side (48.51±32.29 to 33.06±36.47, p=.079) The efficacy of topical TNA in preventing rebound pigmentation after IPL treatment was also statistically significant	No serious adverse events reported	1b
Laothaworn et al*, 2018 [109]	Split Face, DB, RCT	25 24 F 1 M	III-V	3% TA for 8 weeks on one side of face BD QSNYL at baseline and 4 weeks	Vehicle for 8 weeks on other side BD QSNYL at baseline and 4 weeks	8 weeks	mMASI scores, Mexameter™, and participants' evaluation	mMASI score significantly decreased in the combination treatment (p < 0.05), while no significant changes were observed in the laser-alone treatment	Mean MI score Combination group(p = 0.016) Laser alone – not significant Intergroup – not significant More than 80% of the participants noticed a >50% improvement on the side with combination therapy at every follow-up visit	No serious adverse events	1b
Tawfic et al*, 2018 [110]	Split face, RCT	30, F	III , IV	Low-power (12 Watts) fractional ablative CO_2 laser and TA (topically or intradermal injection) after or before laser	Low-power (12 Watts) fractional ablative CO_2 laser	every 4-6 weeks for five consecutive sessions	MASI, MI, and EI	Improvement in MASI score and EI Fractional CO_2 laser alone > fractional CO2 laser and topical TXA, > fractional CO2 laser and intradermal TXA	Improvement in MI Fractional CO_2 laser combined with intradermal injection of TXA > fractional CO_2 laser alone; but not significant Patient satisfaction did not differ among the used three treatment modalities (P-value 0.879)	Minimal complications occurred in the form of mild pain (100%)	1b
Rungsima et al*, 2020 [111]	Split face, DB, RCT	46 44 F, 2 M	III , IV, V	Fractional 1927-nm thulium laser (FTL) both side, TA after treatment to one side	fractional 1927-nm thulium laser (FTL) both side and normal saline solution (NSS) to the contralateral side	4 treatment sessions 6 months follow up	MI, mMASI, patients' self-assessed improvement scores	By the 6th month, significant differences in MI and mMASI scores from baseline were still noted with no significant difference between groups, except in the MI for controls	The patients' self-assessment showed similar patterns	No serious adverse events were reported for either group	1b
Miscellaneous Agents											
Kataoulis et al 2014 [112]	RCT DB	n=37, all females	I-II	Undecylenoyl phenylalanine (UP) 2% cream twice daily for 2 weeks, n=20	Vehicle/ Placebo twice daily for 2 weeks, n=17	12 weeks	Clinical efficacy (5-point scale; 1=mild, 5=severe). Patient assessment (4-point scale)	• UP group 85% (n=17) partial response, 11=moderate and 6=marked improvement. No patient showed complete clearance. • Vehicle group□ 23.5% partial improvement, 76.4% remained stable or worsened. • The difference in response was significant. Lightening of skin lesions noted 4 weeks onwards (1st FU)	Most of the patients on active treatment were happy with the result. Seven were "extremely satisfied" (35%), nine were "satisfied" (45%), and four remained "neutral" (20%) when assessing the result.	Minor ADRs noted which resolved spontaneously. UP group (30%) and vehicle group (11.7%) developed transient erythema, burning and stinging.	1b
Channakeshavaiah et al, 2020 [113]	RCT DB	N=40, M:F 7:33	IV-V	30% Metformin lotion (n=20)	TCC (hydroquinone 2% + tretinoin 0.025% + fluocinolone acetonide 0.01%), [n=20]	Once at night for 8 weeks	MASI, Global improvement scale (1-4), Patient satisfaction	• MASI scored reduced significantly in both groups at 8 weeks. Inter-group difference was not statistically significant (p=0.1)	Global improvement and Subjective assessment scores were comparable between both groups.	Metformin group □ No ADR; TCC □ 10% burning sensation, 5%--> burning with redness; p<0.001.	1b
Lyons et al, 2018 [114]	DB Split Face PC	N=15, all female	II-III	Topical Epidermal Growth Factor (EGF) serum	Placebo	Twice daily for 8 weeks	Physician Global Aesthetic Improvement Scale (GAIS), MelasQoL	Improvement in Melasma (GAIS) noted in 73.4% (topical EGF) side compared to 13% (placebo side).	73% Melasma patients showed improvement in MelasQoL.	No ADRs reported with topical EGF or placebo	3b
Mohamed et al, 2018 [115]	OL Comparative Split Face	N=22, all females	IV	Fractional Er:YAG laser + topical corticosteroids (mometasone)	Fractional Er:YAG laser	Both sides of face treated with 6 laser sessions, 2 weeks apart. Mometasone applied on left	MASI, Histopathology (MPSA-Melanin particle surface area), Immunochemistry (number of MART1 positive cells)	• MASI score, MPSA and number of MART-1 positive cells reduced significantly on both left and right sides of face. • However, better improvement on combined T/t side (left). Combined therapy was more beneficial for Fitzpatrick skin type 3 than type 4.	-	No serious ADR detected with either treatment modality.	3b

						side only after each session, once at night for 1 week.					
Bavarsad et al, 2021*[116]	DB RCT PC	N=22, all females	IV-V	Cream containing 0.05% tomato lycopene and 3.45% wheat bran extract, (n=11)	Placebo, (n=11)	Twice daily for 3 months	MASI score, rate of skin discoloration, size of melasma	● MASI score and rate of skin discoloration reduced significantly in intervention group (vs. placebo). Significant improvement started 6 weeks onwards.	Size of melasma reduced significantly in study group. No recurrence occurred one month after end-of-treatment.	No significant ADRs reported in either group.	1b
Lee et al, 2002 [117]	DB PC RCT	N=47, all females	IV	Group B (n=16)- 2% LM (Lincomycin) mixed with 0.05% BV (Betamethasone valerate) Group C (n=16)- 2% LM + 0.05% BV+ 2% LA (Linoleic acid)	Placebo, n=15 (Group A)	Once at night for 6 weeks	MASI score, Objective assessment	● MASI score reduced significantly in Group C, compared to Group A. No statistically significant difference between Group A and Group B.	43.7% in Group C reported moderate improvement in objective assessment, compared to 12.5% in Group B and none in Group A.	No significant adverse effects reported.	1b
Murtaza et al,2016 [118]	RCT OL	N= 148. M:F= 24: 124	IV	Group A= 20% trichloro-acetic acid peel (once weekly) plus 5% topical magnesium ascorbyl phosphate cream (once daily), n=74	Group B= 20% trichloro-acetic acid peel (once weekly), n=74	Both arms continued for 6 weeks.	MASI score	Significant MASI score reduction was seen in 81.1% patients in Group A, compared to 66.2% patients in Group B (p=0.04)	-	No significant adverse effects reported.	1b
Draelos et al, 2015 [119]	Split Face Randomized cohort	N=60 women	II-III	Cohort 1= Topical lignin peroxidase twice daily vs. no treatment Cohort 2= Topical lignin peroxidase twice daily vs. generic HQ	Cohort 1= No treatment; cohort 2= generic HQ	12 weeks	Dermospectrophotometer, Investigator (MASI) and subjective assessment	● Significant improvement in skin texture, roughness and overall appearance with lignin peroxidise vs no treatment (cohort 1) at week 2. ● Significant reduction in MASI score and dermospectrophotometer score improvement with Lignin peroxidise (vs no treatment). Cohort 2= parity between Lignin peroxidise and HQ, but Lignin peroxidise statistically superior with respect to skin texture and roughness.	-	No significant adverse effects reported.	3b
Yousefi et al, 2014[120]	DB PC RCT	N=93, 82 patients completed the study	IV-V	Topical zinc sulfate 10% solution	Topical hydroquinone 4% solution	Topical preparations applied OD for 2 months, followed up for 3 months post treatment using only sunscreens	Melasma Area and Severity Index (MASI)- Baseline, 2 and 5 months, Adverse drug reaction assessment	The MASI score fell significantly in both groups, but a greater decrease was seen in those who received hydroquinone (43.5 ± 15.5% vs 18.6 ± 20.8%, p < .001).	-	Post-inflammatory pigmentation occurred in 5.2% of the zinc group and irritation in 30.9% of the hydroquinone group.	1b
Bagatin et al, 2020 [121]	RCT	N=42	V	Group A (n=14)= Topical olive extract containing hydroxytyrosol, Group B (n=14)= Systemic olive extract containing hydroxytyrosol,	Group C (n=14)= Control group	90 days, once daily treatment	Melasma Area and Severity Index (MASI), Melanin index and erythema index	All parameters improved more in oral treatment arm, compared to topical and control groups, but not statistically significant. However, oral treatment evaluated paired by time showed a significant reduction in mMASI (p <0.0001) and melanin index (p = 0.0466) after 60 days.	-	No significant ADR reported	1b
Mohammad et al, 2014 [122]	Split Face, Comparative	N=30	IV-V	Picolinamide cream 5%, once at night, on right side of face	Hydroquinone cream 2%, once at night, on left side.	8 weeks, once daily application	Amount of epidermal melanin (colorimeter), amount of skin erythema	The epidermal melanin content reduced significantly with both creams. However, NO significant difference observed between two sides.	No significant reduction in skin erythema in either group.	Both topical applications were safe.	3b
Zubair and Mujtaba, 2009 [123]	Randomized, comparative (3-arm)	N=90	V	Group B (n=30)- 4% Liquiritin Group C (n=30)- 2% Liquiritin	Group A (n=30) 4% Hydroquinone	16-weeks, once at night application	MASI, size of melasma lesion, photographic improvement	73.3% , 96.7% and 86.7% patients improved with 4% HQ, 4% Liquirtin and 2% Liquirtin respectively. Topical Liquirtin 4% is significantly more effective than topical 2% Liquirtin and 4% HQ. Topical 2% Liquirtin is significantly more effective than 4% HQ.	-	No patient developed any complication	1b
Arrowitz et al, 2019 [124]	DB, RCT, Split Face	N=59	II-III	Group A (n=31)- Topical thiamidol (0.2%) vs control (split face). Group B (n=28)- Topical thiamidole (0.2%) vs topical HQ (2%).	-	12 weeks, once at night application	Modified MASI (mMASI), Self-assessment of pigmentary changes (Griffith 10-point scale).	Improvement with thiamidol was significantly more compared to control. Thiamidol side showed significantly reduced mMASI compared to 2% HQ. 79% patients improved with thiamidol, compared to 61% with HQ.	96.4% and 57.1% patients perceived improvement with thiamidol and HQ respectively.	No ADR reported	1b
Sanchez et al 2009 [125]	RCT OL	96 females (66- Dioic acid (DA) group) (30- Hydroquinone (HQ) group)	III	1 % dioic acid cream BD	2 % HQ cream BD	12 weeks	MASI	Significant differences between the MASI scores from baseline to the end of the study in both groups: ● DA (14.52 ± 3.4 vs. 6.05 ± 1.2, P 1⁄4 0.001) ● HQ (15.22 ± 2.4 vs. 6.34 ± 1.3, P 1⁄4 0.001) No significant differences between treatments	-	Side-effects were similar for both medications Pruritus was more common in patients with HQ. Acneiform reaction was more prevalent in patients with DA	2b
Thirion et al [126]	RCT DB	27 females	III	Composite whitening product (Thiospot intensive) BD. Mixture of ethyl linoleate, thioctic acid (a-lipoic acid), octadecenedioic acid, lactic acid and ethylhexyl methoxycinnamate	Non- skin lightening skincare formulation (Eucerin) BD.	12 weeks	Clinical and biometrological assessments: Visual pigmentation gradings on a 4-level linear scale (0: absent, 1: discrete 2: moderate 3: intense). ● Three complementary assessments were performed using Mexameter ● Visioscan VC98 Corneomelametry test	A significant reduction in the clinical rating of melasma pigmentation rated 2.60 ± 0.50 to 1.65 ± 0.67 (P < 0.001) was reached after 3 months in the whitening product group. No significant changes in the clinical pigmentation rating (2.71 ± 0.49) was seen in non-skin lightening product group at 3 months. The value of the M index progressively decreased during treatment by the whitening prod- uct (Table I). The reduction reached significance (P < 0.001) after 2 ()10%) and 3 months ()19%). No significant lightening effect was observed in the control group.	The intra-epidermal melanin quantification by the ULEV method revealed a significant reduction (P < 0.001) after 2 months ()29%) and 3 months (44%) of treatment with the whitening product. No significant changes were observed in the control group.	The amount of melanin in the stratum corneum as assessed by corneomelametry decreased significantly after 2 months ()10%, P < 0.01) and 3 months ()21%, P < 0.001) of treatment with the whitening product No significant changes were yielded in time in the control group.	1b
Adalatkhah et al 2015[127]	RCT DB	74 women: 2 groups	-	1% flutamide cream OD *Sunscreen (SPF 30)	4 % HQ cream *Sunscreen (SPF 30)	4 months	● Melasma Area and Severity Index (MASI) ● Mexameter melanin assay ● Patient satisfaction: 1 – improvement of melasma patches. 2 – satisfaction with drug and potential side effects 3 – skin succulence improvement 4 – skin darkness improvement; and 5 – overall satisfaction with treatment.	● Mean standardized total patient satisfaction score was 28.8 (standard deviation [SD] 17.2) in flutamide group patients versus 18 (SD 15.5) in control group (*P*<0.01). Regardless of treatment group, the skin darkness assessed upon MASI scales was reduced over the treatment course (*P*<0.001). ● Using mixed effects, longitudinal modelling showed better treatment efficacy based on MASI scale for flutamide group compared to the HQ group (*P*<0.05). However, longitudinal analysis of mexameter scores did not reveal any significant difference in melanin measurements between flutamide and HQ.	-	-	1b
Pratchyapurit et al 2016 [128]	RCT DB	38 females	Thailand	Combination of Diacetyl boldine (DAB) cream at night: 4% DAB with licorice extract, ascorbic acid, GA salicylic acid, alpha-arbutin DAB/TGF-b1 biomimetic oligopeptide-68/sunscreen cream in the morning: 4% DAB , 0.05% TGF-b1 biomimetic oligopeptide-68, ascorbic acid and broad spectrum UVA and UVB filters	2 and 4 % HQ	12 weeks	Manual MASI score and MASI score with instrumentally graded darkness at baseline, 6th week, and 12th week.	● Melasma showed improvement at the 6th week and 12th week as compared with baseline (P < 0.05). ● Each formula showed either more efficacy or exerted faster action on pigment reduction than HQ.	About 2.6% of subjects graded themselves markedly improved, 76.3% moderately improved, and 21.1% slightly improved.	None developed severe reaction. Most subjects had temporary, mild skin reaction.	1b
Alvin et al 2011 [129]	RCT	50 patients: 2 groups	-	75% mulberry extract oil OD	Placebo	8 weeks	MASI Mexameter reading Melasma quality of life score (MelasQOL)	The mean MASI score significantly improved from 4.076 (± 0.24) at baseline to 2.884 (± 0.25) at week 8 for the 75% mulberry group while the placebo group showed an improvement of a lesser magnitude. Mexameter readings for the mulberry group showed a significant drop from	The MelasQOL score also improved tremendously for the 75% mulberry group, falling from 58.84 (SD: ± 3.18) at baseline to 44.16 (SD: ± 4.29) at week 8, unlike the placebo group that showed a less dramatic improvement from 57.44 (SD: ± 4.66) at baseline to 54.28 (SD: ± 4.79) at week 8.	Only mild itching was reported in four patients from the 75% mulberry extract oil group 12 cases of either itching or erythema reported from the placebo group	1b

								355.56 (± 59.51) at baseline to 312.52 (± 57.03) at week 8 compared to the placebo group.			
Jiang et al 2018 [130]	DB, PC, RCT	25 female subjects with moderate to severe melasma	II-IV	Trifecting night cream OD with sunscreens and cleansers	Sunscreens and cleansers alone	8, 16, 24, and 28 weeks	MASI, IGA, Investigator's Melasma Severity Assessment, Investigator's Melasma Pigment Intensity Assessment Standardized digital photographs and self-assessment questionnaires	Statistically significant improvement in all clinical grading parameters, starting from Week 16. The improvements achieved after 24 weeks of product usage were largely sustained during the four-week regression period at week 28.	None	Mild erythema, itching, and dryness in 6 patients	1b
Levy et al 2005 [121]	Split-faced prospective trial	22 women with bilateral epidermal/ mixed melasma	French women i-vi	Topical application of Amelan M® (Kojic acid, phytic acid, buthyl methoxydibenzoylmeth ane) cream to one side of the face OD	Topical application of Mela D® (Mexoryl SX®, kojic acid, Lipohydroxyacid® (LHA)cream to other side of the face OD	Week 4, week 16	Modified MASI, Mexameter, Standardised photographs	Superior efficacy of Amelan M® over Mela D®	None	irritation and dryness of the skin in 18.2% with Amelan M® and 4.5% with Mela D®.	2b
Viyoch et al*, 2010 [132]	DB, RCT	60	IV	Trans-4-(aminomethyl) cyclohexanecarboxylic acid/potassium azeloyl diglycinate/niacinamide BD	Emulsion based control BD	8 weeks treatment	MASI, absolute melanin value between hyperpigmented skin and normal skin (RMV) moisture content, pH, and redness (erythema value)	The significant differences in MASI between the test and control groups were observed at weeks 4 (P = 0.005) and after 8 weeks of treatment P (0.027)	The significant differences in RMVs between the test and control groups were observed after 6 weeks of treatment, P (0.006)	The incidence of patients with AEs was not significantly different	1b

DB : Double Blind, RCT: Randomized Controlled Trial, UV: Ultraviolet, VL: Visible Light, HQ : Hydroquinone, MASI : Melasma Area Severity Index, FAHT : Fluocinolone Acetonide Hydroquinone Tretinoin, FA : Fluocinolone Acetonide, GSS : Global Severity Score, TC: Triple Combination, SB : Single Blind, OD : Once-a-day, BD: Twice-a-day, OL : Open Label, HA: hydrocortisone acetate, GA: Glycolic Acid, VAS: visual analogue scale, RA: Retinoic Acid, TXA: Tranexamic Acid, AZA : Azelaic acid FLT : Fractional Laser Therapy ,TTT: Triple Topical Therapy, TCC: Triple Combination Cream, QSNYL: Q-Switched Nd-YAG Laser, PDL: Pulse Dye Laser, IPL: Intense Pulsed Light, IGA: Investigator's Global Assessment, TA : Tranexamic Acid, PGA: Physician Global Assessment, MI : Melanin Index, mMASI : modified Melasma Area Severity Index, MelasQol: Melasma quality of life scale, PC : Placebo Controlled, Global Aesthetic Improvement Scale (GAIS), MPSA-Melanin particle surface area, RMV- Relative melanin value.

Grading of recommendation as per OCEBM – levels of evidence (March 2009). Level of evidence as per OCEBM 2011 – 1: systematic review of randomized trials, 2: randomized trial, 3: nonrandomized controlled cohort/follow- up study, 4: case series; case–control; or historically controlled studies. OCEBM: Oxford Centre for Evidence-Based Medicine [129]

1a : Systematic review (with homogeneity) of RCTs; 1b Individual RCT (with narrow confidence intervals); 1C All or none study

2A Systematic review (with homogeneity) of cohort studies; 2B Individual Cohort study (including low quality RCT, e.g. <80% follow-up); 2C"Outcomes" research; Ecological studies; 3A Systematic review (with homogeneity) of case-control studies ; 3B Individual Case-control study; 4-Case series (and poor quality cohort and case-control study

Supplementary Table 2: Summary of the studies included: systemic agents

Author, Year	Study design	Sample size/ gender	Skin phototype	Intervention arm	Comparison arm	Follow-up duration
Elkamshoushi *et al.*, 2021[137]	RCT	*N*=60 Female Group A=20 Group B=20 Group C=20	III-V	Oral TXA 250 mg twice daily×12 weeks (group A)	Oral TXA 250 mg twice daily + HQ 4% cream HS×12 weeks (group B) Oral TXA 250 mg twice daily×12 weeks with two sessions of 1064 nm low-fluence QSNd: YAG 4 weeks apart (group C)	36 weeks
El Hadidi *et al.*, 2021[138]	RCT (opaque envelope method)	*N*=45 (40) Female Group A=15 (14) Group B=15 (13) Group C=15 (13)	III-IV	Oral TXA 250 mg twice daily×8 weeks (group A)	ID TXA 100 mg/ml every 2 weeks×8 weeks (group B) ID T XA 4 mg/mL every 2 weeks×8 weeks (group C)	12 weeks
Minni *et al.*, 2020[142]	RCT (triple blinded)	*N*=130 (120) Group A=65 (61) (F—60, M—5) Group B=65 (59) (F—60, M—5)	III-VI	Oral TXA 250 mg twice daily + oral ranitidine 150 mg twice daily + sunscreen thrice daily + FbTC cream (HQ 2%, tretinoin 0.025%, 0.01% fluocinolone, acetonide 0.01%) on affected areas×2 hours nightly×12 weeks (group A)	Oral calcium lactate twice daily + oral multivitamins twice daily + sunscreen thrice daily + FbTC cream on affected areas×2 hours nightly×12 weeks (group B)	12 weeks and 24 weeks
Sahu *et al.*, 2020[143]	RCT	*N*=67 (60) (F—55, M—5) Group A=22 (20) Group B=25 (20) Group C=20	No mention	Oral TXA 250 mg twice daily + sunscreen×8 weeks (group A)	Topical TXA twice daily + sunscreen×8 weeks (group B) Modified Kligman's regimen (HQ 2%, 0.05% tretinoin, fluocinolone 0.01%) QHS + sunscreen×8 weeks (group C)	8 weeks

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Supplementary Table 2: Contd...

Author, Year	Study design	Sample size/ gender	Skin phototype	Intervention arm	Comparison arm	Follow-up duration
Shihab *et al.*, 2020[144]	RCT	*N*=50 Females Group A=25 Group B=25	IV-V	Oral TXA 250 mg twice daily + HQ 4% cream + sunscreen×20 weeks (group A)	Oral placebo twice daily + HQ 4% cream + sunscreen×20 weeks (group B)	48 weeks
Agamia *et al.*, 2020[135]	RCT	*N*=60 Females Group A=30 Group B=30	III-V	Oral TXA 250 mg once daily + sunscreen SPF 50×12 weeks (group A)	Oral TXA 250 mg daily + 1064 nm QSNd: YAG laser sessions every 2 weeks×12 weeks + sunscreen SPF 50 (group B)	24 weeks
Khurana *et al.*, 2019[139]	RCT	*N*=64 (F—54, M—10) Group A=32 Group B=32	IV-V	Oral TXA 250 mg twice daily×12 weeks (group A)	Localized microinjections TXA (4 mg–8 mg) once every 4 weeks×3 sessions (group B)	Once every 4 weeks×12 weeks
Yaghoobi *et al.*, 2019[140]	RCT	*N*=69 (59) Group A=34 (29) (F—28, M—1) Group B=35 (30) (F—28, M—2)	No mention	Oral TXA 250 mg twice daily×12 weeks (group A)	HQ 4% cream twice a day×12 weeks (group B)	24 weeks
Colferai *et al.*, 2018[145]	RCT	*N*=47 (37) (F—36, M—1) Group A=20 Group B=17	No mention	Oral TXA 250 mg twice daily + sunscreen SPF 50×12 weeks (group A)	Oral placebo twice daily + sunscreen SPF 50 (group B)	12 weeks
Del Rosario *et al.*, 2018[146]	RCT	*N*=44 (39) Females Group A=22 (18) Group B=22 (21)	III-V	Oral TXA 250 mg twice daily + sunscreen×12 weeks and then sunscreen only×next 12 weeks (group A)	Oral placebo twice daily + sunscreen×12 weeks and then sunscreen only×next 12 weeks (group B)	Once every 4 weeks×12 weeks and then at 24th week
Patil *et al.*, 2018[141]	RCT	*N*=90 Group A=30 (F—24, M—6) Group B=30 (F—22, M—8) Group C=30 (F—24, M—6)	IV-VI	Oral TXA 250 mg twice daily×12 weeks (group A)	TXA solution (5 mL) soaks twice daily×12 weeks (group B) TXA cream twice daily×12 weeks (group C)	12 weeks

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Supplementary Table 2: Contd...

Author, Year	Study design	Sample size/ gender	Skin phototype	Intervention arm	Comparison arm	Follow-up duration
Shetty *et al.*, 2018[147]	RCT	*N*=40 (37) Group A=20 (19) Group B=20 (18)	II-V	Oral TXA 250 mg twice daily + sunscreen SPF 30×12 weeks (group A)	Intradermal injections of TXA 0.05 ml (4 mg/ml) in each cm of melasma, once at three-week intervals×12 weeks + sunscreen SPF 30 (group B)	12 weeks
Rafi *et al.*, 2017[148]	RCT	*N*=140 Group A=70 Group B=70	No mention	Oral TXA 250 mg twice daily + sunscreen SPF 30×8 weeks (group A)	HQ 2% cream nightly + sunscreen SPF 30 (group B)	8 weeks
Padhi *et al.*, 2015[149]	RCT (open label)	*N*=40 Group A=20 (F—17, M—3) Group B=20 (F—15, M—5)	No mention	Oral TXA 250 mg twice daily + FbTC (0.01% fluocinolone acetonide, 0.05% tretinoin, and 2% HQ) (group A)	FbTC alone (group B)	8 weeks
Shin *et al.*, 2013[136]	RCT	*N*=48 (44) Females Group A=24 (23) Group B=24 (21)	III-IV	Oral TXA-based medication 750 mg/day (125 mg TXA, 53 mg coated ascorbic acid, 40 mg L-cysteine, 4 mg calcium pantothenate, and 1 mg of pyridoxine hydrochloric acid) × 8 weeks + low-fluence QSNd: YAG laser (two rounds at 4-week intervals) (group A)	Low-fluence QSNd: YAG alone at the same interval (group B)	8 weeks
Karn *et al.*, 2012[133]	RCT	*N*=260 Group A=130 (F—109, M—21) Group B=130 (F—108, M—22)	III-V	Oral TXA 250 mg twice daily + topical HQ + sunscreen×12 weeks (group A)	Topical HQ + sunscreen (group B)	12 weeks
Chowdhary *et al.*, 2021[150]	Comparative study	*N*=131 Group A=66 (F—58, M—8) Group B=66 (F—51, M—15)	IV	Group A oral TXA 250 mg once daily for 16 weeks	Group B—oral TXA 500 mg twice daily for 16 weeks	12 weeks

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Supplementary Table 2: Contd...

Author, Year	Study design	Sample size/ gender	Skin phototype	Intervention arm	Comparison arm	Follow-up duration
Lima *et al.*, 2020[155]	RCT	*N*=44 Females Group A=22 Group B=22	II-IV	Oral pycnogenol 75 mg twice daily + sunscreen SPF 50 + topical triple combination (4% HQ + 0.05% tretinoin + 0.01% fluocinolone) at bedtime×60 days (group A)	Oral placebo twice daily + sunscreen SPF 50 + topical triple combination at bedtime×60 days (group B)	24 weeks
Handog *et al.*, 2009[154]	RCT	*N*=60 (56) Females Group A=30 (27) Group B=30 (29)	III-V	Oral procyanidin 24 mg (with 6 mg b-carotene, 60 mg ascorbic acid, and 15 IU D-a-tocopherol acetate) twice daily + sunscreen SPF 24×8 weeks (group A)	Oral placebo (starch) twice daily + sunscreen SPF 24×8 weeks (group B)	8 weeks
Goh *et al.*, 2018[159]	RCT	*N*=40 (33) Females	III-IV	Oral Polypodium leucotomos extract 240 mg, two capsules twice daily + 4% HQ cream + sunscreen SPF 50 + × 12 weeks (group A)	Oral placebo 2 capsules twice daily + HQ 4% cream + sunscreen SPF 50 + × 12 weeks (group B)	4 weeks, 8 weeks, 12 weeks
Piyavatin *et al.*, 2020[161]	RCT	*N*=57 Females Group A=29 Group B=28	III-VI	Oral TS6 synbiotics (L. lactis, L. acidophilus, L. casei, B. longum, B. infantis, B. bifidum, fructooligosaccharide, skim milk powder, lactose, maltodextrin, citric acid) 1 sachet daily×12 weeks (group A)	Oral placebo (skim milk powder, lactose, maltodextrin, citric acid) 1 sachet daily×12 weeks (group B)	12 weeks
Rassai *et al.*, 2017[162]	RCT	*N*=30 Females Group A=15 Group B=15	III-IV	Oral finasteride 5 mg/tablet once daily at night + HQ 4% cream + sunscreen×12 weeks (group A)	Oral placebo (a combination of starch and sweetening matter) + HQ 4% cream + sunscreen×12 weeks (group B)	12 weeks

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Supplementary Table 2: Contd...

Author, Year	Scoring system	Primary endpoint	Secondary endpoint	Adverse effects	Level of evidence as per OCEBM 2011
Ellkamshoushi *et al.*, 2021[137]	*mMASI *Dermoscopic examination *Digital clinical photographs	**Mean mMASI score:** lowest in group B (2.34±2.37) followed by groups A (6.38±4.04) and C (7.24±4.95); **mean percentage of mMASI score improvement:** highest in group B (77.47 + 19.07) followed by groups A (35.91±24.13) and C (24.94±27.79) (P <0.001)	There was a significant reduction of telangiectasia in the three groups	Pruritus and irritation, post-inflammatory hyperpigmentation, and gastritis	Ib
El Hadidi *et al.*, 2021[138]	*mMASI *Patient satisfaction *Melanin index (MI) *Erythema index (EI)	**mMASI at 8 weeks:** significant reduction noted in the three groups (group A 43% P=0.002, group B 44% P=0.003, group C 20% P=0.005); **mMASI at 12 weeks:** no statistically significant difference between the three groups	**Melanin Index:** significantly reduced in the three groups: group A (P 0.016), group B (P=0.005), and group C (P=0.003) **Erythema Index:** significant improvement in group A (P=0.028) but was statistically insignificant for groups B and C **Patient satisfaction level:** no statistically significant difference among the three groups	**Oral TXA:** slight abdominal discomfort, nausea, hypomenorrhea **Intradermal TXA:** burning sensation during injections and transient erythema and edema on the injection site that subsided within 48 hours	Ib
Minni *et al.*, 2020[142]	mMASI	**12th week**: group A (65.6%) with marked improvement vs group B (27.1%) **24th week :** group A 65.6% with sustained/ continued improvement despite stopping treatment	None	Erythema and burning: most common reported side effects from both groups; GI complaints (i.e., acidity, diarrhea, abdominal pain, vomiting, and hypomenorrhea) common in oral TXA group	Ib
Sahu *et al.*, 2020[143]	MASI	**Group A:** significant difference in MASI at the 4th (P=0.040) and 8th (P<0.0001) weeks from baseline and percentage decrease in MASI of 25% **Group B:** no significant difference between 8th week and baseline and percentage decrease in MASI of 5% **Group C:** significant difference in MASI at the 4th (P<0.0001) and 8th (P<0.0001) weeks from baseline and percentage decrease in MASI of 30%	None	**Oral TXA:** headache, severe abdominal bloating Topical TXA: erythema, and burning Modified Kligman's: acneiform like eruption, erythema, burning	Ib

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Supplementary Table 2: Contd...

Author, Year	Scoring system	Primary endpoint	Secondary endpoint	Adverse effects	Level of evidence as per OCEBM 2011
Shihab *et al.*, 2020[144]	*mMASI *Patient satisfaction survey *MI	**mMASI after 20** weeks: group A 55% reduction vs group B 10.9% **mMASI 12 weeks after discontinuation**: group A 42% decrease compared with baseline vs. group B 4.7%	**Melanin Index:** Decreasing trend starting week 2 and continuing to week 12, greater in group A vs B. At week 24, there was an increase in MI but remained lower in both groups compared with baseline. **Patient satisfaction:** significant improvement in groups A vs B (P=0.05)	**HQ cream:** erythema and pruritus on the first few days but resolved upon continued application. **Oral TXA:** changes in menstrual cycle	Ib
Agamia *et al.*, 2020[135]	*mMASI *Dermoscopic examination *Wood's lamp examination	**mMASI score at 12 and 24 weeks:** Both groups had a statistically significant decrease in mMASI; group B had a statistically higher response as to mMASI change than group A. Sixty percent of group B had melasma clearance before completing the sessions	Moderate agreement between Wood's lamp and dermoscopy in melasma classification was statistically significant; the epidermal type of melasma showed the best response (P=0.048); telangiectasia significantly improved in both groups of patients	**Oral TXA group:** GIT upset, Change in menstrual periods	Ib
Khurana *et al.*, 2019[139]	*mMASI *Patient grading Evaluation	**mMASI:** group A=57% improvement (P<0.01) vs group B=43.5% (P=0.047); both arms showed a significant decrease from baseline to end of 12th-week treatment, but the improvement obtained by the oral TXA group over the IL group was statistically significant	Subjective response to treatment (patient grading evaluation) Group A: 24/32 had>50% and 8/32 had>75% improvement. Group B: 14/32 had>50%, 3/32 had>75%, and 15/32 had<50% improvement. At the 24-week follow-up, two (6.25%) in group A vs three (9.37%) in group B had a recurrence.	**Group A:** two patients (6.25%) had gastritis and one patient (3.12%) had oligomenorrhea at the end of 12 weeks; no change in coagulation parameters noted. **Group B:** no major side effects except for mild pain and erythema for 2–3 days	Ib
Yaghoobi *et al.*, 2019[140]	*MASI *Patient satisfaction survey (PSS)	**MASI**: no statistically significant difference between both groups (P=0.185)	**PSS**: no significant difference between the two groups (P=0.1)	**Group A:** gastrointestinal problems and hypomenorrhea **Group B:** irritant contact dermatitis and xerosis	Ib

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Supplementary Table 2: Contd...

Author, Year	Scoring system	Primary endpoint	Secondary endpoint	Adverse effects	Level of evidence as per OCEBM 2011
Colferai *et al.*, 2018[145]	*mMASI *MELASQoL *Colorimetry	**Improvement of melasma:** group A 50% vs group B 5.9% (P<0.005) **mMASI score reduction** in group A was statistically significant at the end of the treatment (P<0.001)	**MELASQoL reduction:** statistically significant at the end of the treatment (P<0.001). **L value increase** in group A after treatment: statistically significant (P=0.033)	**Oral TXA:** GI symptoms (35%) such as diarrhea and nausea; altered menstruation (10%)	Ib
Del Rosario *et al.*, 2018[146]	*mMASI *MELASQoL *MI	**mMASI reduction:** group A 49% vs group B 18%	**Melanin index** decreased for both groups but was more notable in group A. **MELASQoL:** no significant difference between the two groups	No thromboembolic issues or other serious AEs in either group	Ib
Patil *et al.*, 2018[141]	*MASI *Physician Global Assessment (PGA) * Visual Analogue Scale (VAS)	Group A was more efficacious compared with the other groups. The difference was statistically significant (P<0.05)	None	**Group A:** headache (6.7%), nausea (6.6%)	Ib
Shetty *et al.*, 2018[147]	*mMASI *Patient's Global Assessment (PGA)	Higher clinical efficacy was observed with group B compared with group A (35.6% vs. 21.7%, P<0.05)	**PGA:** good improvement in 63.2% of cases in group B	**Group B:** erythema and wheal at the site of injection in all patients lasted for 4–6 hours	Ib
Rafi *et al.*, 2017[148]	MASI	Both groups showed a decline in MASI score; however, the results were significantly greater in group A (P<0.001)	None	**Group A:** nausea, vomiting and diarrhea Group B: erythema, hyperpigmentation, burning, allergic contact dermatitis, itching	Ib
Padhi *et al.*, 2015[149]	MASI	Faster reduction in pigmentation in group A vs group B with results statistically significant at 4 weeks (P=0.014) and 8 weeks (P<0.0001)	None	None	Ib
Shin *et al.*, 2013[136]	*mMASI *MI	Mean mMASI score 4 weeks after the second treatment decreased significantly in both groups from baseline; overall clinical improvement: greater number in group A patients scored as grade 3 (51–75% improvement) and 4 (>75% improvement)	**Melanin indices** decreased in both groups but were not statistically significant	No serious side effects	Ib

Contd...

Supplementary Table 2: Contd...

Author, Year	Scoring system	Primary endpoint	Secondary endpoint	Adverse effects	Level of evidence as per OCEBM 2011
Karn *et al.*, 2012[133]	MASI	**Group A:** significant decrease in the mean MASI from baseline to 8 and 12 weeks ($P<0.05$ for both) **Group B:** significant decrease in the mean score at 8 weeks ($P<0.05$) but insignificant at 12 weeks ($P>0.05$)	None	**Group A:** oligomenorrhea (14.7%), belching (9.2%), abdominal cramps (6.9%), palpitation (one patient) and urticarial rash with angioedema (one patient); no serious systemic complication.	Ib
Chowdhary *et al.*, 2021[150]	MASI	Group A reduction in mean MASI score at the initial 4 weeks was not statistically significant, and it decreased significantly at 8 weeks onwards, while in group B it decreased significantly at 4 weeks and the percentage reduction of mean MASI score at 16 weeks was significantly more in group B	None	One patient in group A and two patients in group B reported mild epigastric discomfort , three patients in Group B experienced transient oligomenorrhea that improved after the study period.	Ib
Lima *et al.*, 2020[155]	*mMASI *MELASQoL *Colorimetric indices *Global aesthetic improvement scale (GAIS)	Both groups exhibited a reduction in mMASI scores ($P<0.01$), but the reduction was more superior for group A ($P<0.05$)	Both groups exhibited a reduction in MELASQoL scores and color contrast ($P<0.01$); Reduction in colorimetric contrast was superior for group A ($P<0.05$); GAIS improvement of 86% for group A and 55% for group B	None	Ib
Handog *et al.*, 2009[154]	*MASI *MI *Global evaluation by patient and investigator *Clinical photographs	MASI scores showed a significant improvement in group A ($P<0.001$)	**Melanin index:** significant decrease in group A ($P<0.0001$) **Physicians' and patients' global assessments:** moderate to obvious clinical improvement in group A, no improvement to slight improvement in group B	A metallic taste in one subject	Ib

Contd...

Supplementary Table 2: Contd...

Author, Year	Scoring system	Primary endpoint	Secondary endpoint	Adverse effects	Level of evidence as per OCEBM 2011
Goh *et al.*, 2018[159]	*mMASI *MI *EI *MELASQoL	**mMASI reduction**: statistically significant in group A vs group B noted by 8 weeks ($P \leq 0.05$); marked improvement noted further by 12th week. Group A achieved ≥75% improvement (31.3%) vs group B (6.3%).	**Melanin Index** improvement from baseline till the end of study: group A 9.5% vs group B 15.1% (difference not statistically significant) **Erythema index** at the end of the treatment: slightly reduced in both, group A 6.34% vs group B 1.25%. **MELASQoL** with marked but not significant improvement in both groups; group A showed 4×decrease as early as week 4 compared with group B	None	Ib
Piyavatin *et al.*, 2020[161]	*mMASI *MI *EI	**mMASI score:** Group A showed a significant difference (P = <0.001) vs group B	**Melanin Index and Erythema Index** scores in group A showed a significant difference vs group B	No mention	Ib
Rassai *et al.*, 2017[162]	MASI	No significant difference between the satisfaction of the two groups (P=0.338)	None	None	1b

RCT=randomized controlled trial, TXA=tranexamic acid, QSNY=Q-switched Nd-YAG, MASI=melasma area severity index, mMASI=modified melasma area severity index, HQ=hydroquinone. Grading of recommendation as per OCEBM—levels of evidence (March 2009). Level of evidence as per OCEBM 2011—1: systematic review of randomized trials, 2: randomized trial, 3: nonrandomized controlled cohort/follow-up study, and 4: case series, case–control, or historically controlled studies. OCEBM: Oxford Centre for Evidence-Based Medicine[134]