Melasma treatment: a systematic review

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Abstract

Melasma is a common chronic refractory disorder of pigmentation affecting people with darker skin types. Overall prevalence varies between 8.8% and 40%, depending on the ethnicity of the population and the geographical area. Therapeutic management of melasma is challenging, with high recurrence rates which significant impacts on the quality of life. No single treatment is universally efficacious. Systemic treatments with tranexamic acid and polypodium leucotmatous had promising results, although the former was related to systemic side effects. Microneedling and peeling were also efficacious, although their superiority to topical hydroquinone, the gold standard in melasma treatment, remains to be established. Similarly, laser and light devices have been beneficial. However, recurrence rates remain high in all treatment groups. Combination therapies, either in double or triple combinations yielded the best results when compared to single terapies

dermatoscopic evaluation, in order to select the best treatment option, targeted at each melasma subtype.

Key words: melasma, tranexamic acid, peeling, microneedling, laser, intense pulsed light

Introduction

Melasma, previously referred to as chloasma, is a common chronic refractory disorder of pigmentation affecting people with darker skin types, most commonly Fitzpatrick phototypes III-IV. Based on the ethnic makeup of the population, reported prevalence varies between 8.8% and 40%. (1,2) Clinically, it manifests as symmetric reticulated hypermelanosis and it can appear in three predominant facial patterns: centrofacial, malar, and mandibular.(3)

in the skin: epidermal, typified by a light brown coloration, dermal, exhibiting a bluish grey colour or mixed, seen in a dark brown shade.(4) However, *in vivo* reflectance confocal microscopy showed a heterogenous distribution of melanophages, thus indicating that all (5) It is now thought that melasma is the result of a complex interaction between epidermal melanocytes, keratinocytes, dermal fibroblasts, mast cells, vascular endothelial cells, and hormonal, genetic, as well as UV influence.(6) Histopathologically, melasma is characterized by solar elastosis, basement membrane disruption, increased vascularization and increased mast cell count, which strongly indicate that melasma should also be regarded as a photoaging skin disorder.(7)

In a study by Rodríguez-Arámbula et al, conducted on 20 female patients with malar melasma, histopathological examination revealed significantly higher inflammatory infiltration of CD4+ T cells, CD68+ macrophages and mast cells, as compared to unaffected skin. Additionally, genetic and immunohistochemical analyses showed significant elevations in the expression of IL-17 and COX-2. This indicates that malar melasma contains chronic inflammatory cells and mediators which can be exacerbated by environmental stimuli, of which cumulative sun exposure is the most important. This might explain the recurrence of melasma as well as the favourable responses to topical anti-inflammatory treatments.(8)

DNA hypermethylation in melasma lesions were described by Campuzano-García et al. They showed significantly increased levels of DNA methyltransferases (DNMT1 and DNMT3) in melasma lesions as compared to perilesional skin. Additionally, DNMT levels decreased after the use of sunscreen in combination with either 0.05% retinoic acid, 4% niacinamide, or placebo,

which correlated with clinical improvement. Therefore, DNA methylation might also be involved in melasma etiopathogeny, which impacts on the future treatment measures.(9)

Due to treatment and outcome scoring system heterogeneity, we focused on the objective assessment of the therapies involved, categorized according to the procedure employed: topical creams and peelings, systemic, as well as physical treatments such as microneedling, lasers, intense pulsated light, high intensity focused ultrasound. We further analyzed treatments in categories of single, as well as double and triple combination treatments in search for the best associations. We summarized the results of the RCTs in Tables 2-6. In the treatment columns (A, B, C) we did not include any mention of priming before peeling procedures or SPF daily application considering that all patients used SPF as part of their routine melasma treatment.

Results

A total of 492 articles were initially identified in the literature search, of which 162 were duplicates and 224 did not meet the inclusion criteria and were therefore removed. We selected 87 randomized controlled trials (RCTs), 9 reviews and 1 meta-analysis (Figure 1). A total of 4681 patients with melasma were included, for which different treatment measures were employed: systemic treatments (n=20), microneedling (n=16), peelings (n=10), topical creams and solutions (n=56), lasers (n=24), intense pulsated light (n=7

melasma treatments in their multitude and variability, in the case of systemic treatments, which have been used since as early as 2009, we decided to expand our search period and 6 additional RCTs were included: 2 for TXA, 1 for PLE, 1 for melatonin and 1 for procyanidin + vitamins A, C, E (13 30).

For PLE studies, in the comparison with placebo by Martin et al, the results were superior in the PLE group than in the placebo group(24). However, according to Ahmed et al, significant decrease in MI and MASI scores were noticed in both groups(14). This might be explained by the fact that all the patients also applied daily sunscreen. Furthermore, Chuah et al compared the effectiveness of PLE in addition to hydroquinone (HQ) 4% cream(15). They showed the superiority of PLE + HQ 4% cream, as compared to HQ 4% cream alone at weeks 8 and 12 of treatment, although at day 84 the difference was no longer statistically significant, even though the combination group had a 33% higher improvement of melasma. This might be explained by the high recurrence rates of melasma, irrespective of the treatment measure applied. Nevertheless, no adverse events were reported by the patients who were treated with PLE.

-control

study, in addition to a topical lightening cream and found no difference in melasma improvement between the two groups(18). Similarly, the effects of melatonin, either topical or systemic or both, as well as procyanidin + vitamins A, C E have been scarcely studied. A significant decrease in MASI scores was obtained for the treatment and for the placebo groups, which can be explained by the beneficial effect of sunscreen application, as well as the low effectiveness of the systemic treatment. Mild, reversible adverse events have been reported in the melatonin, as well as procyanidin treatment groups.

TXA was the most studied agent, in different concentrations and dosages, as well as different delivery methods: oral tablets, topical creams, as well as cocktails for microneedling procedures. For its systemic effects, 12 RCTs have been conducted: either TXA versus placebo, or in addition to laser treatment, topical treatment, or part of microneedling sessions. In the placebo comparison, the TXA group had better results than the placebo group, although not statistically significant(16,17). Furthermore, recurrence rates were high in both groups. Oral TXA was used as an adjuvant tool to topical treatments and compared to the effect of topical treatments alone. In the HQ 4% cream combination(21,23,29), as well as in the TC cream combination(25,26), the

superiority of the combined treatment as compared to the topical treatment alone has been demonstrated. Similarly, oral TXA in combination with QSNY laser have demonstrated better results, as compared to oral TXA alone(13,27). However, relapses still occured in either combination comparisons. TXA delivery systems were also compared: in the microneedling versus oral delivey method, the latter had significantly superior results in one study(22) and comparable results in the other(28). With regard to TXA dosage, one study compared the effects of either 500 mg, 750 mg, 1000 mg or 1500 mg daily(30). There were no significant differences between the 4 groups in terms of efficacy or safety profile. However, the rates of improvement positively correlated with treatment time and dosage. Important adverse events have been reported, especially after the oral delivery method of TXA: gastrointestinal upset, changes in menstrual periods, headache (Table 2).

Microneedling

16 RCTs evaluating the effects of microneedling on melasma have been included in our review(31 43). All studies showed a significant decrease in melasma scores as compared to baseline. Further comparisons between microneedling cocktails, combinations with topical treatment, lasers and peeling have been assessed.

Cassiano et al conducted an interesting study on a group of 20 females: they performed two 3 mm punch biopsies, one before and one 7 days after the microneedling session. Histologically, they discovered significant melanin reduction, while clinically a significant decrease in mMASI score was noted(32).

former rendered superior results in a population with a majority of mixed type melasma(22) and the latter showed similar results in a population with a predominant epidermal type of melasma(28).

Regarding the cocktails used for microneedling sessions, Iraji et al demonstrated the superiority of a glutathione combination solution with 0.4 % TXA and 3% vitamin C and the absence of melasma relapse in either group at week 24(35). Additionally, Feng et al compared the efficacy of microneedling with a combination of TXA and reduced glutathione to topical application of HQ cream, with significantly better results in the glutathione-TXA microneedling group(42).

Microneedling therapy, combined with either topical TXA solution, HQ 4% cream or QSNYL demonstrated superiority to the topical and laser therapy alone(39 41). However, it did not significantly improve the effects of peeling(31).

Peeling

Different peeling combination solutions have been tested for the treatment of melasma, including the following acids: salicylic acid (SA), glycolic acid (GA), azelaic acid (AzA), ascorbic acid (AsA), phytic acid (PA), mandelic acid (MA), trichloracetic aci
All studies showed a significant decrease in melasma scores as compared to baseline(44 51).

GA 20% peel in combination with topical AA 20% cream was superior to the topical treatment alone(45). Additionally, the combination of topical ascorbic acid cream 5% and LFQSL with peeling agents were superior to the topical and laser treatments alone(50,51).

In the single versus multiple acid peeling solutions, there was no difference between GA peel and a combination of AzA, PA and resorcinol peel; neither between GA peel and combination of GA and TCA peel(46,47). However, the combination of TCA 20-25% and Jessner peeling rendered superior results to TCA alone(44).

Topical treatment

Topical treatments have been extensively studied in the treatment of melasma(52 73). Either as single active ingredients or in different combinations, they have all been proved efficacious in decreasing melasma scores and have maintained a relatively high safety profile.

Hydroquinone cream was compared to several other topical treatments: TXA 5%, both conventional(54,74) and liposomal(55), lignin peroxidase(58), petroselium crispum solution(65), 0.7% and 1.4% silymarin cream(68), 4% diacetyl boldine serum(69) and cosmetic product combination cream(57), all of which rendered comparable results to HQ cream formulas (2%, 3%, 4%). Conversely, in RCTs comparing HQ topical treatment to 1% flutamide cream(52) and 0.2% thiamidol cream(53), HQ was inferior in efficacy. However, in the HQ versus 5% methimazol cream comparison, the former maintained superior results. Erythema, dryness, burning sensation, pruritus were the most frequently reported adverse events in the HQ groups.

Cysteamine 5%, as well as licorice extract 4% were also efficacious in melasma treatment, however their effects were only compared to placebo(60,66,70), thus their superiority to other topical treatments has not been demonstrated as of yet. Triamcinolone injections, however, seem to yield better results than the Kligman formula containing HQ 5%, tretinoin 0.1%, dexamethasone 0.1%(59).

TXA combinations appeared to have a significant impact on hypervascular, inflammatory melasma(61). Azelaic acid 10% combined with d-panthenol 10% was superior to other azelaic acid formulas(67).

Lasers and Light Therapy

Different light devices have been used in the treatment of melasma(75 80), either fractionated intense pulsed light (IPL) or conventional IPL, both with comparable MASI score decrease(80). Also, different fluences have been utilised, 10 J/ cm^2 and 13 J/ cm^2, both with significant improvement from baseline(75). Combination therapies rendered superior results as compared to IPL alone: in association with microdermabrasion(76), topical TXA 2%(77) or triple combination cream(79).

Laser therapy has been extensively studied in melasma treatment(47,51,81 97). Various devices have been employed: fractional ablative CO2 laser, fractional thulium laser, fractional picosecond laser, picosecond alexandrite laser, copper bromide laser, ablative pixel Erbium YAG laser (APEYL), pulsed dye laser (PDL), low-fluence Q-switched Nd: YAG laser (LFQS), long-pulse Nd: YAG laser (LPNY), Q-switched Nd: YAG laser (QSNY), fractional erbium YAG laser (FEYL), pixel Q-switched Nd: YAG laser (PQSNY), quick pulse-to-pulse laser (Q-PTP), super

skin rejuvenation device (SSR). These can be included into four main categories: pigment-specific (Q-switched and long-pulsed lasers, IPL), vascular (pulsed dye and Copper bromide lasers), fractional and ablative lasers(98). Among these, the non-ablative types are preferred in melasma treatment for their lower incidence of post-inflammatory hyperpigmentation due to direct damage to the skin. Q-switched lasers selectively target melanin chromophores, while IPL is believed to determine the upward shedding of melanosomes destryed by QS laser. Vascular lasers might prove to be useful in inflammatory, hypervascular melasma(3).

The majority of the studies compared laser therapy alone to combination therapy, the latter rendering significantly better results(81,91,95). Similarly, combination therapy had significantly better results than topical therapy alone(83 85) or it rendered similar improvement rates(93,96). In a RCT by Hammami et al, Kligman formula for triple combination cream (TCC) was superior to copper bromide laser(88).

In the laser versus laser comparisons, different technology devices have been evaluated. FEYL combined with QSNYL and TCC cream was superior to QSNYL and TCC(82). Dual toning performed with LFQSNYL and LPNYL 1064 nm had significantly better results than QS toning with LFQSNYL(86). In a triple comparison between SSR, PQSNYL and APEYL, the latter had superior results, although not statistically significant as compared to the other two. Additionally, the effects on different types of melasma were studied: SSR and PQSNDY were significantly efficacious against all types of melasma, with slightly better results against epidermal measma. In contrast, APEYL was significantly efficacious in dermal and mixed melasma, while in epidermal melasma the results were not statistically significant(99).

Discussion

Systemic treatment

Nowadays there are many systemic therapies that can be used as an adjuvant in melasma treatment. However, their efficacy in melasma has not been clearly demonstrated.

Oral PLE is one of the a valid options and it can be used as an adjuvant to topical treatment of melasma, especially in association with HQ cream. Further studies are necessary in order to assess the recurrence rates and the possibility of maintaining the systemic treatment with PLE

after topical treatment cessation, in order to avoid relapses. Dietary carotenoids, melatonin, either topical or systemic or both, as well as procyanidin + vitamins A, C E seem the least effective of the systemic treatments(18 20). However, additional studies following patients for longer periods might be useful. Oral TXA had better results than placebo, although not statistically significant(16,17). Oral TXA in combination with HQ 4% cream, as well as TC cream, rendered superior results than the topical treatment alone(23,25,29). In terms of delivery methods, oral TXA seems to have better results than microneedling(22). Additionally, in terms of TXA dosage, no significant differences were found between the use of either 500 mg, 750 mg, 1000 mg or 1500 mg daily(30).

Microneedling

Microneedling is a minimally invasive, collagen induction therapy that consists in delivery of fine needles into the skin, either through needle rollers, stamping or electric-powered pens. It enhances transdermal drug delivery and has been used in dermatology for scar, striae and rhytides therapy(100).

Microneedling has been repeatedly proven to be an effective measure in melasma treatment, showing results even after as early as 7 days, from a histological viewpoint(32). Microneedling with TXA 0.4% rendered inferior results to GA peeling, silymarin cream(33), HQ 4% cream(37) and similar results to microneedling with vitamin C 40%(43). In the oral versus intradermal delivery of TXA, the former yielded superior results in an Indian cohort with majoritary mixed type of melasma(22), while the latter showed similar results between the two treatment groups, also in an Indian cohort, but this time with a predominant epidermal type of melasma(28) which might indicate that oral TXA is more efficacious against dermal and mixed melasma. The addition of glutathione to TXA cocktails used for microneedling procedures rendered superior results and zero recurrence rates.(35) In a study by Feng et al, microneedling with glutathione in combination with TXA was superior to HQ topical application(42). However, the full article was not accessible, therefore these results need further confirmation. Microneedling has also been used as combination therapy with HQ 4% cream, QSNYL and the results were superior to both topical and laser therapy alone.(39 41)

Tolerability is quite low, especially when dermapen is used, with adverse events varying from transient erythema, burning sensation, to pain, edema and ecchymosis(34). These local reactions are however, operator dependent.

Peeling

Chemical peelings have been used for their ability to generate epidermal remodelling and can be classified as superficial, affecting the epidermis through the papillary dermis, medium, involving the papillary to the upper reticular dermis and deep, penetrating through the mid-reticular dermis.(101) However, in the treatment of melasma, the use of deep or medium-depth peelings is not encouraged in dark-skinned patients, because of the risk of hyperpigmentation.

epidermis-papillary dermis), medium-depth (papillary to upper reticular dermis) and deep subtypes based on the depth of their penetration (mid-reticular dermis).

In a meta-analysis by Dorgham et al, TCA and Jessner's solution were more efficacious than topical HQ in reducing the severity of melasma, while GA was better than TCA. Additionally, GA was similar to tretinoin, vitamin C iontophoresis, and amino fruit acid. Also, SA and LA were comparable to Jessner's solution in efficacy(102).

Most frequently used as combination therapy, chemical peelings had superior results in association with topical creams(45,50) rather than with microneedling(31) or laser(51).

Topical treatment

Topical treatments have been the mainstay of melasma treatment. Photoprotection is the most important and it has been used as an adjuvant to other melasma treatments, since both UV and visible light can cause sustained hyperpigmentation in all skin types. Hydroquinone has been considered a first-line treatment for melasma and triple combination creams containing hydroquinone have become increasingly popular, as they yielded superior results. Kligman formula was the first TCC, containing HQ 5%, tretinoin 0.1% and dexamethasone 0.1%. The most recent TCC is Tri- Luma, which contains HQ 4%, tretinoin 0.05%, 0.1% fluocinolone acetonide and is FDA-

burning sensation, dryness, pruritus and scaling have been most frequently reported after topical HQ treatment(53,54,62,64,65).

Many other active ingredients have been studied, of which 1% flutamide(52) and thiamidol 0.2%(53) seem to have superior results to HQ, with no adverse events reported. TXA 5%(54,55,74), lignin peroxidase(58), petroselium crispum solution(65), silymarin cream(68), 4% diacetyl boldine serum(69) and cosmetic product combination cream(57) had comparable results to HQ cream formulas, which make them a valid alternative to HQ. Furthermore, TXA combinations seem to be more efficacious against hypervascular, inflammatory melasma(61). Also, azelaic acid 10% combined with d-panthenol 10% had better results than other azelaic acid formulas(67).

Lasers and Light Therapy

IPL therapy uses a flash lamp light source with wavelengths between 515 and 1200 nm and it selectively targets melanosomes, with the added advantage that it can simultaneously treat epidermal and dermal melasma(104). However, IPL effectiveness has not been convincingly demonstrated(77,80).

Among laser devices, QSNYL is the preferred choice for dermal and mixed types of melasma. Its two wavelengths, of 532 and 1064 nm, as well as a spot size of up to 10 mm allows for a deeper penetration of the laser beam and selective photothermolysis of melanosomes. This results in cell death, hyperinflammatory state and damage to the basement membrane, which determines exacerbation of melasma and relapse. This is why QSNYL is not recommended as first or second line treatment for melasma. It is, however, suggested that it can be used in recalcitrant cases, as a last resort, after other treatments have failed(105,106). On the other hand, LFQSNYL, also known as laser toning, uses a low-fluence, multi-pass technique, by which the cell membrane and nucleus remain intact, which results in melanocyte downregulation and hyperactive melanocyte cutoff(106). In a RCT by Kong et al, none of the patients in the LFQSNYL treatment group relapsed at week 16(89). Conversely, Vachiramon et al had 8 patients who relapsed after LFQSNYL treatment; they only included patients with mixed melasma(51).

A new class of lasers that generate picosecond- domain pulses, available in different wavelengths, of 532 nm, 755 nm and 1064 nm, determine melanin fragmentation by photoacoustic, rather than phototermal effect, thus determining even less inflammation than the LFQSNYL(104). Lee et al demonstrated picosecond 755 laser superiority to QSNYL(92).

Fractional resurfacing lasers, either ablative or non-ablative, creates different columns of microthermal damage in the skin, which determines lower inflammation and risk of dyspigmentatin(104). Vanaman et al and Wanitphakdee et al demonstrate their efficacy in melasma(95,97).

As an antivascular treatment in melasma, PDL, QSNYL and IPL, either as monotherapy or combined with systemic or topical TXA, seems to be efficacious in cases of melasma with increased vascularity(107).

Conslusion

PLE and TXA have been demonstrated to be an efficacious treatment, especially in association with topical HQ and TCC. Regarding tolerability, PLE is the safer option, while TXA has been linked to mild-to-moderate side effects.

Microneedling with a combination of TXA and glutathione has new and encouraging results that might prove superior to the gold standard so far, HQ cream and might also lower the recurrence rates. Additionally, oral TXA seems to have superior results to intradermal TXA in patients with dermal and mixed types of melasma. Further studies are needed to determine their effects, especially on the long term. Adverse events vary from mild to moderate and are operator dependent.

Chemical peelings have demonstrated high efficacy when combined with either topical or laser therapy. Used as monotherapy, TCA 20-25% with Jessner
results. Transient adverse events are expected during and immediately after the peeling seession. The use of deep and medium-depth peelings is highly discouraged in dark-skinned patients because the risk of hyperpigmentation.

Hydroquinone and triple combination creams containing HQ, like Kligman formula and Tri-Luma remain one of the best treatment options for melasma. Mild adverse events have been

associated with HQ application. TXA 5%, lignin peroxidase, petroselium crispum solution, silymarin cream, and 4% diacetyl boldine serum seem to be an efficacious alternative to HQ products, with comparable results. Newer products, containing 1% flutamide or 0.2% thiamidol had encouraging results, with no adverse events reported and apparently superior to HQ.

A plethora of laser and light devices have become available in the last few years and many of them have been used in melasma treatment. Post-treatment hyperpigmentation and high recurrence rates associated with QSNYL led to the appearance of LFQSNYL and picosecond lasers, which determined less and less inflammation of the skin. Fractional and antivascular lasers have also proved their efficacy, the latter especially in cases of melasma with increased vascularity.

There is a lack of studies following melasma patients on the long term. Of course, as presented in the studies we have reviewed, the immediate results are impressive and statistically significant. However, in a few of the studies following patients for at least 2 months after the cessation of treatments applied, recurrence rates are as high as 100%, which is of great concern and requires immediate search for alternative therapeutic measures. Combination treatments have been proved time and again to be the best solution, either in double or triple combinations. Treatment

order to determinate the epidermal, dermal or mixed type of melasma, as well as the degree of vascularity.

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Table legends

Table 1. Melasma treatment and mechanism of action.

Table 2. Systemic treatments.

Table 3. Microneedling.

Table 4. Peeling.

Table 5. Topical treatments.

Table 6. Laser and light treatments.

Table 1. Melasma treatment and mechanism of action.

MELANOGENESIS AND MELANOSOMAL TRANSFER TO KERATINOCYTES	EXCESS REACTIVE OXYGEN SPECIES AND INFLAMMATION
aloesin	acidified amino acid peels
alpha lipoic acid	alpha tocopherol
antisense oligonucleotides	carotenoid
arbutin	coffeeberry extract
ascorbic acid	curcumin
azelaic acid	epigallocatechin-3-gallate
cinnamic acid	glutathione
dimethyl hydroxy furanone	hesperidin
ellagic acid	

Table 2. Systemic treatments.

Reference	Year	Patients: nr, ethnicity	Comparison	Treatment A	Treatment B	Treat. Duration	Melasma Type	Efficacy/ Outcomes	Tolerability/ Adverse Events	Recurrence rates
Agamia et al(13)	2020	60, Egyptian	single x double	oral TXA 250 mg	oral TXA 250 mg + Qs-Nd: YAG laser (1064 nm)	oral TXA 250 mg daily, laser biweekly, for 3 months	10 epidermal 4 dermal 46 mixed	Significant decrease in mMASI score at 6 months in both groups, with group B showing a significantly better response than A.	Gastrointestinal upset, change in menstrual periods in both groups. Long-standing erythema, itching/discomfort and punctate leukoderma after laser treatment.	3 in group A, 4 in group B.
Ahmed et al(14)	2013	33, Hispanic	single x single	PLE 240 mg	Placebo	three times daily, for 12 weeks	N/A	Significant decrease in MI and MASI scores in both groups.	No serious adverse events.	N/A
Chuah et al(15)	2018	40, Asian	single x double	4% hydroquinone cream + oral PLE	4% hydroquinone cream	daily, for 12 weeks	N/A	Significant decrease in mMASI scores in both groups at weeks 4, 8, 12. mMASI score in group A at week 8, 12 was significantly lower than in group B, but at day 84 there were no significant differences between the two groups.	Mild itching and stinging sensation in both groups.	N/A
Colferai et al(16)	2018	37, Brazilian	single x double	oral TXA 250 mg	oral placebo	oral TXA 250 mg twice daily, for 12 weeks	N/A	Significant decrease in MASI, MELASQoL and colorimetry scores in group A and in MELASQoL score in group B at week 12.	Gastrointestinal symptoms, change in menstrual flow, headache in group A.	N/A
Del Rosario et al(17)	2018	39, Americans	single x double	oral TXA 250 mg	oral placebo	oral TXA 250 mg twice daily, for 3 months	N/A	49% reduction in mMASI score in group A vs. 18% in group B at month 3. 26% reduction in mMASI in group A Vs. 19% reduction in group B at month 6.	Gastrointestinal symptoms, change in menstrual flow, headache, myalgias in both groups, somnolence, arthralgias, blurry vision in group A.	Increase in mMASI scores from week 12 to 24 in both groups, with final values lower than at baseline.
Gan et al(18)	2015	44, Asian	single x double	oral dietary carotenoids 800 mg + lightening cream	oral placebo + lightening cream	once daily, for 84 days	N/A	Significant decrease in median mMASI score in both groups, with no significant difference between the groups. Significant improvement in erythema scores in both groups, with significantly better scores in group A.	Stinging, burning, pruritus in both groups.	N/A
Hamadi et al(19)	2010	46, Iranians	single s double	A: topical metalonin; B: topical metalonin + sunscreen	C: oral melatonin, 3 mg + topical melatonin D: HQ 4% cream	daily, for 90 days	N/A	Significant decrease in MASI scores in all groups.	Mild, transient drowsiness.	N/A
Handog et al(20)	2009	56, Filipino	single x single	Oral procyanidin 24 mg + vitamins	Placebo	twice daily, for 8 weeks	56 epidermal	Significant decrease in MASI scores in both groups.	Metallic taste, reversible on discontinuation in group A.	N/A

				A+C+E: 6 mg b-carotene, 60 mg ascorbic acid,15 IU of D-a-tocopherol acetate						
Karn et al(21)	2012	260, Nepalese	single x double	TXA 250 mg + HQ cream	Placebo + HQ cream	twice daily, for 12 weeks	173 epidermal 28 dermal 59 mixed	Significant decrease of the MASI scores in group A at weeks 8 and 12 and in group B at week 8.	Group A: oligomenorrhea, belching, abdominal cramps, palpitation, urticarial rash with angioedema. Group B: exogenous ochronosis.	N/A
Khurana et al(22)	2019	64, Indian	single x single	microneedling with TXA 0.4%	oral TXA 250 mg	A: monthly, B: twice daily, for 3 months	17 epidermal 3 dermal 44 mixed	Significant decrease in MASI score in group B as compared to A.	Group A: mild pain and erythema. Group B: gastritis, oligomenorrhea.	3 patients in group A and 2 in group B at 6 months
Lajevardi et al(23)	2017	88, Iranian	single x double	oral TXA 250 mg + HQ 4% cream	HQ 4% cream	TXA 250 mg three times daily, cream nighlty, for 3 months	N/A	Significant decrease in mean MASI score in group A compared to B. Significantly higher patient satisfaction in group A than B.	Severe abdominal pain, flank pain, edema of the hands and feet, nausea, vomiting, and headache in group A.	Relapse rate of 30% and 26%, in groups A and B, at 6 months.
Martin et al(24)	2012	21, multiracial	single x single	PLE	Placebo	twice daily, for 12 weeks	N/A	Significant decrease of MASI and MELASQoL scores in group A as compared to B.	No serious adverse events.	N/A

										although lower than baseline.
Shin et al(27)	2013	48, Korean								

Table 3. Microneedling.

Reference	Year	Patients: nr, ethnicity	Comparison	Treatment A	Treatment B	Treatment C	Treat. Duration	Melasma Type	Efficacy/ Outcomes	Tolerability/ Adverse Events	Recurrence rates
Balevi et al(31)	2017	41, Turkish	single x double	30 % SA peel	30 % SA peel + microneedling (mesoneedles) with vitamin C	N/A	A,B: every 2 weeks for 2 months	41 mixed	MASI scores significantly decreased in both groups, but with no significant difference between them. Significant decrease in MelasQoL scores in Group A compared to Group B.	Mild to moderate burning sensation in Group B during injections.	N/A
Cassiano et al(32)	2019	20, Brazilian	single x double	microneedling (Dermaroller 1.5 mm) + SPF 50 sunscreen	SPF 50 sunscreen	N/A	for 7 days	N/A	mMASI, colorimetry, and quality of life parameters improved only in group A. Histologic assessment: significant reduction in melanin density, pendulous melanocytes and basement membrane damage per histological field.	N/A	N/A
Elfar et al(33)	2015	60, Egyptian	single x single	microneedling with 0.4% TXA	Topical Silymarin cream 14 mg/ ml	50% GA peeling	A: weekly; B: twice daily; C: every 2 weeks, for 12 weeks	30 epidermal 13 dermal 17 mixed	Statistically significant difference with the best results in mMASI scores in group C>B >A. There was statistically significant difference between A<B, A<C, group A showing weaker response than B and C.	Group A: burning pain and wheal at the site of injection, erythema. Group B: no side effects. Group C: post inflammatory hyperpigmentation Significant differences between group A and groups B and C, groups B and C being the safest; also between group B and C where group B was the safest.	N/A
Feng et al(42)	2018	180, Chinese	single x double	microneedling with tranexamic acid + reduced glutathione	topical hydroquinone cream	N/A	N/A	N/A	Significantly higher efficacy in group A than B.	N/A	N/A
Hofny et al(34)	2019	23, Egyptian	double x double	microneedling 2 mm with dermapen + PRP on the right side of the face	microneedling with mesoneedles + PRP on the left side of the face	N/A	monthly, 3 sessions	18 epidermal 5 mixed	MASI and mMASI scores decreased significantly. A statistically significant decrease was noted in the hemi-MASI score on each side of the face following PRP treatment, but there was no significant difference on comparing both sides.	The majority of the patients experienced more pain with mesoneedles than with dermapen. All the patients observed less downtime with mesoneedles than with dermapen.	N/A
Iraji et al(35)	2019	30, Iranian	double x double	microneedling (mesoneedles) with TXA 0.4% + vitamin C	microneedling (mesoneedles) with TXA 0.4% + vitamin C	N/A	every 2 weeks, 6 sessions	6 epidermal 5 dermal 19 mixed	Significantly more reduction of mMASI score with cocktail A than B at week 12. Patient satisfaction was significantly higher for cocktail A than B.	Erythema, edema and ecchymosis.	no relapses at week 24

				3% + glutathione 2% on the right half of the face	3% on the left half of the face						
Kaleem et al(36)	2020	60, Pakistanese	single x double	microneedling with TXA 0.4% on the left side of the face	microneedling with saline 0.9% on the right side of the face	N/A	every 2 weeks for 12 weeks	20 epidermal 33 dermal 7 mixed	Mean of H-mMASI score showed significant reduction in group A compared to group B.	Erythema, swelling, and burning were documented as temporary side effects on both sides.	N/A
Pazyar et al(37)	2019	41, Iranian	double x double	microneedling with TXA 0.4% on the right side of the face + topical 4% HQ cream on the left side of the face	microneedling with TXA 1% on the right side of the face; topical 4% HQ cream on the left side of the face	N/A	microneedling: every 2 weeks, cream: twice daily, for 12 weeks	26 epidermal 1 dermal 14 mixed	Significant decrease in MASI score for group A, group B, and HQ cream at week 12 with no significant difference between groups A and B. Significantly better results in the HQ group than 0.4% TXA group at weeks 8 and 12. Higher patient satisfaction rates in group A>B and in HQ>A, but not statistically significant.	All patients experienced injection site burning pain, one patient reported urticaria. No adverse effect was seen in the HQ group.	6 patients in group A and 2 in Group B at week 24
Saki et al(38)	2018	37, Iranian	single x single	hydroquinone 2% cream	microneedling with TXA 0.4 %	N/A	cream nightly for 3 months; monthly microneedling sessions, 3 in total	13 epidermal 6 dermal 12 mixed	Colorimetry measurements for melanin value: significant reduction in both groups, with significantly better results in group B than A at week 4, but not at week 20. Significantly better patient satisfaction rates in group B than A.	N/A	N/A
Tehranchinia et al(39)	2018	55, Iranian	single x double	microneedling with TXA 10% + topical 4% hydroquinone	topical 4% hydroquinone	N/A	cream nightly for 12 weeks; microneedling sessions every 4 weeks, 4 in total	55 epidermal	Significant decrease in mean MASI scores at week 16 in both groups. Significantly better therapeutic outcomes and patient satisfaction rates in group A than B.	Erythema and pruritus in both groups.	N/A
Ustuner et al(40)	2017	16, Turkish	single x double	1,064-nm QS-Nd:YAG laser + microneedling with vitamin C	1,064-nm QS-Nd:YAG laser	N/A	every 4 weeks for 4 months	12 mixed 4 dermal	Significantly lower mean MASI scores, significantly better clinical response as evaluated by the clinician in group A than B at months 1-4. Significant decrease in mean MelasQoL-TR scores in group A.	Transient erythema, slight hyperpigmentation in both groups.	5 patients in group A and 7 in group B
Xu et al(41)	2017	28, Chinese	single x double	microneedling + topical 0.5% TXA solution	topical 0.5% TXA solution	N/A	once weekly for 12 weeks	N/A	Brown spots scores measured by Visia, MI were significantly lower in group A than B at week 12. Physician evaluations of photographs showed better results in group A. Subjective satisfaction scores on both sides increased significantly, with better results in group A.	No obvious adverse reactions.	N/A
Zhao et al(43)	2020	17, Chinese	single x single	microneedling with TXA 10%	microneedling with vitamin C 40%	N/A	weekly, 8 sessions	5 epidermal, 6 dermal, 6 mixed	Significant decrease in MASI scores in both groups.	Mild erythema, localized congestion.	1 patient at month 2.

Table 4. Peeling

Reference	Year	Patients: nr, ethnicity	Comparison	Treatment A	Treatment B	Treatment C	Treat. Duration	Melasma Type	Efficacy/ Outcomes	Tolerability/ Adverse Events	Recurrence rates
Abdel-Meguid et al(44)	2017	24, Egyptian	single x double	TCA 20% 25% + solution	TCA 20% 25%	N/A	biweekly, 6 sessions	14 epidermal, 10 mixed	Significant decrease in MASI score in both groups, with significantly better results in group A.	Erythema, burning sensation, discomfort, pruritus, hyperpigmentation, crustation in both groups.	N/A
Dayal et al(45)	2017	60, Indians	single x double	GA peel + 20% AA cream	20% AA cream	N/A	A: every 3 weeks, 8 peeling sessions; B: twice daily, for 24 weeks	60 epidermal	Significant decrease in MASI and MelasQoL scores after week 12 in both groups, but with significantly better results group A.	Erythema, pruritus, burning sensation, postinflammatory hyperpigmentation and scaling in both groups.	N/A
Faghihi et al(46)	2017	41, Iranian	single x single	20% AA + 10% resorcinol + 6% phytic acid peel on the right side of the face	50% GA peel on the left side of the face	N/A	every 2 weeks, 6 sessions	19 epidermal 22 mixed	Marked improvement in MASI scores in both groups. Significantly lower patient discomfort after procedure in group A compared to B.	Group A: No complications. Group B: burning sensation and dyspigmentation.	N/A
Garg et al(47)	2019	30, Indians	single x double x double	35% GA full-face peel	35% GA full-face peel followed by 10% TCA spot peel	35% GA full-face peel followed by 20% TCA spot peel	every 2 weeks, 4 sessions	epidermal, mixed	Significant reduction of MASI scores in all groups.	Erythema, pruritus, burning sensation, transient hyperpigmentation.	N/A
Mahajan et al(48)	2015	40, Indian	single x single	TC cream	GA peel + 20% AA cream	N/A	for 3 months	20 epidermal 13 dermal 7 mixed	Significant reduction in MASI and VAS scores after 6 and 12 weeks of treatment in both groups.	Irritation, increased dryness, photosensitivity in both groups.	N/A
[redacted] et	2016	148, Pakistanese	single x double	20% TCA peel + 5% magnesium ascorbyl phosphate cream	20% TCA peel	N/A	A, B: weekly, cream once daily; for 6 weeks	148 epidermal	Significant MASI score reduction both groups.	N/A	N/A
Sahu P et al(50)	2017	60, Indians	single x double	20% TCA peel + 5% ascorbic acid cream	20% TCA peel	N/A	A, B: every two weeks, cream nightly, for 12 weeks	60 epidermal	Statistically significant improvement in: MASI, MelasQoL, percentage decrease in MASI, in group A compared to group B.	Post peeling erythema, burning and stinging sensation, post-inflammatory hyperpigmentation in both groups. Pruritus in group B.	

Vachiramon et al(51)	2015	12, Thai	single x double	LFQS on one side of the face	LFQS + 30% GA peel on the contralateral side	N/A	weekly, 5 sessions	12 mixed	Mean relative LI index reduced significantly at week 4 in both treatment groups, but increased at week 8 and week 12. Significant relative LI, MASI score reduction in group B compared to group A.	Burning and stinging sensation on both sides of the face. Superficial skin peeling in group B. Hyperpigmentation, guttate hypopigmentation on the background of hyperpigmentation in both groups.	at week 8 and week 12

Table 5. Topical treatments.

Reference	Year	Patients: nr, ethnicity	Comparison	Treatment A	Treatment B	Treatment C	Treat. Duration	Melasma Type	Efficacy/ Outcomes	Tolerability/ Adverse Events	Recurrence rates
Adalatkhah et al(52)	2015	74, Swedish	single x single	1% flutamide cream	4% hydroquinone cream	N/A	nightly, for 4 months	N/A	Significant decrease in MASI scores in both groups, with better results in group A. Significantly higher patient satisfaction in group A as compared to B.	N/A	N/A

						phytic acid: 5% + 4N-butyl resorcinol: 5% + ferulic acid: 2%					
Nofal et al(68)	2019	42, Egyptian	single x single x single	silymarin 0.7% cream	silymarin 1.4% cream	hydroquinone 4% cream	nightly for 3 months	34 epidermal 3 dermal 5 mixed	Significantly reduced MASI scores in all groups.	Erythema, burning sensation, scaling in group C. None in groups A or B.	N/A
Pratchyapurit et al(69)	2016	38, Thai	single x single x single	DAB 4% serum	HQ 4% cream	HQ 2% cream	for 12 weeks	15 epidermal 25 mixed	Significant improvement in MASI and MI scores in all groups.	Erythema, pruritus, skin exfoliation, dryness and hyperpigmentation in all groups.	N/A
Shamsi et al(70)	2016	44, Iranian	single x single	4% licorice extract cream	placebo	N/A	for 12 weeks	N/A	Significant reduction in mMASI scores in both groups.	N/A	N/A
Taghavi et al(71)	2019	20, Iranian	single x single	topical liposomal hydroquinone 4%	conventional hydroquinone 4%	N/A	daily, for 3 months	N/A	Significant reduction in MASI scores in both groups.	N/A	N/A
Vachiramon et al(72)	2020	21, Thai	single x single	HIFU	2% hydroquinone cream	N/A	HIFU monthly, 3 sessions in total, cream nightly, for 20 weeks	21 mixed	Significant reduction of relative lightness index and MASI in both groups, but with no significant differences between the groups.	Burning sensation, scaling, erythema in both groups.	no recurrences after 3 months
Zhang et al(73)	2019	90, Chinese	single x single x single	herbal cream	arbutin cream	placebo	twice daily for 12 weeks	N/A	Significant decrease in MASI scores in groups A and B, with better results in group A. Significantly reduced EI and density of inflammatory cells in group A.	Mild erythema and pruritus in group B.	N/A

Table 6. Laser and light treatments.

Reference	Year	Patients: nr, ethnicity	Comparison	Treatment A	Treatment B	Treatment C	Treat. Duration	Melasma Type	Efficacy/ Outcomes	Tolerability/ Adverse Events	Recurrence rates
Abdel-Raouf Mohamed et al(81)	2019	22, Egyptian	single x double	FEYL on the right side of the face	FEYL + topical mometasone on the left side of the face	N/A	laser biweekly, 6 sessions, cream nightly	22 epidermal	Significant decrease in: MASI scores, basal hyperpigmentation on HE staining, MPSA/ESA percentage on MF staining, MART- 1-positive- stained cells in both groups. MASI scores were significantly lower in group B than A.	N/A	N/A
Alavi et al(82)	2017	41, Iranian	double x triple	QSNYL-FEYL + topical Klingam formula cream	QSNYL + topical Klingam formula cream	N/A	laser biweekly, 4 sessions, cream nightly	N/A	Significantly lighter skin colour and decrease in melanin content in both groups with significantly better results in group A than B.	None reported.	N/A
Badawi et al(83)	2018	30, French	single x double	FEYL + 4% HQ cream	4% HQ cream	N/A	laser biweekly, 6 sessions, cream twice daily	15 epidermal 6 dermal 9 mixed	Significantly higher decrease in the degree of pigmentation on the 4-point scale and MASI scores in group A than B.	Transient and mild erythema, burning sensation, and itching were reported in both groups. Superficial crusting in group A.	2 patients in both groups.
Bae et al(75)	2015	20, Korean	single x single	10 J/cm2 fluence IPL	13 J/cm2 fluence IPL	N/A	weekly, 6 sessions	N/A	Significant decrease in MASI scores and melanin index in both groups, with no significant differences between the groups.	Transient and mild erythema, burning sensation in both groups.	N/A
Barolet et al(76)	2018	7, Canadian	single x double	microdermabrasion + photobiomodulation LED device	microdermabrasion	N/A	weekly, for 8 weeks	7 dermal	Statistically significant pigment reduction in group A than B. Significant reduction in MASI score in group A at week 12.	N/A	N/A
Chalermchai et al(84)	2018	30, Thai	single x double	fractional picosecond 1,064 nm laser + 4% HQ cream	4% HQ cream	N/A	laser monthly, cream daily	N/A	Significantly decreased mMASI scores at the 12-week visit in group A than B.	Transient mild erythema, mild skin desquamation, mild burning sensation in group A.	N/A
Choi et al(86)	2015	360, Korean	single x double	dual toning: LFQSNYL + LPNYL 1064 nm	QS toning= LFQSNYL	N/A	weekly, 10 sessions	N/A	Significant median decrease of mMASI in group A as compared to B. Significantly lower adverse events in group A than B.	Mottled hypopigmentation and rebound hyperpigmentation in both groups.	N/A
Choi et al.(85)	2017	74, Korean	single x double	picosecond laser with dual-wavelengths (1 064 and 595 nm) + 2 % HQ cream	2% HQ cream	N/A	laser weekly, 5 sessions, cream daily for 7 weeks	N/A	Significant improvement in RL*I, significant decrease of mMASI scores, better subjective satisfaction rates in group A than B.	Mild dermatitis in both groups. Mild pain during laser treatment and mild erythema in group A.	30/39 in group A and 27/39 (69.23%) in group B at week 18.
Chung et al(77)	2016	13, Korean	single x double	IPL + topical TXA 2%	IPL	N/A	monthly, 4 sessions	N/A	Significant decrease in MI and mMASI in group A.	None reported.	N/A

Garg et al(99)	2019	60, Indian	single x single x single	SSR 540 nm	PQSNYL 1064 nm	APEYL 2940 nm	at 3 weeks interval, 5 sessions	22 epidermal 12 dermal 26 mixed	Significantly decreased mMASI scores in all 3 groups, with better results in group C.	group A: transient dryness. Group B, C: post-inflammatory hyperpigmentation, acne brakouts. Group C: herpes labialis.	N/A
Guo et al(87)	2019	12, Chinese	single x single	QSNYL 1064-nm Q-PTP mode on the right side	QSNYL 1064-nm single-pulse mode on the left side	N/A	at 4 weeks interval, 5 sessions	N/A	Significant decrease in mean mMASI scores at week 4 and 12 in both groups.	Significantly lower pain and erythema in group A compared to B. Urticaria and petechiae in group B.	3 patients at week 12.
Hammami et al(88)	2015	16, French	single x double	copper bromide laser + Kligman formula triple combination cream	Kligman formula triple combination cream	N/A	laser at 2-3 weeks interval, 4 sessions, cream daily for 4 months	N/A	Significantly better decrease in MASI scores in group B than A at the end of the treatment.	N/A	100% recurrence rates at 6 months follow-up.
Hassan et al(78)	2018	28, Egyptian	single x single	PDL on the right hemiface	IPL on the left hemiface	N/A	at 3-5 weeks interval	20 epidermal 8 mixed	Significant reduction in hemifacial mMASI scores in both groups with no significant difference between them. Better patient tolerance and satisfaction in group B than A.	Mild erythema, edema and pain during and after treatment, microcrust formation, post-inflammatory hyperpigmentation in both groups.	N/A
Kong et al(89)	2017	17, Korean	single x double	PDL + LFQSNYL	LFQSNYL	N/A	QSNY weekly, 9 sessions, PDL at 4 weeks interval, 3 sessions	N/A	Significant decrease in MASI scores in both groups.	Mild burning sensation and erythema in both groups. Focal purpura, postinflammatory hyperpigmentation in group A.	1 patient at week 16 in group A.
Laothaworn et al(90)	2018	25, Thai	single x double	1064-nm QSNYL + 3% TXA cream	1064-nm QSNYL	N/A	laser at 4 weeks interval, 2 sessions, cream twice daily for 8 weeks	14 mixed 11 epidermal	Significant decrease in MASI scores in group A. Significant decrease in mean MI in group A at week 4.	Mild erythema and burning sensations in both groups.	Rebound at week 8 shown by increased MI starting after week 4 in both groups.
Lee et al(91)	2015	8, Taiwanese	single x double	QSNYL 1,064 nm	QSNYL 1,064 nm + ultrasonic application of topical vitamin C	N/A	monthly, 4 sessions	N/A	Significant improvement in group B compared to A in both patient and physician assessment.	None reported.	No rebound at 3 month follow-up.
Lee et al(92)	2018	12, Taiwanese	single x single	picosecond 755 nm alexandrite laser	QSNYL 1064 nm	N/A	monthly, 4 sessions	dermal, mixed	Significant improvement in group A compared to B, according to both physician and patient assessment.	Temporary erythema.	None reported.
Nourmohammadi	2019	37, Iranian	single x double	HQ 4% cream +	HQ 4% cream	N/A	laser at 3 week	N/A	Significant reduction in darkness at week 3 in	Erythema and burning	N/A

et al(93)				fractional CO2 laser			interval, 3 sessions, cream		group A and at week 6 in group B. Reduction in homogeneity became significant at week 6 in both groups.	sensation.	
Shakeeb et al(79)	2018	96, Pakistanese	single x single x double	triple combination cream	IPL	IPL + triple combination cream	cream nightly, IPL biweekly, for 2 months	96 epidermal	Significantly better MASI score reduction in group C than A or B.	N/A	N/A
Tawfic S et al(94)	2019	28, Egyptian	single x double	fractional ablative CO2 laser	fractional ablative CO2 laser + microneedling with TXA 10%	N/A	every 4-6 weeks, 5 sessions	N/A	Significant reduction in mean MASI, MI and EI scores in group A. Significant reduction in mean MASI score in group B.	Mild burning sensation in both groups. Post-inflammatory hyperpigmentation in group B.	N/A
Vachiramon et al(51)	2015	18, Thai	single x double	LFQSNYL + IPL	LFQSNYL	N/A	LFQS weekly, 5				

Figure legends

Figure 1. Literature search and article selection.