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Review

Unmasking Melasma: Confronting the Treatment Challenges

Ena Parać [1] and Zrinka Bukvić Mokos [2,*]

[1] Children's Hospital Zagreb, Klaićeva 16, 10000 Zagreb, Croatia; enaparac7@gmail.com
[2] Department of Dermatology and Venereology, School of Medicine, University Hospital Centre Zagreb, University of Zagreb, Kišpatićeva 12, 10000 Zagreb, Croatia
* Correspondence: zrinka.bukvic.mokos@mef.hr

Abstract: Melasma, also known as chloasma and the "mask of pregnancy", is a common acquired pigmentary disorder characterized by irregular, hyperpigmented brown-to-grey patches primarily situated on the face. It typically affects women of reproductive age, especially those exhibiting Fitzpatrick skin types III to V. The precise etiopathogenesis of melasma is complex and has not been fully elucidated; however, ultraviolet radiation, hormonal factors, and genetic predispositions significantly contribute to the melanin production increase associated with this condition. Due to the multifactorial aetiology, resistance to various therapeutic options, and high recurrence rate, treating melasma is challenging. Hydroquinone has long been considered a gold standard in melasma treatment due to its ability to inhibit tyrosinase; however, it has faced scrutiny after concerns about its adverse effects. Current treatment strategies include various topical and systemic therapies, procedural interventions, as well as combinations of these methods. For optimal results, both photoprotection and a treatment plan that targets different pathogenic mechanisms should be used. Additionally, treatment should be tailored to patient characteristics, such as skin type, the severity of the condition, and compliance. This review summarises current treatment options, focusing on long-term therapy and the latest advancements in managing this challenging condition.

Keywords: melasma; depigmenting agents; hydroquinone; UV radiation

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1. Introduction

Melasma is a common acquired and relapsing pigmentary disorder presenting with irregular, hyperpigmented brown-to-grey patches symmetrically distributed on sun-exposed areas, primarily the face. It typically affects women of reproductive age, especially those exhibiting Fitzpatrick skin types III to V [1]. The prevalence of this condition varies considerably across different populations, ranging from 1.5% to 33% [2]. It is predominantly observed in individuals of East Asian, Middle Eastern, African, and Latin American descent [3]. While hyperpigmentation resulting from inflammation or sun exposure naturally fades after the triggering factor is removed, the pigmentation in melasma tends to persist [4].

The precise etiopathogenesis of melasma is complex and has not been fully elucidated; however, ultraviolet radiation, hormonal factors, and genetic predispositions significantly contribute to melanin production increase. Ultraviolet (UV) radiation upregulates melanocyte-stimulating hormone (MSH) receptors on melanocytes, thereby increasing hormone binding and subsequently enhancing melanin production. Furthermore, prolonged exposure to UV radiation induces dermal inflammation and triggers fibroblast activation. The activated fibroblasts subsequently secrete stem cell factor (SCF), which binds to the upregulated c-kit (stem cell growth factor receptor) in the epidermis. This interaction leads to the activation of the tyrosine kinase pathway, initiating melanogenesis. Additionally, UV-induced changes in the basement membrane, solar elastosis, mast cell count increase, and hypervascularization underlie the condition [5,6] (Figure 1). Hormonal influence in melasma pathogenesis has been evidenced by its increased occurrence in pregnant women

and those on hormone replacement therapy (HRT) and oral contraceptive pills (OCP). In fact, 10–20% of patients taking OCT develop melasma [7]. Since melasma is a common finding in pregnant women, it is often deemed the "mask of pregnancy", with studies reporting a prevalence ranging from 36.4% to 70% [8]. During pregnancy, elevated levels of oestrogen, progesterone, and melanocyte-stimulating hormone (MSH) promote melanogenesis through various regulatory pathways [9]. It has been shown that the epidermal layer of melasma lesions contains a greater number of progesterone receptors (PR), whereas the dermal layer exhibits a greater abundance of oestrogen receptors (ER). The interaction of oestrogen with its receptors on keratinocytes and melanocytes activates tyrosinase and thereby promotes melanogenesis. In addition, oestrogen can upregulate the expression of α-melanocyte-stimulating hormone (α-MSH) and PDZ domain protein kidney 1 (PDZK1), thereby boosting tyrosinase synthesis and promoting melanin production [5]. The impact of progesterone requires further clarification [3]. However, sex steroid hormones are unable to induce hyperpigmentation alone; instead, they work synergistically with UVB radiation [6]. This "mask of pregnancy" or chloasma gravidarum, typically resolves spontaneously within a year following delivery. Nevertheless, it may persist permanently in around 30% of women [8]. The genetic predisposition for developing melasma is highlighted by a positive family history in a subset of patients. In fact, according to studies, 55–64% of patients with melasma report family members affected by the condition [10]. Along with sun exposure, a positive family history is the most prevalent risk factor identified in men, and in women, it is pregnancy [2]. Familial melasma is characterized by a longer duration and is less likely to be triggered by hormonal contraceptives [4].

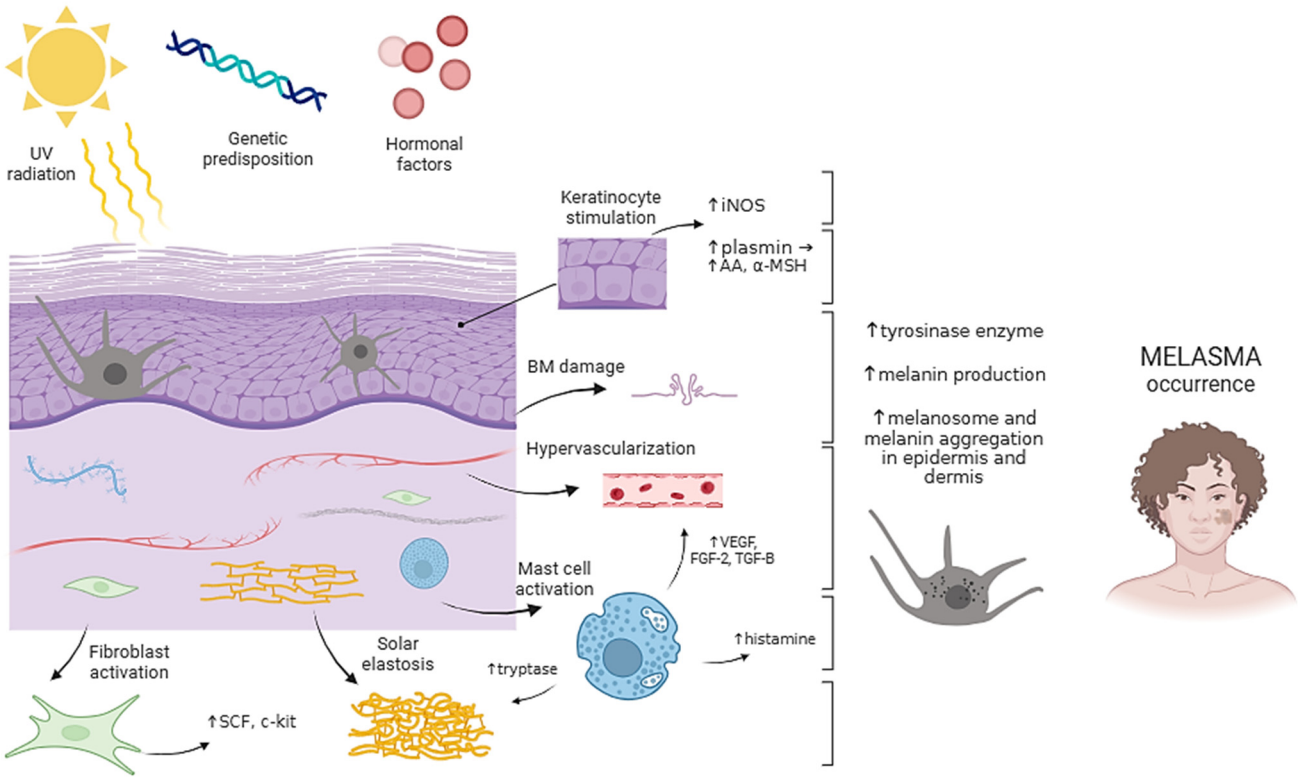

Figure 1. Pathogenesis of melasma. UV radiation, genetic predisposition, and hormonal factors are key contributors to melasma development. Chronic sun exposure in susceptible individuals triggers a complex interplay between dermal and epidermal cells, ultimately leading to increased melanin production and hyperpigmented patches characteristic of melasma. Abbreviations: AA—arachidonic acid; BM—basement membrane; FGF-2—fibroblast growth factor 2; iNOS—inducible nitric oxide synthase; SCF—stem cell factor; TGF-B—transforming growth factor B; UV—ultraviolet; α-MSH—alpha-melanocyte stimulating hormone. Created with Biorender.com.

According to the regions affected by melasma, there are three primary clinical patterns: centrofacial, malar, and mandibular. Centrofacial melasma is the most common type, and it affects the nose, cheeks, forehead, chin, and upper lip, while sparing the nasolabial folds and philtrum. Malar melasma is confined to the malar cheek area, while the mandibular type appears along the jawline [2]. Therefore, symmetrically distributed and irregularly shaped macules and patches of melasma primarily affect the face, with less frequent occurrences on the neck and forearms [11].

Given its localization, chronic course, and tendency to recur, melasma may significantly negatively impact patients' emotional and social well-being, though the correlation between the severity of melasma and quality of life is inconsistent across studies [12,13].

Due to the multifactorial aetiology, resistance to various therapeutic options, and high recurrence rate, treating melasma is challenging and often unsatisfactory. Sun protection using broad-spectrum sunscreen and protective clothing is a crucial component of melasma treatment. Ideally, sunscreens containing physical blockers such as zinc oxide and titanium dioxide are recommended. Treatment should be tailored to individual characteristics such as skin type, severity, and patient compliance. There are numerous approaches available, and in order to achieve optimal results, a treatment plan should target different pathogenic mechanisms [10,11]. Hydroquinone has long been considered a gold standard for treating melasma due to its ability to inhibit tyrosinase; however, it has faced scrutiny after concerns about its adverse effects. Current treatment strategies include different topical and systemic therapies, procedural interventions such as microneedling, chemical peels, and laser treatments, as well as combinations of these approaches [10]. To determine the severity of the disease and the efficacy of therapeutic options, several scales are used, with the most commonly applied being the Melasma Area and Severity Index (MASI), modified Melasma Area and Severity Index (mMASI), Melasma Severity Scale (MSS), and Melasma Severity Index (MSI) (Table 1) [14].

This review focuses on different therapeutic options for melasma, with the emphasis on the challenges when maintaining therapeutic effects after the initial therapy, and long-term efficacy and safety of future treatment strategies.

Table 1. Commonly used scoring systems for melasma.

Scoring System	Parameters	Formula	Total Score
MASI	A: area of involvement (0: absent; 1: <10%; 2: 10–29%; 3: 30–49%; 4: 50–69%; 5: 70–89%; 6: 90–100%);	0.3A (D + H) forehead + 0.3A (D + H) right malar + 0.3A (D + H) left malar + 0.1A (D + H) chin	0–48
	D: darkness (0: absent; 1: slight; 2: mild; 3: marked; 4: severe)		
	H: homogeneity (0 = no pigment; 1 = specks; 2 $\leq$ 2 cm patches; 3 $\geq$ 2 cm patches; 4 = homogeneous)		
mMASI	A: area of involvement (0: absent; 1: <10%; 2: 10–29%; 3: 30–49%; 4: 50–69%; 5: 70–89%; 6: 90–100%);	0.3A $\times$ D forehead + 0.3A $\times$ D right malar + 0.3A $\times$ D left malar + 3A $\times$ D chin	0–24
	D: darkness (0: absent; 1: slight; 2: mild; 3: marked; 4: severe)		
MSS	Intensity of pigmentation	NA	1: mild; 2: moderate; 3: severe
MSI	p: pigmentation (0: no visible pigmentation; 1: barely visible pigmentation; 3: moderate pigmentation; 4: severe pigmentation)	0.4 (a $\times$ p^2) left face + 0.4 (a $\times$ p^2) right face + 0.2 (a $\times$ p^2) nose	Scoring of pigmentation: 0–4 Scoring of area of involvement: 0–4
	a: area of involvement (1: $\leq$10%; 2: 11–30%; 3: 31–60%; 4: >60%)		

Abbreviations: MASI—Melasma Area and Severity Index; mMASI—modified Melasma Area and Severity Index; MSS—Melasma Severity Scale; MSI—Melasma Severity Index; NA—not applicable.

2. Topical Therapy

Topical preparations, including photoprotection, generally serve as the first-line treatment for melasma. A combination of different topical therapies with different mechanisms of action is favoured over monotherapy.

2.1. Photoprotection

Irrespective of the chosen therapeutic approach, photoprotection is essential for melasma treatment. Prolonged and rigorous photoprotection is essential to avoid the progression of existing hyperpigmentation, prevent the formation of new patches, and reduce the risk of relapses [15]. Photoprotection entails reducing sun exposure (especially during the middle of the day), wearing protective clothing, hats, and sunglasses, finding shade, and applying a broad-spectrum sunscreen with a Sun Protection Factor ≥ 30, with reapplications every 2 h when outside [16]. Since long-wave UVA radiation and high-energy visible light have recently been shown to contribute to the pathogenesis of melasma, sunscreens containing inorganic filters and iron compounds are recommended. However, since physical sunscreens often leave white residues, they may be cosmetically unappealing, which could result in reduced usage. Therefore, water-based and easy-to-apply formulas are more likely to ensure better compliance [17]. Additionally, tinted sunscreens that contain pigmentary iron oxides can provide camouflage, positively affecting patients' quality of life [18]. Personalized photoprotection is an important approach that takes into account genetic factors, skin phototype, personal preferences in terms of sunscreen formulation, lifestyle, pollution levels, geographical location, work setting, and underlying skin conditions [19]. In order to achieve adherence, patient counselling and education are necessary.

2.2. Hydroquinone and Triple-Combination Therapy

Hydroquinone (HQ) is a topical depigmentation agent that has long been the mainstay of the treatment of melasma. It blocks melanin synthesis by inhibiting tyrosinase, an enzyme responsible for the hydroxylation of L-tyrosine into 3,4-dihydroxyphenylalanine (L-DOPA) and the oxidation of L-DOPA to dopaquinone, both necessary steps for forming eumelanin and pheomelanin [20]. Additionally, HQ contributes to melanosome and melanocyte degradation [21]. This hydroxyphenolic compound has typically been used at concentrations of 2–5% [16]. However, a more effective formulation, known as Kligman's formula, has emerged. It uses a triple-combination therapy with HQ, a retinoid and a corticosteroid, usually consisting of HQ (4%), tretinoin (0.05%), and fluocinolone acetonide (0.01%). The effectiveness of the triple-combination therapy has been demonstrated to be slightly superior compared to using HQ alone at 4% or in dual combination with either of the other agents [22]. This therapy may show improvements or achieve clearance in up to 60–80% of melasma patients [16]; therefore, it is a first-line treatment option by many practitioners [23]. HQ faced controversies due to the side-effect profile of the drug. Namely, both irritant and allergic contact dermatitis, colloid milium, guttate hypomelanosis, changes in nail colour, paradoxical post-hyperpigmentation, and corneal degeneration have been described [24]. Moreover, a cutaneous condition known as exogenous ochronosis appeared as a complication of long-term HQ therapy. This disorder marked by black-bluish pigmentation, although rare, was even observed at low concentrations of HQ (1–2%) [24,25]. As a result, due to concerns regarding exogenous ochronosis and proposed carcinogenic risks in animal studies, the US Food and Drug Administration (FDA) banned over-the-counter hydroquinone. Since 2020, HQ is only available through prescribed formulations or newly approved medications [16,24].

2.3. Azelaic Acid

Azelaic acid (AZA) is a saturated dicarboxylic acid used in topical treatments for various dermatological conditions, such as acne, rosacea, and hyperpigmentation disorders. It is found in both over-the-counter and prescription products in the form of gels and creams containing 5% to 20% AZA. Besides its antioxidant and anti-inflammatory properties, AZA's inhibition of tyrosinase makes it beneficial in treating melasma [26,27]. AZA may be incorporated into a treatment plan either as monotherapy or in combination with other medications like oral tranexamic acid (TXA) [28]. A randomized controlled trial by Tehrani et al. [29] compared AZA 20% with HQ 5% to HQ 5% alone, showing superior efficacy of combination treatment in melasma reduction.

A meta-analysis by Albzea et al. [30] compared AZA to HQ in terms of efficacy and safety in melasma treatment. According to their results, AZA was more effective than HQ in improving Melasma Area and Severity Index (MASI) scores. However, there was no significant difference in pigmentation reduction, and both treatments had similar rates of reported adverse events, including stinging, burning, erythema, and scaling [27].

2.4. Retinoids

Retinoids such as tretinoin, adapalene, tazarotene, and isotretinoin act as depigmenting agents by accelerating keratinocyte turnover, inhibiting tyrosinase, and decreasing melanosome transfer [21,24]. Additionally, their ability to alter the stratum corneum and permeability barrier may enhance transepidermal penetration of other depigmenting agents [31]. Tretinoin or all-trans-retinoic acid (ATRA) at 0.05–1% is a widely used retinoid for treating melasma. It may be used as monotherapy; however, noticeable results require almost 6 months of regular application [16]. Studies evaluating the efficacy of tretinoin 0.1% cream versus placebo in Caucasian and African American patients with melasma showed significant improvement in depigmentation in the Caucasian group after 24 weeks of tretinoin treatment. In contrast, this improvement was only marginal in the African American group [32,33]. Another randomized controlled trial assessed the efficacy of a combination of topical retinoids compared to placebo. The study showed a significant (70%) improvement in MASI scores on the treated side, similar to the improvement typically seen with HQ [34]. A combination of ATRA and a low concentration of HQ improves the effectiveness of HQ and reduces the unpleasant adverse effects that are associated with higher concentrations of HQ [35].

2.5. Corticosteroids

Corticosteroids inhibit cytokines like endothelin-1 (ET-1) and granulocyte-macrophage colony-stimulating factor (GM-CSF), as well as prostaglandins, all of which promote melanin production [16]. In addition, their anti-metabolic effect leads to decreased turnover of the epidermis, thereby producing mild depigmentation [36]. However, topical corticosteroids are rarely used alone in melasma treatment because of their potential adverse effects, including skin thinning, acne-like eruptions, facial hypertrichosis, and telangiectasias [36,37]. Compared to other corticosteroids, fluticasone exhibits lower atrophogenic properties. Fluocinolone acetonide, hydrocortisone, dexamethasone, fluticasone, and mometasone furoate are still preferred components of triple-combination therapy [38].

2.6. L-Ascorbic Acid

Ascorbic acid, widely known as vitamin C, is an antioxidant found in various cosmeceuticals, and it is well known for its depigmentation properties. Its effectiveness in skincare formulations is limited by its low permeability and susceptibility to rapid oxidation [39]. Therefore, esterified forms of ascorbic acid, such as magnesium ascorbyl-2-phosphate (MAP), are often used because of their greater stability and lipophilic nature, which consequently leads to better penetration through the stratum corneum [40]. Ascorbic acid prevents UV-induced pigmentation by inhibiting tyrosinase through interaction with copper at the enzyme's active site and blocking the oxidative polymerization of melanin

precursors [41]. Furthermore, it stimulates collagen synthesis and provides photoprotection by preventing the absorption of UV radiation [42,43]. Trials comparing ascorbic acid to HQ showed somewhat superior results of HQ in melasma treatment, although treatment with ascorbic acid still showed improvement in pigmentation and had minimal side effects [44]. The use of ascorbic acid in melasma treatment has been effective, especially when combined with Q-switched Nd:YAG laser therapy, as it has been shown to boost its effects [45]. Also, combinations with mesotherapy, iontophoresis, vitamin E, tranexamic acid, or fractional Q-switched ruby laser show greater treatment success than using vitamin C alone [46–50]. Adverse effects of topical vitamin C therapy may involve contact dermatitis but are rarely reported [39].

2.7. Kojic Acid

Kojic acid (KA) is a naturally derived fungal metabolite that has shown benefits in melasma treatment because of its skin-lightening properties. In addition to its antioxidant properties, KA chelates copper ions and inhibits tyrosinase activity [51]. It is typically available in concentrations ranging from 1 to 4%, and optimal results are often achieved by combining KA with other depigmentation products [52]. A double-blind comparison demonstrated that the combination of 2% KA, 2% HQ, and 10% glycolic acid led to greater melasma improvement than 2% HQ and 10% glycolic acid alone [53]. KA as monotherapy may not be as effective. In a comparative study, KA 0.75% was inferior to HQ 4% cream in achieving depigmentation [54]. A similar result was obtained when comparing KA 2% cream to modified Kligman's formula [55]. However, it is a useful agent in patients who are either intolerant or respond poorly to first-line therapies. The cosmetic use of KA is generally associated with few adverse effects, with irritant contact dermatitis (seen mostly in the sensitive skin types), being the main one [52].

2.8. Tranexamic Acid

Tranexamic acid (TXA) is a synthetic derivative of lysine that has become widely used to treat melasma via topical, oral, and injectable preparations. Treatment success typically depends on TXA formulation and concentration. Liposomal formulations containing 2–5% TXA are typically used, and their effects are evident after 2 to 3 months of continuous application [38,56]. Recent studies comparing TXA 5% cream to different concentrations of HQ 2–4% showed similar reductions in MASI with TXA and HQ after 12 weeks of treatment. However, patients in the TXA group reported higher satisfaction levels and fewer adverse effects [57–59]. Despite positive outcomes, the topical form of TXA is not suitable for monotherapy and is less successful than its oral and injectable counterparts [10,60]. Cosmeceuticals containing a combination of depigmenting agents such as TXA, KA, and niacinamide are safe therapeutic options with very high patient satisfaction [61].

2.9. Niacinamide

Niacinamide, the amide form of vitamin B3, has recently been studied in the treatment of various dermatologic conditions due to its anti-inflammatory and antioxidant properties [62]. The mechanism by which niacinamide regulates pigmentation is not entirely understood. It is proposed that niacinamide and its metabolites are involved in melanosome transfer signalling [63]. The effect of skin depigmentation using 4% niacinamide cream is nearly comparable to HQ 4% cream [64]. Besides photoprotection, combination with other topical agents or methods boosts niacinamide's effectiveness [61,63]. It is typically a well-tolerated agent, but prolonged use may lead to pruritus, erythema, and a mild burning sensation [64].

A recent study found that changes in the nicotinamide nucleotide transhydrogenase (NNT) could influence melanin production in the skin. Specifically, the inhibition of NNT activity may lead to increased skin pigmentation, a mechanism that is independent of UVB radiation [65]. Newly recognized pathways may pave the way for new therapeutic interventions.

Further research is needed to specifically investigate pure niacinamide for treating pigmentation in melasma [66].

2.10. Arbutin

Arbutin is a compound made of D-glucose bound to HQ that is naturally found in different plant species. Due to its skin-lightening properties, it is a component of various cosmeceuticals [67,68]. Most studies suggest that arbutin competitively inhibits tyrosinase or irreversibly inactivates it, which blocks the production of melanin [68]. Arbutin has a similar inhibitory effect on tyrosinase to HQ; however, it is less efficacious than KA. Additionally, it prevents melanosome maturation [69]. In comparison to HQ, arbutin is less toxic to melanocytes [70]. Deoxyarbutin (dA) is a synthetic form of arbutin that is more stable and more potent than natural arbutin. A recent randomized controlled study compared a 2% dA to a 4% HQ serum over 12 weeks and showed a similar decrease in the melanin index and therefore, similar depigmenting properties in both groups. However, there is a concern about dA metabolizing to HQ, which could potentially lead to toxicity [71]. Lastly, although arbutin may be more effective at higher concentrations, there is a risk of paradoxical hyperpigmentation [40].

3. Oral Therapy

3.1. Oral Tranexamic Acid

Oral TXA is safe, effective, and a convenient therapeutic option for melasma that may be used alone or in combination with other treatments. Its efficacy has been documented in a number of studies [56,60]. TXA is a valuable antifibrinolytic agent as it inhibits the conversion of plasminogen to plasmin (a molecule responsible for fibrin degradation). Besides its use in surgical settings, it is beneficial in blocking keratinocyte–melanocyte interactions. Essentially, UV radiation and hormones activate the plasmogen activator system in keratinocytes and epidermal basal cells, leading to plasmin formation. This, in turn, produces inflammatory mediators such as arachidonic acid (AA) and prostaglandins that increase melanocyte tyrosinase activity. Additionally, plasmin-induced increase in α-melanocyte stimulating hormone (α-MSH) and fibroblast growth factor (FGF) further contributes to melanin synthesis [69,70]. Therefore, TXA reduces melanocyte response to UV radiation. Furthermore, by inhibiting vascular endothelial growth factor (VEGF), TXA also reduces angiogenesis that is implicated in the pathogenesis of melasma [72]. A recent meta-analysis by Feng et al. [73] revealed significant reductions in MASI scores following oral TXA treatment, suggesting that TXA as monotherapy or adjuvant therapy may be superior to standard treatment. However, no significant differences were detected in the melasma index (MI) and erythema index (EI) between standard treatment methods and TXA. The study also suggested that oral TXA may provide better results than topical or intradermal injections of TXA. To date, there is no official guideline for TXA use in melasma [74]. Oral TXA at a dosage of 250 mg twice daily appears to be a good treatment option, while being much lower than the dose used for haemostasis. Interestingly, studies that employed higher doses of oral TXA showed similar results in MASI and MI scores as those with lower doses [73]. One study compared a combination of oral TXA and 3% topical TXA versus oral TXA and 20% AZA. Both groups had a good therapeutic response, but the combination of oral and topical TXA showed a better improvement in the mean MASI score [75]. Furthermore, the effect of oral TXA is enhanced when paired with other procedures, such as Q-switched Nd:YAG laser [76].

A minimum of 3 months may be necessary in order to see the results of oral TXA. Further research is required to assess the ideal length of treatment. According to expert opinions, oral TXA may be taken for up to 6 months [74]. It is a promising option for moderate-to-severe recurrent melasma and for refractory melasma [77,78].

The most commonly reported adverse effects of oral TXA are gastrointestinal discomfort and menstrual irregularities. Before initiating treatment, patients should be evaluated for any risk factors for thrombosis or thromboembolism [79,80].

3.2. Glutathione

Glutathione (GSH) is a tripeptide consisting of glycine, cysteine, and glutamate. It is a valuable antioxidant in aerobic organisms. GSH is becoming regarded as a skin-lightening agent due to its inhibition of tyrosinase and the ability to shift melanogenesis from eumelanin to pheomelanin [15]. It may be administered as a topical, oral, or intravenous agent. However, despite a recent increase in publicity regarding intravenous GSH, there is no evidence to prove its benefits and it may, on the contrary, be associated with life-threatening reactions such as anaphylaxis and Stevens–Johnson syndrome (SJS) [81,82]. Regarding oral GSH, a randomized controlled trial in 60 young participants showed that 250 mg of GSH twice daily over 4 weeks reduced the MI and the development of lentigines in the GSH group. This suggests that GSH might influence new melanin production rather than existing pigment [83]. Another trial that assessed a combination of topical and oral GSH showed a superior skin-lightening effect with the two agents than with monotherapy [84].

Topical and oral GSH have no significant side effects and are usually well tolerated. Further studies are needed to assess the benefits of GSH in melasma treatment [82].

The aforementioned topical and oral treatment options are presented in Table 2.

Table 2. Selected clinical results of the currently available topical and oral treatment strategies in melasma.

Author, Year [Reference Number]	Study Design	Examinees/Patients	Treatment Method	Wks/ Mo	Method of Assessment	Results
Chan, R. et al., 2008 [22]	Multicentre, randomized, controlled, investigator-blinded, parallel comparison study	251	TC (fluocinolone acetonide 0.01%, HQ 4%, tretinoin 0.05%) vs. HQ 4%	8 wks	GSS, patient satisfaction	GSS: mild or no melasma in 64.2% of the TC patient group vs. 39.4% in HQ group ($p < 0.001$). Patient satisfaction: 70.8% in the TC group vs. 49.6% in the HQ group.
Akl, E. et al., 2022 [28]	Randomized controlled study	50	Liposomal AZA 20% cream + oral TXA (250 mg daily) vs. HQ 4% cream + oral TXA (250 mg daily)	3 mo	mMASI, DLQI	mMASI: better improvement in liposomal AZA group vs. HQ group ($p < 0.001$). QoL: better improvement in liposomal AZA group vs. HQ group ($p < 0.001$) Liposomal AZA 20% was more tolerable ($p < 0.0001$).
Tehrani, S. et al., 2012 [29]	Double-blind randomized clinical trial	64	AZA 20% cream + HQ 5% vs. HQ 5% alone	4 mo	MASI	AZA 20% + HQ 5%: quicker and more effective therapeutic response. MASI score reduction: from 9.35 to 2.9 in the AZA + HQ group and from 9.58 to 4.02 in the HQ group.
Griffiths, C.E.M. et al., 1993 [32]	Double-blind, randomized, vehicle-controlled clinical trial	38	Topical tretinoin 0.1% vs. vehicle	40 wks	Clinical evaluation, colorimetry, patient self-assessment	Clinical improvement: 68% in the tretinoin group vs. 5% in vehicle group ($p = 0.0006$). Colorimetry: lightening by 0.9 units (tretinoin group) vs. by 0.3 units (vehicle) ($p = 0.01$). AE: erythema and desquamation in 88% (tretinoin group) vs. 29% (vehicle).
Espinal-Perez, L.E. et al., 2004 [44]	Randomized, double-blind, split-face study	16	5% L-ascorbic acid cream vs. 4% HQ cream	16 wks	Calorimetry, subjective evaluation, digital photography	Colorimetry: no statistically significant difference. Subjective evaluation: "good" or "excellent" in 93% in the HQ-treated skin vs. 62.5% in the ascorbic acid-treated skin ($p < 0.05$). Skin irritation: 8.75% of HQ-treated skin vs. 6.25% of ascorbic acid-treated skin.
Monteiro, R.C. et al., 2013 [54]	Randomized, controlled trial	60	4% HQ cream vs. 0.75% KA + 2.5% vitamin C	12 wks	MASI	MASI: significantly decreased in both groups ($p \leq 0.001$, respectively). AE: erythema in 6.7% of patients receiving 4% HQ cream and 3.3% of patients receiving 0.75% KA cream.
Bhagwat, P.V. et al., 2017 [55]	Comparative clinical study	60	Modified Kligman's formula (2% HQ, 0.025% tretinoin, 0.01% fluocinolone acetonide cream) vs. 2% KA + octinoxate + allantoin containing gel	3 mo	MASI, colour photography	MASI mean reduction: MKF (2.08, 26.22%, $p < 0.0001$) vs. 2% KA group (6.67, 66.5%, $p < 0.0001$). Better efficacy in MKF vs. 2% KA group ($p < 0.0001$).

Table 2. *Cont.*

Author, Year [Reference Number]	Study Design	Examinees/Patients	Treatment Method	Wks/ Mo	Method of Assessment	Results
Atefi, N. et al., 2017 [57]	Randomized, double-blinded clinical trial	60	Topical TXA 5% vs. topical HQ 2%	12 wks	MASI	MASI: significantly lower in both groups AE: none in TXA group, erythema and skin irritation in the HQ group ($p = 0.131$). Patient satisfaction: 33.3% in TXA group vs. 6.7% in HQ group ($p = 0.015$).
Janney, M. et al., 2019 [58]	Prospective, randomized, single-blind study	100	Topical 5% TXA vs. 3% HQ cream	12 wks	Serial digital photographs, MASI, patient satisfaction score	Reduction of MASI: 27% (TXA group) vs. 26.7% (HQ group); no significant difference between the groups ($p > 0.05$) Patient satisfaction: higher in TXA group ($p = 0.03$) AE: mild irritation (3/50, TXA group), mild erythema and irritation (19/50, HQ group).
El-Husseiny, R. et al., 2020 [59]	A split-face comparative clinical trial	100	TXA 5% cream vs. HQ 4% cream	12 wks	Photography, Wood's light, Hemi-MASI, MELASQoL histopathology	Significant improvement on both TXA 5% and HQ 4% sides of the face. Hemi-MASI, MELASQOL scores, and Antera Average Level of Melanin: no significant difference between the two treatments ($p > 0.05$). Area % of melanin: significant reduction with TXA 5% compared to HQ 4% ($p = 0.000$).
Navarrete-Solís, J. et al., 2011 [64]	Double-blind, left–right randomized clinical trial	27	4% niacinamide cream vs. 4% HQ cream	8 wks	Chromametry, calorimetry, MASI, histopathology	Chromametry: pigment improvement in both groups. Calorimetry: no statistical differences between sides ($p = 0.78$). MASI reduction: 70% with H vs. 62% with niacinamide. Histopathology of niacinamide-treated side: significantly decreased epidermal melanin ($p < 0.0007$), decreased inflammatory infiltrate ($p = 0.01$), reduced solar elastosis. AE (erythema, pruritus, burning): mild in 18% (niacinamide) vs. moderate in 29% (HQ).
Anwar, A.I. et al., 2021 [71]	Double-blind randomized controlled study	59	2% dA serum vs. 4% HQ,	12 wks	Skin brightness (L* value; chromameter) MI, EI (Mexameter®)	Both 2% dA and 4% HQ showed significant skin depigmentation (increase in L* value and decrease in melanin index) at the end of the study ($p < 0.05$).
Nguyen, J. et al., 2021 [72]	Randomized, double-blind, placebo-controlled trial	17	Oral TXA (250 mg) vs. placebo	12 wks, follow-up at 24 wks	Clinical photographs, EI (Mexameter®)	EI: greater median decrease in TXA group vs. placebo; no statistically significant difference ($p = 0.53$ and 0.37, respectively). Clinical improvement only in TXA group.

Table 2. *Cont.*

Author, Year [Reference Number]	Study Design	Examinees/Patients	Treatment Method	Wks/ Mo	Method of Assessment	Results
Malik, F. et al., 2019 [75]	Interventional comparative study	100	Oral TXA (250 mg twice daily) + topical 3% TXA vs. oral TXA (250 mg twice daily) + topical 20% AZA	6 mo	MASI	2 and 4 mo: no significant difference ($p = 0.20$, $p = 0.89$) 6 mo: mean MASI significantly lower in oral + topical TXA group (6.06 ± 5.06 vs. 10.62 ± 7.43, $p = 0.001$).
Zhu, C.-Y. et al., 2019 [80]	Multicentre prospective clinical trial	72	Oral TXA at doses of 500 mg, 750 mg, 1000 mg, or 1500 mg daily	8 wks	Clinical and VISIA® photographs, MASI, MI, blood and coagulation tests	Efficacy: all doses effective for improvement; correlated with dosage and treatment time MASI, MI: no significant differences between doses. Blood tests: D-dimers and FDP within normal range. AE: irregular menstruation, upset stomach; no significant differences between different dose groups.
Arjinpathana, N. and Asawanonda, P. 2012 [83]	Randomized, double-blind, placebo-controlled trial	60	Oral GSH (500 mg/day, in two divided doses) vs. placebo	4 wks	MI (Mexameter®) UV spots, skin evenness, and pore size (VISIA® system), self-reported satisfaction	MI: significant reductions in the GSH group, no changes in the placebo group/increase on the face ($p = 0.021$ and 0.036, respectively). UV spots: a smaller increase with GSH vs. placebo. Skin evenness and pore size: improved in GSH group, not statistically significant. Satisfaction: higher in the GSH group (average 3.06/4) vs. placebo group (average 2.13). AE: minimal; flatulence (GSH), constipation (placebo).
Wahab, S. et al., 2021 [84]	Double-blind, randomized, controlled clinical trial.	46	Group 1: topical and oral placebo Group 2: topical GSH and oral placebo Group 3: topical placebo and oral GSH Group 4: topical and oral GSH Topical preparation: serum containing 2% GSH and vitamin C Oral preparation: 600 mg GSH, 50 mg alpha lipoic acid, 4 mg zinc picolinate	8 wks	MI (Mexameter®) Skin brightness (L* score; chromameter)	Combination therapy showed significantly lower MI and higher L* scores compared to monotherapies and placebo ($p < 0.05$). L* score: statistically significant in the combination group ($p < 0.05$).

Abbreviations: AE—adverse effects; AZA—azelaic acid; dA—deoxyarbutin; DLQI—dermatology life quality index; EI—erythema index; GSH—glutathione; GSS—Melasma Global Severity Score; hemi-MASI—Hemi-Melasma Area and Severity Index; HQ—hydroquinone; KA—kojic acid; L*—luminosity axis; MASI—Melasma Area and Severity Index; MelasQoL—Melasma Quality of Life; mMASI—modified Melasma Area and Severity Index; MI—melanin index; MKF—modified Kligman's formula; mo—months; QoL—Quality of Life; TC—triple combination; UV—ultraviolet; wks—weeks.

4. Procedural Therapy

Procedural interventions serve as a second-line treatment option for patients unresponsive to topical therapy or as an adjunct to topical treatments when these alone are insufficient. While procedural therapies offer promising results, maintenance is crucial for sustained improvement. Although effective, procedures may cause some pain and discomfort, temporary redness, swelling, irritation, post-inflammatory hyperpigmentation, and on rare occasions, allergic reactions and infections.

4.1. Platelet-Rich Plasma

Treatments with platelet-rich plasma (PRP) have gained popularity in recent decades due to their regenerative potential. The use of an autologous serum containing increased concentrations of platelets and growth factors helps regenerate stem cells and remodel soft tissues. PRP's applications in dermatology are wide and include hair restoration, scar and striae treatment, and skin rejuvenation [85]. Furthermore, it has recently been introduced as a treatment option for melasma [86]. There are two reported mechanisms by which PRP improves melasma: one is increased synthesis of extracellular components that leads to increased skin volume; and the other is decreased melanin synthesis [87]. Furthermore, the anti-inflammatory properties of PRP may enhance this effect [85]. Treatment is usually achieved by delivering PRP through microneedling or intradermal injections.

A meta-analysis by Zhao et al. [88] showed the highest satisfaction rate among participants treated with the combination of PRP and microneedling. Thus, it outperformed both PRP as monotherapy and intradermally administered PRP. Nevertheless, an analysis of all included studies revealed that the mean modified MASI (mMASI) score decreased by 1.18 after treatment.

One recent study compared intradermal TXA to intradermal PRP in 40 participants by injecting TXA into one side of the face, and PRP into the other. Although both treatments resulted in a significant reduction in the mMASI score, this was more prominent on the PRP-treated side, showing that intradermal PRP may have superior efficacy in treating melasma [89].

Furthermore, a study by Gamea et al. [90] showed that intradermal injections of PRP enhanced the effect of topical TXA in a liposome-based cream. However, another study reported no added advantage of PRP in patients who received topical TXA treatment [91].

Adverse effects of PRP therapy are minor; a small number of patients may experience temporary redness, local congestion, discoloration, and hyperpigmentation [88].

Interpreting studies on PRP treatment is challenging; there is a lack of standardized preparation protocols for PRP, different clinical endpoints are used, and PRP is often employed in combination with other methods [92]. Finally, PRP is a safe option with high patient satisfaction. Since its use in melasma is a new concept, additional research has yet to determine its regular application.

4.2. Intralesional Tranexamic Acid

Intralesional delivery of TXA is achieved through two routes: transepidermal (using microneedling) and intradermal (using localized microinjections). This method offers controlled administration of therapy, avoids systemic adverse effects of oral TXA, and provides better availability in the skin compared to topical TXA [38,93]. Most commonly, solutions prepared for intralesional administration use TXA at a concentration of 4 mg/mL [38].

Microneedling is performed at a usual depth of 1.5 mm using a dermapen or a dermaroller, which therefore allows better absorption of topical TXA into the dermal layer. It is usually well tolerated and has a limited adverse effect profile. Some patients report erythema, pain, pruritus, and a burning sensation after the treatment, all of which typically subside within a few hours to a few days. Studies have shown that although microneedling on its own is beneficial in patients with melasma, the addition of TCA in the treatment regimen leads to a greater reduction in MASI scores [94,95]. On the contrary, results of some studies suggested no additional benefit of adding microneedling with TXA

to a 4% HQ regimen [96,97]. Nevertheless, despite discrepancies in clinical trials, a recent meta-analysis supports the use of microneedling with TCA over topical TCA alone [73].

Intradermal injections, or mesotherapy, uses small needles to deliver TXA into the dermis, with injections placed 1 cm apart. Studies have shown that intradermal TXA leads to a significant improvement in MASI score, especially if combined with other treatments [98,99]. Additionally, higher concentrations of TXA are not superior to injections with 4 mg/mL TXA [100]. Due to a high rate of recurrence in melasma, it may not be sufficient to use intradermal TCA solely for maintenance therapy; combination with another therapeutic option (along with photoprotection) may be necessary [101]. In conclusion, intralesional TXA is an effective method for improving melasma. It acts directly on the affected skin region, and it is safe and minimally invasive. Patients may experience burning pain at the injection site, along with local erythema and swelling, which generally resolves within 1–2 h after the injection. Additionally, minimal pain, bruising, and irritation may occur [98–101]. Long-term 48-week administration of 4 mg/mL TXA demonstrated only local adverse effects, with systemic adverse effects being avoided due to the TXA dose being considerably lower than the antifibrinolytic dose [101]. However, there are no standardized treatment intervals, as the sessions are still being determined by the treating physician [93].

4.3. Chemical Peels

Chemical peels use exfoliative agents to induce skin regeneration by increasing the turnover of epidermal keratinocytes. They are commonly employed for both cosmetic and therapeutic purposes, such as acne and acne scars, pigmentation disorders, and signs of skin ageing. Chemical peels can be categorized into three groups based on their depth of penetration into the skin layers, namely superficial, medium-depth, and deep peels [101–103].

When considering melasma, they are usually not the primary treatment option and are mainly used as an additional therapy. Agents that are frequently used are 15% or 20% trichloroacetic acid (TCA), 30%, 50%, or 70% glycolic acid (GA), 20% or 30% salicylic acid (SA), and Jessner's solution [15]. They are generally safe, effective, and can even achieve results faster than topical agents [104,105]. However, conventional exfoliative agents may potentially cause irritation, epidermal necrosis, and post-inflammatory hyperpigmentation (PIH) [106]. It is important to note that post-inflammatory hyperpigmentation is more common in individuals with darker skin types, the same group that suffers from melasma more often [107]. Pigmentary complications arising after chemical peels in darker-skinned patients are usually associated with TCA. Furthermore, the use of TCA in this group is less preferred due to the risk of scarring [108]. Moreover, a limitation of alpha hydroxy peels is the need for neutralization, and it may be challenging to determine the exact timing for it [109]. Newly introduced agents like amino fruit acid and phytic acid may overcome the disadvantages of traditional chemical peels, including overpeeling, burning sensation, and the need for neutralization [38,109].

4.4. Laser and Light-Based Therapy

Laser and light-based therapies use light energy to treat various clinical and cosmetic skin conditions. To achieve a clinical effect, laser light must use the appropriate wavelength in order to be absorbed by the chromophores in the skin. The endogenous chromophore melanin has a broad absorption spectrum, ranging from about 630 nm to 1100 nm [110]. Therefore, various devices with appropriate wavelengths have been studied in hyperpigmentary disorders, including melasma. They accelerate melanin removal, rather than target its production [11]. Laser treatments are one of the newer methods used for melasma treatment; however, they are usually not recommended as first-line therapy and may offer benefit to resistant and recurrent cases, as well as in combination treatments [110,111]. Laser therapy may be associated with erythema, scaling, burning sensation, oedema, and in patients with darker skin types, PIH and hypopigmentation [16,112]. To date, there is still no consensus on the laser treatment regimen and the required number of sessions.

Intense pulsed light (IPL) is a light-based device that, unlike lasers, emits noncoherent and noncollimated light pulses of different wavelengths, ranging from 515 to 1200 nm. This allows for selective absorption in the melanosomes and simultaneous targeting of multiple layers of the epidermis and dermis [16,110]. Additionally, IPL's pulse duration is measured in milliseconds, which allows for a wider heat distribution and reduces the risk of PIH. A recent meta-analysis reported high patient satisfaction and a significant reduction in MASI following combined therapy with IPL [113]. A randomized controlled trial that evaluated the effectiveness of IPL therapy in combination with triple-combination therapy (TCC) versus TCC alone showed considerable improvement in the IPL/TCC group compared to the controls. In the IPL/TCC group, there was a 49.4% reduction in MASI scores at 6 months, which persisted as a 44.9% reduction at 12 months [114]. Another recent retrospective study on fifty patients with melasma, who were treated exclusively with IPL, demonstrated a statistically significant correlation between IPL treatments and reductions in MASI scores [115]. Therefore, IPL may be beneficial in patients with refractory melasma when combined with effective topical therapy, preferentially in lighter skin types and in epidermal melasma [116]. Typical side effects include minor tingling sensation and erythema, both of which usually subside within a day. In a small number of patients, increased energy levels may cause mild exfoliation of the skin, though it generally resolves without leaving scars in a week [113].

Q-switched lasers are among the most extensively studied lasers in melasma treatment. Their beams are highly effective at targeting melanin and exist in different wavelengths, namely at 694 nm (Q-switched ruby laser), 755 nm (Q-switched alexandrite laser), and 532 nm or 1064 nm (Q-switched Nd:YAG laser) [11]. At present, the most commonly utilized Q-switched laser is low-fluence Q-switched (LFQS) Nd:YAG laser, also known as laser toning [117,118]. This technique selectively heats and destroys melanosomes and melanin within keratinocytes while preserving the cell membrane and the nucleus [119]. Treatments with LFQS Nd:YAG laser are effective, especially when combined with other topical agents, oral TXA, or chemical peels [77]. In order to achieve a good clinical effect, multiple treatments should be performed within a short period of time, such as weekly [116]. A recent network meta-analysis suggests that LFQS Nd:YAG laser paired with topical medications is superior to all other laser treatments [120]. Nevertheless, this laser carries a risk of mottled hypopigmentation and melasma relapse three months after treatment. Although combined treatments avoid recurrence, long-term studies are needed [121].

Fractional lasers include non-ablative (NAFL) and ablative fractional lasers (AFL). Their beams are absorbed by water-containing tissues and create columns of thermal injury that are intertwined with unaffected skin zones. Most commonly employed are fractional ablative 2940 nm Er:YAG laser, fractional ablative CO_2 laser, and fractional non-ablative 1550/1540 nm laser [110]. NAFL laser with the highest water absorption coefficient, the 1927 NAFL thulium laser, shows the best response after a single treatment and is effective in treating patients with darker skin types [122]. Generally, NAFLs are favoured in darker skin types because they carry a lower risk of PIH than other laser treatments [123]. AFLs are usually not advised in melasma treatment due to the high incidence of both adverse effects and relapses. Typical adverse effects include a burning sensation, temporary erythema, swelling, and superficial crust formation. A small number of patients may experience reversible PIH, acne, and oral herpes [124]. If a specialist opts for an AFL treatment, low-fluence CO_2 lasers are preferred, typically in combination therapy [110,124].

Recent studies on procedural treatments for melasma are presented in Table 3.

Table 3. Selected recent clinical results of the currently available procedural treatments in melasma.

Author, Year [Reference Number]	Study Design	Examinees/Patients	Treatment Method	Wks/ Mo	Method of Assessment	Results
Balevi, A. et al., 2017 [48]	Randomized, mono-blinded study	50	30% SA peel + vitamin C mesotherapy vs. 30% SA peel alone, every 2 wks	2 mo; follow-up for 6 mo	MelasQoL, MASI	MelasQoL: greater reduction in SA + vitamin C group ($p < 0.046$, respectively) MASI: greater decrease in SA + vitamin C group, without significant difference AE: burning sensation
Pazyar, N. et al., 2022 [50]	Prospective, double-blind, split-face, randomized controlled clinical trial.	24	TXA (50 mg/mL) + ascorbic acid (50 mg/mL) vs. TXA (50 mg/mL) + placebo, every 2 wks	12 wks, follow up-for 12 wks	MASI, pain levels	MASI: significantly lower in the intervention group at weeks 8 and 12 ($p < 0.001$, respectively) Pain levels: notably higher in the intervention group
Zhang, C. et al., 2022 [125]	Retrospective analysis	80	Oral TXA (250 mg) vs. PRP + oral TXA (250 mg)	3 mo, follow-up at 3 and 6 mo	MASI, serum levels of VEGF, ET-1, and MSH, AE, recurrence rates	Total efficacy: 73.68% (TXA group) vs. 90.48% (PRP +TXA group), ($p < 0.05$, respectively) AE: in 5.26% (TXA group) vs. 7.14% (PRP + TXA group) Disease recurrence: similar at 3 months; lower in PRP + TXA at 6 months (4.76% vs. 21.05%), ($p < 0.05$) VEGF, ET-1, and MSH: greater changes in oral TXA group compared to PRP + oral TXA
Tuknayat, A. et al., 2021 [126]	Open-labelled prospective trial	40	PRP administered intralesionally 1/month	3 mo, 3-mo follow-up	mMASI, patient satisfaction, AE	mMASI: 54.5% average reduction at 6 months Patient satisfaction: >90% were pleased or very pleased No relapse during follow-up AE: xerosis (35%) and pruritus (25%); no serious adverse effects
Adel, S. et al., 2021 [127]	Randomized prospective split-face study	20	PRP + IPL vs. PRP alone, every 2 wks	6 wks	MASI, mMASI, patient and physician satisfaction on a 4-point scale	MASI: decrease from 16.3 ± 7.7 to 10.9 ± 6.3 (33%) ($p < 0.05$) mMASI: decrease on both PRP (22.86%) and PRP + IPL (23.85%) side; not statistically significant (p-value > 0.05) Patient and physician satisfaction: no statistically significant difference (p-value > 0.05)
Sirithanabadeekul, P. et al., 2019 [128]	Randomized, split-face, single-blinded prospective trial	10	PRP injected intradermally vs. normal saline; every 2 wks	6 wks, follow-up at 10 wks	mMASI, EI, MI (Mexameter®), melanin levels (Antera® 3D), patient satisfaction	MI, EI: no statistically significant changes Melanin levels: significant reduction on the PRP-treated side (from 0.61 ± 0.02 to 0.57 ± 0.03) at week 6 ($p = 0.038$) mMASI: significantly greater mean improvement on the PRP side (1.03 ± 0.44) ($p = 0.042$) Patient satisfaction: improvement at every visit in PRP-side, no change on the saline-treated side

Table 3. *Cont.*

Author, Year [Reference Number]	Study Design	Examinees/Patients	Treatment Method	Wks/ Mo	Method of Assessment	Results
Abd Elraouf, I.G. et al., 2023 [89]	Prospective, split-face, randomized, controlled clinical trial	40	Intradermal TXA (4 mg/mL), vs. PRP; every 4 wks	8 wks	Digital photography, mMASI,	Mean mMASI: decreased from 4.59 to 2.49 (45.67%) on the TXA side vs. from 4.72 to 2.17 (53.66%) on the PRP side; significant improvement on both sides ($p < 0.001$) AE: pain and erythema more common in TXA, but not statistically significant
Gamea, M.M. et al., 2022 [90]	Randomized controlled trial	40	Topical TXA 5% in liposome base (twice daily) vs. topical TXA 5% in liposome base + intradermal PRP every 3 wks	12 wks	mMASI, patient satisfaction surveys	mMASI: mean improvement from 11.7 to 4.8 in TXA group vs. from 12.1 to 3.6 in TXA + PRP group Patient satisfaction: greater in TXA + PRP ($p = 0.024$, $p = 0.029$)
Batra, J. et al., 2022 [93]	Randomized controlled trial	40	Oral TXA (250 mg, twice daily) vs. transepidermal TXA solution (4 mg/mL) (using a dermaroller) at 2-week intervals	12 wks + 12 wks follow-up	MASI, patient satisfaction	MASI: similar decrease in both groups (oral TXA: 3.10 ± 3.38, Group B: 3.09 ± 1.32) ($p < 0.0001$, respectively) Patient satisfaction: slightly higher percentages of "very good" responses in oral TXA group Relapse uncommon in both groups
Saleh, F. et al., 2019 [94]	Randomized controlled trial	42	4% topical TXA + microneedling vs. microneedling alone; every 2 wks	12 wks	MASI, photographic evaluation, histopathological evaluation, immunohistochemistry	MASI: decreased in both groups, mean reduction percentage higher in TXA + microneedling group (62.1% vs. 22.5%) ($p = 0.001$) Clinical improvement: better in TXA + microneedling ($p = 0.001$) Histopathology: greater reduction in epidermal melanin and dermal melanophages in TXA + microneedling group A substantially higher % reduction in MART-1-positive cell number in TXA + microneedling (60.8%) vs. microneedling alone (37.5%) ($p = 0.001$)
Kaur, A. et al., 2020 [95]	Prospective, randomized, open-label, split-face study	40	Microneedling + 10% TXA vs. microneedling + distilled water; every 2 wks	6 wks, follow-up at 8 wks	Clinical images, mMASI, patient satisfaction scores, AE	Mean mMASI: mean improvement of 65.92% (microneedling + TXA) vs. of 20.75% (microneedling+ distilled water) AE: minor (erythema, dryness, burning, pruritus); patients could not differentiate between sides Patient satisfaction: higher on microneedling + TXA side
Zaky, M.S. et al., 2021 [96]	Prospective, randomized, open-label trial	50	Topical 4% HQ nightly vs. microneedling + topical 4% TXA, every other week	8 wks	mMASI	mMASI: decreased by 54.8% in HQ group ($p < 0.001$) vs. by 57.4% in TXA + microneedling group ($p < 0.001$)

Table 3. *Cont.*

Author, Year [Reference Number]	Study Design	Examinees/Patients	Treatment Method	Wks/ Mo	Method of Assessment	Results
Shamsi Meymandi, S. et al., 2020 [97]	Single-blind, randomized clinical trial	60	microneedling + topical 4% TXA (monthly) vs. topical 4% HQ (nightly)	12 wks	MASI, patient and physician assessments	MASI: no significant difference between groups (decrease from 12.89 ± 5.16 to 6.84 ± 4.31 in microneedling + TXA group vs. decrease from 13.56 ± 4.88 to 7.16 ± 4.38 in HQ group) ($p < 0.01$) Patient satisfaction > physician satisfaction in both groups ($p < 0.01$)
Kaleem, S. et al., 2020 [98]	Non-randomized clinical trial	60	TXA (4 mg/mL) vs. normal saline injections, 2-week intervals	12 wks	H-mMASI, patient satisfaction	H-mMASI: decrease from 3.19 ± 2.57 to 1.52 ± 1.20 (TXA side) ($p < 0.05$) vs. from 3.19 ± 2.57 to 1.52 ± 1.20 (saline side) ($p < 0.05$); on TXA side remained at 1.62 ± 1.27 at follow-up (maintenance effect) Patient satisfaction: 90% good to excellent satisfaction with TXA, poor response on the saline side
Agamia, N. et al., 2021 [76]	Comparative study	60	Oral TXA (250 mg/day) vs. oral TXA + Qs-Nd laser (1064 nm, 2 J/cm², every 2 weeks)	3 mo	mMASI score, dermoscopy	mMASI: substantially greater decrease in oral TXA + Qs-Nd laser group ($p = 0.036$) dermoscopy: significant improvement in telangiectasia (both groups) AE: transient in both groups Clearance of melasma in 60% of TXA + Qs-Nd laser group before end of scheduled sessions
Micek, I. et al., 2022 [118]	Clinical trial	40	1064 nm Qs-Nd:YAG Laser pulse length 5 ns, 6–8 mm in diameter, energy density 1.7–3.5 J/cm^2, 5 Hz.	9 treatments (7 to 14-day intervals), 1-year follow-up	MI, EI (Mexameter MX18®), mMASI, participant self-assessment	MI, mMASI: significant reduction ($p < 0.0001$) EI: significant reduction ($p < 0.001$) Participant satisfaction: 70% met expectations Maintained improvement in melasma at one-year follow-up No serious AE reported
Ertam Sagduyu, I. et al., 2022 [129]	Randomized controlled trial	39	Jessner peeling vs. 1064 nm Qs-Nd:YAG	4 weeks	MASI	MASI change: Jessner peeling group (3.35 ± 3.92), vs. Qs-Nd:YAG group (4 ± 4.46), no significant difference between the groups

Abbreviations: AE—adverse effects; EI—erythema index; ET-1—endothelin-1; FDP—fibrin degradation products; H-mMASI—Hemi Modified Melasma Area and Severity Scoring; HQ—hydroquinone; MART-1—melanoma antigen recognized by T cells-1; MASI—Melasma Area and Severity Index; MelasQoL—Melasma Quality of Life; mMASI—modified Melasma Area and Severity Index; MI—melanin index; mo—months; MSH—melanin stimulating hormone; PRP—platelet-rich plasma; Qs-Nd:YAG—Q-switched neodymium–yttrium aluminium garnet; SA—salicylic acid; VEGF—vascular endothelial growth factor; wks—weeks.

The treatment modalities for melasma discussed in the text are illustrated in Figure 2.

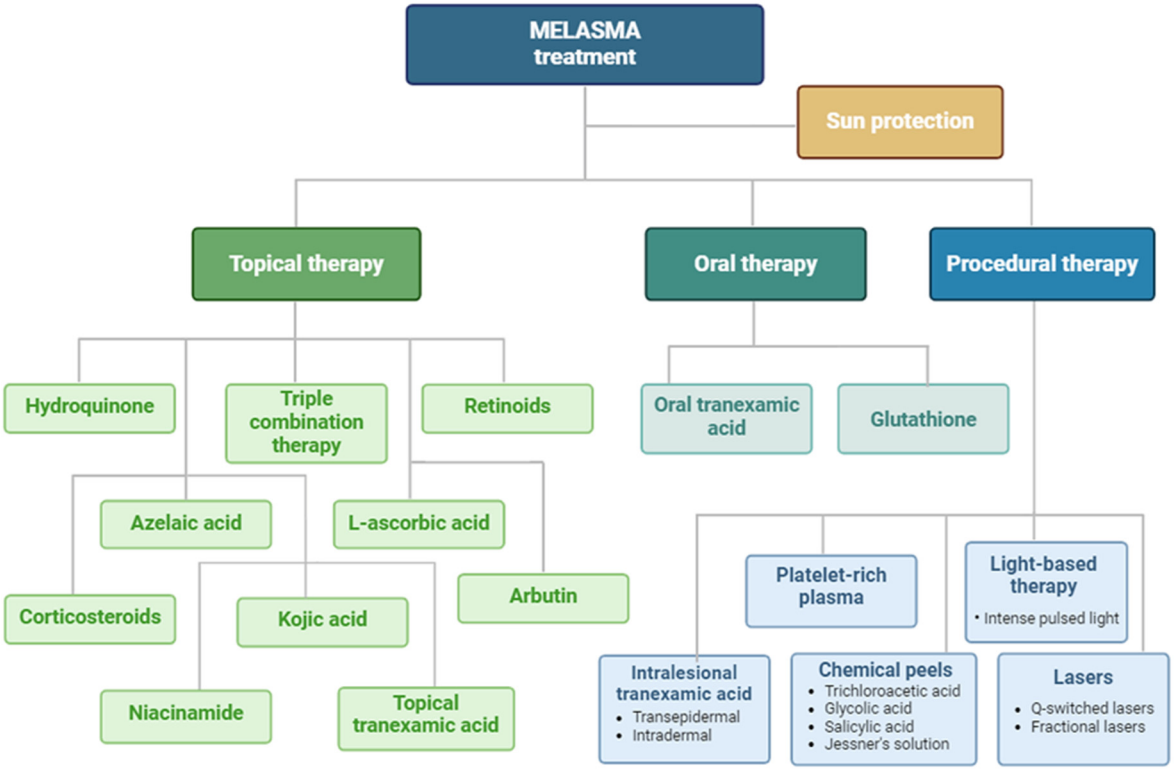

Figure 2. A schematic representation of described therapeutic options in melasma. Created with Biorender.com.

5. Novel Strategies in Melasma Treatment

Due to the ongoing challenges in melasma treatment, innovative approaches such as nanotechnology aim to improve the absorption of topical agents and increase their efficacy in the skin. Nanoparticles (NPs) facilitate better availability, stability, and controlled release of prescribed treatments [130].

Lipid nanoparticles are new drug delivery systems that include solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). They may improve skin hydration and elasticity, enhance drug delivery and protect against its degradation [131]. Studies have demonstrated that HQ-loaded SLNs yielded greater drug accumulation in the skin than conventional HQ. Additionally, HQ encapsulation in SLNs reduces systemic absorption, consequently diminishing adverse effects [132]. Similarly, HQ-loaded NLCs and AZA-loaded NLCs showed beneficial prolonged drug release and reduced skin irritation [133,134].

Nanoemulsions and microemulsions are colloidal delivery systems that are able to transport both hydrophilic and lipophilic molecules through the skin layers [135]. A recent study showed that nanoparticles loaded with AZA and hyaluronic acid may improve drug deposition, inhibit tyrosinase, and lower cytotoxicity [136]. Another study revealed increased drug release and stability of HQ-loaded microemulsions compared to conventional HQ [137].

Liposomes are vesicles composed of lipid bilayers that easily interact with the cell membrane and distribute both hydrophilic and hydrophobic drugs [131]. In a study on patients with melasma, a liposomal serum containing AZA, retinol, and 4-n-butylresorcinol led to substantial improvements in their MASI scores [138]. On the contrary, the results of another study suggested that although liposomal HQ produced a good therapeutic effect, no advantage over conventional HQ was noted [139].

Niosomes are unilamellar or multilamellar vesicles composed of nonionic surfactants. They are characterized by a rigid membrane bilayer, offering several advantages over

liposomes, such as better chemical stability, drug containment, and affordability [131,140]. Niosomal formulations of KA and HQ demonstrate a gradual and more consistent drug release [141].

Transferosomes are highly deformable vesicles composed of a lipid bilayer and membrane-softening components. This recent innovation enables transferosomes to enter the stratum corneum with ease and improves transepidermal drug delivery [142]. Therefore, depigmenting agents encapsulated in transferosomes seem to inhibit melanogenesis more efficiently while also being safe [143].

Finally, the application of nanotechnology has gained considerable attention over the last decades, particularly due to its wide use in the cosmetic industry. NPs have been scrutinized due to their complex chemical and physical properties, potential interactions, and questionable toxicological profiles [144]. The ability of NPs to form reactive oxygen species (ROS) when exposed to UV light has raised fears about their possible long-term toxicity [130]. Additionally, the effects on health and the environment, such as potential transport through sewage systems and biomagnification, have been questioned [145]. These concerns resulted in several regulations published by the European Commission, with the final regulation issued in 2009 [146]. It integrated the latest technological advancements in the cosmetic industry, including those related to nanomaterials. This ensured further research data on nano-enhanced products, improved transparency for customers, and rigorous safety standards. However, there remains a need for additional regulations concerning lipid-based nanoparticles, as they are currently researched and marketed more liberally [134]. Nowadays, various coatings are applied to NPs to minimize reactions that result in ROS formation [130]. Ultimately, nanotechnology offers better penetration through the stratum corneum, greater stability of active ingredients, and reduced toxicities through controlled drug release. However, its long-term efficacy and advantages over first-line treatment options have yet to be fully determined [134].

6. Maintenance Therapy

Since melasma shows a pronounced tendency to recur, maintaining the therapeutic effect after the initial treatment is a real challenge. Furthermore, topical lightening agents are often associated with irritative dermatitis, which can result in post-inflammatory hyperpigmentation.

The cornerstone of maintenance therapy is strict photoprotection. A broad-spectrum sunscreen with SPF 50+ that shields against UVA, UVB, and visible light, preferably with iron oxides for enhanced protection, should be used. Sunscreen must be applied to the entire face every day, regardless of the season, and a broad-brimmed hat should be worn outdoors to further shield the skin from the sun. Exposure to heat sources at work and home should be reduced, as heat can exacerbate melasma. Any known triggers that worsen the condition should be identified and avoided [147].

Non-hydroquinone bleaching agents such as azelaic acid, topical retinoids, niacinamide, and kojic acid are recommended for maintenance therapy. A hydroquinone 2% cream can be applied intermittently for a limited time, considering the potential risk of irritative dermatitis and ochronosis [148]. A limited number of studies support the intermittent application of a triple-combination (TC) cream, consisting of hydroquinone (4%), tretinoin (0.05%), and fluocinolone acetonide (0.01%) (twice weekly). One notable study conducted by Arellano et al. aimed to evaluate the effectiveness of two different 6-month maintenance regimens in preventing the recurrence of melasma after an initial 8-week treatment with a TC cream. One regimen involved applying the TC cream twice weekly, and the other one involved applying the TC cream once weekly combined with the daily application of a broad-spectrum sunscreen. Both maintenance regimens effectively sustained the improvements achieved during the initial treatment phase. Additionally, both regimens were generally well tolerated by patients, with some experiencing mild, manageable irritation that did not lead to discontinuation of the treatment [149].

7. Conclusions

Melasma is a distressing dermatologic condition that frequently requires a comprehensive approach to control its chronic and relapsing nature. Treatment of this pigmentary disorder should be tailored to each patient and take into account factors such as skin type, personal medical history, melasma severity, and patient preferences. Various therapeutic options are available, including topical and oral depigmenting agents, chemical peels, and laser and light-based therapies. Moreover, different procedural interventions and innovative methods for drug delivery are continuously being developed.

However, melasma is quite often resistant to therapy. It is more challenging to treat in individuals with Fitzpatrick skin types III–V, a genetic predisposition, or a family history of the condition. Other factors that worsen the prognosis include having the condition for over two years without improvement, long-term use of topical steroids, developing ochronosis from extended hydroquinone use, undergoing multiple treatments like lasers or microneedling, seeing multiple doctors indicating stubborn disease, and having mixed-type melasma [147].

Irrespective of the chosen therapeutic approach, photoprotection is essential for preventing the worsening of the condition, recurrence following therapy, and the emergence of new lesions.

First-line treatment usually includes a topical 4% HQ cream on its own or as part of a TC alongside a retinoid and a corticosteroid. However, prolonged use may be associated with adverse effects, including atrophy, perioral dermatitis, and ochronosis. Other depigmenting agents such as TXA, AZA, and KA are becoming increasingly popular due to their effectiveness in managing melasma. Nevertheless, the greatest benefits are observed when agents are combined with other drugs or methods such as microneedling, microinjections, energy-based devices, and other skin-lightening and resurfacing techniques. Recent advancements in nanotechnology may secure the improved efficacy of applied treatment and reduce adverse effects. The mentioned therapeutic options often yield equivocal results in clinical trials. Therefore, further research is needed to refine treatment protocols for long-term control of this condition.

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