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Treatment modalities of melasma

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Abstract
Melasma represents a common chronic relapsing pigmentary condition, affecting sun-exposed regions, particularly women within the reproductive age. This manuscript critically reviews the current understanding of photoprotection, topical and oral therapies, as well as procedures such as peels, laser treatments, and microneedling, which are the primary strategies for managing and preventing melasma.

Keywords: Treatment, topical, systemic, microneedling, laser, melasma

Introduction
Melasma mostly affects photoexposed regions, particularly women within the reproductive age, however no definitive therapy exists, substantially diminishing quality of life along with poor self-esteem that contributes to social challenges, anxiety, as well as depressive symptoms [1].

Melasma resulting from pregnancy or photosensitizing medications often improves after the triggering cause is eliminated; nonetheless, the majority of cases endure a chronic condition characterized by seasonal variations and recurrences following effective therapy, necessitating ongoing management post-treatment. Generally, melasma diminishes with age and typically resolves in most women post-menopause, but extrafacial melasma could last for a longer duration [2].

The predominant clinical manifestation in 50–80% of patients stands for the centrofacial pattern, targeting the forehead, nose, as well as upper lip, but the philtrum, cheeks, and chin are excluded. The malar pattern is confined to the malar cheeks, while mandibular melasma occurs on the jawline as well as chin. The latter is believed to manifest in older persons and could be more associated with significant photodamage [3].

An emerging pattern known as extra-facial melasma could manifest on non-facial regions of the body, such as the neck, sternum, forearms, as well as upper extremities. The therapy of this condition is complex due to the inadequate knowledge of its pathophysiology, chronic nature, and recurrence rates, despite its prevalence. Alongside conventional treatments for melasma, there are intriguing novel therapeutics, including topical, oral, and procedural modalities [3].

Melasma
The phrase “facial hyperpigmentation” or “melasma” derives from the Greek term “melas,” which translates to “black.” It also denotes "chloasma gravidarum" or "the pregnancy mask." Melasma, or chloasma, presents as symmetric hyperpigmented macules as well as patches on the facial skin. Melasma often affects the primary sun-exposed skin regions, especially the face or neck [5]

The often affected areas involve the cheeks, chin, forehead, nose, upper lip, as well as temples, however the seldom affected regions could include the sternal area as well as extensor surfaces of the arms. This disease is regarded as a benign condition primarily with cosmetic consequences; yet, it may adversely affect self-esteem along with self-image, thereby impacting an individual's quality of life [6].

Melasma mostly affects women between the ages of 20 and 40, exhibiting a female to male ratio of 9:1.5. Possible melasma causes may involve hormonal factors (e.g., pregnancy, oral contraceptives, hormone replacement treatment) as well as ultraviolet light exposure.

Melasma manifests in individuals of various racial and ethnic origins; yet, its incidence is greater among those with darker skin tones [7].

- **Pathophysiology**

The primary etiology is being exposed to sunshine. Ultraviolet light stimulates the synthesis of alpha-melanocyte-stimulating hormone, corticotropin, interleukin 1, as well as endothelin 1, thus producing melanin through intraepidermal melanocytes. Extended UV exposure causes dermal inflammation while activating fibroblasts, elevating stem cell factors in the melasma dermis, leading to enhanced melanogenesis [8].

Other essential factors contributing to melanin production [9]:

1. Proopiomelanocortin (POMC) and its derivatives expression by skin cells.
2. Melanocortin-1 receptors (MC1-R) number on melanocytes.
3. Diacylglycerol (DAG) production by plasma membranes, thus activating protein kinase C.
4. Nitric oxide (NO) release, thus activating the cGMP pathway.
5. Cytokines and growth factors release via keratinocytes.

Five primary etiopathogenic mechanisms have been identified in melasma. [9]:

1. Inadequate melanocytes' activation.
2. Melanin and melanosomes' accumulation within the epidermis as well as dermis.
3. Higher mast cells' level as well as solar elastosis.
4. Basement membrane alterations.
5. Vascularization increase.

Melasma Treatment

Photoprotection as well as provoking factors' avoidance

A. Modifying the Patient's Lifestyle: Through trying to avoid peak sunshine hours (in tropical regions, between eleven AM and four PM), staying within shaded areas for activities, along with utilizing sunshades such as parasols as well as wide-brimmed hats [10].

B. Sunscreens

- **Topical sunscreen agents:** The UVB as well as UVA filters are classified into organic (chemical absorbers) and inorganic (physical blockers) agents [11].
- **Inorganic agents (physical blockers):** Physical sunscreens include minerals like titanium dioxide or zinc oxide. These particles induce solar light scattering and reflection. The titanium dioxide represents the predominant type utilized, offering broad-spectrum protection against UV radiation and is undetected when included into cosmetic formulas because of its particle size [12].
- **Organic agents (chemical absorbers):** Chemical sunscreens stand as aromatic molecules conjugated with a carbonyl group, enabling the absorption of high-energy ultraviolet radiation (UVR) and subsequent energy release as lower-energy rays, thus avoiding the harmful UVR penetration through the skin [12].
- **Systemic sunscreen agents:** The carotenoids, tocopherol, and vitamin C intake in meals or supplements has effectively provided dietary photoprotection against UV-induced erythema (sunburn). The photoprotective qualities result from their antioxidant activity [13].

Topical products:

A. Phenolic agents:

Hydroquinone stands as the predominant bleaching chemical and the benchmark for melasma therapy. HQ represents a hydroxy phenolic molecule, obstructing the conversion of dopa to melanin via tyrosinase inhibition; it also impedes RNA and DNA synthesis in melanocytes while destroying melanosomes, making it cytotoxic to both melanosomes as well as melanocytes [14].

The HQ efficacy is closely correlated with the preparation concentration, the vehicle utilized, as well as the end product's chemical stability. HQ concentrations range from 2% (available over the counter), yet formulations beyond 5% have shown significant irritation without enhancing effectiveness and are not advised, with an exception for refractory conditions. The negative effects of these preparations are often negligible with regulated usage and monitoring [15].

Optimal outcomes are achieved when hydroquinone is utilized in conjunction with a retinoid as well as corticosteroid. The predominant triple combination cream consists of 4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide. Combination use with other agents need a prescription from a dermatologist. Approximately 35% to 45% of hydroquinone is systemically absorbed following its use topically [16].

B. Combination HQ formulas

The skin-lightening efficacy of HQ may be augmented by including several topical medications, including tretinoin as well as corticosteroids. Tretinoin enhances epidermal transfer along with cellular turnover, promotes the epidermal absorption of hydroquinone, inhibits steroid atrophy, while preventing hydroquinone oxidation. Corticosteroids inhibit melanin synthesis and alleviate the irritation induced by hydroquinone and/or tretinoin [17].

Combination treatments often exhibit a more efficient bleaching result compared to monotherapies, with therapy generally commencing with one of these formulations applied nightly, followed by maintenance with HQ 2% treatment. The combination formulae include the Kligman and Willis formula, Pathak's formula, Westerhof's formula, as well as Katsambas's formula [18].

C. Nonphenolic topical compounds

- **Azelaic acid:** At a concentration of 10–20%, bi-daily application could effectively treat melasma with few adverse effects; the majority of cases have minor but temporary skin irritation and dryness when starting the therapy [19].
- **Kojic acid:** Kojic acid is utilized at concentrations of 2% to 4%, either alone or in conjunction with tretinoin, hydroquinone, and/or a corticosteroid. Kojic acid, despite being less efficient alone compared to 2% hydroquinone, seems to exhibit a synergistic effect when combined with 10% glycolic acid as well as 2% hydroquinone [20].

- **L-Ascorbic Acid (Vitamin CIt is often utilized for treating melasma at concentrations between 5 and 10% and could be combined with other**

depigmenting agents, involving hydroquinone. Additional benefits of vitamin C include its antioxidant effects, anti-inflammatory qualities, as well as photoprotective capabilities [21]

- **N-butylresorcinol**: It has shown to be effective in skin whitening. Both in vitro and in vivo results indicate its significant inhibitory effect on tyrosinase activity [22].
- **Topical Retinoids:** typically administered at a dosage of 0.05%–0.1% once overnight [23].
- **Arbutin**: While treating melasma, it is often utilized at doses between 1% and 6%, mostly in conjunction with other whitening agents and treatments [24].
- **Niacinamide**: It is a crucial precursor of coenzymes like nicotinamide adenine dinucleotide (NADH) as well as nicotinamide adenine dinucleophosphate (NADPH), possessing significant antioxidant properties. In Melasma cases, a 4% concentration of niacinamide has resulted in a 62% decrease in Hemi-MASI after eight weeks [25].
- **Malassezin**: A natural indole molecule originated from Malassezia furfur, it has been shown to promote apoptosis of melanocytes, exhibit dose-dependent activation of apoptotic markers, while reducing melanin formation in melanocyte cultures [26].
- **Alpha tocopheryl ferulate**: It has shown effectiveness as regards UVR absorption as well as a marked melanogenesis inhibition, probably through an indirect tyrosine hydroxylase suppression [14].
- **Topical Tranexamic acid:** Topical TXA stands as a therapeutic option for face melasma with fair effectiveness and safety. The combination of TXA with either fractional CO2 laser or micro needling resulted in markedly superior outcomes compared to their individual use [27].
- **Antithyroid drugs such as (methimazole and propylthiouracil**) are utilized for hyperthyroidism and have lately garnered attention for their topical depigmenting effects in melasma patients. It has shown depigmentation properties in many animal models as well as clinical trial studies. In contrast to hydroquinone, antithyroid medications induce depigmentation via blocking peroxidase, rendering them noncytotoxic. [28].
- **Other agents**: Certain compounds were recognized for their influence on melanin pigmentation and occasionally utilized in formulations involving N-acetyl glucosamine, thiotic acid (alpha-lipoic acid), gentisic acid, soybean extract, as well as paper mulberry extract [14].

Systemic agents

A. Tranexamic acid

A randomized study compared oral TXA 250 mg administered twice daily with placebo, both alongside sunscreen, for treating moderate to severe melasma; results indicated a 49% decrease in m-MASI score for the TXA group against 18% for the placebo group after three months. It was suggested that TXA could be evaluated for treating individuals developing moderate to severe melasma unresponsive to normal therapy [29].

B. *Polypodium leucotomos* extract

Additional Antioxidants Oral *Polypodium leucotomos* extract (PL) at a dosage of 480 mg daily has shown to possess photoprotective effects against visible light. PL, antioxidant properties, suppress UV-induced COX-2 enzyme levels, while regulating immunological as well as inflammatory responses [30].

C. Glutathione: it has been proposed for treating melasma owing to its antioxidant qualities, resulting in the suppression of tyrosinase. Furthermore, it elevates intracellular levels of cysteine as well as N-acetylcysteine, converting melanogenesis from eumelanin to pheomelanin. It is globally given for skin pigmentation orally or intravenously; however, intravenous administration should be avoided to prevent the risk of allergy and Stevens-Johnson syndrome [31].

D. Melatonin: A free radical scavenger that increases antioxidant enzymes (glutathione) while inhibiting the alpha MSH receptor [32].

E. Antihistamines: Either H1 receptor antagonists or H2 receptor antagonists as its effect on reducing mast cells in the superficial skin layers. Mast cell stabilization is a potential treatment target for therapy [33].

Aesthetic procedures and chemical peels

A. Chemical peels

Alpha-hydroxy acids (AHAs), specifically glycolic acid at concentrations of 50%–70%, are administered in peels every 2–3 weeks for a total of 4–6 sessions. Light Jessner's peels are similarly applied every 2–3 weeks for 4–6 sessions, while trichloroacetic acid (TCA) at concentrations of 25%–35% is utilized once. These treatments may be employed alone or in conjunction with other depigmenting agents [31].

Glycolic acid peels cpi;d serve as a beneficial complement to topical therapy, particularly following a patient's two-week pretreatment with hydroquinone, thus reducing the likelihood of post-procedural hyperpigmentation. It is important to note that the reaction of melasma to chemical peels is somewhat unpredictable, exhibiting a propensity for pigmentation alterations following the procedure, particularly in those with darker skin tones. Following the peel, a maintenance regimen with 2% hydroquinone could be advised [31].

B. Dermabrasion

Cases developing resistent melasma, particularly those with a significant dermal component, have been effectively treated with localized or full-face dermabrasion extending to the upper or mid dermis utilizing a 16-mm diameter coarse grit diamond fraise. Fewer than 1% of cases had hypertrophic scars or persistent hypopigmentation. Microdermabrasion stands as a straightforward and safe procedure, as studies indicate that cases of melasma exhibited mild to moderate improvement, reduced melanization with uniform distribution of melanosomes, and enhanced collagen density with organized collagen bundles, which were the predominant histological changes observed [34].

C. Mesotherapy

Mesotherapy with vitamin C promotes collagen synthesis, exhibits antioxidant properties, while diminishing hyperpigmentation by inhibiting melanin formation. Stem cells derived from bone marrow are a crucial element in whitening serums and anti-wrinkle formulations due to their proliferative potential. They have

become integral to whitening treatments [35].

D. Microneedling

The combination of skin needling with a depigmenting serum is more successful in improving melasma than utilizing a topical depigmenting serum alone. Superior enhancement was seen in individuals undergoing microneedling compared to those receiving microinjections. This is due to microneedling's ability to administer medications deeper into the skin [36].

E. Stem cell-derived exosomes in treating melasma and its percutaneous penetration

Research indicates that exosomes produced from human umbilical cord mesenchymal stem cells (hUCMSC-Exos) may function as an innovative cell-free treatment approach in regenerative and aesthetic medicine. It may effectively address melasma; nevertheless, the integrity of the skin barrier is a significant obstacle. hUCMSC-Exosomes may enhance the symptoms of melasma safely and efficiently. In comparison to microneedles, NAFL and PBASM may also effectively enhance penetration. These results require investigation and clinical implementation [37].

F. Lasers and intense pulsed light (IPL)

Melanin serves as the principal chromophore, whereas melanosomes containing melanin are the major targets of lasers. IPL sources equipped with filters for targeting pigmented lesions have also been utilized. Lasers that target water chromophore could be employed under certain circumstances for the vaporization of lesions or for enhanced penetration of depigmenting chemicals [38].

The European Society of Laser in Dermatology's position statement on laser therapy for hyperpigmented lesions indicates that PDL and IPL, which target the vascular component, could be employed exclusively for skin phototypes I to II, with fractional non-ablative laser being acceptable to a lesser amount. Conversely, it was noted that Q-switched ruby, QS alexandrite, or QS Nd:YAG lasers provoke almost constant post-inflammatory hyperpigmentation (PIH) and recurrences in melasma. Consequently, QS lasers were deemed unsuitable for melasma treatment. In all cases, meticulous caution was advised while treating melasma with lasers or IPL sources [39].

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