Advances in management of melasma

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Abstract:
Melasma is one of the most common pigmentary disorder worldwide with a still unresolved Pathogenesis and treatment continues to be challenging. Increased sun exposure and genetic Factor are considered the two most important etiological factor. Estrogen, progesterone and increased melanocyte stimulating hormone are also involved. Melasma treatment can be Very frustrating as many modalities can turn out to therapy. Most patient seek medical help much after the onset of the Condition, making treatment even more difficult. Sunscreen and topical depigmenting agent Remain mainstay of therapy. Chemical peel and light sources are beneficial as adjunct. There have been numerous advance in the understanding and management of melasma.

Keyword: melasma pathogenesis, melasma Factor, hydroquinone

Introduction:
Melasma is a common, therapeutically challenging, and universally relapsing sickness of hyperpigmentation that's most customarily located in girls and people with Fitzpatrick Skin Types III thru VI. The pathogenesis of melasma is complicated and protean. Contributing elements which can be frequently implicated inside the etiopathogenesis of this circumstance encompass a genetic predisposition, excessive ultraviolet radiation exposure, and hormonal influences. Therapeutic interventions for melasma encompass a multimodality technique incorporating photoprotection agents, topical and oral skin lighteners, and resurfacing procedures. Given our increasing understanding of the pathogenesis of melasma, new and powerful remedies are increasing our healing armamentarium. This article evaluations new and rising oral and topical melasma

Etiology of melasma is multifactorial, the management of this condition is usually challenging. Currently, the gold standard treatment for melasma is topical hydroquinone cream and broad-spectrum sunscreens. Hydroquinone is a tyrosinase inhibitor for blocking the conversion of DOPA to melanin. [1]

Figure no 1: Melasma

EPIDEMIOLOGY
Melasma is a common dyschromia that often motivates the search for dermatological care. Its population prevalence varies according to ethnic composition, skin photo type, and intensity of sun exposure. In a 2010 population-based study, 1,500 adults from several Brazilian states was surveye. According to a survey of 77,343 diagnoses performed at dermatological consultations in Brazil that was conducted by the Brazilian Society of Dermatology (BSD) in 2006, melanodermias (among them, melasma) [5]

Clinical manifestations
The characteristic appearance of melasma is that of bilateral light-to-dark brown asymptomatic macules distributed on the malar cheeks, forehead, upper lip and/or mandible with an irregular border. This typical appearance means that the diagnosis is usually
straightforward and can be made clinically. Clinical examination using a Wood’s lamp that emits black light (UVA1) and dermoscopy may be used to aid in diagnosis and determining the level of melanin deposition

Several pattern of melasma:
Centrofacial – It is present on the cheeks, nose, forehead and upper lip and is present in approximately 50–80% of cases
Malar – present over the nose and malar cheeks
Mandibular pattern – Present over the mandible and chin
Extrafacial – This pattern is variable, but is predominantly Presented on the upper extremities, often on sun-exposed sites. [10]

![Clinical patterns of facial melasma](image)

Types of melasma:
1. Epidermal Melasma:
   The light or dark brown colour
   Melanin deposition in the basal and supra basal layer of epidermis
2. Dermal Melasma:
   Blue gray colour, deposition melanin granule in dermis
3. Mixed melasma (Epidermal and Dermal):
   face is most commonly affected
   Rarely pigmentation on V of the neck or may be confined to forearm [link]

Pathophysiology of melasma:
Factor causing melasma:
1. Hormones
2. Sun exposure
3. Pregnancy
4. Certain medications
5. Hypothyroidism
6. Vitamin B12 deficiency

1. Hormones:
Melasma is often associated with the lady hormone estrogen and progesterone. It is common in Pregnant women. Women taking birth control pills (oral contraceptives) Estrogen also increases the quantity of a pigment-forming enzyme called tyrosinase in the body. Individuals with melasma have greater numbers of progesterone receptors in the affected areas of skin. This means that these individuals have skin that is particularly sensitive to increased progesterone levels
Melasma has been discover to aggravate during pregnancy. Because of an increase in the placental, ovarian, and pituitary hormones. Melasma is also common among women using estrogen-containing oral contraceptive pills and hormone replacement therapy and among men using estrogen derivatives in the remidie of prostatic cancer this is due to the presence of estrogen receptors on
melanocytes which stimulate the process of melanogenesis. This is mediated with the aid of using induction melanogenic enzymes such as tyrosinase, TRP1, TRP2, and MITF by estrogen through cyclic AMP-protein kinase. Estrogen also mediates upregulation of PDZ domain protein kidney 1 (PDZK1) expression in the hyperpigmented skin of melasma patients. PDZK1 is a member of sodium-hydrogen exchanger regulatory factor family NHERF3. There occurs an increase in tyrosinase, cyclic AMP-responsive element binding protein, and MITF in melanocyte and also an increase in melanosome transfer.

2.sun exposure:
Visible light and melasma
Ultraviolet radiations are taken in considered the selective causative factor of the relapse in melasma and a strict prevention of sun exposure is recommended. When you divulge your skin to ultra violet light, it triggers the body to produced greater pigment. Sometimes, this pigment seems unevenly, causing the blotchy patches and brown spots of radiation, whether ultraviolet, visible light, or infrared (heat) light; Ultraviolet and infrared radiation from the sun are key in making melasma worse. UVA rays can cause damage to your skin. Most sunscreens protect against a broad spectrum of UV rays but do not offer UVA ray protection. The more melanin make your skin appearance darker or solar-tanned. Sometimes the sun causes an uneven increased in melanin production, which produces abnormal colouring (pigmentation) of the pore and skin. The solar rays’ can also cause a permanently stretching of small blood vessel, giving your skin a mottled, reddish appearance.

3. Pregnancy:
particularly the excess of estrogen and progesterone, is the main cause of melasma during pregnancy. Sometimes melasma can be permanent but it usually fades after birth. occurrence of melasma during pregnancy. Chloasma is derived from the Greek word colazine meaning to be green.
Melas, also Greek, means black. Because the pigmentation is never green in appearance.[7]

4.Certain medications
Antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics, retinoid, hypoglycaemic, antipsychotics, targeted therapies and some other drugs. The great common culprits are non-steroidal anti-inflammatory drugs (NSAIDs), tetracycline, and psychotropic drugs.

5. Hypothyroid
Several study had shown association between melasma and thyroid disorders, specially hypothyroidism and thyroid is postulated that this can be due to impact of these hormones on inducing the production of inflammatory cytokines. Higher circulating levels of pro-inflammatory cytokines have been seen in patients with hyperthyroidism. It thus reinforces that melasma can be triggered by conditions associated with skin inflammation.[8]

6. Diet B12 deficiency:
Deficiency of vitamin B-9 (folic acid) and B-12 (cobalamin) can cause pigmentation troubles leading to patchy skin. Deficiencies of vitamins that take place due to reduced intake of vegetables and fresh fruits can therefore make you skin appear dull and darkish.

Dermal pathology in melasma

![Dermal pathology in melasma](image)

**Figure 3:** Demonstrated pathologic changes in the dermis of lesional melasma including basement membrane disruption, pendu Diagram lous melanocytes, melanophages, mast cells, stem cell factor, solar elastosis, and neovascularization.
Table: 1 Cell Differentiation in Dermal Pathology in Melasma

<table>
<thead>
<tr>
<th>Cells</th>
<th>Definition</th>
<th>Role of Each Cell Involved in Dermal Pathologic Process</th>
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<tbody>
<tr>
<td>Pendulous melanocytes</td>
<td>- Melanocytes that protrude into the dermal layer and related to the hyperactivity of melanocytes</td>
<td>- Loss of basement membrane and cadherin expression by chronic UV exposure lead melanocytes to migrate deeper into the dermis</td>
</tr>
<tr>
<td>Melanophages</td>
<td>- Melanin-containing macrophages</td>
<td>- The phagocytized melanin in cytoplasmic granules within dermis layer leading to persistent of pigmentation</td>
</tr>
<tr>
<td>Fibroblasts</td>
<td>- Dermal resident cells, which can produce collagen and other fibers</td>
<td>- Upregulate the tropoelastin mRNA gene expression and elastin production by chronic UV radiation</td>
</tr>
<tr>
<td>Mase cells</td>
<td>- Inflammatory cells that mediate inflammatory responses</td>
<td>- Trypsinase can activate the pro-collagenase enzymes leading to collagen degradation and elastic materials</td>
</tr>
<tr>
<td></td>
<td>- The granules contain of several cytokines such as trypsinase and histamine, which can be stimulated by the UV exposure</td>
<td>- Produce VEGF leading to neovascularization</td>
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<tr>
<td></td>
<td></td>
<td>- Produce inflammatory mediators such as TNF-α, TGF-β, IL-8</td>
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**Abbreviations:** IL-8, interleukin-8; MMP, matrix metalloproteinase; mRNA, messenger ribonucleic acid; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; UV, ultraviolet; VEGF, vascular endothelial growth factor.

**Treatments For Melasma**

There are several treatment for the cure melasma

- Topical Hypo pigmenting
- Physical Therapy
- Laser Therapy

**TOPICAL THERAPIES:**

**Hydroquinone:**

Hydroquinone, or 1,4-dihydroxybenzene, lighten skin by stopping tyrosinase activity, which leads to a reduction in the transfer of melanosomes within keratinocytes and increased melanosome destruction is commonly used in topical concentration of 2% to 4% but can be compounded to reach higher concentrations. Although these higher concentrations may be more efficacious, there is also an increased risk of side effects, including irritant dermatitis, which can lead to subsequent hyperpigmentation. Long-term use, specially of high concentration, has the potential to cause exogenous ochronosis. Hydroquinone reduce melanin pigment manufacturing through inhibition of the tyrosinase enzyme, which is involved in the initial step of the melanin pigment biosynthesis pathway. Hydroquinone takes several month to take impact.[9]

**Retinoids**

Topical Retinoids have demonstrated advantage in the treatment of melasma by promoting keratinocyte turnover, reducing melanosome transfer, and decreasing melanin levels via epidermopoeisis. When blended with other topical treatments, reti-noids can help to facilitate penetration into the epidermis and increase local drug bioavailability, which enhances overall brightening capabilities. High con-centrations should be used with caution because of irritation and further dyspigmentation [12]

**Kojic acid**

Kojic acid is a fungal metabolite that inhibits Catecholate activity of tyrosinase, used in a 1–4% Cream base, alone or in combination with tretinoin, HQ, and/or corticosteroids. Although kojic acid alone is less effective than HQ 2%, (36) in combination With glycolic acid 10% and HQ 2%, it seem to have A synergistic action [12]

**Azelaic acid**

Azelaic acid (AzA) is a naturally occurring by product Of the metabolism of Pityrosporum ovale and is Associated with hypomelanosis seen in tinea versicolor. In vitro, azelaic acid reversibly inhibits tyrosinase Activity and may also interfere with activity. Azelaic acid does not Appear to affect normal melanocytes, but has an Antiproliferative effect on abnormal melanocytes. AzA Has antibacterial and anti-keratinizing activities. At 10–20% concentration, twice-daily application may Treat melasma with minimal side effects; most patients Report a mild but transient irritation of the skin at the Beginning of treatment. A recent study suggests that 20% azelaic acid cream applied twice daily may be More effective than hydroquinone 4% in reducing mild melasma

**Triple Combination Creams**

The gold standard TCC is the Kligman formula, which is a combination of a retinoid, hydroquinone, and cortico-Steroid. In a study of 120 patients with facial melasma who Applied either TCC cream, consisting of Hydroquinone 4%, tretinoin 0.05%, and fluocinoloneAcetonide 0.01%, once daily, or hydroquinone 4% cream Twice daily for 8 week, an improvement of more than75% was achieved by 73% of those using TCC compared With 49% of those using hydroquinone cream[2]
Chemical peels:
Superficial chemical peeling agents are useful in the Management of epidermal melasma and can be used in Combination with other forms of melasma treatment. The peel solution is selected according to patient’s Needs, skin type and sensitivities. Because of their Superficial action, superficial peels can be utilized in Nearly all skin types .Medium-depth peels may be an alternative Treatment in refractory case of severe melasma. All Types of chemical peels, but mainly alpha-hydroxy Acids, beta-hydroxy acid, salicylic acid, Jessner’s original And modified solutions, and trichloroacetic acid are Used alone or in combination with other depigmenting agent. It has to be emphasized that the response of Melasma to chemical peels is rather unpredictable and there is a tendency for changes in pigmentation after chemical peel, especially in dark skin individuals.

Antioxidant Therapy In Melasma

Vitamin C
Vitamin C, or ascorbic acid, is a potent antioxidant with a myriad of research on its function in various diseases. It is a ROS scavenger and can regenerate various other antioxidants. Vitamin C and magnesium ascorbyl phosphate (MAP), a vitamin C derivative, have been investigated for their role in treating melasma.
Oral vitamin C supplementation has been studied for treatment of hyperpigmentation issues.
Vitamin C cream has been investigated as a topical treatment for melasma, by both direct skin and ultrasounda software. In a comparison of hydroquinone and ascorbic acid cream for melasma, there was significantly greater subjective [6]

Laser Therapy:
Switched Nd:YAG Laser-Tissue Interaction
The Q-switched Nd:YAG laser is the laser of choice for dealing with dermal and mixed epidermal-dermal pigmented lesions, specially in darkish pore and skin.[The laser’s ability to specially target melanosomes in melanocytes, keratinocytes and melanosomes, its ultra-short pulse width (in nanoseconds) and adjustable spot size are key factors that allow effective targeting of dermal pigment.Depth of penetration and selectivity are functions of the wavelength of a laser. The Q-switched Nd:YAG laser has two wavelengths – extended wavelength of 1064 nm and a narrow wavelength of 532 nm. The longer wavelength of 1064 nm is ideal for dermal lesions due to its deeper penetration and bad absorption in epidermal melanin. These lasers have a large spot size up to 10 mm, which also permit deep penetration of the laser beam. Depth of penetration is directly proportional to the spot size of the beam, as greater photons are possible to remain within the space. The mechanism of movement of those lasers includes both a photothermal impact and photomechanical/photo acoustic phenomenon that is based on the principle of selective photothermolysis. To achieve successful effect and minimum side effects, it is necessary to do laser therapy

Some Herbal Treatment For melasma:
Cucurma longa:
Active ingredient : Curcumin
Mechanism : Turmeric has UV protective quality, is an antioxidant and antimutagen, and has anti-inflammatory properties . One study found that curcumin inhibited tyrosinase and melanin production, both of which contribute to melasma Another study found that turmeric had the potential of reduction of hyperpigmentation as well as antioxidant properties , and this not give the side effects [17]

Figure no 4: Effect of turmeric on melasma
Alovera:
Active ingredient: aloin
Aloesin is extracted from aloe vera plant. It competitively inhibits the conversion of tyrosine to DOPA (dihydroxyphenylalanine) DOPA to Dopachrome. A dose-dependent skin-lightening effect was noted when aloesin was applied four times daily for 15 days on UV-irradiated human forearm skin. Aloe vera is a medicinal plant that’s been used to treat various health conditions for thousands of years. It’s usually safe to use also vera directly from the plant or you can buy it in gel form. Aloe vera creams, gels, and ointments contain the clear gel found in aloe vera leaves. These products can be applied topically to treat various skin conditions. Aloe is sold in capsule or liquid form to take internally to promote health and well-being. Aloin causes melanin aggregation leading to skin lightening via alpha adrenergic receptor stimulation.

Fig no 5: Alovera

Extraction:
For the preparation of ethanol and methanol extracts, fresh leaf gel was dried in the oven at 80 °C for 48 h, and then powdered. Twenty grams of this powder was soaked in 200ml. of each of the solvents namely ethanol and methanol for 24 h. The contents were then filtered through Whatman filter paper no. 1, and the filtrate was evaporated to dryness. This dried extract was further powdered and then dissolved in distilled water. Acetone extract was prepared in a similar manner except that the extracted powder was dissolved in 0.15N NaOH and was further neutralized with 0.15N HCl. Natural or store-bought aloe Vera gel is known to relieve many inflammation issues in the skin. It is highly moisturising, deeply hydrating and gentle in nature. So much so that clinical trials have shown that liposome-encapsulated aloe Vera has shown to relieve melasma in pregnant women. It works by rehydrating dry skin, penetrating deep into the skin’s layer to nourish it and protect it from the harmful effects of UV exposure.

Liquorice extract for melasma:
(Glycyrrhiza glabra) – the Active ingredient is glabridin

Figure no 6: Liquorice
Liquorice root includes energetic elements which inhibit tyrosinase, the enzyme that reasons pigmentation brought on with the aid of using solar exposure.

Extraction Method:
Procedure for the extraction of plant compounds the use of chloroform and methanol changed into done as followed: air dried leaves, stems, and roots had been floor the use of mortar and pestle. An quantity of one hundred fifty g of grounded plant substances had been macerated three times until the solvent come into clear liquid. Each maceration process changed into done for 24 hours. The extracts had been filtered and air dried. The dried filtrates had been than store in the glass tubes. Extraction of plant compounds the use of water because the maximum polar solvent is carried out with the aid of using grinding plant substances, which then one hundred fifty g of the grounded fabric changed into boiled in 250 ml of water for 30 minutes. The resulted filtrate changed into then saturated in water bath.[20]

**Black tea water for melasma:**

![Black tea](image1)

Black tea water may be used as a spot-lightening treatment. The astringent residences of tea soothe and calm inflammatory pigmentation and it's also very moisturising in nature. Use a cotton ball to dab steeped black tea onto darkish patches of melasma to your face. Do this two times to get result Preparation of tea extracts.

BT (China), GT (Korea), and WT (China) leaves had been acquired from an oriental medicinal herb market (Korea). The leaves (six hundred g of every type) had been boiled in 6 L of distilled water for two h in a heating extractor (COSMOS-660; Kyungseo Machine, Korea), concentrated, and powdered through lyophilization. Yields of the BT, GT, and WT extracts had been 10.2, 21.3, and 20.0%, respectively.

![Orchid](image2)

**Figure no7:**Black tea

**Figure no 8: Orchid**
Orchid extracts for melasma:
Primarily utilized in Korean skincare staples, orchid extracts have been known to relieve melasma-related hyperpigmentation in women. While it didn’t completely heal them, the components did reduce the size of the dark patches and toned the overall complexion of the skin. The better way to utilise this ingredient for your skin is in the form of serums, nourishing creams, gentle scrubs, and hydrating mask. [20]

Red lentils for melasma
Active ingredient: antioxidant

Figure no 9: Red lentils
Rich in antioxidants, red lentils (masoor dal) can treat melasma-induced hyperpigmentation as well. A DIY face mask prepared with mashed lentils has been used in Ayurvedic beauty practices as a skin brightening treatment. To make your own mask, soak red lentils in water overnight and blend it into a thick paste the next morning. Apply the paste on your face for 20 minutes and rinse with cold water. Follow it up with a light moisturiser to counter any dryness.

Extraction
Red lentils had been ground in a coffee mill and defatted with hexanes in a Soxhlet equipment for 6–8 h. Phenolic compound had been extracted from the raw material using 80% (v/v) acetone at a solid-to-solvent ratio of 1:10 (w/v) at 50 °C for 30 min [23]. Extraction was carried out in Erlenmeyer flask using a shaking water bath (Elpan 357, Wrocław, Poland). The extraction was repeated 2×, supernates combined, and acetone evaporated under vacuum at 40 °C using a Büchi rotary evaporator. Residual water in the extract was eliminated by lyophilization. The prepared extract was stored at −20 °C until analysed. [22]

Tomato paste for melasma:

Figure no 10: Tomato paste
Active ingredient : Lycopene 
Tomato paste is especially useful in treating melasma cause by sun exposure. Lycopene, a primary compound found in tomatoes, is known to protect the skin from short term and long term photo damage caused by UV exposure. A mask made out of tomato paste and olive oil used tow time a week can help fade melasma in a gentle way[18]

**Linolic acid** : obtain from the sunflower stopping of melanogenesis newer liposomal formulation of 0.1% enhanced the efficacy of decrease concentrations is possible by enhanced the penetration of linolic acid in melanocytes

**Conclusion** :
At present, there’s no universally powerful remedy for melasma. The mainstay of remedy is locate of sunscreens at the side of topical medicines that Suppress melanogenesis. Topical hydroquinone on my own Or in strong fixed-dose triple aggregate topical Therapy is the primary line of remedy; chemical peels Are taken into consideration second-line remedy for refractory Cases, and laser and mild are taken into consideration the third-line Treatment. Nowadays, there aren’t anyt any managed research Investigating the efficacy and protection of a couple of novel And experimental agent

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