MELASMA: A COMPREHENSIVE REVIEW OF ETIOLOGY, PATHOGENESIS AND TREATMENT OPTIONS

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ABSTRACT:

Melasma is a common hyperpigmentation disorder characterized by brown, symmetrical facial pigmentation, typically affecting women of childbearing age. Despite its significant impact on patient outcomes and quality of life, the pathogenesis of melasma is multifactorial and poorly understood. This comprehensive review article aims to provide an updated overview of the current understanding of melasma, including its epidemiology, clinical manifestations, risk factors, and pathophysiology.

We discuss the role of genetic factors, hormonal influences, ultraviolet (UV) radiation, and inflammatory mediators in the development of melasma. Additionally, this review explores the diagnostic methods and assessment tools used to assess the severity of melasma and its impact on the patient. In addition, we explore the latest advances in treatment options, including topical therapies, chemical peels, lasers, and emerging therapies such as tranexamic acid and micro-needling.

Finally, we discuss the importance of sun protection and patient education as essential components of melasma management. By integrating current research findings, clinical guidelines, and new therapies, this review aims to provide dermatologists, healthcare professionals, and researchers with an overview comprehensive overview of melasma, thereby facilitating improved patient care and better outcomes in the management of this difficult dermatological illness.

KEYWORDS: *Melasma, pigmentation, laser, melanocytes, tyrosinase, fibroblast growth factor.*

1. INTRODUCTION

Melasma is a most common acquired hyperpigmentation disorder characterized by the development of brown or greyish-brown pigmented spots in areas exposed to the sun such as parts of the face, including the forehead, cheeks, upper lip and chin. In addition to females of reproductive age, men and people of diverse ethnicities can also be affected by this disease [1].The disease significantly impacts the level of comfort and dignity in affected individuals especially dark brown skin types. In terms of histology, there are three types of melasma: epidermal, dermal, and mixed. It is known as an epidermal type when there is an increase in pigment throughout the epidermis layers, particularly in the basal and supra-basilar layers of the epidermis. Melanophores are found in the superficial and deep dermis of the dermal subtype. As a result of the dermatological findings, it is possible to see solar elastosis and an increased number of blood vessels. The histological features that are characteristic of epidermal and dermal types of melanomas are often combined in mixed melasma [2]

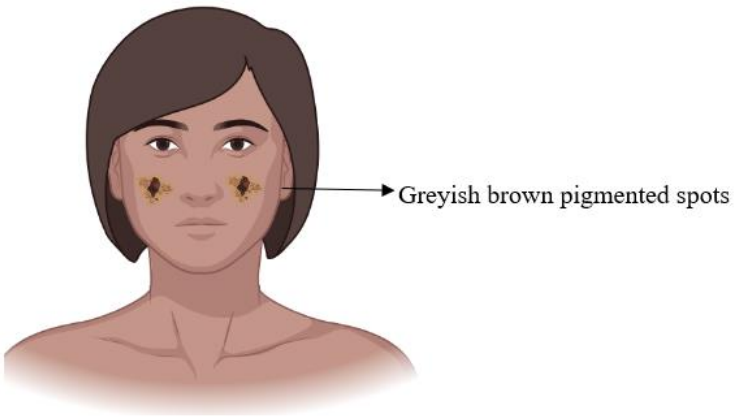

Fig 1. Melasma

1.1CLASSIFICATION OF MELASMA:

The hyperpigmented patches can appear anywhere on the face and neck, ranging from a single lesion to multiple patches that are typically symmetrical. The most common areas where these patches appear are the forehead, cheeks, dorsum of the nose, upper lip (moustache-like melasma), chin, and rarely on the V-neck region. The severity of the lesion can vary, and it is often used to differentiate between the three clinical types of melasma.

(1) Centro-facial pattern: Affects the forehead, cheeks, nose, upper lip, and chin (50-80% of cases). It is distinguished by epidermal hyperpigmentation. Melanocyte hypertrophy with enlarged dendritic cells and cytoplasmic organelles. Mast cell proliferation, vascularity, and elastosis are all increased.

(2) Malar pattern: This pattern is limited to the malar cheeks and can involve the nose.

(3) Mandibular pattern: This pattern can be observed on the mandible ramus (jawline) and it may extend to the chin. Melasma with a mandibular pattern is most commonly seen in post-menopause women.

Melasma variants have been documented on various sun-exposed parts of the body, and an additional categorization known as "extra-facial" melasma has arisen. This categorization pattern includes non-facial body components such as the forearms.

This novel variety appears as hyperchromic, uneven, symmetric skin depigmentation in older, menopausal women. It is more frequent in hormone replacement patients [3].

1.3 EPIDEMIOLOGY:

Melasma is a commonly occuring disorder that causes hyperpigmentation in female sex aged 20-40, with a 9% female and 1.5% male incidence. It mainly triggers the hormones (oral contraceptives, hormone replacement therapy, pregnancy) and exposure to UV light. The prevalence is observed in patients with dark complexions [4]. In a study, melasma prevalence ranges from 1% to 50% in the general and high-risk populations. It typically occurs between the ages of 20-30, but can also affect those in their 40s. Melasma, a skin condition that affects pregnant women, has a prevalence ranging from 15 to 50 percent. According to a study conducted in Brazil and India, the ratio of melasma incidence is 39:1 and 4:1, respectively. The worldwide prevalence of melasma varies across different locations, with Latino women having a prevalence of 8.8%, Saudi women 2.9%, and Ethiopian women 1.5%. These findings were reported in a research study conducted by Rabin Jung Thapa et al. in 2022[5].
In a recent case-control study conducted in Indonesia in men, they investigated that testosterone levels in melasma patients are significantly lower when compared with normal humans [6]. In a study they conducted an analytic retrospective and case-control study in 30 melasma patients and normal people they concluded that the serum levels of the luteinizing hormone are higher and there was an increase in MASI score among patients with melasma compared to the normal people [7].

A survey was conducted on new melasma patients from January 2015 to December 2018 with the proportion of 99.3% of women and 7 men patients treated was 46-55 years. 34.9% of the patients with melasma were due to UV radiation 65.2% of the patients had malar melasma type and 83.4% of the patients had mixed melasma type. The prevalence seen in sunscreen therapy patients was 99.5% and Tretinoin 0.05% patients were 31.8% [8].

In a study, they have taken pregnancy-induced melasma patients to assess the non-hydroquinone non-retinol pigment correcting serum (LYT2). LYT2 antisera showed there was a decrease in the pigmentation in the melasma patients which suggests its use as an alternative to hydroquinone therapy [9]. In a meta-analysis, they determined that 5% cysteamine has shown effective in treating melasma disorder. [10]. In meta-analysis melasma patients have a significant effect negative impact on their quality of life, especially young patients and females, who suffer from sexual difficulties, and various other psychological problems like depression, anxiety, sleep disturbances and adjustment problems [11].

1.4ETIOLOGICAL FACTORS [12]**:**
The exact cause of melasma is unknown, but there are several factors that may contribute to its development. Some of these factors include heredity, pregnancy, cosmetic usage, sun exposure, antiepileptic drugs, oral contraceptives, and thyroid hormone dysfunction. These are all crucial components to consider when investigating the causes of melasma:

1) **Genetics/Heredity:** Melasma affects between 33% to 50% of persons who indicate that someone else in their family has it. Melasma affects the majority of identical twins.
2) **Pregnancy:** It is unknown what causes "the mask of pregnancy" in pregnant women. Experts believe that elevated levels of oestrogen, progesterone, and melanocyte-stimulating hormones during the three months of pregnancy may have a role.
3) **Cosmetics:** Some cosmetics have the potential to trigger a phototoxic response.
4) **Sun exposure:** UVA, UVB, and visible light promote lipid peroxidation in cellular membranes, resulting in the production of free radicals that drive melanogenesis
5) **Phototoxic pharmaceuticals (medications that increase sensitivity to sunlight):** Some antibiotics, nonsteroidal anti-inflammatory medicines (NSAIDs), diuretics, retinoids, hypoglycaemics, antipsychotics, targeted treatments, and other medications fall under this category. It has been reported that the skin care products also cause skin irritation.
6) **Antiseizure medications:** Medication that prevents seizures may be a cause of melasma. Clobazam is an example of an antiseizure drug.
7) **Oral Contraceptive treatment (birth control):** Melasma is commonly reported in those who take oestrogen and progesterone-containing oral contraceptives.
8) **Hormones:** Hormones such as oestrogen and progesterone may be used in some cases. Melasma has been observed in postmenopausal women who have been administered progesterone. If you are not pregnant, your melasma lesions most likely have high amounts of oestrogen receptors.
9) **Oestrogen/Diethyl stilbestrol:** Diethyl stilbestrol is a man-made (synthetic) hormone oestrogen. It's frequently utilised in prostate cancer therapies. There is also another link between elevated oestrogen and melasma.
10) **Thyroid hormone:** Hypothyroidism is a disorder in which your thyroid gland is hypoactive.

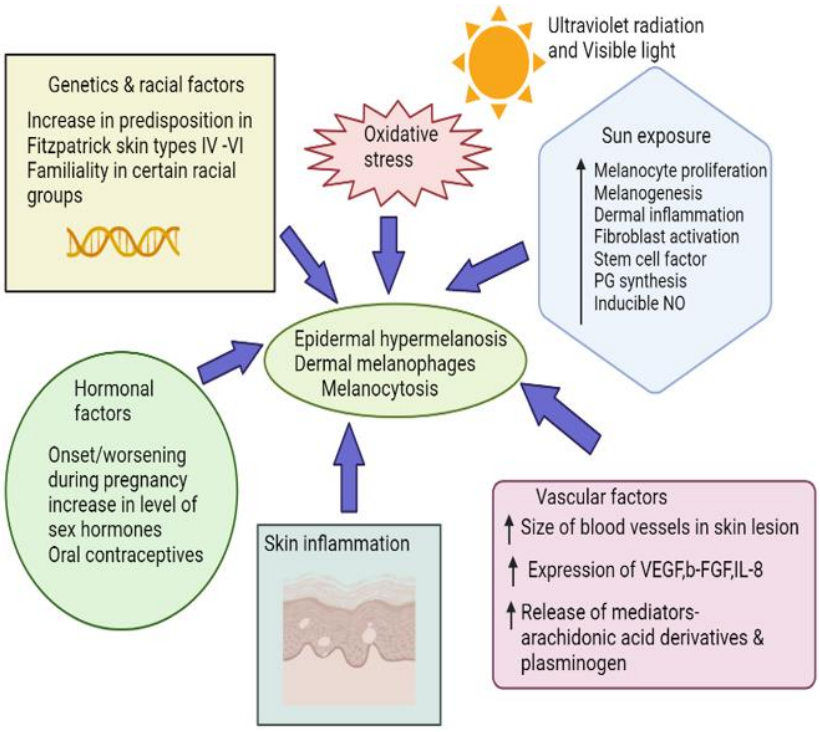

Fig 2. Etiological factors associated with melasma

1.5 PATHOGENESIS

Melasma pathogenesis is extremely complex; nonetheless, various research in recent decades has shed an entirely new perspective on it. Diseases used to be believed to be limited to melanocytes; however, we now know that they include keratinocyte interactions, abnormal melanocyte activation, accumulation of melanin and melanosomes in the epidermis and dermis, a rise in the number of mast cells, elevated vascularization, basal membrane damage, skin extracellular matrix anomalies and premature ageing (solar elastosis) [13].

A)Photoaging, Solar Elastosis, and Extracellular Matrix Abnormalities:

Solar elastosis (actinic elastosis) is a pathological disorder characterised by the buildup of elastic fibres and the degradation of elastic tissue as a result of overexposure to sunlight (photoaging of the skin). UVA radiation that penetrates deeper into the layers of the skin plays an important part in the progression of this degenerative phase.

In all, 93% of melasma victims had moderately to serious solar elastosis. When melasma-affected skin was contrasted to healthy skin, there was a considerably larger degree of disruption of the extracellular matrix, and consequently solar elastosis. Kwon et al. contend that melasma should be regarded not just as a melanocyte illness, but additionally as a pathological condition directly connected to premature ageing of the skin.

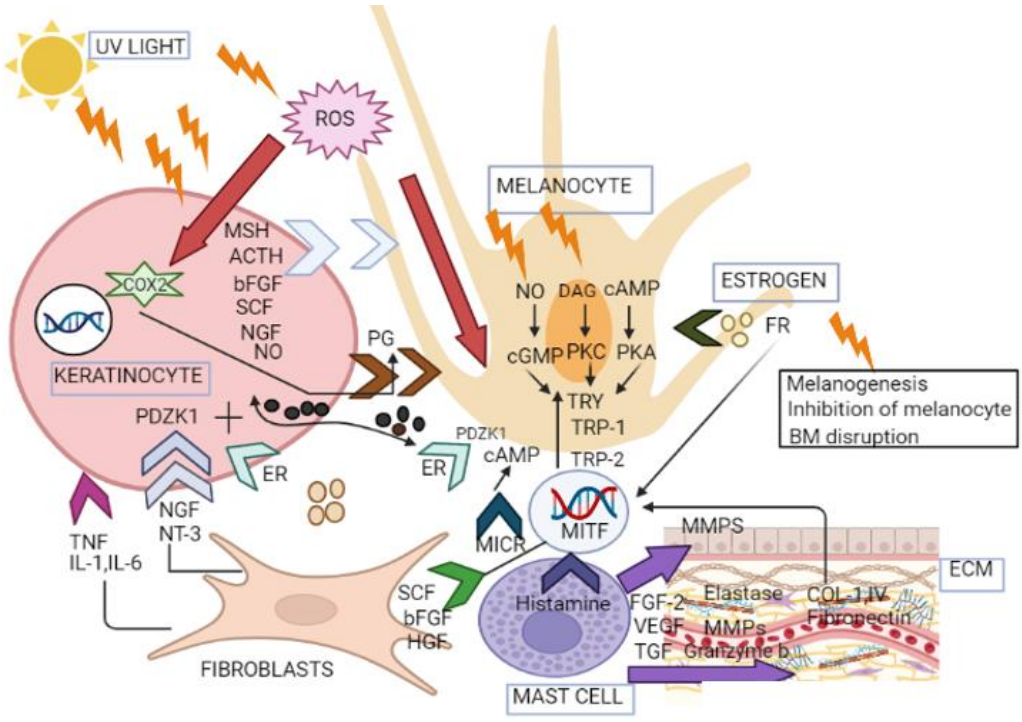

Fig 3. Pathogenesis of Melasma

B) Increased Melanogenesis and Abnormal Melanocyte Activation:

Melasma is a skin condition characterized by hyperactive melanocytes. These melanocytes connect with keratinocytes and produce an epidermal melanin unit. UVB radiation is a major contributor to hyperpigmentation, promoting keratinocytes to generate growth factors. There are several growth factors that play a role in melanin production.

These include stem cell factor (SCF), basic fibroblast growth factor (bFGF), interleukin 1 (IL-1), endothelin 1 (EDN1), inducible nitric oxide synthase (iNOS), α-melanotropin (α-MSH), adrenocorticotropin (ACTH), and prostaglandin E2 (PGE2). These compounds stimulate the production of melanin in both direct and indirect ways. UV radiation also contributes to melanin production. It causes an overexpression of melanocortin 1 receptors (MC1R), which increases the affinity of hormones and results in higher melanin synthesis. The pituitary gland secretes proopiomelanocortin (POMC) which breaks down into MSH and ACTH, both of which stimulate MC1R receptors and activate tyrosinase. There are several signalling pathways that control melanogenesis, including cAMP/PKA/CREB/MITF, NO/cGMP/PKG, and PLC/DAG/PKCβ.[13]

C)Role of Fibroblasts in melasma:

Fibroblasts in the skin release Wnt signalling modulators, that enhance melanogenesis and melanosome translocation. Fibroblasts isolated from photodamaged skin generate pro-melanogenic growth factors such as keratinocyte growth factor (KGF) or hepatocyte growth factor (HGF) and SCF. These findings imply that fibroblasts may play a role in the diverse aetiology of melasma.

D)UV-induced cyclooxygenase-2 (COX-2) is another significant component in the formation of excessive melanogenesis. Kim. et.al studied how inhibition of the COX-2 expression affected melanin synthesis and melanogenic factor expression.

They discovered that cells transformed with COX-2 siRNA that reduced COX-2 expression produced less tyrosinase, tyrosinase-related protein 1 (TRP1), TRP2, glycoprotein 100, and MITF. Furthermore, COX-2 inhibitors reduced melanin synthesis generated by -MSH, making COX-2 inhibitors a major treatment alternative in this illness.

Although being exposed to sunlight on the entire face, melasma often appears exclusively in areas with a high concentration of sebaceous glands (cheeks, forehead, and upper lip). The reason for this is possibly due to the sebaceous glands' ability to synthesise pro-inflammatory cytokines and growth factors that regulate melanogenesis. The development of the sebocyte cell line in conjunction with human melanocytes stimulates melanogenesis, indicating that sebocyte-secreted substances may play an essential part in this process. Rapidly enhanced superoxide dismutase (SOD) activity and reduced glutathione levels in melasma individuals suggest the existence of oxidative stress.

E)Increase in Mast cells:

Studies have shown that the amount of mast cells in skin affected by melasma is significantly higher than in healthy skin. These mast cells are usually found in areas of skin with increased elastosis, and the amount of elastin in skin exposed to UV radiation corresponds to the number of mast cells present. Research suggests that mast cells play a role in the production of elastic fibers in solar elastosis either by directly stimulating fibroblasts or indirectly through other types of cells.

In addition, after exposure to UV radiation, mast cells release tryptase, granzyme B, and stimulated extracellular matrix metalloproteinases (MMP). These chemicals contribute to the breakdown of collagen IV and basement membranes. Histamine is also released from mast cells in response to ultraviolet radiation, which binds to the histamine 2 receptor and stimulates the tyrosinase pathway. This leads to melanogenesis, which may explain the direct relationship between inflammation and the appearance of skin discoloration.[14]

F)Increase in Vascularity:

The growth of new blood vessels in healthy skin is minimal. However, it may increase in some pathological conditions such as chronic inflammation or prolonged exposure to UV radiation. Studies have shown that skin with melasma has a higher density of blood vessels compared to normal skin[15].This is because there is an increase in the number of mast cells, which stimulate the growth of blood vessels by releasing b-FGF, VEGF, and TGF-(transforming growth factor). Additionally, VEGF levels are elevated in keratinocytes and melanocytes have functional VEGF receptors. VEGF promotes the production and release of arachidonic acid metabolites and phospholipase A2. On the other hand, VEGF receptors are found on vascular endothelial cells, which trigger melanogenesis by generating EDN1, resulting in MITF phosphorylation and an increase in tyrosinase levels. Researchers have found a statistically significant correlation between the number of blood vessels and melasma hyperpigmentation. Furthermore, the levels of angiogenic factors increase in proportion to the size, density, and diameter of blood vessels in the affected skin. Telangiectatic erythema is another characteristic of melasma skin that can be targeted for treatment.[16]

G) Disruption of Basement Membrane:

MMP2 and MMP9 are released and activated from mast cells in response to UV radiation, which corresponds with the degradation of collagen IV and VI in the basement membrane. Melasma is persistent and recurring because of disruption to the basement membrane, which causes melanocytes and melanin molecules to move into the dermis. As a result, a major issue is the proper selection of therapy and the cautious application of laser methods, which, if applied improperly, may aggravate the progression of the disease[17].

1.6 DIAGNOSIS:

Wood’s Lamp Examination:

In lighter skin types, a Wood's lamp evaluation can help or confirm melasma detection. During Wood's light examination, epidermal melasma tends to intensify, this may aid in distinguishing between epidermal and dermal subtypes. Light is absorbed by abundant melanin in the basal and supra-basal areas of epidermal melasma. Melasma that does not enhance in colour under Wood's light is most likely dermal. A mixed pattern describes lesions that include both enhancing and non-enhancing patches. According to one study, even though a Wood's lamp examination revealed epidermal melasma in certain individuals, all samples studied demonstrated enhanced melanin accumulation in the epidermis and dermis. This study found that patients with visible epidermal melasma on Wood light inspection may have huge melanin in the dermis, implying that the majority of instances are genetic[18].

Dermoscopy:

Dermoscopy is a non-invasive optical method that plays a crucial role in diagnosing melasma and demonstrating melanin pigment deposition in the skin. It allows for variable magnification of 6-400 times. Reticular melanin pigment located in the dermis can be observed in the perifollicular and pseudo follicular areas. On the other hand, exogenous ochronosis has a diffuse brown background with blue-grey amorphous areas that obscure some follicular openings. It also exhibits irregular, brown-grey globular, annular, and arciform structures or a ‘wormlike’ pattern.

The main histological changes include pigmentation spots, globules, prominent vascularity changes, and telangiectasias (superficial cutaneous vessels of arteriolar, venule, or capillary origin).

Immunohistochemistry:

Melasma is a condition in which the skin may show high levels of stem cell factor in the dermal layer and c-kit in the epidermal layer. Additionally, there may be high levels of vascular endothelial growth factor, which could be the reason for the changed blood vessels observed in melasma.

Hormonal assay:

The hormonal assay can be assayed in melasma patients by the imbalances of the hormonal levels of FSH, LH, MSH, Progesterone, TSH and prolactin hormone estimations [19].

Reflectance confocal microscopy:

Reflectance confocal microscopy (RCM), also known as confocal laser scanning microscopy (CLSM) or skin computer tomography (CT), is a technique used for evaluating various skin conditions. It constructs 3-D models from sets of images obtained at different depths. This method has shown a good correlation with histopathological results while preserving the normal functions of cells and tissues.

Under RCM, Riehl's melanosis exhibits several noticeable aspects, including bright round-to-polygonal formations indicating epidermal infiltration of inflammatory cells, basal layer vacuolization and degeneration manifested as veiled papillary rims, and destruction of the high refractive ring-like structure surrounding the dermal papillae. Additionally, it shows the presence of pigment incontinence, which is characterized by a significant number of melanophages visible as brilliantly refractile, plump, oval to stellate-shaped cells and monocytes infiltrated in the superficial dermal layer. Other features include dilated arteries with conspicuous circular or linear black canalicular features, slightly refractory and round-to-polygonal cells around dermal arteries indicating perivascular inflammatory cell infiltration, dilated infundibulum with black round or oval lumina, and highly refractive material within the designated infundibula [20].

1.7 MELASMA AREA SEVERITY INDEX (MASI)

The Melasma Area Severity Index (MASI) score is a formula used to measure the severity of melasma. The face is divided into four regions: the forehead, right malar region, left malar region, and chin. To determine the severity of melasma, three variables are assessed in these regions: total area involved (A), intensity of darkness (D), and homogeneity of pigmentation (H). By evaluating these variables, the severity of melasma can be determined more accurately.[21]

A numerical value is assigned for the corresponding percentage area of involvement (A) as follows:

0 = no involvement;
1 = 1-10% involvement;
2 = 10-29% involvement
3 = 30-49% involvement
4 = 50-69% involvement
5 = 70-89% involvement
6 = 90-100% involvement

The intensity of darkness of melasma (D) is determined by comparing the darkness of melasma to the normal skin colour. It is graded on a scale of 0-4where
0 = normal skin colour without any hyperpigmentation;
1 = barely visible hyperpigmentation;
2 = mild hyperpigmentation;
3 = moderate hyperpigmentation;
4 = severe hyperpigmentation.
Homogeneity of hyperpigmentation (H) is again graded on a scale of 0-4where
0 = normal skin colour without any hyperpigmentation
1 = specks of pigmentation
2 = small patchy areas of hyperpigmentation measuring less than 1.5cm in diameter
3 = patches of hyperpigmentation measuring more than 2cm in diameter
4 = uniform skin pigmentation without any clear areas in between.
Melasma area severity index score is finally calculated by adding the intensity of darkness (D) and homogeneity of pigmentation (H) the sum of which is multiplied by the numerical value corresponding to the percentage of the area of involvement. This value is then multiplied by the percentage of the four facial areas, i.e; the forehead, right malar region, left malar region, and chin (10-30%).

This formula for calculating the MASI score is:
Forehead 0.3 (D+H) A + right malar region 0.3(D + H) A + left malar region 0.3 (D+H) A + chin 0.1 (D+H) A ……(1)
The Melasma area severity score index ranges between 0 and 48.

MODIFIED MELASMA AREA SEVERITY INDEX SCORING

Recently, Pandya et al., and colleagues developed a modified MASI scoring system. They discovered that this revised scale is a dependable method for measuring the severity of melasma. They determined that the area of skin affected by melasma and its darkness were the only necessary factors for assessing its severity. Homogeneity was removed, and the score range was from 0 to 24. The modified MASI score is easier to perform than the original version.

Modified MASI score = 0.3 A(f) D(f) + 0.3 A(lm) D(lm) + 0.3 A(rm) D(rm) + 0.1 A(c) D(c) - (2)

Where A area of involvement,
D = intensity of darkness,
f = forehead,
l m = left malar region,
rm = right malar region,
c = chin.
The area of involvement is scored as:
0 = absent;
1 = < 10% involvement;

2 = 10% - 29% involvement;
3 = 30% - 49% involvement;
4 = 50% - 69% involvement;
5 = 70% - 89% involvement;
6 = 90% - 100% involvement.
The intensity of darkness is graded on a scale of 0 to 4:
0 = no pigmentation,
1 = slight pigmentation,
2 = mild pigmentation,
3 = marked pigmentation,
4 = severe pigmentation.[21]

Differential diagnosis of melasma:

Types of Melasma	**Diagnosis**
Post-inflammatory hyperpigmentation [22]	Lichen planus, Psoriasis, Atopic dermatitis, Acne vulgaris
Caf'e – aulait macules	Neurofibromatosis, McCune-Albright syndrome, ring chromosome disorder, tuberous sclerosis, Fanconi anemia, Bloom syndrome, and Silver-Russell syndrome.
Naevus of Ota [23]	Blue-grey macules distributed from trigeminal nerve branches, mainly in infants and puberty.
Hori's Naevus	It is mainly seen in 20-70 years in Asian women. It is distributed primary zygomatic area, forehead, upper eyelids and alar nose. Blue-grey or grey-brown macules.
Medication-induced hyperpigmentation	It is distributed usually on the face, and arms, Slate-grey is seen in shins, scars, and mucosal membranes. Acanthosis nigricans, Ephelides, Solar Lentigines, Exogenous ochronosis, Periorbital hyperpigmentation, Maturational dyschromia, Erythema dyschromia perstans Drugs such as minocycline, amiodarone, anti-malarial, heavy metals, anti-viral, anti-psychotics, and clofazimine can cause hyperpigmentation in melasma individuals.

1.8 PREVENTION [23]

Melasma is a condition that currently has no cure and no surefire way to prevent it. However, there are treatments available to reduce pigmentation and prevent hyper-melanosis from spreading to other areas of the skin. One of the most effective ways to prevent pigmentation and damage is to limit sun exposure. Although there is no concrete evidence, some people have found success in preventing melasma by following these tips:

1) Avoid the sun, especially between the hours of 10 am and 4 pm.

2) Wear protective clothing, such as long-sleeved shirts.

3) Apply broad-spectrum sunscreens with a sun protection factor of at least 50, in combination with a UV protector.

4) Include foods rich in vitamins D, B, and C in your diet to help prevent melasma.[23]

1.9TREATMENT:

The chronic and relapsing nature of melasma makes its management challenging [24]. While there is no definitive cure for melasma, several treatments can help manage and improve the condition. It's essential to consult a dermatologist before starting any treatment, as the appropriate approach depends on the severity of melasma and individual skin characteristics. Here are some common treatments for melasma:

A)Topical treatments

Hydroquinone:

Hydroquinone or dihydroxy benzene is used as a topical agent as the first-line treatment of melasma. Hydroquinone can inhibit the conversion of DOPA by inhibiting the tyrosinase enzyme which leads to a decrease in the melanocytes by affecting the melanogenesis pathway. 2-4% of hydroquinone cream has shown effectiveness in melasma patients. However, it also showed adverse effects such as skin irritation, erythema, and contact dermatitis[24].

Niacinamide:

Niacinamide, also known as nicotinamide, is a biologically active form of vitamin B3 that can be found in the roots and yeast of several vegetables. It is essential in the production of co-enzymes like nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH), which have potent antioxidant activity. Studies conducted in vitro have shown that niacinamide can interfere with cell signalling pathways between keratinocytes and melanocytes, thus reducing melanogenesis and significantly decreasing melanosome communication to keratinocytes. Moreover, topical application of niacinamide can increase protein and ceramide synthesis, as well as keratinocyte. differentiation to stabilize epidermal barrier function, improve skin texture and reduce fine lines. In addition, it promotes anti-inflammatory effects on the skin [25].

L-cysteamine:

L-cysteamine is a compound that contains aminothiol and has antioxidant and depigmenting properties. It works by inhibiting the enzymes peroxidase and tyrosinase. Additionally, it acts as a chelator for iron and copper while increasing the levels of glutathione within cells. L-cysteamine is produced naturally as an intracellular breakdown product of L-cysteine.

Azelaic acid:

Azelaic acid is a topical medication that has shown cytotoxic effects. But it also acts as a tyrosinase inhibitor by inhibiting DNA synthesis in melanoma cell lines without causing any harmful adverse effects.20% Azelaic acid cream is safer than the 4% hydroquinone cream with similar adverse effects.

Tranexamic acid:

Tranexamic acid is an anti-fibrinolytic agent that has been used orally and topically to treat melasma. It inhibits the activation of plasmin, an enzyme responsible for breaking down blood clots which in turn reduces the production of prostaglandins. In a previous study, 5% tranexamic acid showed that there was a decrease in endothelin-1 and VEGF help to increase the vascularity in the skin.

Kojic acid:

Kojic acid or 5- hydroxy-2-hydroxy methyl-4- pyrone is a naturally occurring component obtained from fungi particularly *Aspergillus oryzae* and *Aspergillus flavus*. Kojic acid acts by inhibiting the tyrosinase enzyme and reduces melanin production leading to skin lightening effect. It may cause erythema and contact dermatitis. Kojic acid has shown safer and more effective treatment compared with 2% hydroquinone and also decreased the MASI score.

Arbutin and Deoxy Arbutin:

Arbutin is a natural tyrosinase blocker and a derivative of HQ. It is used in combination with lasers or ellagic acid to treat melasma. It is also used in hydrogel masks and has no adverse reactions. Arbutin has a lower toxicological profile than HQ. It binds to tyrosinase competitively and reversibly without affecting tyrosinase mRNA transcription. Deoxy arbutin is a synthetic derivative of arbutin that acts as a safer and more potent skin-lightening agent. It inhibits tyrosinase in a similar manner as HQ.[26]

Liquorice:

Glabridin, the primary component of liquorice's hydrophobic portion, has the potential to suppress tyrosinase activity. Furthermore, additional liquorice components, including liquiritin and isoliquiritin, may release melanin and eliminate epidermal melanin. Even though numerous depigmentation creams containing liquorice extracts are offered over the counter, there is no scientific proof of their effectiveness in the treatment of melasma [26].

Curcuminoids:

Calebin-A (CBA) is a curcuminoid derivative derived from the turmeric root (Curcuma longa). CBA (20μM) effectively inhibited MSH-stimulated melanogenesis in B16F10 murine melanoma cells, according to current studies. CBA did not affect intracellular tyrosinase activity or direct tyrosinase enzyme activity, and it did not affect intracellular -glucosidase activity. CBA enhanced the acidity of cellular organelles while inhibiting melanosome formation by drastically lowering the amounts of matured melanosomes.

Tretinoin:

Tretinoin, a retinoid (RA), suppresses transcription of the major enzyme in melanin formation, tyrosinase. Tretinoin is utilised as a chemical peel and plays an essential part in the triple-combination cream [27].

Corticosteroids:

Topical corticosteroids have anti-inflammatory properties which have an anti-metabolic impact on melanocytes, leading to reduced epidermal turnover and, as a result, a modest

pigment-reducing effect. The active ingredient in triple-combination creams is corticosteroids.

Triple formulations containing various corticosteroids, such as dexamethasone, hydrocortisone 1%, mometasone, and fluorinated steroids, have demonstrated effectiveness. Fluorinated steroids, such as 0.01% fluocinolone acetonide and fluticasone, are more efficient and less hazardous than non-fluorinated steroids [27].

Glycolic acid (GA):

Glycolic acid is an α-hydroxy acid which disrupts cell adhesion, which leads to desquamation, and the inhibition of melanin production by tyrosinase activity is caused by glutaric acid. Typically used in peels. The combination of HQ + GA+HA is effective in treating melasma at 79. 25% of cases, and there are no known indications of its recurrence after strict sun exposure [28].

Ascorbic acid:

Ascorbic acid, a well-known antioxidant, inhibits melanogenesis in the melanogenesis pathway by binding copper and inhibiting tyrosinase, inhibiting the oxidative polymerization of melanin intermediates. 5% L-ascorbic acid shows 62.5% efficacy in treating melasma patients without side effects [28].

Retinoids:

All-trans retinoic acid (ATRA), 13-cis retinoic acid (isotretinoin), retinol, retinaldehyde, tazarotene, and adapalene have been shown to inhibit tyrosinase, reduce melanin transmission, and promote the effects of cellular pigmentation. It is thought to have a brightening effect. Promotes keratinocyte turnover, increases the permeability of the stratum corneum, and finally distributes melanin.

Glutathione:

Glutathione (γ-L-glutamyl-l-cysteinyl glycine) is an amino acid glutamic acid, cysteine, and glycine that contains low molecular weight thiol-containing tripeptides in almost all living bacterial cells and human cells. Reduced glutathione is an important antioxidant, and it has been reported that plasma glutathione level is significantly reduced in melasma patients compared to normal people. Its effectiveness in the treatment of melasma includes the tyrosinase enzyme by chelating copper ions, the migration of tyrosinase to the pre-melanosomes, the transition of melanin formation processes from eumelanin to pheomelanin, and erasing. It is thought to be due to its unique antioxidant effect. Prevents free radical peroxide, tyrosinase activation and melanin formation [29].

Vitamin E:

Vitamin E, also known as α-tocopherol, is an essential antioxidant that is present in tissues, membranes, and plasma. It is comprised of four naturally occurring tocopherols and tocotrienols molecules. Alpha-tocopherol is the most abundant form of vitamin E found in humans. It has the ability to protect against harmful UV rays and can cause depigmentation by inhibiting tyrosinase, increasing intracellular glutathione levels, and preventing lipid peroxidation in melanocyte membranes. Ferulic acid, a compound found in α-tocopherol, tocopherol, and ferulic acid, can absorb UV light and has been found to be highly effective in reducing melanogenesis. Topical α-tocopherol is typically used in combination with vitamin C for skin-lightening purposes and is found in cosmetics in amounts less than 5%. In a double-blind study, the combination of topical vitamins E and C showed significant

improvement in melasma and contact dermatitis-pigmented lesions, and was more effective than either vitamin alone. Allergic or irritating reactions are rare with topical application.

Rucinol:

Rucinol (4-n-butyl resorcinol), a phenol derivative, inhibits tyrosinase and tyrosinase-related protein (TRP-1). 0.1-0.3% rucinol when applied twice daily application has shown improvement in melasma patients. Side effects such as stinging, burning, erythema, dryness, flaking and desquamation were mild [29]

B) Laser therapies in melasma:

Nd: YAG laser: is a type of laser that uses low-fluence Q-switch Nd for collimated laser beams. In recent years, YAG lasers have become popular for skin treatments, particularly in Asian countries. This laser is frequently used for non-ablative skin rejuvenation and treatment of melasma, causing minimal thermal damage and inflammatory response in the affected area of pigmentation. This therapy is referred to as minimized selective photo-thermolysis (MSP). The most common side effects of this therapy include pain, erythema, and temporary swelling. In rare cases, partial macular depigmentation, diffuse hyperpigmentation, or patchy depigmentation may occur [30].

The Med Lite C6 Q-switch Nd(133): another YAG laser that is used for skin treatments. It has been proven to be an effective treatment for refractory dermal melasma when used in combination with 7% alpha-arbutin and broad-spectrum sunscreen for 10 weeks. Therefore, lasers can be used alone or in combination with topical additives for effective skin treatments.

1064 nm Q-switched Nd. YAG laser (134):

A retrospective analysis was conducted to evaluate the effectiveness of treating melasma in 25 women using low pulse energy YAG laser (134). The results showed that 11 out of 25 patients (44%) experienced significant clinical improvement. Among these, 7 (28%) showed near complete clinical improvement, while 5 showed moderate clinical improvement. Only 2 patients showed minimal or no improvement. These findings indicate that using Q-switched Nd: YAG laser treatment with low pulse energy can be an effective and simple treatment for some East Asian patients with melasma [30].

1550 nm fractional laser (135):

It is important to be cautious while using non-ablative agents fractional 1550 nm laser therapy due to its potential side effects. The study evaluated the efficacy and safety of this treatment on 20 female patients with moderate to severe melasma and skin types ranging from II to V on the Fitzpatrick scale. The study was conducted over eight weeks and was a randomized controlled-blinded trial that compared the results with those obtained from triple therapy. After three weeks of treatment, the laser group reported significantly higher treatment satisfaction and recommendations ($p<0.05$). However, after six months, melasma recurred in 5 patients from both groups. The laser group experienced side effects such as erythema, burning, facial edema, pain, and peeling.

Copper bromide plus/ yellow lasers (578nm & 511nm):

It is an anti-angiogenic laser that has recently become available. It has been successfully used in the treatment of melasma, especially in cases of marked telangiectasia in Asian skin [30].

C)Herbal Treatments:

Aloe:

Leaf gel is a natural remedy used for treating minor burns and sunburns. Aloe vera gel has numerous beneficial properties, including antifungal, anti-inflammatory, and hepatoprotective effects. It contains various isolates, such as barbaloin, aloesin, and aglycones like Aloenin, 2"-O-feruloyl aloesin, isoaloeresin D, and aloe resin E. These isolates have potent tyrosinase inhibitory properties, with aloesin showing the highest inhibition. The lyophilized gel has an IC50 of 10.53 and 6.08 mg mL-1 for methanol extracts. It is more valuable compared to other molecules derived from aloe [31].

Morus alba:

Morus alba, or white mulberry, contains flavonoids that exhibit antioxidant and tyrosinase inhibitory activity. The mulberry extract's tyrosinase inhibitory effect is due to HQ and kojic acid. Oxy-resveratrol and mulberroside-A are derived from the root of M. alba. They inhibit monophenolase production and fungal tyrosinase activity in melanin synthesis, and they have antipyretic, hepatoprotective, and antihypertensive effects. The leaves of the white mulberry contain polyphenols that have a decolorizing effect. Mulberroside F exhibits 51.6% inhibition at a concentration of 1μg/ml with an IC50 value of 0.29μg/ml.

Panax ginseng:

Panax ginseng is an herb that contains ginsenosides that have various therapeutic benefits. P-coumaric acid isolated from fresh leaves of Panax ginseng was used for inhibition of L-tyrosine oxidation catalyzed by fungal tyrosinase. Panax ginseng berry isolate is floral ginsenosides [FGA], ginsenosides [GRd], and ginsenosides Re [G Re]. Of these three, floral ginsenosides [FGA] are Microphthalmia-related factors. The importance of ginseng lies in its many pharmacological roles, including B. Anticancer action and its efficacy, Anti-oxidant, anti-ageing, anti-stress, and anti-fatigue. Due to the free radical activity of DPPH, we observed a strong antioxidant activity of Pg AuNPs. Panax ginseng leaves also have whitening, skin-protecting and moisturizing properties. The IC50 value of Panax ginseng extract is 3.65mM.

Ginkgo Biloba:

Ginkgo biloba is a plant that belongs to the Ginkgoaceae family. The most abundant extract from this plant is EGb 761. It contains quercetin and kaempferol derivatives, as well as terpenes (6%) from the tree leaves that have flavone glycosides (33%) that minimize flavone glycosides. When exposed to UVB, mouse cells tan, but Ginkgo biloba has anti-inflammatory and anti-vascular effects, as well as antioxidant and tyrosinase activity. Therefore, it is used to treat various medical problems such as poor blood circulation, high blood pressure, weak memory, and depression. Ginkgo water extract inhibits tyrosinase activity by 50% at 2.25 mg/ml IC50. Also, extracts from ethanol and ethanol-ether mixtures show 50% inhibitory activity with an IC50 value of 75 [31].

Azadirachta Indica:

Azadirachta indica exhibits activity against tyrosinase enzymes and also exhibits anti-oxidant and anti-bacterial properties. It consists of Iso-meldenine, nimbin, nimbinene,6-desacetylnimbinene, nimbandiol and azadirachtin.

Santalum album:

Sandalwood is a plant that possesses numerous medicinal properties such as anti-inflammatory, antiseptic, antispasmodic, carminative, diuretic, emollient, antihypertensive, and memory-enhancing agents, among others. Sandalwood oil has protective, smoothing, and moisturizing properties, which help to prevent wrinkles. Additionally, it inhibits the oxidase 5-lipoxygenase and contains a DPPH radical scavenger activity. The main ingredient of sandalwood oil is α-santol, which is a potent tyrosinase inhibitor with an IC50 value of 171μg/ml. When comparing kojic acid to arbutin, α-santol is a more effective tyrosinase inhibitor.

Magnolia officinalis:

Magnolia officinalis *[Magnoliaceae]* has antispasmodic, anticancer, antioxidant and antidiabetic properties. Magnolia officinalis plant extract inhibits melanogenesis through pre-translational regulation of tyrosinase gene expression. It also exhibits depigmenting action. Fermented methanol bark extract exhibits anti-tyrosinase activity and reduces melanogenesis by 99.8% at a concentration of 200μg/ml.

CONCLUSION:

To sum up, this review sheds light on the complex and multifaceted nature of melasma, which includes its intricate root causes, diverse risk factors, and evolving treatment methods. While we have made significant progress in our understanding of the mechanisms behind melasma, further research is essential to discover new therapeutic avenues. The multitude of interventions discussed in this review emphasizes the importance of a personalized, interdisciplinary approach to managing this challenging pigmentary disorder. As we strive for a more comprehensive understanding of melasma, ongoing research is critical to advance both our knowledge and the effectiveness of therapeutic strategies, ultimately improving the quality of life for individuals affected by this condition [31].

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