Benha Journal of Applied Sciences (BJAS) **print: ISSN 2356–9751**
Vol. (10) Issue (1) (2025), (31- 39) **online: ISSN 2356–976x**
http://bjas.bu.edu.eg
Medical and Health Science

Melasma: Pathophysiology, Clinical Picture and Treatment Lines Overview

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Abstract:

The appearance of many people can be drastically altered by melasma, a pigmented skin condition that affects a large portion of the population. This condition is characterized by symmetric hyperpigmentation and manifests as irregular brown to -brown macules on the face, specifically the cheeks, forehead, nasal bridge, upper lip, mandible, and upper arms. Skin inflammation (as in contact dermatitis and aesthetic operations) and environmental (sunlight) and hormonal (pregnancy, sex hormones) variables all contribute to this condition in those who are already genetically prone to it. A localized hypermelanogenic phenotype is induced and maintained by an interplay of structural and functional changes in the upper dermis, basement membrane, and epidermis in melasma-affected skin, in addition to hyperfunctional melanocytes. Treatment results are not always considered adequate, and melasma care is difficult because of the complicated etiology and recurrence of the condition. Recurrence may be caused by sun exposure, thus treating hyperpigmentation alone may not be beneficial unless combined with regenerative methods and photoprotection. Thus, the treatment plan begins with risk factor management and the implementation of strong UV protection measures. Subsequently, several techniques like as topical treatments, chemical peels, laser and light therapies, microneedling, and systemic therapy are used. The purpose of this paper is to provide a synopsis of melasma's pathogenesis, clinical presentation, and therapeutic options.

Key words: Melasma ; Clinical Picture ; Lines Overview.

Melasma

Acquired pigmentary disorder melasma (sometimes spelled chloasma) most often affects the face. Sunlight and hormones are mostly blamed for this condition, which disproportionately affects women and people of color. There are three main types of symmetric reticulated hypermelanosis on the face that may be identified clinically as melasma: centrofacial, malar, and mandibular. Between fifty and eighty percent of cases have a centrofacial pattern that primarily impacts the upper lip, nose, and forehead while ignoring the philtrum, cheeks, and chin. Mandibular melasma covers the jawline and chin, but the malar pattern only appears on the face's malar cheeks. The second one is associated with serious photodamage and is more likely to happen in the elderly. An emerging pattern called extra-facial melasma may show up on areas of the body other than the face, such as the neck, sternum, forearms, and upper limbs. Although this illness is prevalent, there is still a lack of thorough knowledge of its pathophysiology, which makes treating it problematic. Additionally, the disorder is chronic and has high recurrence rates. Aside from the more conventional methods of treating melasma, there are also some exciting new options, including as oral, topical, and procedural therapy [(1)].

• Onset of disease

Melasma has several potential causes. Scientific studies in both humans and animals have shown that exposure to ultraviolet radiation may bring on or worsen the illness. By stimulating melanogenesis and activating inducible nitric

oxide, ultraviolet radiation is believed to produce reactive oxygen species (ROS). Researchers have shown that oxidative stress indicators are greater in melasma patients compared to healthy individuals. Keratinocytes and fibroblasts may promote melanogenesis after exposure to visible and ultraviolet radiation. The production of stem cell factor (SCF), a ligand for the tyrosine kinase receptor, c-kit, which has downstream effects on the proliferation of melanocytes, is a key mechanism in both visible light and UV-induced pigmentation. The keratinocyte byproduct vascular endothelial growth factor (VEGF) may also support human melanocytes in vitro. Melasma is thought to have an elevated melanocyte activity due, in part, to this. Recent studies on gene and protein expression have also shown a decrease in expression of genes related to lipid metabolism in skin lesions, which might indicate that altered barrier function plays a role in the development of melasma [(2)].

Melasma is more likely to occur in families when the problem runs in the family, lending credence to the idea that the disorder may have a hereditary component. There is a favorable family history in 55-64% of individuals with this illness, according to some experts. Although there hasn't been a genome-wide analysis of the genes involved, the results thus far point to pigmentary, inflammatory, hormonal, and maybe vascular responses as the likely culprits. A favorable family history is more common in patients with darker skin types (IV-VI) than in those with lighter skin types (II and III) according to the Fitzpatrick skin type (FST) system [(3)].

Because of the correlation between hormonal changes and melasma, it is clear that hormonal medications, such as oral contraceptives, contribute significantly to the development of this skin condition. There is some evidence that perimenopausal symptoms are shared by extra-facial melasma. An immunohistochemistry analysis of the dermis and epidermis of both the afflicted and unaffected surrounding skin revealed a significant upregulation of progesterone receptor expression in the affected skin's epidermis. Furthermore, dermal and vascular estrogen receptor protein expression was upregulated, the relevance of which is unclear at this time. No other clinical problems have been reliably linked to melasma. There has been some investigation into endocrinological problems, such thyroid illness, and its possible link to melasma. However, the frequency of thyroid diseases in these studies is not higher than in the general population [(4)] ,[(5)]

• Showcase in the clinic

Hyperpigmented patches with uneven boundaries, ranging from light to dark brown or brownish grey, are the hallmark of melasma. Hyperpigmented patches may be seen anywhere from a single lesion to many patches, often arranged in a symmetrical pattern on the forehead, cheeks, dorsum of the nose, upper lip, chin, and, on rare occasions, the V region of the neck and forearms. Postmenopausal women are more likely to get extra-facial melasma. There are three patterns that melasma may take on, depending on where the lesions are located (Figure 1): centrofacial, malar, and mandibular [(6)]

The pattern that occurs most often is known as the centrofacial pattern. The face, including the brow, cheekbones, upper lip, nose, and chin, is affected. The malar pattern incorporates the nose and cheeks. The ramus of the mandible is involved in the mandibular pattern.

There is a strong association between the depth of the melanin pigment and the four forms of melasma that may be identified based on Wood's light inspection of the skin [3].

Under Wood's light, the pigmentation on the skin becomes lighter brown. An increase in melanin in the basal, suprabasal, and stratum corneum layers is a hallmark of this condition, according to histology. Under Wood's light, the skin appears pale or bluish-grey, and the pigmentation is not enhanced. Melanophages make up most of the dermal cells in both the outer and inner dermis, according to histology [7].

Mixed: a dark brown color. Under Wood's light, certain regions show enhanced pigmentation and others do not. There are numerous dermal melanophages, and the epidermis has an increase in melanin [8].

Uncertain: a Wood's light examination does not help those with dark-brown complexion or skin type VI.[9].

It may be challenging to treat individuals with apparent epidermal melasma since dermal melanin deposition is prevalent and cannot be seen during a Wood's lamp examination. In clinical studies, individuals with melasma are often evaluated using the Melasma Area and Severity Index (MASI). One subjective tool for determining melasma area and darkness is the modified MASI [10].

• Therapy channels as shown in fig. 2 [11]

The application of medication directly to the skin.

Hydroquinone 2-5% has long been the go-to topical medication for treating melasma, although other methods have also been used. You should think about other topical medications like azelaic acid, kojic acid, and tranexamic acid before you choose a chemical peel or laser treatment for your melasma. These have shown significant reductions in the condition. By far, the most successful formulation has been Kligman's formula, which includes hydroquinone, tretinoin, and dexamethasone in a cream base. This formulation is still considered the best option for treating melasma since it improves or eliminates the condition in 60-80% of individuals but may cause skin irritation, redness, peeling, or dryness, particularly in sensitive individuals [12]

Retinoic acid

The hydroxyphenolic chemical hydroquinone (HQ) has been the go-to medicine for melasma treatment for a long time. Its efficacy is based on its capacity to bind to copper and block tyrosinase, so preventing DOPA from being converted into melanin. Additionally, HQ is involved in the breakdown of melanosomes and melanocytes. A cream combining 4% HQ, 0.05% tretinoin, and 0.01% fluocinolone acetonide was shown to be somewhat more effective than using 4% HQ alone or with only one additional component, according to the research. Irritative contact dermatitis, characterized by redness, swelling, itching, and scaling, is the most often reported side effect. Although it may occur at varying concentrations of HQ, this is a common short-term adverse event that has been seen in 70% of patients, typically with 4% or greater dosages of HQ [13].

Vitamin A

A reduction in melanosome transfer and an acceleration of melanin removal may be achieved with the use of retinoids, which promote keratinocyte metabolism and regeneration. On top of that, they improve transepidermal penetration, which means that other topical drugs can reach deeper layers of skin. One of the most well-known retinoid treatments for melasma, tretinoin (0.05-0.1%) is still widely used but it may induce excessive dryness or exfoliation. Consistent use for at least 24 weeks is usually necessary to see

noticeable clinical improvement, however. Adapalene, tazarotene, and topical isotretinoin are among the retinoids that have been used in conjunction with hydroquinone to treat melasma [14]

Anti-inflammatory drugs

Glucocorticoids have a direct role in UV-B-induced melanogenesis by blocking the action of cytokines and prostaglandins such endothelin 1 and granulocyte macrophage colony-stimulating factor (GM-CSF), which in turn increase melanin synthesis. There have been promising treatment outcomes with the topical use of a strong or very strong corticosteroid alone. Because of the risk of skin shrinkage, face hypertrichosis, acne-like eruptions, telangiectasias, rosacea, and perioral dermatitis, topical corticosteroids are seldom used alone to treat melasma. Hydrocortisone, dexamethasone, mometasone furoate, fluocinolone acetonide, and fluticasone are the corticosteroids most often used in triple combination treatments for melasma [15].

Treatment with a triple combination

The most researched method for treating melasma so far is a combination of hydroquinone, retinoid, and corticosteroid because of the improved tolerance and effectiveness of this combination. The combination's effectiveness is due to the complementary effects of its constituent parts. After around three weeks of twice-daily use, you should start to see some results. Tretinoin is helpful because it inhibits hydroquinone oxidation and increases the skin's receptivity to other substances. Topical corticosteroids have three functions: reducing irritation from the other two components, inhibiting melanin formation, and decreasing cellular metabolism all at once [16]

Using chemicals to peel

Chemical peels are often used to treat melasma because they administer exfoliative chemicals that encourage skin regeneration and tissue remodeling. Level one of the remodeling process affects the epidermis via the papillary dermis; level two includes the papillary to the upper reticular dermis; and level three penetrates via the mid-reticular dermis As showin in **figs (3,4)** but it may induce dryness or swelling [17].

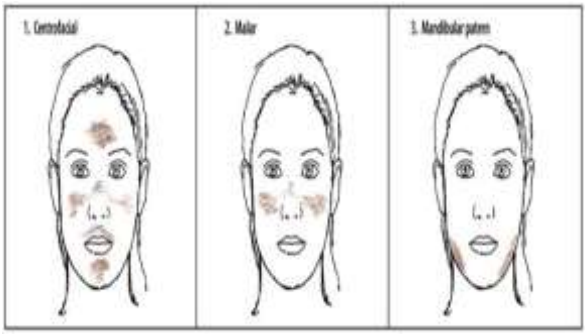

Fig 1: Patterns of melasma based on distribution of the lesions [28]

Plant ferments and active compounds derived from nature

To combat melasma and its negative effects, natural skin-whitening compounds have recently gained attention as possible remedies. The medicinal potential of these plant, marine, bacterial, and fungal extracts is encouraging. Korean red ginseng (KRG) is a plant-based skin-whitening product with 100 positive benefits for melasma and acceptable tolerability. Most agents that suppress melanin synthesis are sourced from the ocean and block the enzymatic activity of tyrosinase. Examples of such agents include Endarachne binghamiae, Schizymenia dubyi, Ecklonia cava

(EC), and Sargassum silquastrum (SS). Kojic acid, a melasma therapy that is successful when taken in conjunction with other drugs, is a naturally occurring metabolite of the fungi Acetobacter, Aspergillus, and Penicillium. Because of their potential to lighten the skin, fermented vegetables have recently gained interest as a potential therapy option. One natural substance that has the potential to replace synthetic and chemical skin-lightening components with fewer adverse effects is fermented aloe vera leaf skin [(18)]. It is both cost-effective and of low-risk but less potent and slower results [(19)]

Additional antioxidants.

Melasma is one of several dermatologic reasons for the widespread use of antioxidants. Amino acids, ascorbic acid, vitamin E, niacinamide, phytic acid, polypodium leucotomos, silymarin, zinc, and amino fruits are some of these compounds. In comparison to glycolic acid peels, which are known to be more irritating and poorly tolerated, amino fruit acid peels, which are carboxylated acidic amino acids, are more effective in treating melasma. Combination therapy with a Q-switched Nd:YAG laser amplifies the benefits of vitamin C in the treatment of melasma. A combination therapy involving 5% niacinamide, 3% Tranexamic Acid (TXA,) and 1% kojic acid resulted in a significant decrease in the melanin index by week 12, compared to both the pre-treatment baseline and control groups. Niacinamide, also known as nicotinamide, is an amide of vitamin B3. It is safe and effective when used alone, especially when compared with hydroquinone. It has also been shown that 10% zinc sulfate used topically is an effective and safe way to treat melasma but In some cases, taking large amounts of antioxidants can have the opposite effect and promote oxidative damage(pro-oxidant effect) [(20)]

Plasma high in platelets

Platelet-rich plasma (PRP) has recently gained popularity as a therapy for melasma, joining a long list of dermatological disorders for which it is used. Because it inhibits melanin formation via delayed extracellular signal-regulated kinase activation, it is an excellent therapy for melasma. In contrast to the TXA-treated side, the PRP-treated side showed a much larger percentage of score decrease but it requires multiple sessions (typically 3–6 sessions) over a period of weeks or months to achieve desired results. In addition, a recent research found that autologous platelet-rich plasma injection plus topical 5% tranexamic acid in a liposome-based cream had a greater impact than tranexamic acid alone [(21)].

comprehensive medical care

Doctors should undertake their own research on systemic therapy dose, possible adverse effects, and safety measures before administering them to their patients. In addition to topical treatments like hydroquinone cream, there are a few systemic therapies that may be used to treat melasma. One of them, orally given P. leucotomos, has the potential to provide substantial therapeutic effects for melasma. The low cost and relative simplicity of prescription for oral tranexamic acid have led to its increased use in primary care but it may induce abdominal discomfort [(22)]

Using tiny needles

Stamping, needle rollers, or an electric-powered pen are often used to inject tiny needles into the skin during microneedling, a minimally invasive treatment also known as percutaneous collagen induction therapy. The use of microneedling may improve transdermal medication delivery. Studying microneedling microinjuries in vitro also seems to trigger genes involved in epidermal differentiation and tissue remodeling. Temporary redness, burning,

discomfort, swelling, and bruising are some of the unpleasant effects that may occur after microneedling. Depending on the operator's expertise and technique, these local responses might be mild or severe [23]

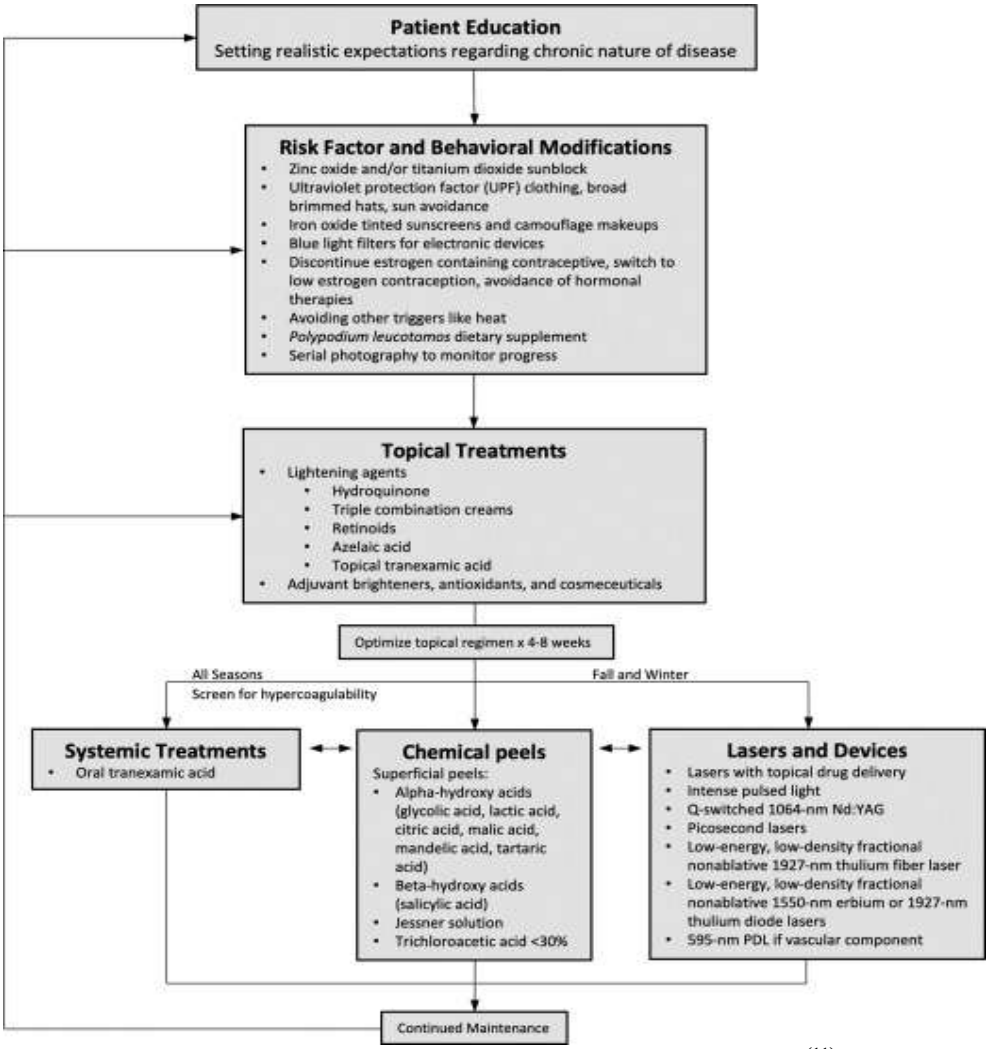

Fig. (2) showing algorithm for treatment of melasma [11] .

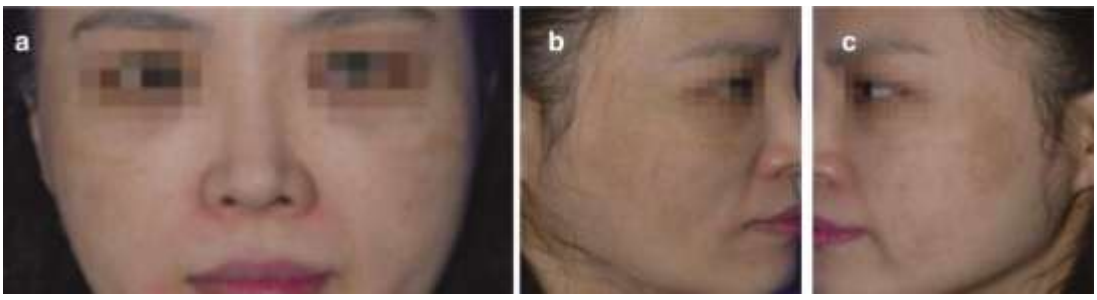

Fig. (3): showing a 38 year old woman with melasma, symmetrical brown melasma is seen on both sides malar cheeks.

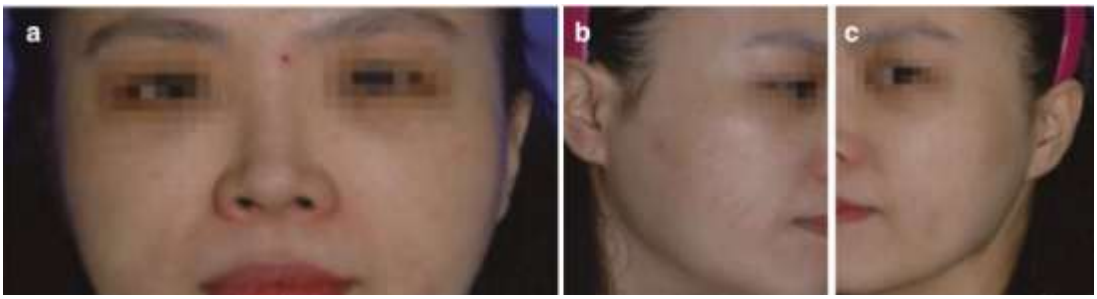

Fig. (4): showing improvemnt of the symptoms after chemical peeling

Therapies that use light, such as intense pulsed light (IPL) and lasers

Various wavelengths ranging from 515 to 1200 nanometers (nm) are emitted by intense pulsed light (IPL) systems. Melanosomes preferentially absorb certain wavelengths within this light range. The fact that IPL technology may target many layers of skin at once (epidermal and epidermal) is another advantage. Mild erythema (skin redness) and a tingling feeling are common side effects, although they usually go away within a day or two. Higher energy levels might cause modest skin exfoliation in some individuals; however, this usually goes away without leaving scars within about a week [24]

Using fractionated resurfacing lasers that do not ablate

When compared to treatments using IPL or Q-switched lasers, NAFLs seem to provide a longer-lasting therapeutic response. When patients use topical tyrosinase inhibitors before and after laser surgery, this becomes much more apparent. Some of the most common adverse effects include redness, swelling, and discomfort. In general, the therapy is thought of as having little downtime and a quick recovery period, and these side effects usually only endure for three to ten days. Many clinical studies have shown post-inflammatory hyperpigmentation (PIH) as a side effect. Potentially resulting from the treatment's heat generation, PIH seems to be linked to the density of the microthermal zones. In contrast to IPL and Q-switched lasers, which may cause recurrence as early as three months after treatment discontinuation, relapses after NAFL treatments typically occur three to six months after treatment [25]

Fractionated resurfacing lasers that are relative (AFL)

Patients with melasma have shown improvement after treatment with fractionated resurfacing lasers. Tissue ablation is achieved by light-energy-absorbed by water molecules in the tissue, which is how CO2 10,600 nm and Er:YAG 2940 nm lasers work. Minimal pigmentation is the result of fractionated ablation's microinjured zones, which improve transepidermal drug delivery (TDD), extract transepidermal melanin, increase dermal elastin tissue, induce neocollagenesis, stabilize the basal membrane, and ultimately reduce interaction between keratinocytes and melanocytes with melanogenic dermal stimulators [26]

picosecond laser treatments: using ultra-short pulses to break up pigment particles in the skin. These lasers deliver energy at high speeds, which helps to shatter melanin into smaller particles that can be cleared by the body more efficiently than with traditional lasers like the Q-switched Nd:YAG laser, safer than traditional lasers, particularly in darker skin types, because of their ability to treat melasma with fewer risks of causing further hyperpigmentation and have improved outcomes especially if used with topical agents [27]

Recent combination therapy [11]:

Tranexamic Acid (TXA) + Q-switched Nd:YAG Laser

Or Niacinamide + Tranexamic Acid (TXA) + Hydroquinone or Chemical Peels + Topical Retinoids

Conclusion:

There are substantial psychological and social ramifications to melasma, yet the disorder is still difficult to cure. Factors such as gender, skin color, and ethnicity all have a role in how a patient responds to therapy, which in turn affects the treatment's effectiveness. A multimodal therapy strategy is necessary to address the several elements that contribute to the development of melasma, including photoprotection, inflammation, vascularity, pigmentation, and hormonal effects. Our knowledge of melasma and its treatment options is expanding because to ongoing research. Topical, oral, procedural, and combination therapy have all witnessed significant advancements in the last ten years. Future therapies for this frequent but difficult disorder may benefit from a better knowledge of the pathophysiology of melasma.

References

[1] Liu W, Chen Q, Xia Y. New Mechanistic Insights of Melasma. Clin Cosmet Investig Dermatol. 2023;16:429-42.

[2] Chen Y, Vellaichamy G, Schneider SL, Kong W, Liu Z. Exposure factors in the occurrence and development of melasma (Review). Exp Ther Med. 2024;27(4):131.

[3] Navya A, Pai V. Comparison of Dermoscope and Woods Lamp as A Tool to Study Melanin Depth in Melasma. Indian Dermatol Online J. 2022;13(3):366-9.

[4] Ogbechie-Godec OA, Elbuluk N. Melasma: an Up-to-Date Comprehensive Review. Dermatol Ther (Heidelb). 2017;7(3):305-18.

[5] Goandal NF, Rungby J, Karmisholt KE. [The role of sex hormones in the pathogenesis of melasma]. Ugeskr Laeger. 2022;184(6).

[6] Rattananukrom T, Suchonwanit P, Thadanipon K, Vachiramon V. A Comparative Study of Dermatoscopic Features of Melasma and Hori's Nevus in Asian Patients. J Clin Aesthet Dermatol. 2022;15(3):16-20.

[7] Massi G, LeBoit PE. Histological Diagnosis of Nevi and Melanoma: Springer Berlin Heidelberg; 2016.

[8] Bostan E, Cakir A. The dermoscopic characteristics of melasma in relation to different skin phototypes, distribution patterns and wood lamp findings: a cross-sectional study of 236 melasma lesions. Arch Dermatol Res. 2023;315(7):1927-38.

[9] Pagan AD, Mitchell K, Yousif J, Henry M. Diagnostic tools for hyperpigmentation disorders in skin of color: An updated review. Dermatological Reviews. 2023;4(1):17-29.

[10] Kristine H, Simone C, Laurence F, Imstepf V, Adatto M, Lehmann M, et al. Skin hyperpigmentation index in melasma: A complementary method to classic scoring systemswilley online library. 2023;22(12): 3405-12.

[11] Guo EL, Wang JV, Geronemus RG, Friedman PM. Combination Treatment Approach to Melasma. Advances in Cosmetic Surgery. 2021;4(1):97-107.

[12] Doolan BJ, Gupta M. Melasma. Aust J Gen Pract. 2021;50(12):880-5.

[13] Jiryis B, Toledano O, Avitan-Hersh E, Khamaysi Z. Management of Melasma: Laser and Other Therapies-Review Study. J Clin Med. 2024;13(5).

[14] McKesey J, Tovar-Garza A, Pandya AG. Melasma Treatment: An Evidence-Based Review. Am J Clin Dermatol. 2020;21(2):173-225.

[15] Mahajan VK, Patil A, Blicharz L, Kassir M, Konnikov N, Gold MH, et al. Medical therapies for melasma. J Cosmet Dermatol. 2022;21(9):3707-28.

[16] González-Molina V, Martí-Pineda A, González N. Topical Treatments for Melasma and Their Mechanism of Action. J Clin Aesthet Dermatol. 2022;15(5):19-28.

[17] Conforti C, Zalaudek I, Vezzoni R, Retrosi C, Fai A, Fadda S, et al. Chemical peeling for acne and melasma: current knowledge and innovations. G Ital Dermatol Venereol. 2020;155(3):280-5.

[18] Jeon G, Ro H-S, Kim G-R, Lee H-Y. Enhancement of Melanogenic Inhibitory Effects of the Leaf Skin Extracts of Aloe barbadensis Miller by the Fermentation Process. Fermentation. 2022;8(11):580.

[19] Kim K, Huh Y, Lim KM. Anti-Pigmentary Natural Compounds and Their Mode of Action. Int J Mol Sci. 2021;22(12).

[20] Correia G, Magina S. Efficacy of topical vitamin C in melasma and photoaging: A systematic review. J Cosmet Dermatol. 2023;22(7):1938-45.

[21] Acar A, Ozturk A, Sokmen N, Unal I, Ertam Sagduyu I. Evaluation of platelet-rich plasma efficacy in melasma. J Cosmet Laser Ther. 2022;24(1-5):36-9.

[22] Feng X, Su H, Xie J. Efficacy and safety of tranexamic acid in the treatment of adult melasma: An updated meta-analysis of randomized controlled trials. J Clin Pharm Ther. 2021;46(5):1263-73.

[23] Bailey AJM, Li HO, Tan MG, Cheng W, Dover JS. Microneedling as an adjuvant to topical therapies for melasma: A systematic review and meta-analysis. J Am Acad Dermatol. 2022;86(4):797-810.

[24] Xu J, Pu Y. Q-Switched Laser Combined with Intense Pulsed Laser in the Treatment of Melasma Based on Reflection Confocal Microscope. Comput Math Methods Med. 2022;2022:4413130.

[25] Piętowska Z, Nowicka D, Szepietowski JC. Understanding Melasma-How Can Pharmacology and Cosmetology Procedures and Prevention Help to Achieve Optimal Treatment Results? A Narrative Review. Int J Environ Res Public Health. 2022;19(19).

[26] Iranmanesh B, Khalili M, Mohammadi S, Amiri R, Aflatoonian M. Employing hyaluronic acid-based mesotherapy for facial rejuvenation. J Cosmet Dermatol. 2022;21(12):6605-18.

[27] Feng J, Shen S, Song X, Xiang W. Efficacy and safety of picosecond laser for the treatment of melasma: a systematic review and meta-analysis. Lasers Med Sci. 2023;38(1):84.

[28] Dessinioti C, Lotti TM, Stratigos AJ, Damevska K, Katsambas AD. Melasma. In: Katsambas AD, Lotti TM, Dessinioti C, D'Erme AM, editors. European Handbook of Dermatological Treatments. Cham: Springer International Publishing; 2023. p. 651-61.