Melasma: Treatment Modalities and New Therapeutic Strategies

Amany Nassar[a], Amira Mohamed Abdelhamid[a*], Mai A Samir[a]

[a] Dermatology Department, Faculty of Medicine, Zagazig University, Egypt

Author Details:

- Amany Nassar MD, Professor of Dermatology, Venereology and Andrology, Faculty of Medicine, Zagazig University, Egypt.

E mail: dramany_nassar@yahoo.com

- Amira Mohamed Abdelhamid*, M.B.B. Ch, Faculty of Medicine, Zagazig University, Egypt

E mail: dr_mero_1985@yahoo.com; AMAbdelhamid@medicine.zu.edu.eg.

Orcid No: 0000-0002-0880-3137

- Mai A Samir, MD, Assistant Professor of Dermatology, Venereology and Andrology, Faculty of Medicine, Zagazig University, Egypt.

E mail: M.a.samir@hotmail.com

Conflict of Interest: The authors declare no competing interests.

Financial Disclosures:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ABSTRACT

Melasma is a common distressing skin condition with symmetrical brown or gray-brown patches on the face. It affects women, especially during their reproductive years, posing not only aesthetic challenges but also psychological impacts, as it can decrease quality of life and self-esteem**.** Various factors contribute to this condition, including family history, exposure to ultraviolet radiation (UV) and hormonal imbalances. Management of melasma is challenging and vary based on the depth and extent of pigmentation, as well as individual patient factors. Our review summarizes the various current therapeutic modalities used in the treatment of melasma and their side effect profile in addition to the new therapeutic strategies that may benefit melasma patients.

Keywords: Melasma, triple combination therapy, laser, peeling, exosomes.

INTRODUCTION

Melasma is a chronic relapsing skin condition, described as irregular brown or gray-brown macules and patches on the face, affecting the cheeks, forehead, nasal bridge, upper lip, and the mandible **(Sheth and Pandya, 2011)**. Melasma is one of the most met dermatoses in dermatology and one of the commonest hyperpigmentary disorders seen in pigmented skin individuals**.** It affects women with Fitzpatrick skin types II to V, especially in their reproductive age, but may affect adolescents, older women, and men with males presenting less than 20% (**Dlova et al., 2019).**

Although the exact causes of melasma are still unclear, the Pathogenesis has been attributed to an interplay between genetic predisposition, hormonal levels, UV light, inflammation, free radical formation and neurohumoral factors, all of which increase melanocyte activity, therefore melanogenesis. Also, certain cosmetic products and lifestyle factors such as diet, smoking, thyroid diseases, and specific medications (e.g antiseizures) can also exacerbate the condition **(Ogbechie-Godec & Elbuluk. 2017).**

Established treatments

Melasma management is challenging due to its complex pathogenesis and recurrent nature with treatment results often unsatisfactory. Now, there is no cure for melasma and treatment tend to be chronic to lessen progression **(Jiryis et al., 2024)**.

The current standard treatment for melasma includes topical approaches, with hydroquinone (HQ) serving as the gold standard as well as triple combination creams (corticosteroid, tretinoin and HQ), chemical peels, lasers and lights, microneedling and systemic therapy (**Pixley et al., 2023)**. Yet, these treatment effectiveness is limited due to the high recurrence rates and adverse effects Such as contact dermatitis and ochronosis with prolonged use and higher concentrations of HQ; menstrual irregularities and increased risk of deep venous thrombosis with Oral tranexamic acid (TXA). Also, burning and peeling of the skin with Chemical peels **(Lee et al., 2019 a)**.

Initial treatment strategies focus on eliminating risk factors, protecting against UV exposure, and using topical lightening agents, but relapse often occurs. In refractory cases, chemical peels and laser therapies may be employed. Overall, treatment aims to inhibit melanin synthesis, reduce melanosome transfer from melanocytes to keratinocytes, and help melanin removal **(Pennitz et al., 2022)**.

1. Photoprotection

Actual management involves photoprotection to prevent worsening of pigmentation, especially darker skin types. Daily use of physical sunscreens containing titanium dioxide and zinc oxide offer broad-spectrum protection against UV and visible light. Moreover, minimizing sun exposure and wearing protective clothing are recommended strategies (**Morgado-Carrasc et al., 2022)**.

2. Topical Treatment

Topical treatments are the mainstay of melasma management, with HQ (2-5%) being the most widely used. Other options including azelaic acid, kojic acid, and TXA can be used before opting for chemical peels or laser therapy. Kligman's formula, comprising HQ, tretinoin, and dexamethasone, is considered the gold standard due to its high efficacy in 60-80% of patients **(Doolan & Gupta, 2021)**.

2.1. Hydroquinone (HQ)

Hydroquinone, has held its reputation as the primary medication for treating melasma. It acts via inhibiting the enzyme tyrosinase, by attaching to copper, thereby reducing melanin production and breaking down melanosomes and melanocytes. A combination cream containing 4% HQ, 0.05% tretinoin, and 0.01% fluocinolone acetonide revealed slightly superior effectiveness compared to using 4% HQ alone or in combination with other ingredient. Although very effective, HQ can cause irritant contact dermatitis in up to 70% of users, especially at 4% or higher concentrations and chronic use can cause exogenous ochronosis (**Gong et al., 2015).**

2.2. Retinoids

Retinoids, a class of vitamin A derivatives, are effective in treating melasma by inhibiting the tyrosinase enzyme, helping epidermal turnover and keratinocytes renewal, enhancing the penetration of other topical medications, and aiding in melanin reduction, Also, they helps decrease the transfer of melanosomes and speeds melanin loss. Tretinoin (0.05–0.1%) is commonly used for melasma treatment, though visible improvement may take at least 24 weeks. Other retinoids, like adapalene, tazarotene and topical isotretinoin, are also used with hydroquinone (**McKesey et al., 2020)**.

2.3. Corticosteroids

Corticosteroids reduce UV-B-induced melanogenesis by inhibiting melanin produced by prostaglandins and cytokines like endothelin-1 and granulocyte macrophage colony-stimulating factor. While topical potent or super potent agents are effective, they are not used alone due to their side effects, such as skin atrophy, facial hypertrichosis, acne-like eruptions, telangiectasias, rosacea, and perioral dermatitis. So, they are often used in combination therapies. Agents like hydrocortisone, dexamethasone, mometasone furoate, fluocinolone acetonide, and fluticasone are crucial in melasma triple combination therapy (**Mahajan et al., 2022)**.

2.4. **Triple Combination Therapy (TC)**

Kligman-Willis introduced the initial triple combination in 1975, which contained hydroquinone 5%, tretinoin 0.1%, and dexamethasone 0.1%. This triple combination has been altered over the years to produce a less irritating combination, such as Tri-Luma (HQ 4%, tretinoin 0.05%, 0.1% fluocinolone acetonide), which is FDA-approved for the treatment of melasma **(Spierings, 2020)**.

This combination is effective due to the synergistic actions of its components, with visible benefits usually appearing after three weeks of twice-daily use. Tretinoin aids by preventing the oxidation of hydroquinone and enhancing the penetration of other agents into the skin. Concurrently, the topical corticosteroid decreases cellular metabolism, inhibits melanin synthesis, and reduces potential irritation caused by the other two components (**Jutley et al., 2014**). The TC cream has demonstrated its safety when used daily for eight weeks followed by a maintenance phase with intermittent application (either twice weekly or a tapering regimen) for six months. Side effects include erythema and scaling, dryness, pruritus and burning (**Taylor et al., 2003)**.

2.5. **Azelaic Acid**:

Azelaic acid is a weak tyrosinase inhibitor that reduces DNA synthesis in melanocytes, helping to treat melasma. It is safe for pregnant and breastfeeding individuals, and side effects such as stinging and itching subside quickly. Twice daily 20% cream can reduce melasma severity by 50% after 8 weeks and has anti-inflammatory effects that help reduce pigmentation **(Farshi, 2011).**

2.6. **Niacinamide**

Niacinamide is a biologically active antioxidant compound, found in vegetables and yeast. It helps reduce melanogenesis by inhibiting melanosome transfer from melanocytes to keratinocytes. Topically, it strengthens the skin barrier, enhances protein and ceramide synthesis, and improves skin texture and wrinkles, while also providing anti-inflammatory effects. Safe for pregnant and breastfeeding individuals and used as a 4–5% cream twice daily, alone or with other lighteners as kojic acid, TXA and arbutin. It can reduce melasma pigmentation by 62% after 8 weeks (**Cassiano et al., 2022)**.

2.7. **Cysteamine**

Cysteamine is an antioxidant with depigmenting properties, inhibiting peroxidase and tyrosinase enzymes, and increasing glutathione levels. It is found naturally as a product of L-cysteine degradation. Studies showed that 5% cysteamine cream, applied nightly for up to 3 hours, can reduce melasma severity (MASI) by 50–59% after 16 weeks. In comparisons with other treatments, cysteamine achieved reductions of 32–52% in MASI, outperforming or matching treatments like HQ and a modified TC therapy in various trials **(Nguyen et al., 2021)**.

2.8. **Other Topical Agents**

Several topical treatments are being evaluated, but limited randomized controlled trials hinder their full assessment. Vitamin C inhibits melanogenesis by interacting with copper in tyrosinase and depleting dopaquinone. Vitamin C (5–20%) is often used combined with other lighteners like kojic acid and arbutin and shown efficacy with Q-switched Nd:YAG laser (**Cassiano et al., 2022)**

Kojic acid (1%–4%), derived from fungi, blocks eumelanogenesis via binding to copper in tyrosinase. It is used in combination with other lighteners and requires 2–4 weeks for initial improvement and 6 months for full effects (**Zachary et al., 2020)**.

Arbutin, a hydroquinone plants derivative, inhibits tyrosinase and prevents melanosome maturation. It is used in concentrations of 1%–6% combined with other lighteners and procedures **(Boo et al., 2021)**

Glycolic acid, an alpha hydroxy acid, promotes skin cell turnover, thinning the epidermis, and increasing melanin dispersion. It helps other active ingredients penetrate the skin and is used in concentrations of 4%–10% in combination with other lighteners like kojic acid and hydroquinone. While effective, glycolic acid may cause irritation, erythema, and burning (**Draelos et al., 2010**).

Metformin, which inhibits melanogenesis by reducing intracellular cyclic adenosine monophosphate, has shown similar efficacy to traditional treatments like TC therapy, despite requiring high concentrations for effectiveness. Methimazole, an antithyroid drug, has depigmenting effects by inhibiting peroxidase and tyrosinase but is less effective than HQ (**Gheisari et al., 2020**). Melatonin, a hormone with antioxidant properties, regulates circadian rhythm and reduces UV-induced free radicals. Patients with melasma have lower serum melatonin and catalase levels, indicating increased oxidative stress. A study found that topical 5% melatonin twice daily with sunscreen for 90 days reduced MASI by 31%, slightly less than HQ 4% with sunscreen, which achieved a 37% reduction (**Sarkar et al., 2020**).

Overall, various topical treatments exist, each with different effectiveness, side effect profiles, and mechanisms of action. Sequential and combination therapies tend to produce better outcomes.

2.9. Chemical Peeling

Chemical peeling involves the application of chemical agents to exfoliate the outer layers of the skin, promoting skin regeneration and improving hyperpigmentation. Chemical peels can be categorized into: superficial, medium, and deep, depending on the depth of skin penetration. For individuals with darker skin types, careful consideration is required, as deeper peels may lead to PIH **(Conforti et al., 2020)**.

Superficial peels, such as glycolic acid, have been shown to effectively treat melasma mainly by promoting exfoliation and penetration of topical medications, and stimulating collagen production. They can provide significant improvement in melasma with a favorable safety profile when performed correctly **(Lee et al., 2019 a)**.

Amino acid peels have been found to be less irritating and better tolerated than glycolic acid peels for melasma treatment. Yet, the effects of chemical peeling may be temporary, necessitating ongoing maintenance treatments and combining peels with topical agents for enhanced efficacy (**Cassiano et al., 2022)**.

2.10. Active Substances of Natural Origin and Plant Ferments

Natural substances with skin-whitening properties have emerged as potential alternatives to synthetic chemicals and their associated side effects for melasma treatments. These extracts, from plants, marine organisms, bacteria, and fungi, possess promising therapeutic qualities **(Wawrzy´nczak, 2023).**

Among the plant-derived agents is the Korean red ginseng that shows good tolerability and efficacy for melasma. Ocean-derived agents like Endarachne binghamiae, Schizymenia dubyi, Ecklonia cava, and Sargassum silquastrum mostly suppresses melanin production by inhibiting tyrosinase enzyme. Kojic acid, derived from fungal metabolites by species of Acetobacter, Aspergillus, and Penicillium, is effective for melasma and often used with other substances**.** Also, fermented plants, especially aloe vera leaf skin, are recognized for their skin-lightening effects with minimal side effects **(Jeon et al., 2022).**

3. Systemic Treatment

Systemic therapies e.g. tranexamic acid and antioxidants offer promising, sustained pigment control for recalcitrant and dermal melasma. Systemic treatments work best with topical agents (hydroquinone, retinoids, azelaic acid) and physical therapies (lasers, chemical peels). While beneficial, they require cautious use due to potential side effects (**Cassiano et al., 2022)**.

TXA is a plasmin inhibitor that reduces melanogenesis by inhibiting plasmin-induced inflammation and vascularization, decreasing prostaglandins and other inflammatory mediators that stimulate melanocyte and blocking the keratinocytes-melanocytes interaction (**Chowdhary et al., 2021)**. Oral TXA is well tolerated and effective for dermal and mixed melasma, with up to 50% MASI score reduction but, side effects as GI discomfort, menstrual irregularities, and rare thromboembolic risk may occur. It is dosed 250–500 mg twice daily for 3–6 months; lower doses (125 mg twice daily) may be effective with fewer side effects **(Feng et al., 2021)**.

Oral Antioxidants e.g. Polypodium Leucotomos Extract which is Photoprotective, reduces UV-induced inflammation, and improves melasma when combined with topical therapy. Vitamins C & E

neutralize oxidative stress, work best in combination with hydroquinone and sunscreens besides, Glutathione which is tyrosinase inhibitor with skin-lightening effects (**Cassiano et al., 2022)**.

4. Microneedling

Microneedling combined with topical interventions has been found to be an effective measure in melasma treatment. Combined with a 4% HQ cream and Q-switched Nd:YAG laser, microneedling has demonstrated superior results when compared to using topical or laser therapy alone. Its adverse effects can range from temporary redness, burning sensation, to pain, swelling, and bruising depending on the skills and technique of the operator (**Wu et al., 2020)**.

5. Lasers and Light Based Therapy

The distinct thermal and absorptive natures of pigmented structures, make light and laser therapies suitable for treatment of melasma without damaging adjacent normal tissues. Laser therapy has emerged as a safe alternative to traditional methods for treating melasma when other treatments are ineffective (**Trivedi et al., 2017)**. Despite technological advancements, the understanding of various laser therapies effectiveness and safety for melasma is still incomplete. Potential adverse events such as erythema, burning sensation, PIH, hypopigmentation, and recurrence may occur **(Jiryis et al., 2024)**. The FDA approved the nonablative fractional 1550/1540 nm laser in 2005 and Lutronic's Spectra laser, the first Q-switched laser, in 2012 for melasma treatment. These lasers bypass the epidermis and penetrate the mid-reticular dermis to stimulate remodeling and neocollagenesis, while at the same time facilitating the removal of dermal melanophages via transepidermal elimination (**Trivedi et al., 2017)**.

5.1. Intense Pulsed Light (IPL)

IPL systems emit a range of different wavelengths between 515 and 1200 nanometer (nm). Within this spectrum of light, some of its wavelengths are selectively absorbed in the melanosomes. Another benefit of IPL is its multiple wavelengths that allow for the targeting of multiple layers of epidermal and dermal melasma simultaneously. IPL is best suited for Fitzpatrick skin types I-III due to the risk of PIH or hypopigmentation in those of darker skin types (**Trivedi et al., 2017).**

Yi et al. (2020) reported that IPL-based combination therapy for melasma can effectively reduce MASI scores and result in higher satisfaction among patients. Typical side effects include mild erythema and a slight tingling sensation, which generally resolves within a day. Some patients may encounter mild skin exfoliation due to the use of higher energy levels, but this usually heals without scarring in about one week.

5.2. Pulsed dye lasers (PDLs)

PDLs are used in melasma due to its vascular element. In **2011**, **Passeron et al**. compared PDL with Tri-Luma cream (TCC) to TCC alone over four months. One month after treatment, greater improvement was observed in the combined PDL and TCC group, only in patients with lighter skin types II and III.

5.3. Low-Fluence Q-Switched 1064 nm Nd:YAG (LFQS)

LFQS laser seems to be one of the best options for treating melasma, especially in darker skin types. Often used in combination with other treatments such as IPL, topical HQ, azelaic acid, chemical peels like Jessner’s formula, glycolic acid, and oral adjuvants such as TA. These lasers, specifically designed to target melanin, are available in various wavelengths, including ruby (694 nm), alexandrite (755 nm), and Nd:YAG (532 nm or 1064 nm) **(Pietowska et al., 2022)**.

Low-fluence treatments utilize the 1064 nm wavelength, which penetrates deeper into the dermis while sparing the epidermis disrupting pigment through a photoacoustic mechanism without harming surrounding cells. However, it requires multiple sessions within a relatively short treatment interval (typically weekly) and has high 3 months recurrence rates (64% to 81%), impacting patient compliance. Side effects e.g., erythema, transient burning, edema and changes in pigmentation, with cases of guttate hypopigmentation occurring in combination with other treatments at rates between 5.5% and 13.6% (**Iranmanesh et al., 2021)**.

5.4. Non-Ablative Fractionated Resurfacing Lasers (NAFL)

NAFLs use a photothermolysis mechanism to create micro-beams that penetrate deep into the skin, generating microscopic thermal zones that impact collagen and keratinocytes leading to the formation of Column-like necroses of keratinocytes, which facilitates the removal of coagulated substances and enables dermal and epidermal melanin clearance within six days. Melanocytes in melasma lesions can remain reduced for up to three months following a single NAFL treatment **(Goldberg et al., 2008)**.

Compared to IPL and Q-switched laser treatments, NAFLs offer longer-lasting results, particularly when used with topical tyrosinase inhibitors both before and after the laser surgery **(Pietowska et al., 2022)**. Relapses after NAFL noted between 3 and 6 months, which occur as early as 3 months post-treatment with IPL and Q-switched lasers. Common side effects including erythema, swelling and pain are short-term side effects lasting for 3 to 10 days, and the treatment is regarded as having low downtime with a fast recovery process. Also, PIH is a reported side effect (**Trivedi et al., 2017)**.

5.5. Ablative Fractionated Resurfacing Lasers (AFL)

Ablative fractionated resurfacing lasers have been documented for melasma treatment. It creates microscopic injury zones, facilitating improved transepidermal drug delivery, extraction of transepidermal melanin, enhancement of dermal elastin tissue, neocollagenesis, basal membrane stabilization, and consequently, reduced interaction between keratinocytes and melanocytes with melanogenic dermal stimulators, leading to less pigmentation (**Iranmanesh et al., 2021)**.

Adopting a fractionated approach minimizes epidermal injury, resulting in fewer side effects and a lower risk of dyspigmentation. However, it is not recommended to use AFLs for melasma treatment due to the likelihood of relapses. In cases where specialists do employ AFL treatments, they prefer a CO2 laser with very low fluency, usually as part of combination therapy (**Sarkar et al., 2017**).

5.6. Picosecond Lasers

Picosecond lasers are advanced devices that produce ultra-short pulses with high precision, breaking down melanin through a photoacoustic rather than photothermal process. This technology is particularly efficient for pigment removal without harming nearby tissues. Operating at various wavelengths (532 nm, 755 nm, and 1064 nm), picosecond lasers have been studied in melasma. Some studies support their use, others note high recurrence rates, indicating a need for further research to fully assess their effectiveness **(Pietowska et al., 2022).**

6. Platelet-Rich Plasma

Platelet-rich plasma (PRP) is an autologous blood product with a platelet concentration higher than normal physiological levels. It is obtained from part of the plasma fraction created after centrifugation of whole blood (**lves & Grimalt, 2018)**

Platelets are small, anucleate cell fragments derived from megakaryocytes that play a role in blood clotting and homeostasis. They contain three types of granules; dense, α, and lysosomal granules, with α granules storing a variety of bioactive factors, e.g., growth factors (GFs), cytokines, and proteins. PRP also has fibrin and leukocytes besides α granule factors **(Lin et al., 2020)**.

The therapeutic potential of PRP lies mainly in the GFs and cytokines it contains including: platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-b), insulin-like growth factor (IGF), serotonin, dopamine, histamine, adenosine, and calcium (**Pixley et al., 2023**). PRP exhibits anti-inflammatory and regenerative properties, through the action of these GFs, which promote angiogenesis, cell proliferation and differentiation of stem cells, fibroblasts, keratinocytes, and endothelial cells. These properties of PRP make it beneficial for various dermatological conditions like alopecia areata, vitiligo, melasma, wound healing, photoaging, and acne scars **(Collins et al., 2021)**.

PRP is an emerging treatment for various dermatologic conditions specifically for such chronic conditions such as alopecia, melasma, and vitiligo. It has emerged as a novel therapy for melasma. It improve skin texture and tone, promote keratinocytes proliferation, and reduce pigmentation by modulating melanocyte activity **(Acar et al., 2022)**. Studies showed that intradermal PRP injection led to a greater reduction in melasma severity compared to TXA. Besides, combining topical TXA with PRP enhances treatment effectiveness compared to TXA alone **(Abd Elraouf et al., 2023).** The therapeutic potential of PRP is linked to the wound healing and angiogenic effects of its growth factors PDGF and TGF-β1/β2 with TGF-β1 believed to inhibit melanogenesis by downregulating tyrosinase activity via transcription factors like microphthalmia-associated transcription factor (MITF) and interfering with ERK pathways activation (**Pixley et al., 2023)**.

Safety, rapid release of platelet-derived growth factors, autologous preparation (obtained from a patient's own blood), and avoidance of disease transmission are some of the benefits that PRP's biological approach may offer (**Abdelgawad et al., 2022)**.

7. Exosomes

Exosomes (EXOs) are small extracellular vesicles (30-150 nm) originating from endosomes, released by various cell types into body fluids. They transport biomolecules like RNA, DNA, proteins, lipids, and metabolites, facilitating intercellular communication and influencing biological processes and disease development **(Olumesi and Goldberg, 2023)**. Initially thought to be cellular waste, research now recognizes exos as vital mediators in cellular signaling. The source of exos is divided into natural and engineered. Natural exos are further divided into human (conventional) sources and the nonconventional sources including animal, plant, and microbial (bacteria; parasitic and fungal) **(Panigrahi et al., 2022)**.

Almost all types of normal cells can produce exosomes, with MSCs being primary for therapeutic applications. However, nonconventional sources such as animal or plant-derived exos are interesting due to their role in interspecies communication, offering new avenues for developing therapeutic agents (**Panigrahi et al., 2022)**.

Exosomes' membranes contain proteins, cholesterol, and lipids, which help in signaling and cargo delivery via receptor-mediated endocytosis. They can modulate immune responses, reduce inflammation, and have regenerative and therapeutic potentials.

MSC-derived exos also inhibit pro-inflammatory cytokines (such as TNF-α and IL-6) implicated in melasma pathogenesis besides their regenerative properties (**Proietti et al., 2024)**

Conclusions: Melasma management is challenging due to its complex pathogenesis and recurrent nature with treatment results often unsatisfactory. Now, there is no cure for melasma and treatment tend to be chronic to lessen progression. Ongoing research into novel treatment modalities and a better understanding of its underlying mechanisms are essential for improving outcomes in affected individuals.

References:

- Abd Elraouf, I.G.; Obaid, Z.M.; Fouda, I (**2023)**. Intradermal Injection of Tranexamic Acid versus Platelet-Rich Plasma in the Treatment of Melasma: A Split-Face Comparative Study. Arch. Dermatol. Res., 315, 1763–1770.
- Abdelgawad, E., Ibrahim, H., Samir, M. (2022). An Insight of Platelet Rich Plasma (PRP) Role in Dermatology: Review Article. The Egyptian Journal of Hospital Medicine, 88(1), 2472-2474. doi: 10.21608/ejhm.2022.236811
- Acar, A.; Ozturk, A.; Sokmen, N.; Unal, I.; Ertam Sagduyu, I (**2022)**. Evaluation of Platelet-Rich Plasma Efficacy in Melasma. J. Cosmet. Laser Ther., 24, 36–39.
- Boo YC. Arbutin as a skin depigmenting agent with antimelanogenic and antioxidant properties. Antioxidants (Basel). 2021;10(7):1129.
- Cassiano, D.P., Espósito, A.C.C., da Silva, C.N. et al. Update on Melasma—Part II: Treatment. Dermatol Ther (Heidelb) **12**, 1989–2012 (2022). https://doi.org/10.1007/s13555-022-00780-4
- Chowdhary B, Mahajan VK, Mehta KS, Chauhan PS, Sharma V, Sharma A, et al. Therapeutic efficacy andsafety of oral tranexamic acid 250 mg once a day versus 500 mg twice a day: a comparative study. Arch Dermatol Res. 2021;313(2):109–17.
- Collins T, Alexander D, Barkatali B. Platelet-rich plasma: a narrative review EFORT Open Rev 2021;6:225-235. DOI: 10.1302/2058-5241.6.200017
- Conforti, C.; Zalaudek, I.; Vezzoni, R.; Retrosi, C.; Fai, A.; Fadda, S.; Dimichele, E.; Dianzani, C. Chemical Peeling for Acne and Melasma: Current Knowledge and Innovations. G. Ital. Dermatol. Venereol. **2020**, 155, 280–285.
- Dlova NC, Akintilo LO, Taylor SC (2019). Prevalence of pigmentary disorders: a cross-sectional study in public hospitals in Durban South Africa. Int J Womens Dermatol.; 5(5):345–8.
- Doolan, B.J.; Gupta, M. Melasma. Aust. J. Gen. Pract. **2021**, 50, 880–885.
- Draelos ZD, Yatskayer M, Bhushan P, Pillai S, Oresajo C. Evaluation of a kojic acid, emblica extract,and glycolic acid formulation compared with hydroquinone 4% for skin lightening. Cutis. 2010; 86(3):153–8.
- Farshi S. Comparative study of therapeutic effects of 20% azelaic acid and hydroquinone 4% cream in the treatment of melasma. J Cosmet Dermatol. 2011;10(4):282–7.
- 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, 1263–1273.

- Gheisari M, Dadkhahfar S, Olamaei E, Moghimi HR, Niknejad N, Najar NN. The efficacy and safety of topical 5% methimazole vs 4% hydroquinone in the treatment of melasma: a randomized controlled trial. J Cosmet Dermatol. 2020;19(1):167–72.
- Goldberg, D.J.; Berlin, A.L.; Phelps, R. Histologic and Ultrastructural Analysis of Melasma after Fractional Resurfacing. Lasers Surg. Med. **2008**, 40, 134–138.
- Gong, Z.; Lai,W.; Zhao, G.;Wang, X.; Zheng, M.; Li, L.; Yang, Q.; Dang, Y.; Liu, L.; Zou, Y. Efficacy and Safety of Fluocinolone Acetonide, Hydroquinone, and Tretinoin Cream in Chinese Patients with Melasma: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Study. Clin. Drug Investig. **2015**, 35, 385–395.
- Iranmanesh, B.; Khalili, M.; Mohammadi, S.; Amiri, R.; Aflatoonian, M. The Efficacy of Energy-Based Devices Combination Therapy for Melasma. Dermatol. Ther. 2021, 34, e14927. [CrossRef]
- Jeon, G.; Ro, H.S.; Kim, G.R.; Lee, H.Y. Enhancement of Melanogenic Inhibitory Effects of the Leaf Skin Extracts of AloeBarbadensis Miller by the Fermentation Process. Fermentation 2022, 8, 580.
- Jiryis B, Toledano O, Avitan-Hersh E, Khamaysi Z (2024): Management of Melasma: Laser and Other Therapies—Review Study. J. Clin. Med; 13, 1468. https://doi.org/10.3390/jcm13051468
- Jutley, G.S.; Rajaratnam, R.; Halpern, J.; Salim, A.; Emmett, C. Systematic Review of Randomized Controlled Trials on Interventions for Melasma: An Abridged Cochrane Review. J. Am. Acad. Dermatol. **2014**, 70, 369–373.
- Lee KC, Wambier CG, Soon SL, Sterling JB, Landau M, Rullan P, et al (2019 a). Basic chemical peeling: superficial and medium-depth peels. J Am Acad Dermatol.;81(2):313–24.
- Lin M-Y, Lin C-S, Hu S, et al. Progress in the use of platelet-rich plasma in aesthetic and medical dermatology. J Clin Aesthet Dermatol. 2020;13(8):28–35.
- lves R, Grimalt R. A review of platelet-rich plasma: history, biology, mechanism of action, and classification. Skin Appendage Disord 2018;4:18–24.
- Mahajan, V.K.; Patil, A.; Blicharz, L.; Kassir, M.; Konnikov, N.; Gold, M.H.; Goldman, M.P.; Galadari, H.; Goldust, M. Medical Therapies for Melasma. J. Cosmet. Dermatol. **2022**, 21, 3707–3728.
- McKesey, J.; Tovar-Garza, A.; Pandya, A.G. Melasma Treatment: An Evidence-Based Review. Am. J. Clin. Dermatol. **2020**, 21, 173–225.
- Morgado-Carrasco, D.; Piquero-Casals, J.; Granger, C.; Trullàs, C.; Passeron, T. Melasma: The Need for Tailored Photoprotection to Improve Clinical Outcomes. Photodermatol. Photoimmunol. Photomed. **2022**, 38, 515–521. [CrossRef] [PubMed]
- Nguyen J, Remyn L, Chung IY, Honigman A, Gourani-Tehrani S, Wutami I, et al. Evaluation of the efficacy of cysteamine cream compared to hydroquinone in the treatment of melasma: a randomised, double-blinded trial. Australas J Dermatol. 2021;62(1):e41–6
- Ogbechie-Godec OA, Elbuluk N (2017). Melasma: an up-to-date comprehensive review. Dermatol Ther.;7(3):305–318
- Olumesi KR, Goldberg DJ (2023): A review of exosomes and their application in cutaneous medical aesthetics. J Cosmet Dermatol.;22(10):2628-2634. doi:10.1111/jocd.15930
- Panigrahi AR, Srinivas L, Panda J. Exosomes: Insights and therapeutic applications in cancer. Transl Oncol 2022;21:101439
- Passeron T, Fontas E, Kang HY, Bahadoran P, Lacour JP, Ortonne JP. Melasma treatment with pulsed-dye laser and triple combination cream: a prospective, randomized, single-blind, split-face study. Arch Dermatol. 2011;147(9):1106-1108. doi:10.1001/archdermatol.2011.255
- Pennitz A, Kinberger M, Avila Valle G, Passeron T, Nast A, Werner RN. Self-applied topical interventions for melasma: a systematic review and meta-analysis of data from randomized,

investigator-blinded clinical trials. Br J Dermatol. 2022 Sep;187(3):309-317. doi: 10.1111/bjd.21244. Epub 2022 May 18. PMID: 35290681.

- Pietowska, Z.; Nowicka, D.; Szepietowski, J.C. 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, 12084. [CrossRef] [PubMed]
- Pixley JN, Cook MK, Singh R, Larrondo J, McMichael AJ (2023). A comprehensive review of platelet-rich plasma for the treatment of dermatologic disorders. J Dermatolog Treat.; 34(1):2142035. doi:10.1080/09546634.2022.2142035
- Proietti I, Battilotti C, Svara F, Innocenzi C, Spagnoli A, Potenza C. Efficacy and Tolerability of a Microneedling Device Plus Exosomes for Treating Melasma. Applied Sciences. 2024; 14(16):7252. https://doi.org/10.3390/app14167252
- Sarkar R, Devadasan S, Choubey V, Goswami B. Melatonin and oxidative stress in melasma – an unexplored territory; a prospective study. Int J Dermatol. 2020;59(5):572–5.
- Sarkar, R.; Aurangabadkar, S.; Salim, T.; Das, A.; Shah, S.; Majid, I.; Singh, M.; Ravichandran, G.; Godse, K.; Arsiwala, S.; et al. Lasers in Melasma: A Review with Consensus Recommendations by Indian Pigmentary Expert Group. Indian J. Dermatol. **2017**, 62, 477–482. [CrossRef]
- Sheth VM & Pandya AG (2011): Melasma: A Comprehensive Update: Part i. J. Am. Acad. Dermatol, 65, 689–697.
- Spierings N. M. K. (2020): Melasma: A critical analysis of clinical trials investigating treatment modalities published in the past 10 years. Journal of cosmetic dermatology, 19(6), 1284–1289. https://doi.org/10.1111/jocd.13182
- Taylor, S.C.; Torok, H.; Jones, T.; Lowe, N.; Rich, P.; Tschen, E.; Menter, A.; Baumann, L.;Wieder, J.J.; Jarratt, M.M.; et al. Efficacy and Safety of a New Triple-Combination Agent for the Treatment of Facial Melasma. Cutis. **2003**, 72, 7.
- Trivedi MK, Yang FC, Cho BK. A review of laser and light therapy in melasma. Int J Women's Dermatol. 2017;3(1):11-20.
- Wawrzy´ nczak, A. Cosmetic and Pharmaceutic Products with Selected Natural and Synthetic Substances for Melasma Treatment and Methods of Their Analysis. Cosmetics **2023**, 10, 86.
- Wu, S.Z.; Muddasani, S.; Alam, M. A Systematic Review of the Efficacy and Safety of Microneedling in the Treatment of Melasma. Dermatol. Surg. **2020**, 46, 1636–1641.
- Yi, J.; Hong, T.; Zeng, H.; Li, P.; Li, P.; Wang, S.; Chen, J.; Li, P.; Zhou, J. A Meta-Analysis-Based Assessment of Intense Pulsed Light for Treatment of Melasma. Aesthetic Plast. Surg. **2020**, 44, 947–952.
- Zachary CM, Wang JV, Saedi N. Kojic acid for melasma: popular ingredient in skincare products.Skinmed. 2020;18(5):271–3