Review Article

Pharmacological Insights into Melasma: Understanding and Evaluating Treatment Modalities

Dr Virendra Kushwaha*, Dr Pooja Agrawal, Dr Sarthak Goel, Dr BK Shoraisham, Dr Anuj Kumar, Dr Sameer Siddiqui
Department of Pharmacology, GSVM Medical College, Kanpur, India.
***Corresponding author's E-mail:** vkushwaha1970@gmail.com

Received: 02-01-2024; **Revised:** 24-02-2024; **Accepted:** 28-02-2024; **Published on:** 15-03-2024.

ABSTRACT

Melasma, a complex pigmentary disorder, is characterized by the development of brown patches on sun-exposed areas of the face. Treatment for this intriguing dermatological condition has evolved over a century, with significant contributions to our understanding of its diagnosis, pathogenesis, and histology. Early classifications, groundbreaking theories, and advancements in the mid-20th century laid the groundwork for exploring the etiopathogenesis of melasma. From genetic predisposition and cutaneous vasculature to hormonal influences and UV radiation, this disorder's multifaceted nature is examined in this study from a pharmacological perspective. Treatment modalities, such as hydroquinone and tranexamic acid, are explored, emphasizing their pharmacological mechanisms and considerations. In conclusion, melasma's complexity demands a holistic approach, integrating pharmacological interventions for comprehensive management.

Keywords: Melasma, Hydroquinone, Tranexamic acid, sunscreen.

INTRODUCTION

Melasma, an intricate pigmentary disorder characterized by the development of brown patches on sun-exposed areas of the face, has undergone a fascinating historical evolution that spans over a century. In the early 1900s, Dr. G. Pernet[1] and Dr. Castellani[2] laid the groundwork for classifying skin pigmentation disorders, coining the term "chloasma" to denote skin discolorations linked to sun exposure[2]. Dr. W.G. Spencer's 1923 lecture introduced a groundbreaking theory connecting melanin to neural tube development, providing early insights into melasma's multifaceted nature[3]. Concurrently, Dr. Gupta added to the vocabulary the term "melanoderma" in 1929, contributing significantly to the understanding of melanin-related disorders[3,4].

In the mid-20th century, particularly the 1960s-1970s, Dr. Sorrel S. Resnik introduced the term "melasma," associating it with pigmentary disorders related to oral contraceptives[5]. Subsequent decades witnessed explorations into hormonal influences, extrafacial manifestations, and genetic predispositions, as well as in 1980s different melasma types and associations with thyroid dysfunction through histological studies were discovered[5]. The late 20th century marked rapid progress in melasma research, with treatment modalities like hydroquinone and retinoic acid gaining popularity. Assessment indices like the Melasma Area and Severity Index (MASI) were developed, and a surge in clinical studies focusing on diverse manifestations significantly enhanced diagnostic capabilities and therapeutic approaches[6].

As we enter the 21st century, Investigations into genetic factors, hormonal influences, and innovative treatment modalities are at the forefront, providing new avenues for targeted therapeutic interventions[7,8]. A global survey examining the role of ultraviolet radiation and hormonal influences underscores the multifactorial nature of melasma, emphasizing the need for a comprehensive understanding. Diverse clinical presentations and the identification of melasma in men further highlight the complexity of the disorder. The purpose of this review is to explore the historical aspects of melasma, its etiopathogenesis and treatment modalities developed so far.

Melasma: Etiopathogenesis and Causative Factors

Factors causing melasma can be divided[9] into

(1) Endogenous Factors- includes Genetic predisposition and cutaneous vasculature

(2) Exogenous Factors- such as sex hormones and UV radiations

Traditionally, Melasma has been classified into

- Epidermal
- Dermal
- Mixed

However, with recent reflectance confocal microscopy studies, there exists serious doubt to existence of "True Epidermal" or "True Dermal" melasma.

A potential genetic predisposition to melasma is indicated by a notable occurrence within families of specific ethnic backgrounds. Research from various regions, including Iran, Singapore, and among Latino men, has reported incidence rates ranging from 10% to as high as 70%[11]. In Southeast Asia, prevalence rates were observed at 40% in

females and 20% in males[12]. A global survey led by Ortonne et al., involving women from nine countries, further highlighted the susceptibility of individuals with Fitzpatrick skin phototypes III and IV, along with a greater likelihood of a positive family history in African-Americans.[13]

Despite the absence of genome-wide studies exploring associated genes, it is proposed that the responsible genes may be linked to pigmentary, inflammatory, hormonal, and potentially vascular responses. The precise molecular mechanisms underlying these associations still require thorough elucidation.

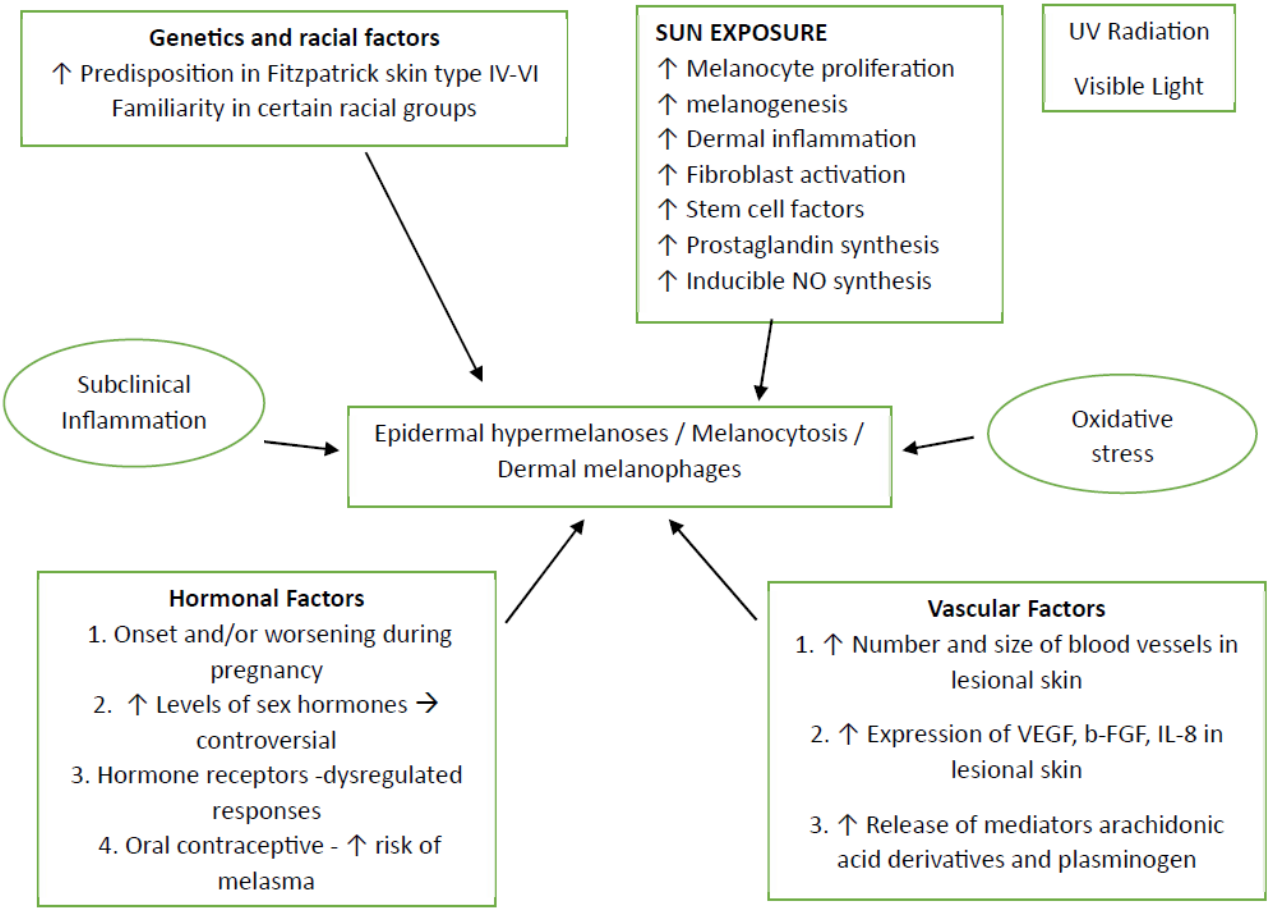

Figure 1: Diagrammatic representation of various factors responsible for melasma[10]

Underlying Ultravoilet Induced Melasma

UV radiation stimulates melanogenesis through direct and indirect effects on keratinocyte-melanocyte interaction. Directly, it induces the formation of endogenous 1,2-diacylglycerols (DAGs), activates protein kinase C-beta, and promotes the production of nitric oxide (NO) and cGMP. Indirectly, paracrine stimulation of melanocytes involves the release of melanogenic factors like basic fibroblast growth factor (bFGF), nerve growth factor (NGF), endothelin-1 (ET-1), and peptides from pro-opiomelanocortin (POMC), such as melanocyte-stimulating hormone (MSH) and adrenocorticotrophic hormone (ACTH)[14]. These factors promote melanocyte proliferation and stimulate melanin synthesis by activating tyrosinase activity and tyrosinase-related protein 1 (TRP-1)[15]. The interaction between melanocortin (MC) and the MC-1 receptor (MC1R) upregulates melanogenesis through the cAMP-PKA-MITF pathway, especially the MITF-M isoform. Enhanced expression of inducible nitric oxide synthase (iNOS) within keratinocytes contributes to melasma melanogenesis[16].

UV-induced dermal inflammation and fibroblast activation result in increased expression of stem cell factor (SCF) and c-kit, influencing melanogenesis in melasma lesions[17]. Fibroblast-derived cytokines play a role in stimulating melanocyte proliferation and melanogenesis. UV-induced synthesis of prostaglandins (PGs) and upregulation of cyclooxygenase-2 (COX-2) are linked to epidermal hyperpigmentation, supporting the consideration of PG analogs as a therapeutic option for vitiligo[17].

Beyond UV radiation, visible light, especially in skin types IV–VI, triggers hyperpigmentation[18]. Many sunscreens designed for UV-A and UV-B protection offer partial defense, emphasizing the superior effectiveness of tinted mineral sunscreens. These formulations protect against both UVR and visible light, proving more effective in preventing melasma relapses[19]. Additional UV mechanisms involve melanogenesis stimulation through disruption of the basement membrane (BM), abnormalities in the extracellular matrix (ECM), and the activation of mast cells[20].

Basement Membrane Disruption: A Relatively Recently Detected Feature of Melasma

Recent investigations have directed attention towards the presence and significance of focal vacuolar degeneration in the basement membrane concerning melasma. Despite a wide range in reported incidences of basement membrane disruption in melasma (ranging from 3% to 95.5%), it is considered a crucial characteristic that helps establish the link between chronic UV exposure and melasma[20]. The presence of **pendulous melanocytes** associated with basement membrane abnormalities has been identified as a distinctive feature of melasma[21].

In a recent study involving melasma patients with Fitzpatrick skin types IV and V, disrupted basement membranes were observed in 95.5% and 83% of skin samples using periodic acid-Schiff-diastase (D-PAS) staining and anti-collagen type IV immunohistochemistry, respectively[22].

This disruption is attributed to elevated levels of matrix metalloproteinase (MMP)-2 and MMP-9 induced by chronic UV exposure, leading to the degradation of type IV collagen and type VI collagen in the skin. Furthermore, recent research has unveiled UV-independent pathways contributing to basement membrane disruption in melasma lesions. Cadherin 11 (CDH11) overexpression is proposed as a factor that can induce basement membrane disruption and dermal changes in melasma, regardless of UV exposure. The disruption of the basement membrane also provides an explanation for the descent of melanocytes and melanin into the dermis, presenting as free melanin or melanophages in the dermis of melasma-affected skin. This phenomenon renders melasma challenging to treat and increases its susceptibility to relapse.[23-25]

Role of Hormones

Melasma's connection with female sex hormones, oral contraceptive pills (OCPs), and pregnancy remains complex and warrants further clarification.

Pregnancy and Melasma: Many individuals experience the onset or exacerbation of melasma during pregnancy, known as "chloasma gravidarum" or "the mask of pregnancy," typically emerging in the second half of gestation. However, melasma may appear before pregnancy or years after childbirth. The reported incidence of melasma during pregnancy ranges from 2.5% to 75%, with a higher occurrence in pregnant women with skin of color (SOC). It is more prevalent in women of black, Hispanic, or Asian descent. Limited epidemiological studies on melasma in Indian women exist, but two studies report an incidence of 2.5–8.5% during pregnancy[26,27].

Oral Contraceptive Pills (OCPs) and Melasma: The documented onset of melasma following OCP use is notable. In a global survey, 25% of 324 women with melasma reported its onset with OCP use[28]. Melasma occurrence has been reported in 11.3–46% of individuals using oral contraceptives across various countries[29]. Evidence suggests OCP-induced melasma may be more common in patients lacking a family history of melasma, with a higher risk of recurrence or worsening during pregnancy. While discontinuing OCPs may benefit those developing melasma, a systematic change in hormonal contraception for melasma patients seems unwarranted.

Hormones, Hormone Receptors, and Melasma: Estrogens and progesterones are implicated in melasma development, though studies report conflicting results due to variations in genetic and ethnic study populations. Studies from the Indian subcontinent show a significant increase in estradiol levels in melasma patients compared to controls, while contradictory results are reported by other authors[30-32]. Recent attention to estrogen's pathogenetic role in melasma includes suggestions of improvement with systemic anti-estrogenic therapy in patients with oligomenorrhea associated with a hyperestrogenic state. Anecdotal reports include extrafacial melasma following topical estrogen application, melasma reduction with anti-estrogen cream, and melasma development in Caucasian men following finasteride treatment[33-35]. Although robust evidence for hormonal pathogenesis in men is lacking, increased luteinizing hormone and reduced testosterone levels have been reported in Indian men with melasma.

Table 1: Proposed Mechanisms of Melanogenesis stimulation by oestrogen- oestrogen receptor interaction in the pathogenesis of melasma[36]

Mechanism	Effect
Direct induction of protein synthesis	Upregulation of tyrosinase, TRP-1, TRP-2, MITF
Activation of the cAMP-PKA pathway	Upregulation of tyrosinase
Overexpression of PDZK1 gene	Enhanced tyrosinase expression and melanosome transfer
Increased expression of MC1R in melanocytes	Upregulation of tyrosinase via cAMP-PKA pathway stimulation

CAMP-PKA, cyclic adenosine monophosphate-protein kinase A; MC1R, melanocortin type 1 receptors; PDZK1, PDZ domain protein kidney 1; TRP-1,2, tyrosinase-related protein 1,2.

Vascular Factors in Melasma

Prominent solar elastosis is observed in lesional melasma skin compared to perilesional skin, and UV-induced dermal inflammation activates fibroblasts, leading to increased melanogenesis. This underscores the significant role of the dermal environment in melasma development[37,38]. Beyond the known involvement of dermal components like the extracellular matrix (ECM), fibroblasts, and mast cells in melanogenesis enhancement through paracrine effects on the melanocyte-keratinocyte unit, recent attention has turned to cutaneous vasculature[39].

Despite hyperpigmentation being the primary clinical feature of melasma, many patients exhibit distinctive telangiectatic erythema specifically in the melasma-affected skin, although perilesional skin may also show increased erythema[40]. Recent research, including colorimetric analysis, immunohistochemical studies, and laser confocal microscopy, indicates that melasma lesions are more vascularized than perilesional skin[41-42]. These vascular changes, often overlooked by the naked eye, become apparent through dermoscopy and advanced instruments like chromameters and spectrocolorimeters.

A comprehensive study in women newly diagnosed with melasma demonstrated a significant increase in the number and size of dermal blood vessels and an upregulated expression of vascular endothelial growth factor (VEGF) in lesional skin compared to perilesional normal skin. UV irradiation is speculated to induce an angiogenic switch, leading to the upregulation of proangiogenic factors like VEGF, basic fibroblast growth factor (b-FGF), and interleukin (IL)-8. VEGF, a major angiogenic factor, enhances melanogenesis through interaction with VEGF receptors in epidermal keratinocytes, followed by the release of mediators, particularly metabolites of arachidonic acid and plasminogen from proliferated vessels[42]. Increased dermal mast cells, leading to the secretion of angiogenic factors like VEGF, FGF-2, and TGF-β that contribute to vascular dilatation, have also been implicated. The moderate efficacy of newer treatment modalities such as tranexamic acid (TEXA), a plasminogen inhibitor, and pulsed dye laser (PDL), which primarily target vascular components, further supports the vascular theory of melasma[43].

Topical Agents

Depigmenting Agents-Depigmenting agents which is considered as the gold standard for melasma treatment, include hydroquinone (HQ), a widely used and well-researched tyrosinase inhibitor with mild to moderate local adverse effects[45,46,47]. Studies by Ennes et al. and Vázquez et al. demonstrated significant improvement when HQ was used in combination with sunscreen[48,49]. Another agent, azelaic acid (AA), a competitive tyrosinase inhibitor, showed efficacy comparable to 4% HQ but with a potentially higher risk of irritant adverse effects. Various trials compared AA with HQ, with conflicting results on superiority[50-54]. Topical vitamin C, known for its ability to chelate copper ions involved in melanogenesis, did not consistently show significant improvement in melasma[55,56].

Rucinol serum, another tyrosinase inhibitor, demonstrated a decrease in melanin index with adverse effects like stinging and burning, which improved with a liposomal encapsulated cream[57,58].

Table 2: Melasma treatments, mechanisms of action, and adverse effects[44]

Modality	Treatment	Mechanism of action	Adverse Effects (AE)
Topical	Iron oxide	Block visible and ultraviolet light	Irritation
	Hydroquinone (HQ)	Tyrosinase inhibitor	Irritation, exogenous ochronosis (with HQ)
	Azelaic acid,		
	Ascorbic acid,		
	Kojic acid		
	Tretinoin	Increased keratinocyte turnover	Irritation, redness
	Corticosteroids	Anti-inflammatory with non-selective inhibition of melanogenesis	Telangiectasias, epidermal atrophy, steroid-induced acne, striae, hypopigmentation
	Ascorbic acid	Inhibition of reactive oxygen species	No significant AE
	Niacinamide	Inhibition of melanosome transfer	Irritation
Oral	Tranexamic acid [also used tropically]	Inhibits plasminogen/plasmin pathway inhibition of melanin synthesis Decreases vascular proliferation	Abdominal bloating, menstrual irregularities, headache, deep venous thrombosis
	Polypodium leucotomos, Glutathione	Inhibition of reactive oxygen species	No significant AE
Procedural	Q-switch ruby laser, Q-switch Nd:Yag laser	Melanosome destruction	Burn, post inflammatory pigment alteration (PIPA)
	Non-ablative fractional lasers	Fractional photothermolysis leading to melanin extrusion	Burn, PIPA
	Chemical peels	Increased keratinocyte turnover	Burn, peeling, PIPA
	Microneedling	Transdermal drug delivery	Erythema, edema, tram-track marks, PIPA
	Intense pulsed light	Extrusion of melanosomes	Burn, PIPA
	Radiofrequency	Cellular biostimulation Transdermal drug delivery	Burn

AE adverse effects, HQ hydroquinone, PIPA post-inflammatory pigment alteration, Nd:YAG neodymium-doped yttrium aluminium garnet

Retinoids- Retinoids play a role in targeting various pathways involved in melanin synthesis and dispersion in the skin, including reducing tyrosinase transcription and melanin synthesis. They have been studied in the context of melasma[59]. Additionally, retinoids enhance epidermal keratinocyte metabolism and turnover, leading to a decrease in melanosome transfer and melanin loss, and facilitating the penetration of other topical therapies[60].

In a 40-week trial, Griffiths et al. compared 0.1% tretinoin cream with a vehicle, with 68% of the treatment group showing improvement. However, the effects were not observed until 24 weeks, and 88% of the treatment group experienced adverse effects from the high concentration of tretinoin. Similar results were obtained in a trial involving African American subjects [61,62]. Leenutaphong et al. failed to show significant improvement using a lower concentration of 0.05% tretinoin cream twice daily compared to vehicle+sunscreen [63].

Adapalene, suggested to be less irritating than tretinoin, showed similar efficacy with fewer adverse effects in a trial comparing adapalene 0.1% gel with tretinoin 0.05% cream once daily+sunscreen [64].

In a recent split-face trial, Truchuelo et al. used a proprietary product containing two different retinoids for melasma treatment, observing a 74% reduction in MASI score after 3 months, with limited adverse effects [65].

Visible Light Protection- Visible light, akin to UV radiation, can induce prolonged hyperpigmentation by generating reactive oxygen species[66, 67]. Consequently, physical blockers in sunscreens may enhance efficacy against both UV and visible light. Castanedo-Cazares et al. demonstrated this by comparing a combination sunscreen with UV-only sunscreen in individuals using 4% HQ cream, showing superior improvement in MASI score, colorimetry, and histopathology in the combination group after 8 weeks[68].

Zinc sulfate, serving as a physical blocker and antioxidant against visible light, has been tested but does not surpass the efficacy of 4% HQ. The zinc sulfate group experienced more dropouts, possibly due to unsatisfactory results[69]

Tropical Tranexamic Acid- The use of topical tranexamic acid (TXA), an antifibrinolytic agent, in treating melasma has yielded varied results. Topical formulations, including 2–5% creams or solutions and intradermal injections (4–100 mg/mL), have been explored. Ebrahimi et al. conducted a randomized split-face trial comparing 3% topical TXA with 3% HQ + 0.01% dexamethasone twice daily for 12 weeks, revealing a higher improvement in MASI in the topical TXA group (74% vs. 65% for HQ + dexamethasone), though not statistically significant[70]. Studies by Banihashemi et al. and Atef et al. also found no significant differences between liposomal TXA and HQ cream, and between topical TXA and 2% HQ, respectively[71,72].

Topical TXA has been investigated as an adjuvant treatment. Laothaworn et al. observed a remarkable improvement (48%) when combining QS-Nd:YAG laser with 3% topical TXA, compared to 20% in the laser-only group[73]. Xu et al. demonstrated successful pigmentation improvement with microneedling combined with 5% topical TXA after 12 weeks[74].

Intradermal injections of TXA, at different concentrations and treatment protocols, have shown mixed results compared to topical HQ or TXA. Budamakuntla et al. compared microneedling and intradermal TXA injections in a 12-week trial, finding no significant difference in mean MASI scores, but suggesting that microneedling may be superior to intradermal injections in achieving >50% improvement[75].

Combined Tropical Agents - The triple combination cream (TCC), comprising hydroquinone (HQ), a retinoid, and a fluorinated corticosteroid, is a proven and safe melasma treatment[76]. In a large-scale trial by Taylor et al., TCC demonstrated superior efficacy compared to dual combinations, achieving complete or near-complete clearing in 77% of subjects, with manageable adverse events [77]. Further investigations into maintenance therapy with TCC revealed a lower relapse rate in subjects treated twice weekly, although transitioning to maintenance therapy posed relapse challenges for most subjects[78].

While TCC remains a prominent option, alternative combination therapies, such as solutions containing glycolic acid (GA) and kojic acid (KA), have been explored[79]. However, caution is advised due to potential increased adverse effects when combining these solutions with HQ.

Chemical Peels

Chemical peels are a routine practice for addressing skin concerns like rejuvenation, solar lentigines, acne, and hyperpigmentation. However, most current melasma studies lack standardized assessment tools, leading to controversial results. Recognized potential adverse effects involve skin irritation and post-inflammatory hyperpigmentation (PIH).[80]

Glycolic Acid Peels

Glycolic acid (GA) peels, commonly used in melasma treatment, do not consistently demonstrate superior efficacy over topical agents but show potential in combination with triple combination cream (TCC). The increased risk of adverse effects, particularly post-inflammatory hyperpigmentation (PIH), associated with GA peels in the treatment regimen should be noted[81].

In split-face trials, comparisons of 2% HQ + 10% GA gel with GA peels versus pretreatment with 8% GA cream, 4% HQ twice daily with GA peels, and GA peels against tretinoin demonstrated no significant difference [81-84]. Notably, a study by Sarkar et al. found a significant decrease (46%) in melasma area and severity index (MASI) in the combination of 30–40% GA peels with TCC compared to TCC alone [79]. However, 10% of subjects in the GA peel group experienced PIH[85].

Erbil et al. compared 20–30% GA peels, 20% azelaic acid (AA) twice daily, and 0.1% adapalene gel once daily versus AA and adapalene alone. Both groups showed a decrease in MASI score, with significantly greater improvement in the intervention group, although with a higher incidence of PIH[86]. Dayal et al. investigated 20% AA twice daily alone versus 20% AA plus GA peels, finding a significant decrease in MASI and Melasma Quality of Life Score at week 12, with higher adverse effects in the combination group[87].

In a recent study comparing different chemical peels, including 35% GA peel, 30% salicylic acid (SA) + 10% mandelic acid (SMA), and 50% phytic acid (PA), the GA peel group showed significantly greater results compared to the PA peel group, with similar efficacy to SMA[88].

Laser and Light Therapies

Laser and light therapies are widely employed for managing hyperpigmentation and skin rejuvenation, despite an increased risk of adverse effects, particularly in individuals with skin of color. Noteworthy studies have reported varying outcomes with different approaches.

Intense Pulsed Light (IPL) treatments have demonstrated significant improvement, with studies by Wang and colleagues and Figueiredo Souza and colleagues showing positive results when combined with topical agents.[89] However, caution is advised due to the potential for adverse effects, as highlighted by Shakeeb and colleagues and observations on Fractionated IPL (F-IPL)[90].

Q-Switched Neodymium-Doped Yttrium Aluminum Garnet (QS-Nd:YAG) Laser therapies, including laser toning, have shown effectiveness in various studies [91-96]. Combining QS-Nd:YAG with other modalities, such as microneedling or chemical peels, has demonstrated improved outcomes[93,97].

Pulsed-Dye Laser (PDL) treatments, targeting the vascular component of melasma, have been explored with positive outcomes reported by Passeron and colleagues[98].

Fractional Laser Therapy, particularly monotherapy, has shown limited efficacy, especially in individuals with darker skin tones, due to the associated risk of hyperpigmentation and recurrence[99,100]. Combining fractional laser with other modalities, such as CO2 laser or QS alexandrite laser, has demonstrated improved results[101,102]. Notably, TCC + CO2 laser has shown higher efficacy compared to either treatment alone [103]

Other laser therapies have been investigated with mixed results. Adverse effects and recurrence rates should be carefully considered in laser and light-based treatments for hyperpigmentation. Further research and long-term studies are crucial to establishing the safety and efficacy of these therapies, especially in individuals with skin of color.

Systemic Agents

Systemic therapies have emerged as potential treatments for melasma, including oral options like tranexamic acid (TXA), plant-based medications, and oral glutathione.

TXA, an antifibrinolytic agent, has shown effectiveness in subjects with refractory melasma, with doses ranging from 500 to 1500 mg daily. Adverse effects include gastrointestinal upset and a risk of deep venous thrombosis. Studies by Karn et al., Wu et al., and others support the efficacy of oral TXA, with improvements ranging from 69% to 100% in various dosages and combinations[104-110]. Recent meta-analyses have favored oral TXA over intradermal injections or topical creams, with notable histological improvements observed[111-113].

Polypodium leucotomos extract (PLE), an antioxidant, has not shown significant benefits in controlled, randomized trials [114-117]

Other systemic agents, such as procyanidin, β-carotene, vitamin C, vitamin E capsules, and melatonin, have demonstrated mild to moderate improvements in melasma[104-106].

CONCLUSION

In summary, addressing the multifaceted challenges posed by melasma demands a comprehensive approach that takes into account the distinct healthcare landscapes of both rural and urban populations. Enhancing widespread awareness is not only a means to bridge the knowledge gap but also an essential step towards ensuring equitable access to information across diverse communities. Public health campaigns and educational initiatives play a pivotal role in disseminating crucial insights about melasma, its causative factors, and available treatment options.

The emphasis on early treatment is a must, not just for the potential improvement in clinical outcomes but also for mitigating the psychological trauma often associated with persistent skin discoloration.

Beyond the physical manifestations, melasma often exerts a notable toll on individuals' psychological well-being. The emotional distress stemming from altered appearance and societal perceptions necessitates a holistic approach to care. Recognizing and addressing the psychological impact of melasma is integral to comprehensive management, acknowledging the interconnectedness of physical and mental well-being.

In conclusion, a comprehensive strategy that spans awareness, early detection, and timely treatment is crucial for effectively managing melasma in diverse populations. Bridging the healthcare access divide between rural and urban settings, coupled with robust educational initiatives, contributes to a proactive and informed community. By prioritizing early intervention and acknowledging the psychological dimensions of melasma, we can enhance the overall well-being of affected individuals, fostering a more inclusive and compassionate approach to skin health.

ACKNOWLEDGEMENT: We extend our sincere gratitude to the authors who contributed significantly to this review article. Their expertise and dedication enhanced the quality of this work. We also thank supporting institutions and the broader scientific community for their contributions.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Pernet G. A section of melanosis cutis. Proc R Soc Med. 1910; 3(Dermatol Sect): 32-39.
2. Castellani A, Chalmers AJ. Manual of Tropical Medicine. 3rd ed. London1919: 2231.
3. Spencer WG. The bradshaw lecture on Melanosis (Melanin: Melanoma: Melanotic Cancer). *Br Med J*. 1923; **2**(3281): 907-913.
4. Carruthers R. Chloasma and the pill. Br Med J. 1967;3(5560):307-12. doi:10.1136/bmj.3.5560.307-a
5. Adamson HG. Melanosis cutis, with melanotic carcinoma. Proc R Soc Med. 1922;15(Dermatol Sect):45-47.
6. Syder NC, Elbuluk N. The history of melasma: its roots and evolution. *Dermatological Reviews*. 2023; 4: 5-11. doi:10.1002/der2.134.
7. Vázquez M, Maldonado H, Benmamán C, Sanchez JL. Melasma inmen. Int J Dermatol. 1988;27(1):25-27. doi:10.1111/j.1365-4362.1988.tb02329.x
8. McKesey, J., Tovar-Garza, A., & Pandya, A. G. Melasma Treatment: An Evidence-Based Review. *American journal of clinical dermatology*, 2020;*21*(2):173–225. https://doi.org/10.1007/s40257-019-00488-w
9. Sonthalia S, Bharti J. Etiopathogenesis of Melasma. In: Sarkar R, ed. Melasma: A Monograph.
10. Kang HY, Bahadoran P, Suzuki I, et al. In vivo reflectance confocal microscopy detects pigmentary changes in melasma at a cellular level resolution. Exp Dermatol. 2010;19:228-33.
11. Sheth VM, Pandya AG. Melasma: a comprehensive update: Part I. J Am Acad Dermatol. 2011;65:689-97.
12. Sivayathorn A. Melasma in Orientals. Clin Drug Invest. 1995;10:34-40.
13. Ortonne JP, Arellano I, Berneburg M, et al. A global survey of the role of ultraviolet radiation and hormonal influences in the development of melasma. J Eur Acad Dermatol Venereol. 2009;23:1254-62.
14. Lee AY. Recent progress in melasma pathogenesis. Pigment Cell Melanoma Res. 2015;28:648-60.
15. Suzuki I, Kato T, Motokawa T, et al. Increase of pro-opiomelanocortin mRNA prior to tyrosinase, tyrosinase-related protein 1, dopachrome tautomerase, Pmel-17/gp100, and P-protein mRNA in human skin after ultraviolet B irradiation. J Invest Dermatol. 2002;118:73-8.
16. Jo HY, Kim CK, Suh IB, et al. Co-localization of inducible nitric oxide synthase and phosphorylated Akt in the lesional skins of patients with melasma. J Dermatol. 2009;36:10-6.
17. Kang HY, Hwang JS, Lee JY, et al. The dermal stem cell factor and c-kit are overexpressed in melasma. Br J Dermatol. 2006;154:1094-9.
18. Passeron T. Melasma pathogenesis and influencing factors—an overview of the latest research. J Eur Acad Dermatol Venereol. 2013;27:5-6.
19. Kwon SH, Hwang YJ, Lee SK, et al. Heterogeneous pathology of melasma and its clinical implications. Int J Mol Sci. 2016;17(6):30-35.
20. Lee DJ, Park KC, Ortonne JP, et al. Pendulous melanocytes: A characteristic feature of melasma and how it may occur. Br J Dermatol. 2012;166:684-6.
21. Raj S, Khopkar U, Kapasi A, et al. Skin in pregnancy. Indian J Dermatol Venereol Leprol. 1992;58:84-8.
22. Torres-Alvarez B, Mesa-Garza IG, Castanedo-Cazares JP, et al. Histochemical and immunohistochemical study in melasma: Evidence of damage in the basal membrane. Am J Dermatopathol. 2011;33:291-5
23. Kim NH, Choi SH, Lee TR, et al. Cadherin 11 involved in basement membrane damage and dermal changes in melasma. Acta Derm Venereol. 2016;96:635-40.
24. Torres-Alvarez B, Mesa-Garza IG, Castanedo-Cazares JP, et al. Histochemical and immunohistochemical study in melasma: Evidence of damage in the basal membrane. Am J Dermatopathol. 2011;33:291-5.
25. Kwon SH, Hwang YJ, Lee SK, et al. Heterogeneous pathology of melasma and its clinical implications. Int J Mol Sci. 2016;17(6):18-23.
26. Kumari R, Jaisankar TJ, Thappa DM. A clinical study of skin changes in pregnancy. Indian J Dermatol Venereol Leprol. 2002;73:141.
27. Kim EH, Kim YC, Lee ES, et al. The vascular characteristics of melasma. J Dermatol Sci. 2007;46:111-6.
28. Sidharth Sonthalia, Jyotirmay Bharti. Etiopathogenesis of Melasma. In: Rashmi Sarkar, Edito. Melasma a Monograph: 2nd Edition. New Delhi: Jaypee Publication; 2018. p.11
29. Handel AC, Miot LD, Miot HA. Melasma: a clinical and epidemiological review. An Bras Dermatol. 2014 Sep-Oct;89(5):771-82. doi: 10.1590/abd1806-4841.20143063. PMID: 25184917; PMCID: PMC4155956..
30. Sidharth Sonthalia, Jyotirmay Bharti. Etiopathogenesis of Melasma. In: Rashmi Sarkar, Edito. Melasma a Monograph: 2nd Edition. New Delhi: Jaypee Publication; 2018. p.12
31. Hassan I, Kaur I, Sialy R, et al. Hormonal milieu in the maintenance of melasma in fertile women. J Dermatol. 1998;25:510-2.
32. Perez M, Sanchez JL, Aguilo F. Endocrinologic profile of patients with idiopathic melasma. J Invest Dermatol. 1983;81:543-5.
33. Mahjour M, Khoushabi A, Feyzabadi Z. The role of oligomenorrhea in melasma. Med Hypotheses. 2017;104:1-3.
34. Snyder A, Schiechert RA, Zaiac MN. Melasma Associated with Topical Estrogen Cream. J Clin Aesthet Dermatol. 2017;10:57-8.
35. Cohen PR. Topical anti-estrogen therapy to treat melasma. J Clin Aesthet Dermatol. 2017;10:16.
36. Famenini S, Gharavi NM, Beynet DP. Finasteride associated melasma in a Caucasian male. J Drugs Dermatol. 2014;13:484-6.
37. Kang WH, Yoon KH, Lee ES, et al. Melasma: Histopathological characteristics in 56 Korean patients. Br J Dermatol. 2002;146:228-37.
38. Kang HY, Hwang JS, Lee JY, et al. The dermal stem cell factor and c-kit are overexpressed in melasma. Br J Dermatol. 2006;154:1094-9.
39. Hernandez-Barrera R, Torres-Alvarez B, Castanedo-Cazares JP, et al. Solar elastosis and presence of mast cells as key features in the pathogenesis of melasma. Clin Exp Dermatol. 2008;33:305-8
40. Kumari R, Jaisankar TJ, Thappa DM. A clinical study of skin changes in pregnancy. Indian J Dermatol Venereol Leprol. 2002;73:141.
41. Kim EH, Kim YC, Lee ES, et al. The vascular characteristics of melasma. J Dermatol Sci. 2007;46:111-6.
42. Kim SJ, Park JY, Shibata T, et al. Efficacy and possible mechanisms of topical tranexamic acid in melasma. Clin Exp Dermatol. 2016;41:480-5.

43. Gddes ER, Stout AB, Friedman PM. Retrospective analysis of the treatment of melasma lesions exhibiting increased vascularity with the 595-nm pulsed dye laser combined with the 1927-nm fractional low powered diode laser. Lasers Surg Med. 2017;49:20-6.

44. Ogbechie-Godec OA, Elbuluk N. Melasma: an Up-to-Date Comprehensive Review. Dermatol Ther (Heidelb). 2017 Sep;7(3):305-318. doi: 10.1007/s13555-017-0194-1. Epub 2017 Jul 19. PMID: 28726212; PMCID: PMC5574745.

45. Draelos ZD, Matsubara A, Smiles K. The effect of 2% niacinamide on facial sebum production. J Cosmet Laser Ther. 2006;8(2):96-101. doi:10.1080/14764170600717704

46. Misra N, Sharma A, Agarwal A, et al. A randomized, open-label study to evaluate the efficacy and safety of oral tranexamic acid in the treatment of melasma in Indian patients. Indian J Dermatol Venereol Leprol. 2019;85:284–290.

47. Sarkar R, Garg V, Bansal S, Sethi S, Gupta C. Comparative evaluation of efficacy and tolerability of glycolic acid, salicylic mandelic acid, and phytic acid combination peels in melasma. Dermatol Surg. 2016;42(3):384–391.

48. Huh CH, Seo KI, Park JY, et al. A randomized, double-blind, placebo-controlled trial of vitamin C iontophoresis in melasma. Dermatology. 2003;206(4):316–320.

49. Tse TW, Hui E. Tranexamic acid: an important adjuvant in the treatment of melasma. J Cosmet Dermatol. 2013;12(1):57–66.

50. Baroero L, Marenco M, Negro C, et al. Tranexamic acid as epigenetic silencing agent of melanin synthesis in a novel in vitro regenerative pig skin model. Dermatol Ther. 2020;33(1):e13168.

51. Ishii N, Momosawa A, Hanada K, et al. Clinical effects of tranexamic acid on melasma and adverse reactions: a systematic review and meta-analysis. Int J Dermatol. 2021;60(3):331–340.

52. Baliña LM, Graupe K. The treatment of melasma. 20% azelaic acid versus 4% hydroquinone cream. Int J Dermatol. 1991;30(12):893–5.

53. 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.

54. Sarkar R, Bhalla M, Kanwar AJ. A comparative study of 20% azelaic acid cream monotherapy versus a sequential therapy in the treatment of melasma in dark-skinned patients. Dermatology. 2002;205(3):249–54.

55. Huh CH, Seo KI, Park JY, Lim JG, Eun HC, Park KC. A randomized, double-blind, placebocontrolled trial of vitamin C iontophoresis in melasma. Dermatology. 2003;206(4):316–20.

56. Espinal-Perez LE, Moncada B, Castanedo-Cazares JP. A double-blind randomized trial of 5% ascorbic acid vs. 4% hydroquinone in melasma. Int J Dermatol. 2004;43(8):604–7.

57. Khemis A, Kaiafa A, Queille-Roussel C, Duteil L, Ortonne JP. Evaluation of efficacy and safety of rucinol serum in patients with melasma: a randomized controlled trial. Br J Dermatol. 2007;156(5):997–1004.

58. Huh SY, Shin JW, Na JI, Huh CH, Youn SW, Park KC. Efficacy and safety of liposomeencapsulated 4-n-butylresorcinol 0.1% cream for the treatment of melasma: a randomized controlled split-face trial. J Dermatol. 2010;37(4):311–5.

59. Romero C, Aberdam E, Larnier C, Ortonne JP. Retinoic acid as modulator of UVB-induced melanocyte differentiation. Involvement of the melanogenic enzyme's expression. J Cell Sci. 1994;107:1095–103.

60. Ortonne JP. Retinoid therapy of pigmented disorders. Dermatol Ther. 2006;19:280–8.

61. Griffiths CE, Finkel LJ, Ditre CM, Hamilton TA, Ellis CN, Voorhees JJ. Topical tretinoin (retinoic acid) improves melasma. A vehicle-controlled, clinical trial. Br J Dermatol. 1993;129(4):415–21.

62. Kimbrough-Green CK, Griffiths CE, Finkel LJ, Hamilton TA, Bulengo-Ransby SM, Ellis CN, Voorhees JJ. Topical retinoic acid (tretinoin) for melasma in black patients. A vehicle-controlled clinical trial. Arch Dermatol. 1994;130(6):727–33.

63. Leenutaphong V, Nettakul A, Rattanasuwon P. Topical isotretinoin for melasma in Thai patients: a vehicle-controlled clinical trial. J Med Assoc Thai. 1999;82(9):868–75.

64. Dogra S, Kanwar AJ, Parsad D. Adapalene in the treatment of melasma: a preliminary report. J Dermatol. 2002;29(8):539–40.

65. Truchuelo MT, Jiménez N, Jaén P. Assessment of the efficacy and tolerance of a new combination of retinoids and depigmenting agents in the treatment of melasma. J Cosmet Dermatol. 2014;13(4):261–8.

66. Liebel F, Kaur S, Ruvolo E, Kollias N, Southall MD. Irradiation of skin with visible light induces reactive oxygen species and matrix-degrading enzymes. J Investig Dermatol. 2012;132:1901–7.

67. Mahmoud BH, Ruvolo E, Hexsel CL, et al. Impact of longwavelength UVA and visible light on melanocompetent skin. J Investig Dermatol. 2010;130:2092–7.

68. Castanedo-Cazares JP, Hernandez-Blanco D, Carlos-Ortega B, Fuentes-Ahumada C, TorresÁlvarez B. Near-visible light and UV photoprotection in the treatment of melasma: a double-blind randomized trial. Photodermatol Photoimmunol Photomed. 2014;30(1):35–42.

69. Yousef A, Khani Khoozani Z, Zakerzadeh Forooshani S, Omrani N, Moini AM, Eskandari Y. Is topical zinc effective in the treatment of melasma? A double-blind randomized comparative study. Dermatol Surg. 2014;40(1):33–7.

70. Ebrahimi B, Naeini FF. Topical tranexamic acid as a promising treatment for melasma. J Res Med Sci. 2014;19(8):753–7.

71. Banihashemi M, Zabolinejad N, Jaafari MR, Salehi M, Jabari A. Comparison of therapeutic effects of liposomal Tranexamic Acid and conventional Hydroquinone on melasma. J Cosmet Dermatol. 2015;14(3):174–7.

72. Atef N, Dalvand B, Ghassemi M, Mehran G, Heydarian A. Therapeutic effects of topical tranexamic acid in comparison with hydroquinone in treatment of women with Melasma. Dermatol Ther (Heidelb). 2017;7(3):417–24.

73. Laothaworn V, Juntongjin P. Topical 3% tranexamic acid enhances the efficacy of 1064-nm Qswitched neodymium-doped yttrium aluminum garnet laser in the treatment of melasma. J Cosmet Laser Ther. 2018;20(6):320–5.

74. Xu Y, Ma R, Juliandri J, Wang X, Xu B, Wang D, Lu Y, Zhou B, Luo D. Efficacy of functional microarray of microneedles combined with topical tranexamic acid for melasma: a randomized, self-controlled, split-face study. Medicine (Baltimore). 2017;96(19):e6897.

75. Budamakuntla L, Loganathan E, Suresh DH, Shanmugam S, Suryanarayan S, Dongare A, Venkataramiah LD, Prabhu N. A randomised, open-label, comparative study of tranexamic acid microinjections and tranexamic acid with microneedling in patients with Melasma. J Cutan Aesthet Surg. 2013;6(3):139–43.

76. Taylor SC, Torok H, Jones T, Lowe N, Rich P, Tschen E, Menter A, Baumann L, Wieder JJ, Jarratt MM, Pariser D, Martin D, Weiss J, Shavin J, Ramirez N. Efficacy and safety of a new triple combination agent for the treatment of facial melasma. Cutis. 2003;72(1):67–72.

77. Torok H, Taylor S, Baumann L, Jones T, Wieder J, Lowe N, Jarret M, Rich P, Pariser D, Tschen E, Martin D, Menter A, Weiss J. A large 12-month extension study of an 8-week trial to evaluate the safety and efficacy of triple combination (TC) cream in melasma patients previously treated with TC cream or one of its dyads. J Drugs Dermatol. 2005;4(5):592–7.

78. Arellano I, Cestari T, Ocampo-Candiani J, Azulay-Abulafa L, Bezerra Trindade Neto P, Hexsel D, Machado-Pinto J, Muñoz H, Rivitti-Machado MC, Sittart JA, Trindade de Almeida AR, Rego V, Paliargues

F, Marques-Hassun K. Preventing melasma recurrence: prescribing a maintenance regimen with an effective triple combination cream based on long-standing clinical severity. J Eur Acad Dermatol Venereol. 2012;26(5):611–8.

79. Guevara IL, Pandya AG. Safety and efficacy of 4% hydroquinone combined with 10% glycolic acid, antioxidants, and sunscreen in the treatment of melasma. Int J Dermatol. 2003;42(12):966– 72.

80. Lim JT. Treatment of melasma using kojic acid in a gel containing hydroquinone and glycolic acid. Dermatol Surg. 1999;25(4):282–4.

81.) Lim JT, Tham SN. Glycolic acid peels in the treatment of melasma among Asian women. Dermatol Surg. 1997;23(3):177–9.

82. Hurley ME, Guevara IL, Gonzales RM, Pandya AG. Efficacy of glycolic acid peels in the treatment of melasma. Arch Dermatol. 2002;138:1578–82.

83. Ilknur T, Biçak MÜ, Demirtaşoğlu M, Özkan Ş. Glycolic acid peels versus amino fruit acid peels in the treatment of melasma. Dermatol Surg. 2010;36(4):490–5.

84. Kumari R, Thappa DM. Comparative study of trichloroacetic acid versus glycolic acid chemical peels in the treatment of melasma. Indian J Dermatol Venereol Leprol. 2010;76(4):447.

85. Sarkar R, Kaur C, Bhalla M, Kanwar AJ. The combination of glycolic acid peels with a topical regimen in the treatment of melasma in dark-skinned patients: a comparative study. Dermatol Surg. 2002;28(9):828–32.

86. Erbil H, Sezer E, Taştan B, Arca E, Kurumlu Z. Efficacy and safety of serial glycolic acid peels and a topical regimen in the treatment of recalcitrant melasma. J Dermatol. 2007;34(1):25–30.

87. Dayal S, Sahu P, Dua R. Combination of glycolic acid peel and topical 20% azelaic acid cream in melasma patients: efficacy and improvement in quality of life. J Cosmet Dermatol. 2017;16(1):35–42.

88. Sarkar R, Garg V, Bansal S, Sethi S, Gupta C. Comparative evaluation of efficacy and tolerability of glycolic acid, salicylic mandelic acid, and phytic acid combination peels in melasma. Dermatol Surg. 2016;42(3):384–91.

89. Wang CC, Hui CY, Sue YM, Wong WR, Hong HS. Intense pulsed light for the treatment of refractory melasma in Asian persons. Dermatol Surg. 2004;30(9):1196–200

90. Goldman MP, Gold MH, Palm MD, Colon LE, Preston N, Johnson LA, Gottschalk RW. Sequential treatment with triple combination cream and intense pulsed light is more efcacious than sequential treatment with an inactive (control) cream and intense pulsed light in patients with moderate to severe melasma. Dermatol Surg. 2011;37(2):224–33

91. Park KY, Kim DH, Kim HK, Li K, Seo SJ, Hong CK. A randomized, observer-blinded, comparison of combined 1064-nm Q-switched neodymium-doped yttrium–aluminum–garnet laser plus 30% glycolic acid peel vs. laser monotherapy to treat melasma. J Clin Exp Dermatol Res. 2011;36(8):864–70.

92. Lee DB, Suh HS, Choi YS. A comparative study of low-fuence 1,064 nm Q-Switched Nd: YAG laser with or without chemical peeling using Jessner's solution in melasma patients. J Cosmet Laser Ther. 2014;16(6):264–70.

93. Ustuner P, Balevi A, Ozdemir M. A split-face, investigator-blinded comparative study on the efficacy and safety of Q-switched Nd:YAG laser plus microneedling with vitamin C versus Q-switched Nd: YAG laser for the treatment of recalcitrant melasma. J Cosmet Laser Ther. 2017;19(7):383–90.

94. Kaminaka C, Furukawa F, Yamamoto Y. The clinical and histological effect of a low-fluence Q-Switched 1,064-nm neodymium:yttrium-aluminum-garnet laser for the treatment of melasma and solar lentigines in asians prospective, randomized, and split-face comparative study. Dermatol Surg. 2017;43(9):1120–33.

95. Jeong SY, Shin JB, Yeo UC, Kim WS, Kim IH. Low-fuence Q-switched neodymium-doped yttrium aluminum garnet laser for melasma with pre-or post-treatment triple combination cream. Dermatol Surg. 2010;36(6):909–18.

96. Wattanakrai P, Mornchan R, Eimpunth S. Low-fluence Q-switched neodymium-doped yttrium aluminum garnet (1,064 nm) laser for the treatment of facial melasma in Asians. Dermatol Surg. 2010;36(1):76–87.

97. Kar HK, Gupta L, Chauhan A. A comparative study on efcacy of high and low fuence Q-switched Nd:YAG laser and glycolic acid peel in melasma. Indian J Dermatol Venereol Leprol. 2012;78(2):165

98. 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):1106–8.

99. . Wind BS, Kroon MW, Meesters AA, Beek JF, van der Veen JW, Nieuweboer-Krobotová L, Bos JD, Wolkerstorfer A. Nonablative 1,550 nm fractional laser therapy versus triple topical therapy for the treatment of melasma: a randomized controlled split-face study. Lasers Surg Med. 2010;42(7):607–12.

100. Kroon MW, Wind BS, Beek JF, Van Der Veen JW, NieuweboerKrobotová L, Bos JD, Wolkerstorfer A. Nonablative 1550-nm fractional laser therapy versus triple topical therapy for the treatment of melasma: a randomized controlled pilot study. J Am Acad Dermatol. 2011;64(3):516–23.

101. Nouri K, Bowes L, Chartier T, Romagosa R, Spencer J. Combination treatment of melasma with pulsed CO2 laser followed by Q-switched alexandrite laser: a pilot study. Dermatol Surg. 1999;25(6):494–7.

102. Angsuwarangsee S, Polnikorn N. Combined ultrapulse CO2 laser and Q-switched alexandrite laser compared with Q-switched alexandrite laser alone for refractory melasma: split-face design. Dermatol Surg. 2003;29(1):59–64

103. Trelles MA, Velez M, Gold MH. The treatment of melasma with topical creams alone, CO2 fractional ablative resurfacing alone, or a combination of the two: a comparative study. J Drugs Dermatol. 2010;9(4):315–22.

104. Karn D, Kc S, Amatya A, Razouria EA, et al. Oral tranexamic acid for the treatment of melasma. Kathmandu Univ Med J. 2014;10:40–3.

105. Wu S, Shi H, Wu H, Yan S, et al. Treatment of melasma with oral administration of tranexamic acid. Aesthet Plast Surg. 2012;36:964–70.

106. Li Y, Sun Q, He Z, Fu L, et al. Treatment of melasma with oral administration of compound tranexamic acid: a preliminary clinical trial. J Eur Acad Dermatol Venereol. 2014;28:393–4.

107. Lajevardi V, Ghayoumi A, Abedini R, Hosseini H, Goodarzi A, Akbari Z, Hedayat K. Comparison of the therapeutic efcacy and safety of combined oral tranexamic acid and topical hydroquinone 4% treatment vs. topical hydroquinone 4% alone in melasma: a parallel-group, assessor- and analyst-blinded, randomized controlled trial with a short-term follow-up. J Cosmet Dermatol. 2017;16(2):235–42.

108. Padhi T, Pradhan S. Oral tranexamic acid with fuocinolonebased triple combination cream versus fuocinolone-based triple combination cream alone in melasma: an open labeled randomized comparative trial. Indian J Dermatol. 2015;60:520.

109. Tan AW, Sen P, Chua SH, Goh BK. Oral tranexamic acid lightens refractory melasma. Australas J Dermatol. 2017;58:e105–8.

110. Sharma R, Mahajan VK, Mehta KS, Chauhan PS, Rawat R, Shiny TN. Therapeutic efcacy and safety of oral tranexamic acid and that of tranexamic acid local infltration with microinjections in patients with melasma: a comparative study. Clin Exp Dermatol. 2017;42(7):728–34

111. Nagaraju D, Bhattacharjee R, Vinay K, Saikia UN, Parsad D, Kumaran MS. Efcacy of oral tranexamic acid in refractory melasma: a clinico-immuno-histopathological study. Dermatol Ther. 2018;31(5):e12704.

112. Na JI, Choi SY, Yang SH, Choi HR, Kang HY, Park KC. Efect of tranexamic acid on melasma: a clinical trial with histological evaluation. J Eur Acad Dermatol Venereol. 2013;27(8):1035–9.

113. Kim HJ, Moon SH, Cho SH, Lee JD, Kim HS. Efcacy and safety of tranexamic acid in melasma: a meta-analysis and systematic review. Acta Derm Venereol. 2017;97(7):776–81.

114. Martin LK, Caperton C, Woolery-Lloyd H, et al. A randomized double-blind placebo-controlled study evaluating the efectiveness and tolerability of oral Polypodium leucotomos in patients with melasma. American Academy of Dermatology Annual Meeting: 16–20 March 2012; San Diego.

115. Ahmed AM, López I, Perese F, et al. A randomized, doubleblinded, placebo-controlled trial of oral Polypodium leucotomos extract as an adjunct to sunscreen in the treatment of melasma. JAMA Dermatol. 2013;149(8):981–3.

116. Goh CL, Chuah SY, Tien S, Thng G, Vitale MA, Delgado-Rubin A. Double-blind, placebo-controlled trial to evaluate the efectiveness of Polypodium leucotomos extract in the treatment of melasma in asian skin: a pilot study. J Clin Aesthet Dermatol. 2018;11(3):14–9.

117. Handog EB, Galang DA, de Leon-Godinez MA, Chan GP. A randomized, double-blind, placebo-controlled trial of oral procyanidin with vitamins A, C, E for melasma among Filipino women. Int J Dermatol. 2009;48(8):896–901.