Pharmacological Insights into Melasma: Understanding and Evaluating Treatment Modalities

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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 and Dr. Castellani laid the groundwork for classifying skin pigmentation disorders, coining the term “chloasma” to denote skin discolorations linked to sun exposure. 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. Concurrently, Dr. Gupta added to the vocabulary the term “melanoderma” in 1929, contributing significantly to the understanding of melanin-related disorders.

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. Subsequent decades witnessed explorations into hormonal influences, extracutaneous manifestations, and genetic predispositions, as well as in 1980s different melasma types and associations with thyroid dysfunction through histological studies were discovered. 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.

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. 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 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%. In Southeast Asia, prevalence rates were observed at 40%.
females and 20% in males. 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. 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

**Underlying Ultraviolet 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). These factors promote melanocyte proliferation and stimulate melanin synthesis by activating tyrosinase activity and tyrosinase-related protein 1 (TRP-1). 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.

UV-induced dermal inflammation and fibroblast activation result in increased expression of stem cell factor (SCF) and c-kit, influencing melanogenesis in melasma lesions. 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. Beyond UV radiation, visible light, especially in skin types IV–VI, triggers hyperpigmentation. 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. 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.
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 melasma20. The presence of pendulous melanocytes associated with basement membrane abnormalities has been identified as a distinctive feature of melasma21.

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, respectively22.

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 relapse23-25.

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 pregnancy26,27.

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 use28. Melasma occurrence has been reported in 11.3–46% of individuals using oral contraceptives across various countries29.

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 progestogens 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 authors30-32. 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 treatment33-35. 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-estrogen receptor interaction in the pathogenesis of melasma36

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Effect</th>
</tr>
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<tbody>
<tr>
<td>Direct induction of protein synthesis</td>
<td>Upregulation of tyrosinase, TRP-1, TRP-2, MITF</td>
</tr>
<tr>
<td>Activation of the cAMP-PKA pathway</td>
<td>Upregulation of tyrosinase</td>
</tr>
<tr>
<td>Overexpression of PDZK1 gene</td>
<td>Enhanced tyrosinase expression and melanosome transfer</td>
</tr>
<tr>
<td>Increased expression of MC1R in melanocytes</td>
<td>Upregulation of tyrosinase via cAMP-PKA pathway stimulation</td>
</tr>
</tbody>
</table>

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 development37,38. 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 vasculature39.
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. Recent research, including colorimetric analysis, immunohistochemical studies, and laser confocal microscopy, indicates that melasma lesions are more vascularized than perilesional skin. These vascular changes, often overlooked by the naked eye, become apparent through dermoscopy and advanced instruments like chromameters and spectrophotometers.

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 (bFGF), 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. 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.

**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. Studies by Ennes et al. and Vázquez et al. demonstrated significant improvement when HQ was used in combination with sunscreen. 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.

Topical vitamin C, known for its ability to chelate copper ions involved in melanogenesis, did not consistently show significant improvement in melasma.

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.

**Table 2: Melasma treatments, mechanisms of action, and adverse effects**

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

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. 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.

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. Leenutaphong et al. failed to show significant improvement using a lower concentration of 0.05% tretinoin cream twice daily compared to vehicle+sunscreen.

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.

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.

Visible Light Protection- Visible light, akin to UV radiation, can induce prolonged hyperpigmentation by generating reactive oxygen species. 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.

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.

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. Ebrahimii 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. 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.

Topical TXA has been investigated as an adjuvant treatment. Laithaworn 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. Xu et al. demonstrated successful pigmentation improvement with microneedling combined with 5% topical TXA after 12 weeks.

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

Combined Tropical Agents- The triple combination cream (TCC), comprising hydroquinone (HQ), a retinoid, and a fluorinated corticosteroid, is a proven and safe melasma treatment. 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. 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.

While TCC remains a prominent option, alternative combination therapies, such as solutions containing glycolic acid (GA) and kojic acid (KA), have been explored. 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).

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.

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. 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. However, 10% of subjects in the GA peel group experienced PIH.

Available online at www.globalresearchonline.net
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 PIH⁹⁰. 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 group⁵⁷.

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 SMA⁹⁸.

### 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.⁹⁵–⁹⁶. Combining QS-Nd:YAG with other modalities, such as microneedling or chemical peels, has demonstrated improved outcomes⁹³,⁹⁷.

**Pulsed-Dye Laser (PDL) treatments**, targeting the vascular component of melasma, have been explored with positive outcomes reported by Passeron and colleagues⁹⁸.

**Fractional Laser Therapy**, particularly monotherapy, has shown limited efficacy, especially in individuals with darker skin tones, due to the associated risk of hyperpigmentation and recurrence⁹⁹,¹⁰⁰. Combining fractional laser with other modalities, such as CO2 laser or QS alexandrite laser, has demonstrated improved results¹⁰¹,¹⁰². Notably, TCC + CO2 laser has shown higher efficacy compared to either treatment alone¹⁰³.

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 combinations¹⁰⁴–¹¹⁰. Recent meta-analyses have favored oral TXA over intradermal injections or topical creams, with notable histological improvements observed¹¹¹–¹¹³.

Polypodium leucotomos extract (PLE), an antioxidant, has not shown significant benefits in controlled, randomized trials¹¹⁴–¹¹⁷.

Other systemic agents, such as procyanidin, β-carotene, vitamin C, vitamin E capsules, and melatonin, have demonstrated mild to moderate improvements in melasma¹⁰⁴–¹⁰⁶.

### 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.

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