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Review Paper

Melasma Management: A Comprehensive Review of Pathogenesis, Conventional Limitations, and the Synergistic Potential of Polyherbal Bioactives

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ABSTRACT

Melasma is an acquired, symmetrical hypermelanosis of the face presenting as light brown to dark macules, with a multifactorial pathogenesis involving UV radiation, hormonal fluctuations, and genetic susceptibility. Conventional pharmacological therapies such as hydroquinone, tretinoin, and topical corticosteroids are frequently utilized but are often associated with adverse effects during long-term use, including irritation, redness, long-term sensitivity, and exogenous ochronosis. Consequently, interest has increased in plant-based therapeutic alternatives that offer improved safety profiles. Glycyrrhiza glabra, commonly known as liquorice, alongside synergistic botanical extracts such as Phyllanthus emblica (Amla), Morus alba (White mulberry), and Camellia sinensis (Green tea), are rich in bioactive phytochemicals, including glycyrrhizin, glabridin, vitamin C, and various flavonoids. These herbal bioactives demonstrate potential anti-melanogenic activity through the direct inhibition of tyrosinase, reduction of oxidative stress, and notable anti-inflammatory effects. This review summarizes the pathophysiology of melasma and the limitations of current therapies and pharmacological properties of polyherbals. The study highlights the therapeutic promise of these polyherbal formulations as a multi-mechanistic, natural agent for melasma management and emphasizes the need for further clinical studies and formulation optimization.

INTRODUCTION

Melasma, also known as chloasma, is a persistent genetic skin condition caused by an excess of

melanin in areas exposed to UV light. It commonly occurs on the face, with the neck and forearms being less affected. The condition presents as

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irregular patches and macules with varying shades from light to dark brown, usually appearing symmetrically [1,2]. It is classified into epidermal, dermal, or mixed types based on the distribution of pigment observed through Wood's lamp examination. It is the most common pigmentary disorder among Asians, affecting women more often, particularly during their reproductive years. Although, about 10 % of cases also occur in men. A study conducted in India by Sarkar et al. found that 20.5 % of male patients had melasma, showing clinical and histopathological similarities to melasma in women [3]. The prevalence of melasma varies across the general population depending on factors such as skin type, sun exposure, and ethnicity. Epidemiological studies have shown a higher incidence in individuals with more pigmented phenotypes, particularly those in Fitzpatrick skin types III–VI. Research indicates increased prevalence among populations from the Middle East, East Asia (including Japanese,

Korean, and Chinese), India, Pakistan, Africa, and the Mediterranean region. In Southeast Asian populations, the reported prevalence is as high as 40 % [4]. Melanin, a complex polymer derived from the amino acid tyrosine, is responsible for the pigmentation of the skin, hair, and eyes in mammals [5]. Through melanogenesis, melanin is produced by melanocytes, which are differentiated in epidermis [6,7]. Melanocytes transfer melanin pigments to surrounding keratinocytes in the skin, resulting in its pigmented tone [8].

Pathogenesis:

Melasma is driven by the hyperactivation of melanocytes, primarily triggered by UV radiation and hormonal shifts that induce oxidative stress and chronic inflammation. This results in the overproduction and uneven deposition of melanin within the epidermal and dermal layers, leading to characteristic facial hyperpigmentation.

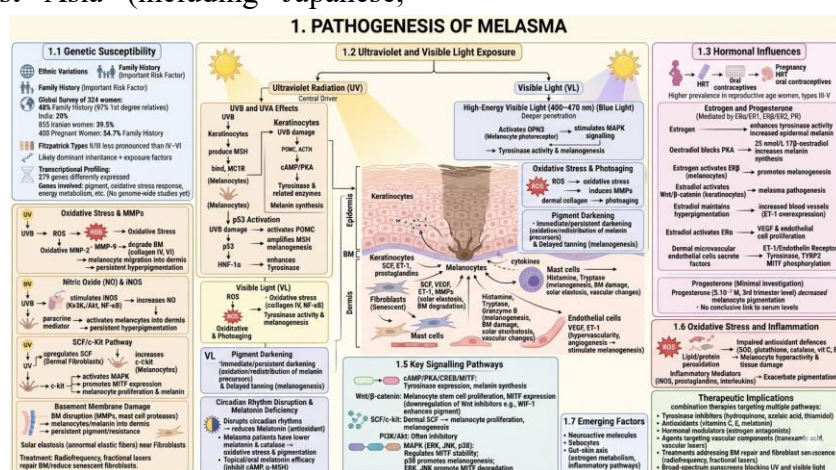


Fig: Pathogenesis of Melasma

Current Treatments:

Treatments for melasma include topical, oral, procedural, and combination treatments. These are

aimed at various aspects of the pathogenesis of melasma including photodamage, inflammation, vascularity, and pigmentation (Table 1). [9]

Table 1 Melasma treatment, mechanism of action and adverse effects

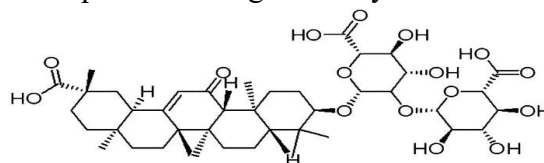
Modality	Treatment	Mechanism of action	Adverse effects (AE)
Topical	Iron oxide	Block visible and ultraviolet light	Irritation
	Hydroquinone (HQ), azelaic acid, ascorbic acid, kojic acid	Tyrosinase inhibitor	Irritation, exogenous ochronosis (with HQ)
	Tretinoin	Increased keratinocyte turnover	Irritation, 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	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
	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
	Radio-frequency	Cellular biostimulation, transdermal drug delivery	Burn

While modern pharmaceuticals are often limited by severe side effects, herbal bioactives provide a promising alternative characterized by higher patient compliance and a significantly reduced toxicological profile

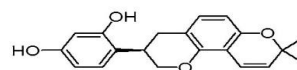
Glycyrrhiza glabra:

Glycyrrhiza glabra extracts play a large role on the skin mainly as a result of its antioxidant activity, especially its strong antioxidant glycyrrhizin, triterpene saponins, and flavonoids. The main attributes are skin whitening, skin depigmentation, lightening of skin, anti-aging, antierythemic, emollient, anti-acne, and photoprotective effects. Gabridin is present in the hydrophobic part of the root extract of Glycyrrhiza and it can reduce

tyrosinase activity in culture on melanocytes and inhibit UVB induction [10]. Two specific studies found that the plant's effectiveness was higher than a placebo but lower than a hydroquinone 4% cream [11,12,13]. Another significant study revealed that when topical treatment of licorice is combined with 5% ascorbic acid, the recovery rate of patients significantly increases [14]



Glycyrrhizic acid



Glabridin

The extract of licorice inhibits the tyrosinase activity by inhibiting oxidation of L-DOPA to an IC₅₀ value of 53 µg/mL. Glabridin content has highest inhibition activity on tyrosinase. The highest inhibitory activity was reported on the first oxidation of tyrosine with IC₅₀ value of 0.9 µg/mL [15].

Phyllanthus emblica:

Phyllanthus emblica is recognized for its nutritional content. A wide range of chemicals are present, including flavonol, glycosides, carbohydrates, mucic acids, amino acids, sesquiterpenoids, alkaloids, flavone glycosides, phenolic glycosides, phenolic acids, and tannins. Phyllanthus emblica fruit juice contains the highest amount of vitamin C and vitamin E as compared to other fruit juice. The extract could inhibit tyrosinase, by inhibiting microphthalmia-associated transcription factor (MITF) and Trp-1 gene expression, but under low concentration of the extract treatment would induce Trp-2 gene expression.

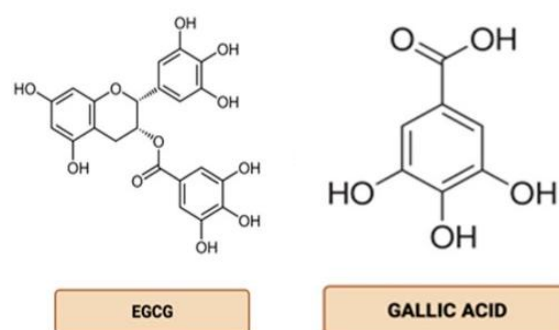
A trial study also studied the effect of this plant in combination with Glycyrrhiza glabra on blurs caused by melasma disease. 50 patients participated in this study, with 23 in the hydroquinone 2% group and 27 in the 7% Phyllanthus emblica and Glycyrrhiza glabra intervention group. The overall results of this study showed that the combination of this plant with Glycyrrhiza glabra compared to 2% hydroquinone was not significantly different in the treatment of melasma patients [16]

Ethanol extract has higher antioxidant and anti-melanogenesis effect [17,18].

Camellia sinensis:

It is commonly known as green tea. It belongs to the Theaceae family. Green tea is made of steamed, dried, rolling leaves to inactivate endogenous polyphenol oxidase [PPO]. The

activities of Camellia sinensis, melanin synthesis, and expression of melanogenic enzyme at the protein and mRNA levels in melan-A cells were evaluated by researchers [19]. Green tea contains active ingredients like -[-]-epigallocatechin-3-gallate[EGCG], [-]-epigallocatechin[EGC], [-]-catechin[C], [-]-gallocatechingallate [GCG], and [-]-epicatechingallate [ECG]. EGCG inhibit melanin production in mouse melanoma cells. All active ingredients do not show potent inhibitory activity but EGCG and gallic acid show higher tyrosinase inhibitory activity by cell proliferation. [20].



Morus alba:

Flavonoids present in Morus alba extract shows antioxidant and tyrosinase-inhibiting properties. Tyrosinase inhibiting activity of mulberry extract is comparable with HQ and kojic acid [21]. Oxyresveratrol and Mulberroside-A derived from M. alba root which strongly inhibit the monophenolase production and inhibit mushroom tyrosinase activity in melanin synthesis [22]. They have properties of fever reduction, liver protection, and blood pressure lowering. The polyphenols in the leaves have properties for depigmentation [10]. Mulberroside F have 51.6% inhibition at 1 µg/mL concentration on 0.29 µg/mL IC₅₀ value [23]

DISCUSSION

The management of melasma remains a significant challenge due to its multifactorial pathogenesis, which involves a complex interplay of genetic

susceptibility, UV radiation, and hormonal fluctuations.

While conventional pharmacological treatments like **hydroquinone, tretinoin, and corticosteroids** are standard, their long-term utility is frequently hampered by adverse effects such as **exogenous ochronosis, epidermal atrophy, and permanent skin sensitivity.** This review highlights a shifting paradigm toward **polyherbal alternatives** that target multiple pathways of melanogenesis with improved safety profiles. The botanical extracts discussed—*Glycyrrhiza glabra*, *Phyllanthus emblica*, *Morus alba*, and *Camellia sinensis*—exhibit potent anti-melanogenic activity through several key mechanisms:

Tyrosinase Inhibition: **Glabridin** from licorice and **Mulberroside-A** from mulberry serve as powerful inhibitors of tyrosinase, the rate-limiting enzyme in melanin synthesis. Notably, the inhibitory activity of mulberry extract has been found comparable to conventional agents like hydroquinone and kojic acid.

Antioxidant Support: Melasma is driven by oxidative stress; therefore, the high **Vitamin C** content in Amla and the **polyphenols (EGCG)** in Green tea provide critical defense by scavenging reactive oxygen species (ROS).

Synergistic Efficacy: Clinical observations suggest that these herbals work best in combination. For instance, combining licorice with **5% ascorbic acid** significantly increases patient recovery rates. Furthermore, a polyherbal intervention using Amla and Licorice showed efficacy comparable to **2% hydroquinone**, suggesting these natural agents can match standard treatments without the same risk of toxicity

CONCLUSION

Melasma is a chronic, relapsing hyperpigmentary disorder characterized by a complex and **multifactorial pathogenesis** involving genetic predisposition, ultraviolet radiation, hormonal

influences, oxidative stress, and inflammatory mediators, which collectively **complicate its therapeutic management.**

Conventional therapeutic agents, including hydroquinone, retinoids, and corticosteroids, remain the cornerstone of treatment; however, their prolonged use is frequently associated with adverse effects and a high rate of recurrence, thereby limiting their long-term clinical applicability. Considering the **multifactorial mechanistics** underlying melasma, a multi-targeted therapeutic approach is imperative. Polyherbal formulations comprising *Glycyrrhiza glabra*, *Phyllanthus emblica*, *Morus alba*, and *Camellia sinensis* exhibit significant potential by modulating key pathways involved in melanogenesis through **tyrosinase inhibition, antioxidant activity, and anti-inflammatory effects.**

Thus, combined herbal formulations represent a rational and promising strategy for holistic melasma management. Nevertheless, further well-designed clinical studies and standardization of formulations are essential to substantiate their efficacy, safety, and long-term therapeutic outcomes.

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