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MELASMA PATHOGENESIS, THERAPEUTIC LIMITATIONS, AND THE EMERGING POTENTIAL OF METFORMIN AND PROPOLIS AS A MULTI-TARGET TOPICAL STRATEGY: A NARRATIVE REVIEW

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ABSTRACT

Melasma is a chronic, relapsing disorder of hyperpigmentation that predominantly affects women of reproductive age, particularly those with darker skin phototypes in regions of high ultraviolet (UV) exposure. Despite its benign nature, melasma exerts a profound psychosocial burden, significantly impairing quality of life. Current therapeutic modalities—including topical hydroquinone, triple combination creams, chemical peels, and laser therapies—remain inadequate due to limited efficacy, high recurrence rates, safety concerns with long-term use, and failure to address the multifactorial pathogenesis of the disease. This narrative review comprehensively examines the pathophysiology of melasma, the molecular mechanisms underpinning melanogenesis, current treatment approaches and their limitations, and the scientific basis for a novel multi-target therapeutic strategy combining metformin hydrochloride and propolis extract. Metformin inhibits upstream melanogenesis signaling through AMPK activation, cAMP reduction, and MITF downregulation, while propolis—a lipophilic resinous bee product rich in flavonoids and polyphenols—exerts direct tyrosinase inhibition alongside antioxidant and anti-inflammatory activities. Together, these agents offer complementary, multi-level inhibition of the melanogenic pathway. The emulgel delivery platform is discussed as a rational co-delivery system capable of simultaneously accommodating both the hydrophilic metformin and the lipophilic propolis extract. This review highlights the scientific and clinical rationale for this innovative combination and identifies key directions for future preclinical and clinical development.

KEYWORDS: Melasma; Melanogenesis; Metformin; Propolis; Emulgel; Topical drug delivery; Hyperpigmentation; Tyrosinase inhibition; AMPK; Drug repurposing.

1. INTRODUCTION

Melasma is a common, acquired pigmentary disorder characterized by symmetrical hyperpigmented macules and patches on sun-exposed facial skin, representing one of the most therapeutically challenging conditions in dermatology.[1,2] Although not life-threatening, the condition disproportionately affects women of reproductive age across diverse ethnic populations, particularly those with Fitzpatrick skin phototypes III–VI, including individuals of Hispanic/Latino, Asian, Middle Eastern, and African descent.[1,2,3] The psychosocial consequences are substantial: validated instruments such as the Melasma Quality of Life Scale (MELASQoL) consistently reveal emotional distress, social avoidance, and reduced occupational productivity comparable to more severe dermatological conditions.[4]

The pathogenesis of melasma is multifactorial, involving the complex interplay of UV radiation, hormonal dysregulation, genetic predisposition, oxidative stress, and inflammatory mediators, all converging to produce melanocyte hyperactivation and excessive melanin deposition.[1,2,5] Despite decades of research, no currently available monotherapy addresses this multifactorial pathogenesis comprehensively. The most widely used depigmenting agent, hydroquinone, carries risks of exogenous ochronosis and has been restricted or banned in several countries, while combination regimens involving corticosteroids risk skin atrophy with prolonged use.[6,7] High recurrence rates of 50–70% upon treatment discontinuation further underscore the unmet clinical need for novel, safe, multi-target therapeutic strategies.[1,6]

Drug repurposing has emerged as a promising paradigm in dermatology, and metformin hydrochloride—the cornerstone antidiabetic biguanide—has attracted growing attention for its pleiotropic anti-melanogenic properties.[8,9,10] Concurrently, propolis, a natural resinous substance produced by honeybees, has been demonstrated to possess potent antioxidant, anti-inflammatory, and tyrosinase-inhibitory activities relevant to hyperpigmentation treatment.[11,12,13] The convergence of these two agents—targeting complementary molecular nodes in the melanogenesis cascade—presents an innovative multi-target approach to melasma pharmacotherapy.

This narrative review synthesizes the current evidence on melasma pathophysiology, existing treatment modalities and their limitations, the molecular basis and evidence for metformin's and propolis's anti-melanogenic activities, and the rationale for their co-formulation in an emulgel topical delivery platform. The review aims to provide a comprehensive scientific foundation for developing and evaluating such a novel therapeutic combination, while identifying critical gaps requiring further investigation.

2. Skin Biology and Melanogenesis

2.1 Skin Structure and the Epidermal Melanocyte Unit

The skin is the largest organ of the human body, constituting approximately 15–16% of total body weight with a surface area of 1.5 to 2.0 m² in adults.[14,15] It is a complex, multilayered organ comprising three principal strata: the outermost epidermis, which serves as the primary barrier against environmental insults; the underlying dermis, which provides structural support through its collagen and elastic fiber network; and the deepest hypodermis, which functions in thermoinsulation and energy storage.[14,15] Beyond its structural role, the skin performs critical physiological functions including thermoregulation, immunological surveillance, and protection against UV radiation, microbial invasion, and chemical insults.[14]

Of particular relevance to pigmentary disorders, the epidermis harbors melanocytes within its basal layer—highly specialized cells responsible for melanin synthesis and the primary cellular targets in the pathogenesis and treatment of melasma.[16] Melanocytes interact intimately with surrounding keratinocytes through cytoplasmic dendrites, facilitating the transfer of melanin-containing melanosomes that ultimately determine skin color.[16,17] Understanding this cellular unit is fundamental to rational drug design targeting hyperpigmentation.

2.2 Melanogenesis: The Molecular Pathway

Melanogenesis is the complex biochemical process by which melanocytes synthesize melanin, the primary determinant of skin, hair, and eye color.[16,17] This process occurs within specialized organelles called melanosomes and is regulated by a cascade of enzymatic reactions, signaling pathways, and transcription factors.[16,17,18]

The melanogenic pathway is initiated by the binding of alpha-melanocyte-stimulating hormone (α-MSH) to the melanocortin 1 receptor (MC1R) on the melanocyte surface, which activates adenylyl cyclase and increases intracellular cyclic adenosine monophosphate (cAMP) levels.[16,17,18] Elevated cAMP activates protein kinase A (PKA), which phosphorylates the cAMP response element-binding protein (CREB), leading to the transcriptional upregulation of microphthalmia-associated transcription factor (MITF)—the master regulator of melanocyte development and melanogenic gene expression.[17,18] MITF subsequently induces the expression of three critical melanogenic enzymes: tyrosinase, tyrosinase-related protein 1 (TYRP1), and dopachrome tautomerase (DCT/TYRP2).[16,17,18]

Tyrosinase is the rate-limiting enzyme in melanin biosynthesis, catalyzing the hydroxylation of L-tyrosine to L-DOPA and the subsequent oxidation of L-DOPA to dopaquinone.[16,17] From dopaquinone, the pathway diverges into two branches: eumelanogenesis (producing brown-black eumelanin) and pheomelanogenesis (producing yellow-red pheomelanin in the presence of cysteine or glutathione).[16,17] The ratio of eumelanin to pheomelanin varies among individuals and is a major determinant of constitutive skin color.[5] In melasma, the dysregulation of this pathway—particularly the overactivation of the cAMP/PKA/CREB/MITF/tyrosinase signaling cascade—results in excessive melanin production and deposition.[16,17,18] Table 1 summarizes this cascade and identifies key therapeutic intervention points.[9,10,11,16,17,18,19]

Table 1: The Melanogenesis Signaling Cascade and Therapeutic Intervention Points.

Step	Molecular Event	Key Molecules	Therapeutic Target
1	UV/hormonal stimulus	UV radiation, α-MSH, estrogen	Photoprotection; hormonal modulation
2	Receptor activation	MC1R, estrogen receptors	Receptor antagonism
3	Second messenger generation	cAMP via adenylyl cyclase	Metformin: Reduces cAMP via AMPK activation
4	Kinase activation	PKA activation; CREB phosphorylation	Metformin: Suppresses PKA/CREB signaling
5	Transcription factor activation	MITF upregulation	Metformin: Downregulates MITF expression
6	Enzyme expression	Tyrosinase, TYRP1, DCT	Gene-level regulation
7	Enzymatic catalysis	Tyrosinase: L-tyrosine → L-DOPA → dopaquinone	Propolis flavonoids: Direct tyrosinase inhibition
8	Melanin synthesis	Eumelanin/pheomelanin production	Antioxidants (shift eumelanin/pheomelanin ratio)
9	Melanosome transfer	Transport to keratinocytes	Metformin: Inhibits melanosome transfer
10	Amplification signals	ROS, TNF-α, IL-1, PGE2	Both agents: Antioxidant and anti-inflammatory effects

3. Melasma: Epidemiology, Pathogenesis, and Clinical Features

3.1 Definition and Clinical Presentation

Melasma (derived from the Greek "melas," meaning black) is a common, acquired, chronic disorder of hyperpigmentation characterized by the development of symmetrical, irregular, light- to dark-brown macules and patches predominantly on sun-exposed areas of the face.[1,2,5] It is also historically referred to as "chloasma" or the "mask of pregnancy" due to its strong association with hormonal changes during gestation.[2] The condition results from hyperfunction of epidermal melanocytes—an increased activity of melanocytes rather than an increase in their number—leading to excessive melanin production and deposition in the epidermis and, in some cases, the dermis.[2,16] The pathogenesis is multifactorial, involving a complex interplay of genetic predisposition, UV radiation exposure, hormonal influences, and various environmental and biological factors.[1,2,5]

Clinically, melasma presents as symmetrical, well-demarcated to slightly irregular, hyperpigmented macules and patches that coalesce over time.[1,2] The lesions are classified into three distribution patterns: the centrofacial pattern (the most common, affecting 50–80% of cases, involving the forehead, cheeks, nose, upper lip, and chin), the malar pattern (limited to the cheeks and nose), and the mandibular pattern (the least common, affecting the ramus of the mandible).[1,2] Less frequently, melasma may occur on extrafacial sun-exposed sites including the forearms, neck, and upper chest.[18] The depth of melanin deposition—epidermal, dermal, or mixed—influences lesion color and response to treatment, with dermal melasma being particularly resistant to topical therapies.[2,6]

3.2 Epidemiology and Risk Factors

Melasma is one of the most prevalent pigmentary disorders worldwide, with a global prevalence estimated to range from 1% in the general population to as high as 50% in high-risk populations.[1,2,3] The condition demonstrates a marked predilection for women of reproductive age (20–40 years), with females accounting for approximately 90% of all cases, although male melasma is increasingly recognized and may constitute up to 10–25% of cases in certain populations.[1,2,3] The prevalence varies significantly across ethnic groups and geographic regions, with the highest rates observed in populations with darker skin phototypes (Fitzpatrick types III–VI), including individuals of Hispanic/Latino, Asian, Middle Eastern, African, and Indian descent.[1,2,3]

Table 2: Global Epidemiology of Melasma.

Region/Population	Prevalence	Key Demographics
General global population	1–50%	Varies by ethnicity and sun exposure
United States (general)	0.18%	Female-to-male ratio 19:1; peak age 41–55 years
US Hispanic population	2.5–8.8%	Higher rates in Latinos
Brazil (women)	15–35%	Predominantly Fitzpatrick III–V
Iran	16–39.5%	High UV exposure regions
India (paddy field workers)	41–46%	Occupational sun exposure
Saudi Arabia	2.9%	Middle Eastern populations
Morocco	Up to 37%	North African populations
Pregnant women (worldwide)	15–50%	Hormone-related onset

Ultraviolet radiation is the single most important triggering and exacerbating factor, stimulating melanocyte activity through direct DNA damage, generation of reactive oxygen species (ROS), and release of melanogenic cytokines from keratinocytes.[1,5] Hormonal influences—particularly estrogen and progesterone—play significant roles, as evidenced by the high prevalence during pregnancy and with oral contraceptive use; estrogen receptors on melanocytes directly stimulate melanogenesis.[1,2,20] Genetic predisposition is reported in 40–60% of patients, with associations in specific genetic polymorphisms and concordance observed in identical twins.[1,2] Recent evidence also demonstrates that visible light (400–700 nm), particularly blue light, can induce sustained pigmentation in darker skin types.[18] Additional contributing factors include medications such as phenytoin and phototoxic agents, thyroid autoimmunity, and psychological stress acting via neuroendocrine mechanisms.[1,2]

3.3 Differential Diagnosis

Melasma must be differentiated from other common causes of acquired facial hyperpigmentation, as accurate diagnosis is essential for appropriate therapeutic selection and prognosis.[1,2,6] Key differential diagnoses include post-inflammatory hyperpigmentation (PIH), solar lentigines, and ephelides (freckles), all of which involve increased melanin deposition but differ in etiology, distribution pattern, clinical course, and response to treatment.[2,6,7]

Post-inflammatory hyperpigmentation occurs secondary to cutaneous inflammation or injury and is localized to areas of prior inflammation, lacking the characteristic centrofacial distribution of melasma.[2,6] Solar lentigines are discrete, well-circumscribed hyperpigmented macules resulting from chronic UV exposure, most commonly observed in older individuals with fair skin.[6,7] Ephelides are small, genetically determined pigmented macules that darken with sun exposure and fade during winter months, distinguishing them from the more persistent pigmentation of melasma. [2,6,7] A structured comparison of these conditions is presented in Table 3.

Table 3: Clinical Distinction Between Melasma and Other Hyperpigmented Disorders.

Feature	Melasma	Post-Inflammatory Hyperpigmentation	Solar Lentigines	Ephelides
Pattern	Symmetrical, bilateral	Localized to prior inflammation	Discrete, well-circumscribed macules	Small, scattered macules
Primary Trigger	Hormonal influences + UV	Cutaneous inflammation or injury	Chronic UV exposure	Genetic predisposition + UV
Typical Location	Cheeks, forehead, upper lip (centrofacial)	Site of preceding inflammation	Face, hands, sun-exposed areas	Face and shoulders
Seasonal Variation	May partially lighten in winter	Variable	Persistent	Darken in summer, fade in winter
Response to Topical Therapy	Gradual improvement	Often responds more rapidly	Limited response	Usually not treated
Most Affected Skin Types	Fitzpatrick III–VI	All skin types	Fitzpatrick I–III	Fitzpatrick I–II

The diagnosis of melasma is primarily clinical, based on characteristic symmetrical hyperpigmented macules and patches on sun-exposed facial areas, supported by a detailed history focusing on hormonal influences, sun exposure, pregnancy, and medication use.[1,2] Adjunctive diagnostic tools include Wood's lamp examination (enhancing contrast between epidermal and dermal melanin deposition), dermoscopy (revealing a reticular or pseudo-network pigment pattern), and, rarely, skin biopsy for diagnostically uncertain or treatment-resistant cases.[2,6]

3.4 Psychosocial Impact and Quality of Life

Despite being a benign condition with no systemic health consequences, melasma exerts a profound negative impact on psychological well-being and quality of life.[1,2,4] Studies utilizing validated instruments—the Dermatology Life Quality Index (DLQI) and the Melasma Quality of Life Scale (MELASQoL)—consistently demonstrate significant impairment of social functioning, emotional health, and daily activities. [4] Balkrishnan et al. reported that the emotional burden of melasma is comparable to more severe dermatological conditions, with patients reporting avoidance of social situations, difficulty in interpersonal relationships, and reduced occupational productivity.[4] This burden is particularly pronounced in populations where facial appearance carries significant cultural importance, including the Middle East, South Asia, and Latin America.[1,2,4]

4. Current Treatment Approaches and Their Limitations

The management of melasma remains one of the most challenging areas in dermatology, as no single treatment modality provides a consistently effective, long-lasting solution.[1,2,3] Current therapeutic strategies aim primarily to reduce melanin production, promote melanin degradation, and inhibit melanosome transfer, with broad-spectrum photoprotection as the cornerstone of all treatment regimens.[1,6]

Topical depigmenting agents—hydroquinone (2–4%), azelaic acid, kojic acid, arbutin, vitamin C, and niacinamide—constitute first-line therapy, though each carries specific limitations including irritation, contact sensitization, instability, or modest efficacy as monotherapy.[6,7] The triple combination cream (Kligman's formula combining hydroquinone, tretinoin, and a corticosteroid) is considered the gold standard but is unsuitable for long-term use due to the risk of skin atrophy and telangiectasia from the steroid component.[6,7] Procedural interventions—chemical peels and laser therapies—carry the risk of post-inflammatory hyperpigmentation, particularly in darker skin types, while oral tranexamic acid presents systemic side effects including thromboembolic risk.[6] Broad-spectrum sunscreen is essential but insufficient as monotherapy.[1,6]

These limitations are compounded by high recurrence rates (50–70% of patients relapse upon treatment discontinuation), safety concerns with long-term hydroquinone use including exogenous ochronosis and regulatory bans in several countries, limited efficacy of most topical agents against dermal melasma, and the absence of agents that address the multifactorial pathogenesis of the disease.[1,2,6,7] These collective shortcomings underscore the pressing need for novel therapeutic approaches combining multi-target mechanisms with an acceptable safety profile for long-term use.

5. Topical Drug Delivery: Principles and The Emulgel Application

5.1 Principles of Percutaneous Drug Delivery

Topical drug delivery involves the application of drug-containing formulations to the skin surface for local or systemic therapeutic effects.[21,22] For dermatological conditions such as melasma, the primary goal is to achieve local drug delivery to the epidermis and dermis while minimizing systemic absorption.[21] The stratum corneum, with its "brick and mortar" architecture of corneocytes embedded in a lipid matrix, represents the principal barrier to percutaneous drug penetration.[21,22,23] Drug molecules traverse this barrier through three potential pathways: the intercellular route (through the lipid matrix between corneocytes), the transcellular route (through corneocytes and intervening lipid layers), and the appendageal route (through hair follicles and sweat glands).[22,23] The physicochemical properties of the drug—including molecular weight, lipophilicity (log P), degree of ionization, and solubility—critically determine the rate and extent of percutaneous absorption.[21,22,23]

5.2 Semisolid Dosage Forms and the Emulgel Concept

Semisolid dosage forms—ointments, creams, gels, pastes, and emulgels—constitute the most widely used vehicles for topical drug delivery.[24,25,26] Vehicle selection is not merely a pharmaceutical convenience; it significantly influences drug stability, release kinetics, skin permeation, and ultimately, therapeutic efficacy.[24,25,26]

Emulgels represent an innovative class of topical dosage forms that combine the properties of emulsions and gels into a single, synergistic delivery system.[27,28] While conventional gels cannot efficiently deliver lipophilic drugs, and emulsions have poor skin retention due to their fluid nature, emulgels address both limitations simultaneously.[27, 28] The emulsion component allows the incorporation of both water-soluble and oil-soluble drugs, while the gel matrix provides enhanced viscosity, improved skin adhesion, prolonged contact time at the application site, and controlled drug release.[27, 28,29]

A typical emulgel formulation comprises an aqueous phase (purified water, hydrophilic polymers such as Carbopol 934/940 or HPMC, and preservatives), an oil phase (vegetable oils, mineral oils, or liquid paraffin containing lipophilic drugs), emulsifying agents (Tween 80, Span 20, or stearic acid), penetration enhancers (propylene glycol, isopropyl myristate, or oleic acid), and preservatives (methylparaben or propylparaben).[27,28] The emulgel platform offers several distinct advantages: dual drug incorporation for both hydrophilic and lipophilic agents; enhanced drug loading capacity; improved spreadability, skin adhesion, and prolonged contact time; controlled and sustained drug release; better stability than conventional emulsions; non-greasy, non-staining, and easily removable properties; thixotropic behavior facilitating easy application; and excellent patient compliance.[27, 28,29]

6. Metformin: Pharmacology and Anti-Melanogenic Mechanisms

6.1 Overview and Primary Mechanism of Action

Metformin hydrochloride (1,1-dimethylbiguanide hydrochloride; molecular formula C4H11N5·HCl; molecular weight 165.63 g/mol) is a synthetic biguanide derivative originally derived from galegine, a natural compound found in *Galega officinalis*, first synthesized in 1922 and introduced into clinical practice in Europe in 1957.[8,9] For over six decades, it has served as the first-line pharmacological agent for the management of type 2 diabetes mellitus.[8,9] Its primary mechanism involves the activation of adenosine monophosphate-activated protein kinase (AMPK), a master cellular energy sensor that suppresses hepatic gluconeogenesis, enhances peripheral glucose uptake, and improves insulin sensitivity.[8,9,10] Additionally, metformin inhibits mitochondrial complex

I of the electron transport chain, increasing the AMP/ATP ratio that triggers AMPK activation.[10]

6.2 Pleiotropic Anti-Melanogenic Properties

Beyond its antidiabetic properties, metformin has garnered considerable attention for pleiotropic effects extending into oncology, cardiovascular disease, aging, polycystic ovary syndrome (PCOS), and dermatological conditions.[9,10,30] In the dermatological context, its pleiotropic profile is particularly compelling: AMPK activation reduces intracellular cAMP levels—a key second messenger in melanogenesis signaling—thereby downregulating MITF expression and inhibiting tyrosinase activity.[9,10,19,30] Furthermore, metformin suppresses NF-κB signaling and reduces pro-inflammatory cytokines, reduces ROS while enhancing endogenous antioxidant defenses, attenuates UV-induced DNA damage, and inhibits melanosome transfer between melanocytes and keratinocytes.[10,19,30]

Key preclinical and early clinical evidence supports this potential. Lehraiki et al. demonstrated that metformin significantly inhibited melanin synthesis in human melanocytes in vitro through cAMP reduction and MITF downregulation.[19] Banavase Channakeshavaiah and Andanooru Chandrappa reported significant improvement in Melasma Area and Severity Index (MASI) scores with topical metformin 30% cream in a preliminary randomized clinical trial, providing important proof-of-concept for topical application in melasma.[31] These converging mechanisms position metformin as a uniquely attractive candidate for dermatological applications targeting hyperpigmentation disorders.

6.3 Formulation Challenges and the Emulgel Solution

Despite its pharmacological promise, metformin's physicochemical properties present formulation challenges for topical delivery. Its high water solubility and negative log P value (−1.43) result in poor partitioning into the lipophilic stratum corneum.[30,31] As a strong base (pKa = 12.4), it exists predominantly in ionized form at skin physiological pH (4.5–6.5), further limiting passive percutaneous penetration.[30,31] The optimal topical concentration has not been definitively established, with studies employing concentrations of 10–30%.[30,31] The emulgel platform directly addresses these limitations: the oil phase provides intimate contact with the lipophilic stratum corneum, and penetration enhancers such as propylene glycol further facilitate drug permeation.[27,28,31] Topical delivery simultaneously avoids the systemic gastrointestinal adverse effects affecting 20–30% of oral users and eliminates hepatic first-pass metabolism.[8,9,30]

7. Propolis: A Natural Anti-Melanogenic Agent

7.1 Origin, Composition, and Bioactive Constituents

Propolis (from the Greek "pro" = in defense of, "polis" = city) is a complex, resinous, lipophilic substance produced by honeybees (*Apis mellifera*) through the enzymatic processing of exudates from buds, leaves, and bark of various plant species, mixed with beeswax and salivary enzymes.[32,33,34] Bees utilize propolis to seal crevices, reinforce hive structure, and maintain a sterile colony environment.[32,33] Propolis has been used in traditional medicine for thousands of years and has gained significant modern scientific interest as a source of bioactive compounds.[33,34]

The chemical composition of propolis is remarkably complex, with more than 500 individual compounds identified to date.[32,33,34] Composition varies with botanical origin, geographic location, season, and bee species, but generally comprises resins and balsams (50–60%), waxes and fatty acids (25–35%), essential oils (5–10%, including terpenes), pollen (~5%), and other organic compounds (~5%, including minerals and vitamins).[32,33] The general chemical composition is presented in Table 4.

Table 4: General Chemical Composition of Propolis.

Component Class	Percentage	Major Compounds	Biological Relevance
Resins and balsams	50–60%	Flavonoids, phenolic acids, CAPE, ferulic acid	Antioxidant, anti-inflammatory, anti-melanogenic
Waxes and fatty acids	25–35%	Beeswax, fatty acids	Lipophilicity, film-forming
Essential oils	5–10%	Terpenes, aromatic aldehydes	Antimicrobial
Pollen	~5%	Proteins, amino acids, vitamins	Nutritive
Other compounds	~5%	Minerals (Fe, Zn, Cu, Mn), coumarins	Supportive activities

The pharmacological activity of propolis is primarily attributed to its polyphenolic content. Flavonoids such as pinocembrin, chrysin, galangin, quercetin, and kaempferol are potent antioxidants that scavenge free radicals, chelate metal ions, and inhibit tyrosinase.[33,34,35,36]Caffeic acid phenethyl ester (CAPE) exhibits potent anti-inflammatory, antioxidant, immunomodulatory, and anti-melanogenic properties.[33,34] Phenolic acids—including caffeic acid, ferulic acid, and p-coumaric acid—contribute significantly to antioxidant and UV-protective properties.[33,34]

Yemeni propolis is of particular scientific interest given Yemen's unique apicultural heritage, with beekeeping centered in regions rich in endemic Sidr (*Ziziphus spina-christi*) and Somr (*Acacia* spp.) flora.[36] Yemeni propolis is expected to possess a distinctive phytochemical profile that may differ from Brazilian, European, and Asian

varieties, representing an understudied natural resource of potential pharmaceutical significance.[36]

7.2 Anti-Melanogenic and Dermatological Properties

Propolis exhibits a broad spectrum of pharmacological activities directly relevant to melasma treatment.[33,34,35] As one of the most potent natural antioxidants, propolis neutralizes reactive oxygen species (ROS) and reactive nitrogen species, chelates transition metal ions that catalyze free radical generation, inhibits pro-oxidant enzymes, and upregulates endogenous antioxidant defense systems—including superoxide dismutase, catalase, and glutathione peroxidase.[33,34,35] This antioxidant capacity is particularly relevant to melasma, where UV-induced oxidative stress is a primary driver of melanocyte hyperactivation.[1,5]

Propolis flavonoids—particularly quercetin and kaempferol—demonstrate direct inhibitory activity against tyrosinase, the rate-limiting enzyme in melanin biosynthesis, by competitively binding to the enzyme's active site and chelating its essential copper cofactors, thereby reducing catalytic activity.[35,36] Additionally, CAPE has been shown to downregulate MITF expression and reduce melanogenic enzyme transcription through modulation of intracellular signaling pathways.[33,34] Propolis exerts anti-inflammatory effects primarily through inhibition of the NF-κB signaling pathway, suppression of COX-2 and lipoxygenase activity, reduced production of pro-inflammatory cytokines and prostaglandins, and inhibition of inducible nitric oxide synthase.[33,34] These properties directly address the inflammatory component increasingly recognized in melasma pathogenesis, including mast cell infiltration, increased vascularity, and elevated pro-inflammatory mediators in lesional skin.[1,5] Furthermore, the wax and lipid components of propolis form a protective emollient film on the skin surface, reducing transepidermal water loss and supporting barrier function.[33]

8. Rationale for the Metformin- Propolis Combination: A Multi- Target Approach

The case for combining metformin and propolis in a single topical formulation is grounded in three mutually reinforcing pillars: mechanistic complementarity, clinical unmet need, and pharmaceutical formulation rationale.

From a mechanistic standpoint, melasma is driven by simultaneous dysregulation at multiple levels—UV-induced ROS generation, hormonal receptor activation, upstream cAMP/PKA/CREB/MITF signaling, downstream tyrosinase enzymatic activity, and inflammatory amplification.[1,2,5] Metformin addresses upstream signaling events through AMPK activation, cAMP reduction, MITF downregulation, and inhibition of melanosome transfer,[9,10,19,30] while propolis targets downstream enzymatic processes through direct tyrosinase inhibition alongside antioxidant protection and anti-inflammatory suppression of melanogenic cytokines.[33,34,35,36] This complementary, multi-level mechanism of action has the potential to achieve more comprehensive and sustained anti-melanogenic efficacy than any single-agent monotherapy—and may address the high recurrence rates that plague current treatments.

Clinically, both agents present favorable safety profiles suited for long-term use: metformin carries a decades-long systemic safety record,[8,9] and propolis demonstrates minimal reported adverse effects in topical applications,[33,34] positioning the combination as a potentially safer alternative to hydroquinone- and corticosteroid-containing formulations for the chronic maintenance treatment that melasma demands. Furthermore, to the best of current knowledge, no previous study has combined metformin hydrochloride and propolis extract in a single topical formulation for any dermatological indication, making this a novel and unexplored therapeutic direction.

From a formulation perspective, no conventional topical dosage form can efficiently accommodate both the highly hydrophilic metformin (log P: −1.43) and the lipophilic propolis extract simultaneously.[27,28] The emulgel dual-phase system uniquely resolves this challenge: metformin is dissolved in the aqueous phase while propolis is incorporated in the oil phase, enabling controlled, simultaneous delivery of both agents to the target site in the skin.[27,28] This represents not only a rational pharmaceutical strategy but also an innovative co-delivery paradigm potentially applicable to other hydrophilic-lipophilic drug combinations.[27,28,29]

9. DISCUSSION

The evidence synthesized in this review highlights both the scientific rationale and the clinical urgency for novel multi-target approaches in melasma management. Current monotherapies fail to address the multifactorial pathogenesis of the disease, and the limitations of hydroquinone—the most effective available agent—create a therapeutic vacuum that demands safer, mechanism-based alternatives.[1,6,7]

Metformin's emerging role in dermatology represents one of the most compelling examples of drug repurposing in the pigmentary disorders space. The mechanistic alignment between AMPK activation and suppression of the cAMP/MITF/tyrosinase axis is well-supported by in vitro data.[19] The clinical trial by Banavase Channakeshavaiah and Andanooru Chandrappa demonstrating MASI improvement with topical metformin 30% cream,[31] while preliminary and limited in scale, provides important proof-of-concept and establishes translational potential. However, the optimal topical concentration, vehicle, and treatment duration for metformin remain undefined, and large, randomized, vehicle-controlled trials are critically needed.

The evidence base for propolis in hyperpigmentation is predominantly in vitro and mechanistic.[33,34,35,36,37] While the antioxidant and tyrosinase-inhibitory properties are

robust at the cellular level, controlled clinical studies evaluating propolis as a standalone depigmenting agent are currently lacking—a significant gap in the literature. The geographic variation in propolis composition also presents a challenge for standardization: Yemeni propolis, derived from a unique botanical source, requires rigorous phytochemical characterization before pharmaceutical applications can be reliably advanced.[36]

The combination strategy proposed here addresses these limitations by harnessing the complementary mechanisms of both agents within a single, rationally designed delivery system. Future studies should prioritize:[14] phytochemical standardization and quality control of propolis extracts;[15] in vitro drug release and permeation studies using human skin models;[1] in vitro anti-melanogenic bioassays for the combination at clinically relevant concentration ratios;[16] accelerated stability studies under ICH guidelines; and[17] progression to well-powered, controlled clinical trials employing validated outcome measures including MASI and MELASQoL.

The incorporation of locally sourced Yemeni propolis also introduces an important dimension of regional relevance and economic potential, particularly for resource-limited settings where affordable alternatives to branded therapies are needed.[38] The synthetic-natural hybrid approach—bridging drug repurposing with ethnopharmacology—represents an emerging and promising paradigm in dermatological therapeutics that warrants further systematic investigation.

Preformulation study is a stage before preparing drugs is the stage of compatibility between excipients and the drug, and after that the various pharmaceutical forms are prepared according to compatibility. the method of preparing drugs from industrial sources applies to natural sources, taking into account that natural sources need to be studied from the beginning, as there is no information available. Therefore, the study must be in accordance with the system of studying compatibility preformulation, then studying the formulation, evaluation, and stability study of pharmaceutical forms in novel drug delivery systems. Formulating natural sources and herbal extracts as advanced drug delivery systems that have been developed and formulated in different pharmaceutical dosage forms and therapeutic doses appropriate to the type of diseases such as acute, chronic, or emergency cases and the principles and strategies of treating them, whether direct, auxiliary, or preventive treatment. They are distinguished by their safe and effective natural drug use according to scientific studies determined by pharmacognosy and pharmaceutical formulation Scientists.[39-67]

10. CONCLUSION

Melasma remains a therapeutically unsatisfying condition, with current approaches constrained by limited long-term efficacy, high recurrence, and safety concerns that preclude extended use. The complex, multifactorial pathogenesis of the disease demands equally multi-faceted therapeutic solutions. This review has presented the scientific basis for a novel combination of metformin hydrochloride and propolis extract, formulated as a topical emulgel, as a rational multi-target therapeutic strategy for melasma. Metformin and propolis operate through complementary, non-redundant molecular mechanisms that collectively address upstream melanogenesis signaling, downstream enzymatic activity, oxidative stress, and the inflammatory microenvironment of melasma lesions. The emulgel platform provides the pharmaceutical means to co-deliver these physicochemically disparate agents to the target site with enhanced patient acceptability. While preclinical and early clinical evidence is promising, rigorous in vitro, in vivo, and controlled clinical investigations are necessary to fully substantiate the potential of this approach. This combination strategy represents a meaningful scientific advance and a potentially impactful contribution to dermatological pharmacotherapy.

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