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A NARRATIVE REVIEW OF PROPOLIS AND METFORMIN IN TOPICAL DERMATOLOGY: FROM MONO-AGENT BIOACTIVITIES TO THE FRONTIER OF EMULGEL-BASED COMBINATION THERAPIES FOR MELASMA

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ABSTRACT

Melasma is a common, therapeutically challenging disorder of hyperpigmentation characterized by a complex pathophysiology involving aberrant melanogenesis, oxidative stress, and inflammation. Current gold-standard treatments are often limited by safety concerns or suboptimal efficacy. This narrative review synthesizes the literature from 2010 to 2026 to evaluate two promising agents for melasma therapy: propolis, a natural resin with multifaceted bioactivities, and metformin, a repurposed drug with a novel melanogenesis-inhibiting mechanism. We systematically examine the pharmacological properties of both agents, including their anti-melanogenic, antioxidant, anti-inflammatory, and photoprotective effects in skin models. The review further explores the evolution of their topical formulations, from conventional creams to advanced nano-delivery systems, highlighting the potential of emulgel technology as a superior platform. Finally, we assess the growing body of evidence supporting multi-target combination therapies for melasma. By consolidating this evidence, we establish the scientific rationale for a novel, unexplored therapeutic strategy: a dual-drug emulgel co-delivering metformin and propolis to synergistically target both upstream signaling and downstream enzymatic pathways in melanogenesis.

KEYWORDS: Melasma, Propolis, Metformin, Emulgel, Topical Delivery, Combination Therapy, Hyperpigmentation, Anti-melanogenic.

1. INTRODUCTION

Melasma is a chronic and relapsing condition of acquired hyperpigmentation that predominantly affects women, significantly impacting their quality of life.[1,4] Its pathogenesis is multifactorial, involving not only the overproduction of melanin but also chronic inflammation, oxidative stress, and vascular factors.[1,2,4] This complexity renders many single-agent therapies, such as hydroquinone, insufficient for long-term management and raises concerns about side effects like ochronosis and irritation.[3,4] Consequently, there is a critical need for novel, multi-targeted therapeutic strategies that are both safe and effective.[4,67]

Recent research has illuminated two distinct and promising candidates for melasma treatment. First, propolis, a natural resinous substance produced by bees, has garnered attention for its rich polyphenolic content and diverse pharmacological properties, including direct tyrosinase inhibition, potent antioxidant activity, and significant anti-inflammatory effects.[1,2,3,5,6,7] Second, the anti-diabetic drug metformin has been repurposed following landmark discoveries demonstrating its ability

to inhibit melanogenesis through the upstream cAMP/CREB/MITF signaling pathway, a mechanism fundamentally distinct from traditional tyrosinase inhibitors.[23,24]

Despite their individual promise, the therapeutic potential of combining these two agents has not been explored. Furthermore, the optimal delivery of both a hydrophilic drug (metformin) and a lipophilic natural extract (propolis) to the skin presents a formulation challenge. Emulgel technology, a hybrid of emulsion and gel, offers a compelling solution due to its ability to incorporate both hydrophilic and lipophilic compounds, enhance skin penetration, and provide superior patient compliance.[9,54]

This narrative review aims to: (1) consolidate the pharmacological evidence for propolis and metformin in skin health, with a focus on their anti-melanogenic mechanisms; (2) evaluate the landscape of formulation strategies for both agents; (3) assess the current state of emulgel technology for dermatological applications; and (4) examine the evidence for combination therapies in melasma. By synthesizing these domains, we aim to provide the scientific foundation for a novel, multi-target approach to melasma treatment.

2. Propolis: A Multi-Target Natural Agent for Skin Health

2.1 Pharmacological Properties Relevant to Melasma

Propolis is a complex mixture of plant exudates, beeswax, and bee enzymes, and its composition varies geographically. Its pharmacological properties are primarily attributed to its rich flavonoid and phenolic acid content, including galangin, chrysin, pinocembrin, and caffeic acid phenethyl ester (CAPE).[1,3,5,7,10]

2.1.1 Anti-Tyrosinase and Anti-Melanogenic Activity

The anti-melanogenic effects of propolis have been extensively documented. Early mechanistic studies by Gheibi et al. demonstrated that propolis extracts (ethanolic, methanolic, hexanolic) directly inhibit mushroom tyrosinase by reducing the thermal and chemical stability of the enzyme, thereby altering its structure and function.[1] Subsequent research has confirmed this direct inhibitory effect. Widelski et al. evaluated European propolis extracts and reported tyrosinase inhibition ranging from 86.66% to 93.25% at 100 µg/mL, which strongly correlated with total polyphenol content and antioxidant capacity.[3] This positions propolis as a direct, downstream inhibitor of melanin synthesis.

However, the mechanism is not always direct. Arung et al. isolated prenylated flavonoids (broussoflavonol F and glyasperin A) from stingless bee propolis that exhibited potent melanin inhibition in B16 melanoma cells without directly inhibiting tyrosinase.[2] This suggests an indirect mechanism, likely mediated through reactive oxygen species (ROS) scavenging, highlighting the multi-faceted nature of propolis's anti-melanogenic action.[2]

2.1.2 Antioxidant and Anti-Inflammatory Activity

Oxidative stress and inflammation are key drivers of melanocyte activation in melasma. Propolis is a potent antioxidant. Karapetsas et al. showed that Greek propolis extracts protected HaCaT keratinocytes from UVB-induced DNA damage and reduced the expression of matrix metalloproteinases (MMPs), key enzymes in photoaging.[4] Similarly, Bae et al. demonstrated that a hydrophilic fraction of Korean propolis, rich in phenylpropanoids like ferulic acid, effectively inhibited ROS production and lipid peroxidation induced by particulate matter.[5] Valverde et al. characterized Brazilian red propolis, reporting potent antioxidant activity (DPPH IC50 of 12–17 µg/mL) and broad-spectrum UV photoprotection, alongside confirmed non-cytotoxicity in skin cells.[6]

The anti-inflammatory effects are largely mediated by CAPE, a major propolis component. Armutcu et al., in a comprehensive review, detailed CAPE's role as a specific inhibitor of nuclear factor-kappa B (NF-κB) activation, preventing the nuclear translocation of its p65 subunit and subsequent production of pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β.[7] This mechanism has been validated in vivo; El-Gammal et al. reported an 86.8% overall response rate in a large clinical trial of a propolis and aloe vera ointment for psoriasis, a chronic inflammatory skin condition.[8] Furthermore, El-Kersh et al. demonstrated that a standardized propolis extract downregulated TLR4, IL-6, and TNF-α in stimulated models and accelerated burn wound healing in rabbits, underscoring its potent anti-inflammatory and regenerative capacity.[9]

2.1.3 Photoprotective and Wound Healing Activities

Propolis offers dual photoprotection. Gregoris et al. demonstrated that propolis possesses both a high Sun Protection Factor (SPF) for UVB and significant UVA absorbance, coupled with strong antioxidant activity, qualifying it as a cosmeceutical-grade sunscreen ingredient.[10] Kim et al. uncovered a novel molecular mechanism, showing that propolis directly inhibits phosphoinositide 3-kinase (PI3K) in UV-exposed dermal fibroblasts, thereby attenuating MMP upregulation and collagen degradation, an effect that extends beyond simple radical scavenging.[11] In wound healing, Conceicao et al. confirmed that topical red propolis enhanced wound contraction and epithelialization in rats, with immunohistochemical analysis showing favorable modulation of collagen, VEGF, and TGF-β3, alongside increased antioxidant enzyme activity.[12] Rosa et al. further supported this with clinical results showing significantly greater wound area reduction with 5% green propolis ointment in chronic ulcers.[13]

2.2 Formulation Strategies for Propolis Delivery

2.2.1 Conventional and Nano-Formulations

Early formulation work focused on conventional semi-solids. Dos Santos et al. developed propolis-loaded emulgels with vegetable oils, demonstrating that the choice of oil (e.g., andiroba oil) significantly influenced dermal permeation and retention.[14] Ramanauskiene et al. confirmed that phenolic compounds from propolis penetrate both the epidermis and dermis from ointments and creams, with ointment bases providing slightly higher penetration.[15] Radic et al. clinically validated a standardized phenolic acids polymer extract (PAPE) in face creams, achieving significant wrinkle improvement.[16]

To overcome limitations like poor water solubility and variable bioavailability, researchers have turned to nano-delivery systems.[22] Spanidi et al. developed a liposome-cyclodextrin system for controlled release of propolis polyphenols, which retained their biological activity in skin models.[17] Viqhi et al. formulated a propolis-loaded nanoemulgel using oleic acid as a permeation enhancer, optimizing for both skin retention and transdermal delivery.[18] Shahab-Navaei and Asoodeh synthesized solid lipid nanoparticles (PSLNs) that preserved the active compounds and demonstrated remarkable antioxidant and antimicrobial activity.[19] Similarly, Vaseghi et al. created propolis-loaded chitosan nanoparticles with high encapsulation efficiency and preserved bioactivity.[20] In the cosmeceutical arena, An et al. developed polymeric nanoparticles that increased collagen production and reduced collagenase activity, leading to significant wrinkle reduction in a clinical trial.[21]

3. Metformin: A Repurposed Drug with a Novel Anti-Melanogenic Mechanism

3.1 Pharmacological Properties in the Skin

Metformin, a first-line drug for type 2 diabetes, has emerged as a promising repurposed agent for various dermatological conditions due to its pleiotropic effects on cellular metabolism and signaling.

3.1.1 Anti-Melanogenic Activity via cAMP Pathway Modulation

The seminal work by Lehraiki et al. fundamentally changed our understanding of metformin's dermatological potential. They demonstrated that metformin inhibits melanogenesis not through AMPK activation, as previously speculated, but by directly reducing cAMP accumulation and subsequent CREB phosphorylation.,[23] This downregulates the master regulator MITF and its downstream targets, including tyrosinase, TRP1, and DCT.[23] Critically, topical metformin induced visible depigmentation in mouse tails and was effective in reconstituted human epidermis, providing the first robust evidence for its use as a topical depigmenting agent.[23]

Liu et al. (2025) expanded on this by showing that metformin also inhibits melanosome transfer from melanocytes to keratinocytes.[24] This effect is mediated through alterations in Rho GTPase expression and cytoskeletal dynamics, which suppress dendrite and filopodia formation.[24] They further identified a dual cAMP-MITF and cAMP-Nrf2 signaling axis, adding another layer to its mechanism.[24]

3.1.2 Anti-Melanoma and Antiproliferative Activity

Metformin exhibits melanoma-selective cytotoxicity through sequential mechanisms. Tomic et al. demonstrated G0/G1 cell cycle arrest at 24 hours, autophagy induction at 72 hours (LC3/Beclin1 upregulation), and apoptosis at 96 hours, with autophagy required for cell death.[25] Normal melanocytes remained resistant, indicating selectivity.[25] Cerezo et al. showed metformin blocks melanoma invasion and metastasis through AMPK/p53-dependent mechanisms, inhibiting invasion without affecting migration, modulating epithelial-mesenchymal transition markers, and suppressing MMP-2/MMP-9 activation.[26] Tseng et al. identified microRNA involvement, with upregulation of miR-192-5p, miR-584-3p, and miR-1246 targeting EFEMP1 and SCAMP3.[27]

3.1.3 Anti-Inflammatory, Antioxidant, and Photoprotective Effects

Metformin's effects extend beyond melanogenesis. In keratinocytes, Tsuji et al. showed that metformin inhibits the NLRP3 inflammasome via AMPK and SIRT1 pathways, suppressing the secretion of mature IL-1β and other pro-inflammatory cytokines.[28] This translated to a significant reduction in psoriasis-like inflammation in a mouse model.[28] Ba et al. confirmed that metformin directly suppresses the NF-κB pathway in keratinocytes by inhibiting IκBα degradation and p65 nuclear localization.[29]

Regarding photoprotection, Ribeiro et al. found that metformin does not act as a direct antioxidant but protects keratinocytes from UVB-induced oxidative damage by inhibiting NADPH oxidase-dependent superoxide production.[30] Chen et al. further demonstrated that metformin attenuates UVA-induced photoaging by suppressing mitophagy and the PI3K/AKT/mTOR pathway.[31] Wu et al. established a crucial role for AMPK in skin tumor suppression, showing that metformin enhances UVB-induced DNA damage repair by increasing the expression of the repair protein XPC.[32]

3.1.4 Wound Healing and Other Dermatological Applications

In diabetic wound healing, Tombulturk et al. demonstrated that topical metformin promotes collagen-I and -III synthesis while inhibiting apoptosis via the p53/c-jun pathway.[33] Zhang et al. showed that metformin lotion promotes scarless wound healing by activating AMPK and inhibiting TGF-β1, reducing

myofibroblast accumulation and collagen overdeposition.[34] Furthermore, a meta-analysis by Yen et al. confirmed metformin's utility as an adjuvant therapy for acne in PCOS, attributed to its reduction of androgen levels.[35]

3.2 Formulation Strategies for Topical Metformin

3.2.1 Clinical Evidence in Melasma

The clinical translation of metformin for melasma has been rapid. Early trials by Mapar et al. showed significant MASI reduction with metformin cream, although it did not statistically separate from placebo, possibly due to study design.[36] However, subsequent trials have been highly promising. Channakeshavaiah and Andanooru compared 30% metformin lotion to triple combination cream (TCC) and found comparable efficacy with zero adverse events in the metformin group.[37] This was reinforced by AboAlsoud et al., who found 30% metformin cream to be comparably effective to Kligman's formula.[38] A systematic review and meta-analysis by Mongkhon et al. concluded that 15% metformin is effective versus placebo, and 30% metformin is equivalent to TCC with a superior safety profile.[39] Most recently, Hussain et al. suggested that 30% topical metformin may offer superior efficacy to 4% hydroquinone.[40]

3.2.2 Advanced Delivery Systems

Metformin's hydrophilic nature (log P = -1.43) poses a challenge for skin penetration. To address this, advanced delivery systems have been developed. Mousa et al. formulated metformin-loaded ethosomes, which exhibited significantly greater antitumor activity in a skin cancer model compared to free metformin gel.[41] Salem et al. developed metformin-loaded bilosomes (bile salt-containing vesicles), which achieved significantly higher permeation flux than the non-formulated drug.[42] Behzatoglu et al. created a thermosensitive in situ hydrogel for burn wounds, providing sustained release at the application site.[43] Clinical studies have also explored physical enhancement techniques. Elkholy et al. and Galal et al. both demonstrated in split-face studies that combining microneedling with topical metformin significantly enhances its clinical efficacy for melasma compared to microneedling with placebo or vitamin C, respectively.[44,45] A systematic review by Afshar et al. identified hydrogels, nanofibers, and microneedles as promising strategies for optimizing metformin bioavailability.[46]

4. Emulgel: An Advanced Platform for Topical Drug Delivery

Emulgels are a hybrid formulation combining the advantages of emulsions and gels. They consist of an oil phase emulsified in an aqueous phase, which is then incorporated into a gel base. This architecture offers several benefits: it is thixotropic, non-greasy, easy to spread and wash off, has a high patient acceptability, and can deliver both hydrophilic and lipophilic drugs simultaneously.[9,54]

4.1 Applications in Dermatology

The versatility of emulgels has been demonstrated across a wide range of dermatological applications. Singh et al. developed a stable and effective diclofenac sodium emulgel with favorable release kinetics, serving as a model for anti-inflammatory formulations.[47] Yilmaz and Borchert further refined NSAID emulgel design by systematically optimizing Carbopol and HPMC concentrations to achieve desired rheological and release properties.[48] Algahtani et al. prepared a curcumin nanoemulgel (56.25 nm droplet size) with significantly enhanced permeation versus conventional hydrogel and superior wound healing.[49]

For antimicrobial therapy, Salem et al. developed a ketoconazole nanoemulgel with droplet sizes below 200 nm, demonstrating enhanced antifungal activity while minimizing systemic absorption concerns.[50] El-Tokhy et al. formulated a poly-delta-decalactone-based nanoemulgel for the synergistic co-delivery of ketoconazole and eugenol, demonstrating significantly improved efficacy at lower drug concentrations.[51] In anti-acne therapy, Najafi-Taher et al. showed in a randomized trial that a tea tree oil nanoemulsion containing adapalene was significantly more effective than a marketed adapalene gel.[52] Alahdab formulated curcumin in a tea tree oil-based emulgel, utilizing the oil phase as both vehicle and therapeutic agent.[53]

4.2 Emulgels for Depigmenting and Natural Products

The utility of emulgels for depigmenting agents and natural products is particularly relevant. Abd El-Aziz et al. developed an alpha-arbutin emulgel that achieved 2.3-fold higher dermal retention compared to an aqueous solution, demonstrating its superiority for delivering hydrophilic depigmenting agents.[54] Suryawati et al. showed that a turmeric extract nanoemulgel significantly reduced inflammatory markers in an atopic dermatitis model, highlighting its potential for inflammatory and pigmentary disorders.[55] Dasari et al. provided proof-of-concept for a polyherbal emulgel combining *Curcuma longa*, *Emblica officinalis*, and *Aloe vera* extracts, demonstrating complementary antioxidant and anti-inflammatory activities.[56] Andleeb et al. further illustrated the potential by loading a plant extract into nanoethosomes and then incorporating them into a gel, achieving enhanced permeation and release.[57]

5. The Era of Combination Topical Therapies for Melasma

The multifactorial pathogenesis of melasma has driven a shift from monotherapy to combination strategies. A network meta-analysis by Wang et al. confirmed that 87% of combination therapy studies demonstrated superior efficacy over single agents, with strategies targeting multiple melanogenic pathways consistently outperforming monotherapies.[67]

5.1 Synthetic-Synthetic Combinations

Synthetic-synthetic combinations have proven highly effective. Abou-Taleb et al. demonstrated that a niosomal cream of tranexamic acid and niacinamide was non-inferior to 4% hydroquinone with significantly fewer adverse reactions and lower relapse rates.[58] Li et al. evaluated a triple-agent serum (tranexamic acid 3%, niacinamide 5%, kojic acid 1%) in 22 patients, achieving improvement in 86.36% of cases.[59] This concept was extended by Soliman et al., whose multi-component serum (niacinamide, tranexamic acid, vitamin C, glycolic acid) was non-inferior to hydroquinone with superior tolerability.[62] Sherif et al. and Gonzalez et al. validated the cysteamine and nicotinamide combination, which leverages both antioxidant and melanosome-transfer inhibition.[60,61]

5.2 Natural Product Combinations

Natural product combinations have also shown equivalence to gold-standard treatments. Costa et al. found that a botanical combination of *Emblica officinalis*, licorice, and belides achieved comparable depigmentation to 2% hydroquinone with fewer adverse events.[63] Aslam et al. reported that an herbal combination of chickpea and melon seed extracts matched the efficacy of 4% hydroquinone.[64] A systematic review by Saeed et al. confirmed the large effect size of botanical products on MASI reduction and their significantly better safety profiles compared to active comparators.[65]

5.3 Multi-Target Pathway Approaches

The most rational combinations target distinct points in the melanogenic cascade. Liu et al. (2025) developed a dual-effect composition targeting both oxidative stress and glycation, achieving significant downregulation of MITF and tyrosinase in 3D skin models and clinical improvement in skin lightness [66]. This approach, targeting upstream signaling (inflammation, oxidative stress) and downstream enzymatic activity, represents the cutting edge of melasma therapy.[66,67]

6. DISCUSSION

This review consolidates the extensive evidence supporting propolis and metformin as two powerful, mechanistically distinct agents for managing melasma. Propolis acts as a multi-pronged agent, providing downstream tyrosinase inhibition, potent antioxidant protection, and anti-inflammatory effects.[1,2,3,5,6] Metformin offers a complementary upstream approach by inhibiting melanogenesis at the signaling level (cAMP/MITF), suppressing melanosome transfer, and providing indirect antioxidant and anti-inflammatory benefits.[23,24,28,29,30]

Individually, both agents have demonstrated clinical promise for melasma. Propolis has proven its efficacy and safety in other inflammatory skin conditions, and its flavonoids are well-established tyrosinase inhibitors.[1,3,8] Metformin, remarkably, has shown in multiple clinical trials to be equivalent to the gold-standard triple combination cream and hydroquinone, with a superior safety and tolerability profile.[37,38,39,40] However, the optimal delivery of metformin remains a challenge due to its hydrophilicity, and while propolis has been formulated in various systems, its potential in an emulgel specifically for melasma is untapped.

The evolution of topical formulations points towards advanced platforms that can overcome the physicochemical limitations of active ingredients. Nanoemulgels and other nano-carrier systems have consistently demonstrated enhanced skin penetration, sustained release, and improved stability.[18,19,42,49] The emulgel platform, in particular, is ideally suited for co-delivering a hydrophilic drug like metformin and a lipophilic extract like propolis, ensuring both agents are delivered to their target sites in the skin effectively.[9,54,55]

The overwhelming evidence supporting combination therapy for melasma provides the final, compelling piece of the puzzle.[58,59,62,67] The success of multi-target formulations that address both upstream triggers (inflammation, oxidative stress) and downstream effectors (melanin synthesis) underscores the need for a rationally designed combination that pairs these two mechanistically complementary agents.[66,67] The combination of metformin (upstream signaling inhibitor) and propolis (downstream enzyme inhibitor and antioxidant) represents a logical and powerful next step in the evolution of melasma therapy.

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.[68-97]

7. CONCLUSION

The literature from 2010 to 2026 provides a robust foundation for a novel therapeutic strategy in melasma. Propolis is a well-characterized natural product with proven anti-tyrosinase, antioxidant, and anti-

inflammatory properties. Metformin is a clinically validated, repurposed drug that inhibits melanogenesis via a unique upstream mechanism and has demonstrated efficacy equivalent to gold-standard therapies. Emulgel technology offers an advanced, patient-friendly platform capable of co-delivering these two agents with complementary physiochemical properties. The convergence of these three pillars justifies the development of a metformin-propolis co-loaded emulgel. Such a formulation would represent a novel approach to combine an upstream signaling inhibitor with a downstream enzyme inhibitor for melasma, addressing the condition's complex pathophysiology through a rational, multi-targeted approach and potentially offering a safe, effective, and innovative treatment option.

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