

Review

Innovative Skin Depigmenting Strategies: A Review

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Abstract

Skin pigmentation results from the melanin production by melanocytes, an essential process for protection against ultraviolet radiation and for maintaining cutaneous homeostasis. Disruptions in this balance lead to pigmentary disorders, such as hyperpigmentation, which is characterized by localized or diffuse darkening of the skin. Its most prevalent forms include melasma, post-inflammatory hyperpigmentation, and solar lentigines, often driven by hormonal, inflammatory, and environmental factors, particularly sun exposure. Despite being clinically benign, these conditions have a significant impact on self-esteem and quality of life. Conventional treatments rely on depigmenting agents such as hydroquinone, retinoids, and corticosteroids, as well as chemical peels, and laser or light-based therapies, frequently used in combination. However, limited efficacy, prolonged treatment durations, and potential adverse effects underscore the need for safer and more effective alternatives. In recent years, research has focused on developing novel approaches, with nanotechnology-based delivery systems and minimally invasive techniques, such as microneedling, standing out as particularly promising fields. In parallel, the growing number of interventional clinical trials reflects an increasing interest in optimizing topical depigmenting strategies. This review summarizes the main types of hyperpigmentation, the depigmenting substances currently used, and emerging therapeutic approaches with potential clinical impact.

Keywords: skin pigmentation; hyperpigmentation types; depigmenting formulations; innovative formulations; nanotechnology; clinical evidence



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1. Introduction

The skin, the human body's largest organ, functions as a barrier against environmental insults and plays essential roles in immune defense and sensory perception [1,2]. Beyond its structural function, the skin actively participates in fundamental processes such as thermoregulation, metabolic regulation, and intercellular signaling, highlighting its complex and dynamic nature [1,2]. Among the diverse physiological processes contributing to skin homeostasis, pigmentation plays a pivotal role. Cutaneous pigmentation is primarily determined by the activity of melanocytes, specialized cells originating from the ectodermal neural crest, which are responsible for the synthesis and distribution of melanin within

the epidermis [3]. Melanin not only defines skin color but also confers photoprotection by absorbing and dispersing ultraviolet (UV) radiation, thereby limiting DNA damage and oxidative stress [3,4].

Melanin synthesis is a dynamic process regulated by environmental, hormonal, and genetic factors, with UV radiation acting as a primary stimulus [3,4]. There are two main types of melanin: pheomelanin, associated with lighter (reddish/brown) skin tones, and eumelanin, responsible for darker pigmentation [3,4]. The latter comprises dark brown/black 5,6-dihydroxyindole (DHI) melanin and light brown dihydroxyindole-2-carboxylic acid (DHICA) melanin. Individual variations in melanin content and sun exposure response are commonly described using the Fitzpatrick scale, which classifies skin phototypes from type I (e.g., I–III corresponding to lighter skin tones) to type VI (e.g., IV–VI corresponding to darker skin tones) [5]. This classification has important clinical implications, as darker phototypes are generally more prone to pigmentary disorders and may require modified therapeutic strategies, whereas lighter phototypes exhibit increased vulnerability to UV-induced damage, necessitating tailored photoprotection. However, while the Fitzpatrick scale provides a useful framework for categorizing skin types, it may not fully capture the diversity of human skin [5].

The melanogenesis process (Figure 1) is tightly regulated by tyrosinase (TYR) and tyrosinase-related proteins (TRP-1/TRP-2), which together control the conversion of tyrosine into eumelanin and pheomelanin [3,6]. TYR, the initiating and rate-limiting enzyme of this pathway, catalyzes the hydroxylation of L-tyrosine to L-3,4-dihydroxyphenylalanine (DOPA) and its subsequent oxidation to dopaquinone (DQ). At this point, the pathway diverges: in the presence of cysteine, DQ reacts to form cysteinyl-dopa, leading to pheomelanin formation. In the absence of cysteine, DQ is converted into dopachrome. Subsequently, dopachrome can undergo spontaneous decarboxylation into DHI, which polymerizes into eumelanin. Alternatively, dopachrome is enzymatically converted by TRP2 into DHICA, which is then oxidized by TRP1 to produce eumelanin. Within melanocytes, TYR, TRP1, and TRP2 function cooperatively as a multienzyme complex to coordinate the type and quantity of melanin generated [3,6]. Dysregulation of any of these enzymes is clinically relevant, as it underlies several hyper- and hypopigmentation disorders with substantial clinical and cosmetic implications [7].

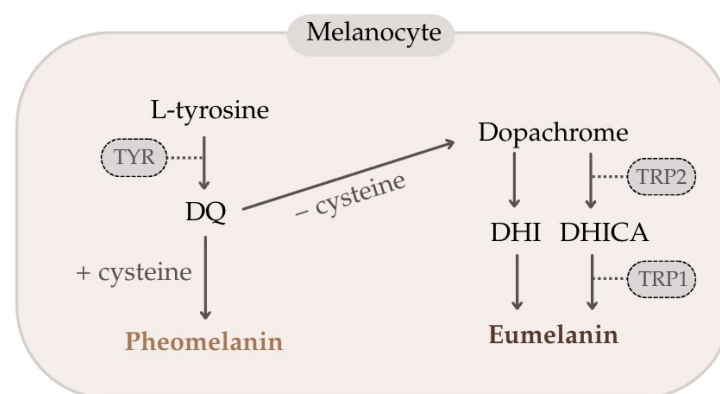


Figure 1. Biosynthetic pathways of eumelanin and pheomelanin in melanocytes. In the presence of cysteine (+ cysteine), DQ is preferentially converted into pheomelanin; conversely, in the absence of cysteine (– cysteine), dopachrome formation leads to eumelanin synthesis via two pathways: DHI and DHICA. TRP2 converts dopachrome into DHICA, while TRP1 catalyzes the subsequent oxidation. DHI formation can occur spontaneously from dopachrome and is less dependent on TRP1/2 activity. Abbreviations: DHI: 5,6-dihydroxyindole; DHICA: 5,6-dihydroxyindole-2-carboxylic acid; DQ: dopaquinone; TRP1: tyrosinase-related protein 1; TRP2: tyrosinase-related protein 2; TYR: tyrosinase.

Hyperpigmentation, characterized clinically by localized or diffuse macules or patches, results from excessive melanin accumulation driven by overactive melanogenic enzymes. This process is influenced by endogenous factors (e.g., hormonal fluctuations, genetic predisposition, and inflammation) and exogenous triggers (e.g., UV radiation and certain drugs) [8,9]. While typically benign, hyperpigmentation can profoundly impact patients' quality of life, often undermining self-esteem and social interactions [10–12].

Epidemiological data highlight that pigmentary disorders are a highly prevalent and impactful global dermatological concern [10–12]. A recent large-scale international survey of approximately 48,000 adults across 34 countries revealed that 50% of respondents reported at least one pigmentary condition, including solar lentigo, axillary hyperpigmentation, post-inflammatory hyperpigmentation (PIH), periorbital hyperpigmentation, melasma, and vitiligo, with notable impacts on quality of life and social perception [10]. These disorders are also among the most frequently reported dermatological conditions in skin of color populations, particularly in individuals with Fitzpatrick skin phototypes IV–VI, in whom lesions tend to be more persistent and refractory to treatment [11]. Consistent with these observations, a prospective cohort study of 140 patients at a private dermatology practice in North Carolina reported that approximately 80% of participants presented with one or more pigmentary disorders [11].

Although therapeutic options such as hydroquinone (HQ) and retinoids are available, their use is often constrained by adverse effects (e.g., irritation, ochronosis, and long-term toxicity) and high recurrence rates [13,14]. Moreover, the safety and efficacy of many emerging or naturally derived treatments remain controversial, with conflicting evidence regarding their long-term outcomes [13,14]. These shortcomings highlight the limitations of existing approaches in providing safe, sustained, and satisfactory outcomes. Innovative approaches to safely and efficiently control pigmentation disorders are needed, given the incidence, psychosocial burden, and limitations of current therapies. Accordingly, this review critically evaluates recent advances in therapeutic approaches for hyperpigmentation (Figure 2), focusing on their potential translation into clinical and cosmetic practice.



Figure 2. Clinical examples of hyperpigmentation in patients with Fitzpatrick skin phototype III/IV. (a) Localized hyperpigmented patches on the malar and infraorbital areas; (b) Pigmentary alterations on the dorsum of the hand. Source: Author's personal collection. All images were obtained following informed consent from the participants.

2. Molecular Pathways Underlying Principal Hyperpigmentation Types

At the molecular level, chronic sun exposure is recognized as the most frequent trigger of hyperpigmentation. UV radiation modulates membrane phospholipids, inducing the formation of diacylglycerol (DAG), which attaches to the regulatory domain of protein kinase C (PKC), specifically the β -isoform, activating it. Subsequently, this enzyme phosphorylates

TYR, significantly increasing its catalytic activity and directly enhancing the rate of melanin synthesis [15]. In parallel, UVA exposure stimulates the generation of reactive oxygen species (ROS), which further enhances TYR activity, while UVB induces DNA damage in keratinocytes, activating p53 and stimulating the production of α -melanocyte-stimulating hormone (α -MSH) and adrenocorticotrophic hormone (ACTH) [15,16]. These peptides bind to the melanocortin-1 receptor (MC1R) on melanocytes, triggering the cyclic AMP–microphthalmia transcription factor (cAMP–MITF) pathway and upregulating melanogenic enzymes (TYR, TRP-1, and TRP-2) [15]. In addition to these direct effects, keratinocytes and fibroblasts exposed to UV also release paracrine mediators such as endothelin-1, basic fibroblast growth factor (bFGF), and stem cell factor (SCF), which support melanocyte survival and pigment production [16]. Beyond UV radiation, visible light, particularly blue light spectrum, also contributes to hyperpigmentation by activating melanocytes through the photoreceptor opsin-3 (OPN3). This activation induces calcium influx and stimulates downstream signaling pathways, such as mitogen-activated protein kinase (MAPK) and cAMP response element-binding protein (CREB). These pathways converge on microphthalmia transcription factor (MITF), sustaining melanogenic gene expression and resulting in prolonged pigment production [16].

Collectively, these biological pathways manifest as several clinically recognizable forms of hyperpigmentation, each characterized by distinct etiologic and therapeutic profiles. The main subtypes relevant to cosmetic dermatology—melasma, post-inflammatory hyperpigmentation (PIH), drug-induced hyperpigmentation (DIH), ephelides, and solar lentigines—are summarized in Table 1 [6,8,17–31]. This table integrates clinical features, underlying pathogenic mechanisms, and representative therapeutic strategies, providing a translational overview that links molecular pathways to clinical decision-making.

Table 1. Overview of the main types of hyperpigmentation, including their clinical features and representative treatment options. Data compiled from [6,8,17–31].

Disorder	Etiology	Lesion Location	Clinical Presentation	Treatment Options
Melasma	UV/visible light-induced melanocyte activation, hormonal factors (e.g., pregnancy, oral contraceptives)	Sun exposed areas, especially face	light- to dark-brown macules/patches, symmetric	Photoprotection; topical agents (e.g., hydroquinone, azelaic acid, kojic acid); oral agents (e.g., tranexamic acid); chemical peels; microneedling; lasers
PIH	Increased melanocyte stimulation secondary to inflammation/injury	Sites of inflammation/trauma	Brown to blue-gray macules/patches, depending on depth	Photoprotection; topical agents (e.g., hydroquinone, retinoids, azelaic acid); chemical peels; lasers/light-based therapies
DIH	Accumulation of drugs or their metabolites within the dermis or epidermis	Sun-exposed areas (may involve nails and mucosae)	Brown, blue-gray, violaceous or yellow pigmentation	Discontinuation/substitution of the drug; photoprotection
Ephelides (Freckles)	Genetic predisposition + UV-induced upregulation of melanocyte activity	Sun-exposed areas	Small 1–3 mm red to tan/light brown, sharply demarcated macules	Photoprotection; chemical peels; cryotherapy; laser therapy ¹
Solar Lentigines	Chronic UV-induced melanocyte hyperplasia	Sun-exposed areas	1–3 cm light yellow to dark brown, flat, well-defined patches	Topical agents (e.g., hydroquinone, retinoids); chemical peels; cryotherapy; intense pulsed light; laser therapy

Abbreviations: DIH, drug-induced hyperpigmentation; PIH, post-inflammatory hyperpigmentation; UV, ultraviolet; ¹ Treatment may be pursued solely for cosmetic concerns.

3. Current Strategies in the Treatment of Hyperpigmentation

In the context of hyperpigmentation management, the terms “treatment” and “therapy” encompass a wide spectrum of interventions, including prescription drugs, cosmetic products, dietary supplements, medical devices, and in-office dermatological procedures. These approaches differ substantially in their regulatory classifications, intended uses, safety profiles, and the level of medical supervision required. Throughout this section, depigmenting strategies are discussed according to their primary mode of application and regulatory status, distinguishing between topical agents used in cosmetic or pharmaceutical formulations, oral agents marketed as dietary supplements or prescription medications, and some procedures that require specialized equipment and professional supervision.

3.1. Main Topical Depigmenting Agents

Topical agents, typically formulated as gels or creams, are the first-line approach for the home-based management of hyperpigmentation and play a central role in treating different hyperpigmentation disorders. These compounds act through distinct pathways, and, for clarity, are generally categorized into four groups according to their primary mechanism of action: tyrosinase inhibitors, inhibitors of melanosome transfer, antioxidants, and agents that accelerate epidermal turnover and desquamation. Among these, tyrosinase inhibitors have been the most extensively studied, as they target TYR and modulate its activity at different levels [32,33]. HQ is considered the gold standard and acts via multiple routes: (i) direct inhibition of TYR activity and interference with tyrosine oxidation, (ii) disruption of melanosome formation and transfer through the dendritic projections, and (iii) melanocyte cytotoxicity mediated by oxidative metabolites, particularly at higher concentrations [32,34]. However, HQ faces distinct regulatory restrictions depending on the jurisdiction: in the European Union, it is prohibited in cosmetic products and may only be used in medical/pharmaceutical preparations, typically under prescription, due to safety concerns and its regulatory classification as a drug [32]. Topical HQ is typically prescribed at 2–5%, alone or in combination with a corticosteroid and a retinoid (known as triple combination cream, TCC), with clinical improvement usually observed within 4–8 weeks [34]. Nevertheless, its use is limited by adverse effects, including erythema and contact dermatitis [32–36]. Safer alternatives include agents such as arbutin and its derivative deoxyarbutin, which inhibit TYR with lower toxicity compared to HQ; kojic acid (KA), a fungal metabolite that chelates copper ions at the active site of TYR while exhibiting antioxidant activity; and azelaic acid (AZA), which inhibits TYR and melanocyte proliferation [32,36–39]. Depending on the concentration, these depigmenting agents can be used as drugs or as cosmetic ingredients. The Scientific Committee on Consumer Safety (SCCS) recommends concentrations of α -arbutin up to 2% in cosmetic products such as face creams [40]. The existing dermatological data also support the safety of kojic acid at a concentration of 2% in cosmeceuticals [41]. Conversely, the poor skin penetrability and low solubility of azelaic acid demand higher concentrations to achieve the desired effect, thus, commercially available creams and gels usually contain 20% of this depigmenting agent [42].

Given that visible pigmentation also depends on the efficiency of melanosomes transfer from melanocytes to surrounding keratinocytes, compounds that interfere with this process provide a complementary strategy to limit pigment distribution across the epidermis [43–45]. Methylophipogonanone B (MOPB) and centaureidin have been reported to induce temporary dendrite retraction in melanocytes, thereby reducing melanosome transfer without affecting melanin synthesis or cell viability [44–47]. Niacinamide is another well-established agent in this category, consistently shown to decrease melanosome transfer and improve skin brightness [43,45,48]. Soybean and soymilk-derived extracts represent another option, as their naturally occurring serine protease inhibitors reduce the activation

of protease-activated receptor-2 (PAR-2) on keratinocytes, a key regulator of melanosome uptake [43–46]. Research has also investigated the role of lectins and neoglycoproteins in this regulatory process, given their ability to modulate recognition and adhesion events between melanocytes and keratinocytes [43–45,49]. Notably, Minwalla et al. [50] utilized flow cytometry and electron microscopy to demonstrate that both lectins and neoglycoproteins inhibited melanosome transfer in co-culture systems, with neoglycoproteins exhibiting stronger, and dose-dependent effects, particularly when applied in combination [50].

Regarding antioxidants, the main agents include vitamin C (ascorbic acid) and its derivatives, vitamin E (α -tocopherol), and niacinamide, all of which can mitigate pigmentation by scavenging ROS and modulating redox-sensitive steps of melanogenesis [33,43–45]. Vitamin C can additionally interact with copper at the tyrosinase active site or with *o*-quinones, thereby limiting the oxidative polymerization of melanin intermediates [43,44]. Plant-derived flavonoids also stand out for their dual role as antioxidants and tyrosinase inhibitors [49,51]. Zuo et al. [51] highlighted that their ability to scavenge ROS and inhibit TYR activity is strongly influenced by the number and position of phenolic hydroxyl groups in their structure, which enhance both antioxidant and depigmenting effects, as observed in compounds such as baicalein, rosmarinic acid, and dihydromyricetin [49,51].

Finally, agents that accelerate epidermal turnover and desquamation contribute to skin lightening by promoting keratinocyte renewal and facilitating the removal of the stratum corneum, where melanin accumulates [33,43,45]. The most employed compounds include retinoids, exfoliating acids, particularly α -hydroxy acids (AHAs, e.g., glycolic and lactic acids) and β -hydroxy acids (BHAs, e.g., salicylic acid), and certain unsaturated fatty acids such as linoleic acid [33,43,45]. AHA are weak organic acids naturally found in fruits, milk, and plants that promote the removal of epidermal cells in the stratum corneum by weakening the ionic bonds that mediate corneocyte adhesion [33,45]. Their effect is concentration-dependent: lower concentrations provide gentle renewal, while higher concentrations induce more extensive peeling and epidermal remodeling [33,45]. Salicylic acid, the main representative of β -hydroxy acids, acts similarly by promoting epidermal exfoliation (in concentrations above 2%). However, this compound has the advantage of being lipophilic, having greater capacity for deeper penetration into the pilosebaceous unit. This property makes it especially useful for oily and acne-prone skin [33,45].

3.2. Oral Therapies

Oral therapies represent an important alternative or adjunct to topical approaches in the management of hyperpigmentation. In this context, oral antioxidants and melanogenesis-modulating agents have been explored for their ability to influence pigmentation through systemic mechanisms, complementing localized skin effects [6,8]. While both topical and oral treatments are suitable for outpatient management, oral agents may offer greater therapeutic potency and improved convenience by eliminating the need for frequent applications [4]. Nevertheless, their use is often associated with several limitations, including higher costs, a delayed onset of action, and an increased risk of systemic adverse effects [4,8]. Therefore, oral agents are usually used as adjuvants to topical therapy [4,8].

Among the available oral agents, tranexamic acid (TXA) is the most widely studied. Beyond its established clinical use for the short-term management of abnormal or excessive bleeding (owing to its modulation of the coagulation cascade)—where it is routinely prescribed (e.g., Traxamac[®] 250 mg) [4,8]—TXA has emerged as a promising dermatological tool. In this field, TXA has been shown to inhibit UV-induced plasmin activity, thereby reducing the production of inflammatory mediators such as arachidonic acid and prostaglandins. This inhibition ultimately attenuates melanin synthesis, a mechanism supported by experimental studies in guinea pig skin models [6].

Glutathione (GSH), a well-known food supplement, has also attracted considerable interest over the past decade as a potential oral depigmenting agent owing to its proposed skin effects [6,8,52,53]. Mechanistically, GSH is thought to suppress melanogenesis by inhibiting tyrosinase through several pathways, including direct copper chelation at the enzyme's active site, interference with tyrosinase transport to premelanosomes, and indirect inhibition via its antioxidant activity [52,53]. Despite these mechanistic insights, the clinical efficacy of orally administered GSH remains controversial, primarily due to its low and variable bioavailability. Conventional oral formulations are susceptible to gastrointestinal degradation and extensive first-pass metabolism, which may substantially limit systemic absorption [52,53]. To address these limitations, alternative delivery strategies such as buccal lozenges and novel formulations have been explored to enhance bioavailability and prolong systemic exposure [53]. In this context, a clinical study by Handog et al. [54] demonstrated that daily administration of oral GSH lozenges for eight weeks resulted in statistically significant reductions in melanin indices, with approximately 90% of participants exhibiting moderate improvement in skin pigmentation and no serious adverse events reported [54]. However, the small sample size and the short intervention period limit the generalizability of these findings. From a safety standpoint, oral GSH is generally regarded as safe and is commonly marketed as a food or dietary supplement. Reported adverse effects are typically mild and transient, including gastrointestinal discomfort, pruritus, erythema, and fatigue [53].

Beyond TXA and GSH, other oral agents, including supplements such as melatonin, and drugs such as cysteamine hydrochloride and isotretinoin, have been investigated as adjunctive options in selected cases of hyperpigmentation [4,6,8,53]. Melatonin has been proposed to exert indirect depigmenting effects through its antioxidant and free radical scavenging properties, whereas cysteamine acts primarily as a tyrosinase inhibitor and hydroxyl radical scavenger [6,8]. However, it is important to note that no official clinical guidelines include melatonin as a standardized or approved therapy for hyperpigmentation. Any use in this context is currently off-label or experimental and is not formally recognized as an approved therapeutic indication by major regulatory agencies. Oral isotretinoin, renowned for its efficacy in acne management, has also been investigated for its potential role in hyperpigmentation [4,53]. Although the precise mechanisms underlying its effects on hyperpigmentation remain incompletely understood, it is important to consider that this teratogen is associated with a well-established adverse effect profile, including xerosis, cheilitis, and dyslipidemia. This underscores the necessity of rigorous patient monitoring, routine laboratory evaluation, and appropriate counseling regarding contraception and overall safety [53]. However, similarly to melatonin, there is no specific indication approved by regulatory agencies, such as the EMA or FDA, for the use of isotretinoin in hyperpigmentation.

The main oral agents reported in the literature, along with their mechanisms of action, are summarized in Table 2 [4,6,8,53].

Table 2. Overview of oral depigmenting agents in hyperpigmentation management. Data compiled from [4,6,8,53].

Depigmenting Agents	Mechanism of Action	Clinical Notes
TXA	Inhibits tyrosinase via reduction of UV-induced plasmin activity	Effective in melasma; often combined with topical therapy
Melatonin	Radical scavenging and antioxidant properties; inhibits the α -MSH receptor	Usually used alone or in combination with 4% hydroquinone
GSH	Inhibits tyrosinase; shifts melanin synthesis toward pheomelanin formation	Oral and topical forms show comparable efficacy in melasma
Cysteamine hydrochloride	Scavenges hydroxyl radicals and inhibits tyrosinase activity	Improves melasma; acts as an adjunctive antioxidant

Abbreviations: GSH, glutathione; MSH, melanocyte-stimulating hormone; TXA, tranexamic acid; UV, ultraviolet.

3.3. Chemical Peels and Laser Therapy

Chemical peels are widely employed techniques to treat hyperpigmentation, serving as a complementary approach to topical treatments [3,4,6,8]. This dermatological procedure, most frequently performed on the face, involves the controlled application of chemical agents to induce exfoliation and remove the superficial layers of the stratum corneum, thereby reducing the visibility of dark patches [6,8]. Common peeling agents and their concentrations reported in the literature include Jessner's solution (14% salicylic acid, 14% lactic acid, and 14% resorcinol in an alcohol base), tretinoin (1–10%), and salicylic acid (20–30%) [6,8]. Trichloroacetic acid (TCA) peels are also used to manage melasma, although higher concentrations may increase the risk of PIH, particularly in darker phototypes [6,8]. The selection of each agent depends on desired depth of action and the patient's skin characteristics, while concentrations may vary according to the specific peeling protocol [6,8].

Peels are generally categorized by depth, with superficial peels being the most common due to their safety and effectiveness, while medium and deep peels are used less frequently due to their higher risks [4,6,8]. Although low-concentration superficial peels may be formulated as cosmetic products for home use, the chemical peels most employed in the clinical management of hyperpigmentation—particularly medium and deep peels—are considered medical procedures. Therefore, they require professional application and supervision, given the potential for adverse effects such as persistent irritation or scarring [6,8].

Laser therapy is another established second-line, in-office therapeutic approach for managing hyperpigmentation, offering a targeted method to reduce melanin and improve skin tone [4]. These modalities are classified as medical device-based procedures and require specialized equipment and trained professionals. Unlike chemical peels, which act via exfoliation, lasers use high-intensity light to selectively interact with melanin, minimizing damage to surrounding tissues [6,8].

Several types of light-based modalities are commonly used in dermatology. Intense Pulsed Light (IPL) uses of a xenon chloride lamp and has shown promise in treating conditions like melasma [6,8]. Another widely used option for hyperpigmentation is the Q-Switched neodymium-doped yttrium aluminum garnet (QS Nd: YAG) laser, available in several commercially produced systems (Fotona d.o.o., Ljubljana, Slovenia), which is highly selective for melanin and thus minimizes damage to the adjacent epidermis [6]. Q-Switched ruby lasers (QSRL) operate through a similar mechanism to QS Nd: YAG but with variable efficacy, while Erbium: YAG lasers produce minimal thermal injury, reducing the risk of PIH and making them appropriate for more sensitive skin types [6,8].

Although laser therapy can provide rapid and effective results, it also carries risks, including irritation, erythema, PIH, or scarring when incorrectly applied [6,8]. Therefore, appropriate laser selection, careful patient assessment, and professional administration are essential to maximize efficacy and minimize adverse effects.

4. Emerging Treatments and Innovative Systems to Encapsulate Depigmenting Agents

4.1. Phytochemicals

Increasingly recognized for their natural origin, phytochemicals offer a promising strategy to manage hyperpigmentation by acting through multiple mechanisms. Many plant-derived compounds, including polyphenols and flavonoids such as ellagic acid, glabridin, and resveratrol, have shown significant potential in protecting melanocytes from UV-induced oxidative stress and inflammation [6,55]. However, most evidence supporting these compounds is derived from *in vitro* and animal models. For instance, the efficacy of glabridin has been studied *in vitro* using mushroom tyrosinase assays and B16F10 melanoma cell lines, whereas the depigmenting potential of resveratrol has been evaluated

in vivo in guinea pig models [55]. Aloesin, a C-glucosylated derivative of Aloe vera, exhibits potent anti-TYR activity by inhibiting L-DOPA oxidation [6,55]. Consistent with other polyphenolic compounds, its depigmenting effects have been primarily validated in in vitro models [55]. However, despite its promising biological activity, the relatively high molecular weight and hydrophilic nature of aloesin limit its permeation through the stratum corneum, which may compromise its clinical efficacy when applied topically [6]. Citrus-derived hesperidin and licorice compounds such as liquiritin also demonstrate anti-TYR and anti-inflammatory effects [6,55]. *Polypodium leucotomos* (PL), a fern extract explored as an oral photoprotective agent, represents one of the few phytochemicals supported by human clinical evidence and has been shown to reduce UV- and visible-light-induced pigmentation and oxidative damage, supporting its use as a systemic adjunct to topical treatments [6].

Nevertheless, despite their versatility and broad biological activity, phytochemicals face notable limitations, particularly related to chemical stability, solubility, and skin penetration. Moreover, although many natural compounds show promising results in vitro, relatively few have advanced to clinical trials, where consistent efficacy must be demonstrated [55]. Overcoming these challenges through optimized formulations, enhanced bioavailability, and rigorous clinical evaluation is essential to fully harness the therapeutic potential of phytochemicals in managing hyperpigmentation.

4.2. Lipid-Based Nanocarriers

Lipid-based nanocarriers have recently gained significant attention as an advanced strategy for improving the delivery of depigmenting agents. By encapsulating active compounds within nanosized lipid matrices, these systems enhance cutaneous permeation, protect cargo from degradation, and allow for the controlled modulation of active ingredient release [56]. The main lipid-based nanocarriers are described in detail in Table 3 [6,8,56–59]. Lipid-based technologies have achieved a higher degree of translational maturity compared to other emerging systems. Several liposome-based formulation have been approved by the U.S. Food and Drug Administration (FDA) for a variety of clinical applications, successfully transitioning from experimental stages to clinical use, thereby demonstrating the translational success of these technologies [58].

Table 3. Main lipid-based nanocarriers for depigmenting agents. Data compiled from [6,8,56–59].

Nanocarrier Type	Composition	Advantages	Limitations	Examples of Encapsulated Actives
Solid lipid nanoparticles (SLN)	Solid lipid	Improve stability; enhanced skin permeation, controlled release	Potential polymorphic transitions of lipids; long-term instability	KA, HQ, N-Acetyl-D-Glucosamine
Nanostructured lipid carriers (NLC)	Solid liquid lipid	Higher drug-loading capacity; lower drug expulsion		Trans-Resveratrol, Deoxyarbutin
Liposomes	Phospholipid bilayers	Increase skin deposition; increase bioavailability; biodegradable	Low encapsulation efficiency; physicochemical instability; low encapsulation efficiency	Arbutin; AZA; 4-n-butylresorcinol;
Niosomes	non-ionic surfactants generally combined with cholesterol	Greater chemical stability; high biocompatibility; low toxicity; low production cost	Physical instability and aggregation; potential leakage or hydrolysis of the encapsulated compounds	Arbutin, KA
Microemulsions	aqueous phase + oil phase, separated by a surfactant layer	Facilitate greater absorption of bioactive compounds	Possible risk of irritation due to high surfactant levels; low viscosity, spreadability and reduced bioavailability	Ascorbic acid
Nanoemulsions		Enhance penetration and stability; suitable for topical applications		KA esters, AZA, kojic monooleate

Abbreviations: AZA, azelaic acid; HQ, hydroquinone; KA, kojic acid; NLC, nanostructured lipid carriers; SLN, solid lipid nanoparticles.

4.3. Polymer-Based Nanocarriers

Polymer-based nanocarriers are nanoscale systems composed of biodegradable and biocompatible polymers (e.g., chitosan, albumin, and gelatin) with particle sizes ranging from 10 to 1000 nm [56]. The main types include polymeric nanoparticles and polymeric micelles, with the former being the most extensively used [56]. These nanocarriers are particularly suitable for topical applications as they can improve drug stability, enhance skin penetration, and provide controlled or sustained drug release [56,57]. Polymeric nanoparticles can be classified as nanospheres (matrix systems) or nanocapsules (reservoir systems), allowing modulation of drug release via diffusion, polymer swelling, enzymatic cleavage, or desorption [56].

Polymers such as chitosan and ethyl cellulose have demonstrated significant promise as nanocarriers for depigmenting agents. In a study conducted by Duarah et al. [60] L-ascorbic acid (50 mg) was encapsulated into ethyl cellulose nanoparticles and subsequently incorporated into a hydroxypropyl methylcellulose gel intended for topical application. The system significantly improved the stability of L-ascorbic acid and provided sustained release for up to eight hours, ensuring prolonged antioxidant and anti-tyrosinase activities within the skin [60]. Despite these advantages, limitations of these nanocarriers include challenges in industrial scale-up and limited toxicity data, requiring further comprehensive safety studies [57]. Although numerous *in vitro*, *ex vivo*, and *in vivo* studies have demonstrated the enhanced therapeutic potential of polymeric nanoparticles for topical skin applications, evidence from human clinical trials remains limited, underscoring the need for further clinical validation and development [61].

4.4. Inorganic Nanocarriers

Inorganic nanocarriers are nanoscale systems with a core-shell structure, composed of metals (e.g., gold, silver, and iron oxide) or non-metals (e.g., diamond, sulfur, and fullerenes) currently being investigated for hyperpigmentation, particularly melasma [8,56]. Notable examples include fullerenes and gold nanoparticles (AuNPs). Fullerenes are spheroidal carbon nanoparticles with a large inner cavity that enables the encapsulation of biomolecules, enhancing topical delivery [8,56]. They exhibit antioxidant and anti-TYR activity and, upon skin contact, distribute intercellularly, improving the absorption and controlled release of active ingredients [8,62]. However, their long-term safety remains under investigation due to potential cytotoxicity and pro-oxidant effects at higher concentrations [8,56,57]. AuNPs are small, stable gold particles with antioxidant properties and excellent biocompatibility [8,56]. Studies have shown that AuNPs, especially those synthesized with *Panax ginseng* leaf extract, can inhibit TYR activity, reduce melanin synthesis, and suppress TYR gene expression, sometimes outperforming arbutin in melasma treatment [8,56,63]. Nevertheless, factors such as particle size, surface charge, and concentration may influence immunogenicity and cytotoxicity, while undefined safety profiles and high production costs limit their broader clinical or cosmetic application [8]. While applications of inorganic nanoparticles in pharmaceutical and biomedical fields are increasing steadily, their behavior regarding the skin barrier remains not fully understood, with conflicting results reported in the literature [64]. To improve translational relevance, human skin should be used as the preferred “gold standard” model for *in vitro* penetration experiments, and more studies are needed to correlate *in vitro* and *in vivo* animal data with human outcomes [64].

4.5. Microneedling

Microneedling is a minimally invasive technique in which fine needles penetrate the epidermis and upper dermis (typically depths of approximately 0.5 mm), inducing a controlled wound-healing response that enhances skin regeneration [6]. In the context of

hyperpigmentation disorders, microneedling has gained attention not only for its regenerative effects but also for its ability to enhance the transdermal delivery of depigmenting agents by transiently disrupting the stratum corneum barrier [6,8].

Several experimental and clinical studies have demonstrated that microneedling-assisted delivery significantly improves the efficacy of topical depigmenting agents compared to topical application alone. Combination protocols involving agents such as rucinol, sophora-alpha serum, triple combination cream, vitamin C, and TXA have been associated with greater reductions in pigmentation severity, particularly in melasma [6,8]. Clinical validation has been provided by randomized and prospective trials. In a randomized controlled study involving 45 patients with facial melasma, microneedling combined with topical TXA resulted in significantly greater reductions in modified Melasma Area and Severity Index (mMASI) scores compared to microneedling combined with metformin or a modified Kligman's formula over an eight-week treatment period, with minimal and transient adverse effects reported [65]. Similarly, a prospective single-blind clinical trial comparing microneedling-assisted delivery of TXA versus vitamin C demonstrated significant MASI reductions in both treatment arms, although no statistically significant differences were observed between groups [66].

Beyond conventional microneedling devices used in clinical settings, microneedle-based delivery systems, particularly dissolving microneedle (DMN) patches incorporating depigmenting agents such as TXA and hyaluronic acid (HA), have emerged as alternative strategies for transdermal delivery [8]. These systems create microchannels in the stratum corneum or dissolve upon application, enabling localized drug deposition, enhanced bioavailability, and reduced systemic exposure [8].

From a translational and regulatory perspective, it is essential to distinguish between these approaches. Conventional microneedling is generally classified as a medical procedure performed in a clinical setting, requiring professional supervision and appropriate device regulation. In contrast, many commercially available microneedle patches are predominantly regulated as cosmetic products intended for home use, with claims typically supported by preclinical data or consumer testing rather than large-scale randomized controlled trials.

Despite its therapeutic potential, microneedling faces certain limitations, including variability in needle penetration depending on skin thickness and operator technique, as well as the risk of transient irritation or post-procedural erythema, and PIH (particularly in darker phototypes). Furthermore, DMN systems face specific challenges such as incomplete microneedle dissolution and manufacturing hurdles related to drug loading, mechanical stability, scalability, and cost [8].

5. Evidence from Clinical Trials on Topical Depigmenting Strategies

Although significant advances have been made in elucidating melanogenesis and developing novel depigmenting formulations, most of the evidence for active ingredients and delivery systems remains preclinical, predominantly derived from *in vitro* and *in vivo* studies, with only a limited number progressing to early clinical evaluation [55]. In general, clinical research on depigmenting agents is still in its infancy, with recent systematic reviews and meta-analyses reporting that available clinical evidence is largely confined to small, short-term studies with heterogeneous endpoints and outcome measures [67,68]. To provide an updated overview of the current clinical research landscape, an evidence map of the main completed and ongoing clinical trials conducted over the past fifteen years (2010–2025) is presented in Table 4. All information was retrieved from the U.S. National Library of Medicine (ClinicalTrials.gov). This analysis includes exclusively interventional studies that investigated topical treatments for hyperpigmentation as the primary

intervention. Therefore, trials in which topical formulations were used solely as adjunctive therapies (e.g., combined with laser or microneedling) were excluded. Only trials with an active or completed recruitment status (i.e., specifically “Completed,” “Active, not recruiting,” “Recruiting,” or “Enrolling by invitation”) were included in Table 4, as these represent trials that have generated or are currently generating clinical data. Data were retrieved up to 22 October 2025, to ensure the inclusion of the most recent records available at the time of analysis.

Table 4. Main interventional clinical trials (2010–2025) evaluating topical treatments for hyperpigmentation, without adjunctive therapies.

NCT ID	Reg. Year/Status	Formulation	Enrollment	Main Findings/Adverse Effects
NCT01542138	2012 (COMPLETED)	Desonide cream (0.05%) Vs. niacinamide cream (4%) Vs. placebo	28 (F)	Results not yet reported
NCT02730819	2016 (COMPLETED)	Topical cream (2013-MCN-333) containing tazarotene (0.075%), AZA (20%), tacrolimus (0.1%) and microfine zinc oxide (10%)	19 (F/M)	Median MASI reduction: −11.7 units (full range: −15.3 to −3.6); all participants showed clinical improvement from baseline; mild and transient adverse effects observed
NCT02905903	2016 (COMPLETED)	TCA (20%, 25%, 30%, 35%)	30 (F/M)	Results not yet reported
NCT03392623	2018 (COMPLETED)	50 SPF sunscreen Vs. niacinamide (4%) Vs. retinoic acid (0.025%)	28 (F)	Results not yet reported
NCT03926845	2019 (COMPLETED)	Topical cream containing isobutylamido-thiazolyl-resorcinol (0.2%) Vs. placebo	200 (F/M)	Results not yet reported
NCT03982849	2019 (COMPLETED)	Silymarin cream (0.7%) Vs. HQ cream (4%)	92 (F)	Results not yet reported
NCT03933774	2019 (COMPLETED)	Tretinoin cream (0.05%) Vs. placebo	25 (F/M)	Both sides showed a reduction in hyperpigmentation (the difference between tretinoin-treated and placebo-treated areas was not statistically significant); local irritation was reported only on tretinoin-treated sites
NCT05119413	2021 (COMPLETED)	New trio (thiamidol + retinoid + topical steroid) Vs. Kligman formula (HQ + retinoid + topical steroid)	40 (F/M)	Results not yet reported
NCT05471947	2022 (COMPLETED)	TCA (15%) + GA (3%)	20 (F/M)	Results not yet reported
NCT05704114	2023 (COMPLETED)	Tazarotene lotion (0.045%)	20 (F/M)	Results submitted, pending quality control (QC) review
NCT05790577	2023 (COMPLETED)	Metformin (30%) + nicotinamide lotion (2%) Vs. Kligman Formula (HQ + retinoid + topical steroid)	88 (F/M)	Results not yet reported
NCT05969587	2023 (COMPLETED)	Cysteamine cream (5%) Vs. HQ cream (4%) + betamethasone valerate cream (0.06%)	28 (F/M)	Results not yet reported
NCT05986123	2023 (RECRUITING)	Topical cream containing a combination of niacinamide, arbutin, <i>Scutellaria baicalensis</i> root extract, <i>Centella asiatica</i> extract and <i>Camellia sinensis</i> leaf extract	25 ² (F/M)	Study ongoing; results not yet available
NCT05998200	2023 (RECRUITING)	Serum with low concentration of AHA (1% GA and LA) and PGA	34 ² (F/M)	Study ongoing; results not yet available
NCT06080035	2023 (COMPLETED)	Topical Cetyl Tranexamate Mesylate	22 (F/M)	Results not yet reported
NCT06153134	2023 (RECRUITING)	Curcuma xanthorrhiza Roxb. cream (10%) Vs. KA cream (2%)	15 ² (F/M)	Study ongoing; results not yet available

Table 4. Cont.

NCT ID	Reg. Year/Status	Formulation	Enrollment	Main Findings/Adverse Effects
NCT06213987	2024 (COMPLETED)	Tretinoin cream (0.025%) Vs. placebo	20 (F/M)	Results not yet reported
NCT07062120	2025 (COMPLETED)	Salicylic acid peel (30%) + 10% nicotinamide cream (Vs. peel alone, cream alone, placebo)	56 (F/M)	Results not yet reported
NCT06780644	2025 (NOT YET RECRUITING)	TCC of flucinolone acetone (0.01%), HQ (4%), tretinoin (0.05%) Vs. TCC of mometasone furoate (0.1%), HQ (4%), tretinoin (0.05%)	56 ² (F)	Study ongoing; results not yet available
NCT06833996	2025 (COMPLETED)	Bakuchiol cream Vs. placebo	22 (F/M)	Results not yet reported
NCT06957834	2025 (COMPLETED)	Eflornithine hydrochloride cream (11.5%) Vs. HQ cream (2%)	20 (F/M)	Results not yet reported
NCT07060157	2025 (NOT YET RECRUITING)	Resveratrol Gel (1%) Vs. TCA (20%)	41 ² (F/M)	Study ongoing; results not yet available
NCT07133204	2025 (COMPLETED)	Cream infused with organic extract of <i>Scutellaria baicalensis</i> .	38 (F/M)	Results not yet reported

Notes: Data from ClinicalTrials.gov registry (U.S. National Library of Medicine). Abbreviations: AHA, alpha hydroxy acid; AZA, azelaic acid; F, female; GA, glycolic acid; HQ, hydroquinone; KA, kojic acid; LA, lactic acid; M, male; MASI, Melasma Area and Severity Index; PGA, polyglutamic acid; QC, quality control; "Reg. Year", year of registration; SPF, sun protector filter; TCA, trichloroacetic acid; TCC, triple combination cream; ² estimated number of participants (study still recruiting).

Although a substantial proportion of these registered clinical trials have not yet reported final outcomes or lack publicly available results, which limits robust comparative analysis, their inclusion is essential. They provide a comprehensive overview of current research activity and highlight innovations that distinguish these formulations from previously studied or commercially available products, particularly through the exploration of novel combinations of active ingredients and the optimization of formulations designed to enhance cutaneous penetration, stability, or local bioavailability.

6. Discussion and Future Directions

In the context of clinical research, topical depigmenting therapies have developed gradually but are still at an early stage, as evidenced by the compiled clinical. Although many different active ingredients have been tested, ranging from traditional agents like HQ and tretinoin to newer substances like cysteamine, niacinamide, and silymarin, most trials remain small-scale, short-term, and methodologically heterogeneous. Common limitations include small sample sizes, brief treatment durations (typically 8–12 weeks), heavy reliance on the MASI as the primary endpoint, and limited follow-up; collectively, these factors constrain comparability across studies and hinder the development of standardized treatment recommendations.

Due to their historical use as first-line topical depigmenting agents, HQ and tretinoin continue to be used as benchmarks in most trials. However, growing safety and regulatory concerns, particularly regarding long-term HQ use, have prompted research into alternative agents with improved multi-target activity and tolerability. Among these, niacinamide, AZA, and plant-derived antioxidants have shown promising results, though they often fail to surpass the efficacy of HQ-based regimens.

The emphasis on combination formulations is a noteworthy trend in recent trials, incorporating keratolytic, antioxidant, or anti-inflammatory components to enhance penetration and address multiple stages of melanogenesis. While these strategies appear to accelerate pigment reduction and improve lesion uniformity, the predominance of short

intervention periods and limited follow-up precludes definitive conclusions regarding long-term efficacy, relapse rates, and sustained pigment control.

Importantly, as shown in Table 4, a sizable fraction of these clinical trials evaluating topical depigmenting formulations are still ongoing or have not yet reported outcome data, limiting the ability to reliably evaluate the clinical efficacy and safety. The absence of published results should not be interpreted as a lack of therapeutic potential; rather, it reflects broader challenges in clinical trial execution and reporting, including prolonged study timelines, complex pigmentation endpoints, and regulatory or logistical delays. Among the few clinical trials with available results, adverse effects were generally mild, with transient erythema, burning, or irritation being the most frequently reported events.

Overall, future research should prioritize well-designed, multicenter clinical trials with larger sample sizes, standardized outcome measures, and extended follow-up periods. Such efforts are essential to clarify the true clinical value of emerging topical depigmenting strategies and to enhance the comparability and reproducibility of results.

7. Conclusions

Skin hyperpigmentation represents a complex and multifactorial dermatological condition driven by the interplay of genetic, hormonal, environmental, and inflammatory factors. Although conventional therapeutic strategies—such as HQ, retinoids, chemical peels, and laser-based procedures—remain central to clinical practice, their utility is frequently constrained by limited long-term efficacy, safety concerns, high relapse rates, and patient tolerability issues. These limitations underscore the need for more effective, safer, and sustainable depigmenting approaches.

Over the past decade, advances have redefined the therapeutic landscape, bridging the fields of dermatology, pharmaceutical technology, and cosmetic science. Progress in the understanding of melanogenesis and its regulatory pathways has fostered the development of innovative depigmenting agents and delivery technologies. In particular, nanotechnology-based systems, including lipid, polymeric, and inorganic nanocarriers, have emerged as potential tools to enhance cutaneous penetration, protect labile actives, enable controlled release, and reduce local or systemic adverse effects. Similarly, minimally invasive strategies, such as microneedling, have shown promise in improving the efficacy of topical agents by overcoming the barrier function of the stratum corneum while minimizing systemic exposure.

Despite these encouraging developments, the translation of emerging technologies into routine clinical or cosmetic practice remains limited by the scarcity of robust clinical evidence. Most available data are derived from preclinical studies or small, short-term clinical trials with heterogeneous designs and outcome measures. As highlighted in this review, well-designed, long-term, and adequately powered clinical trials are still urgently needed to validate the efficacy, safety, and durability of these novel approaches, as well as to establish standardized treatment protocols.

In essence, the future of skin depigmentation will likely depend not only on novel molecules but also on smart delivery systems that interact with the skin's natural complexity. By combining mechanistic insights, pharmaceutical innovation, and rigorous clinical validation, next-generation depigmenting strategies hold the potential to offer more personalized, effective, and evidence-based solutions, aligning therapeutic performance with safety, regulatory standards, and patient-centered expectations.

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Abbreviations

The following abbreviations are used in this manuscript:

AHA	α -Hydroxy acids
ACTH	Adrenocorticotrophic hormone
AuNPs	Gold nanoparticles
AZA	Azelaic acid
bFGF	Basic fibroblast growth factor
BHA	β -hydroxy acids
cAMP-MITF	cyclic AMP–microphthalmia transcription factor
CREB	cAMP response element-binding protein
DAG	Diacylglycerol
DHI	5,6-dihydroxyindole
DHICA	5,6-dihydroxyindole-2-carboxylic acid
DIH	Drug-induced hyperpigmentation
DMN	Dissolving microneedle
DOPA	L-3,4-dihydroxyphenylalanine
DQ	Dopaquinone
FDA	Food and Drug Administration
GA	Glycolic acid
GSH	Glutathione
HA	Hyaluronic acid
HQ	Hydroquinone
IPL	Intense Pulsed Light
KA	Kojic acid
LA	Lactic acid
MAPK	Mitogen-activated protein kinase
MASI	Melasma Area and Severity Index
MC1R	Melanocortin-1 receptor
MITF	Microphthalmia transcription factor
MOPB	Methylophiopogonanone B
MSH	melanocyte-stimulating hormone
NLC	Nanostructured lipid carriers
OPN3	Opsin-3
PAR	Protease-activated receptor
PGA	Polyglutamic acid
PIH	Post-inflammatory hyperpigmentation
PKC	Protein kinase C
PL	<i>Polypodium leucotomos</i>
QC	Quality control
QS Nd: YAG	Q-switched neodymium-doped yttrium aluminum garnet
QSRL	Q-switched ruby lasers
ROS	Reactive oxygen species

SCF	Stem cell factor
SLN	Solid lipid nanoparticles
SPF	Sun protector factor
TCA	Trichloroacetic acid
TCC	Triple combination cream
TRP1	Tyrosinase-related protein 1
TRP2	Tyrosinase-related protein 2
TXA	Tranexamic acid
TYR	Tyrosinase
UV	Ultraviolet

References

- Jin, R.; Luo, L.; Zheng, J. The Trinity of skin: Skin homeostasis as a neuro-endocrine-immune organ. *Life* **2022**, *12*, 725. [CrossRef]
- Nguyen, A.V.; Soulika, A.M. The dynamics of the skin's immune system. *Int. J. Mol. Sci.* **2019**, *20*, 1811. [CrossRef]
- Li, C.; Kuai, L.; Cui, R.; Miao, X. Melanogenesis and the targeted therapy of melanoma. *Biomolecules* **2022**, *12*, 1874. [CrossRef]
- Thawabteh, A.M.; Jibreen, A.; Karaman, D.; Thawabteh, A.; Karaman, R. Skin pigmentation types, causes and treatment—A review. *Molecules* **2023**, *28*, 4839. [CrossRef] [PubMed]
- Alipour, N.; Burke, T.; Courtney, J. Skin type diversity in skin lesion datasets: A review. *Curr. Dermatol. Rep.* **2024**, *13*, 198–210. [CrossRef] [PubMed]
- Nautiyal, A.; Wairkar, S. Management of hyperpigmentation: Current treatments and emerging therapies. *Pigment Cell Melanoma Res.* **2021**, *34*, 1000–1014. [CrossRef] [PubMed]
- Fistarol, S.K.; Itin, P.H. Disorders of pigmentation. *J. Dtsch. Dermatol. Ges.* **2010**, *8*, 187–201. [CrossRef]
- Deb, A.; Sb, S.; B, S.; Hp, S.G.; Aj, R. Advancements in drug delivery for hyperpigmentation: Emerging therapies and future prospects. *Cutan. Ocul. Toxicol.* **2025**, *44*, 329–341. [CrossRef]
- Desai, S.R. Hyperpigmentation therapy: A review. *J. Clin. Aesthet. Dermatol.* **2014**, *7*, 13–17.
- Kerob, D.K.; Passeron, T.; Alexis, A.; Dreno, B.; Wei, L.; Morita, A.A.; Leok, C.; Puig, S.; Schalka, S.; Lim, H.W. Pigmentary disorders, prevalence, impact on quality of life and social stigmatization: Results of the first large international survey. *J. Am. Acad. Dermatol.* **2024**, *91*, AB280. [CrossRef]
- Taylor, A.; Pawaskar, M.; Taylor, S.L.; Balkrishnan, R.; Feldman, S.R. Prevalence of pigmentary disorders and their impact on quality of life: A prospective cohort study. *J. Cosm. Dermatol.* **2008**, *7*, 164–168. [CrossRef]
- Wang, J.Y.; Kabakova, M.; Philip, R.; Stolyar, J.; Berger-Gutierrez, R.; Jagdeo, J. The impact of hyperpigmentation on the lives of patients. *J. Drugs Dermatol.* **2025**, *24*, 668–674. [CrossRef]
- Draeos, Z.D. Skin lightening preparations and the hydroquinone controversy: Hydroquinone and skin lightening preparations. *Dermatol. Ther.* **2007**, *20*, 308–313. [CrossRef] [PubMed]
- Ghasemiyeh, P.; Fazlinejad, R.; Kiafar, M.R.; Rasekh, S.; Mokhtarzadegan, M.; Mohammadi-Samani, S. Different therapeutic approaches in melasma: Advances and limitations. *Front. Pharmacol.* **2024**, *15*, 1337282. [CrossRef] [PubMed]
- Gilchrest, B.A.; Park, H.Y.; Eller, M.S.; Yaar, M. Mechanisms of ultraviolet light-induced pigmentation. *Photochem. Photobiol.* **1996**, *63*, 1–10. [CrossRef] [PubMed]
- Nahhas, A.F.; Abdel-Malek, Z.A.; Kohli, I.; Braunberger, T.L.; Lim, H.W.; Hamzavi, I.H. The potential role of antioxidants in mitigating skin hyperpigmentation resulting from ultraviolet and visible light-induced oxidative stress. *Photodermatol. Photoimmunol. Photomed.* **2019**, *35*, 420–428. [CrossRef]
- Ogbechie-Godec, O.A.; Elbuluk, N. Melasma: An up-to-date comprehensive review. *Dermatol. Ther.* **2017**, *7*, 305–318. [CrossRef]
- Honigman, A.; Rodrigues, M. Differential diagnosis of melasma and hyperpigmentation. *Dermatol. Rev.* **2023**, *4*, 30–37. [CrossRef]
- Qu, Y.; Wang, S.; Xie, H.; Meng, X.; Cui, B.; Xiao, Z. Melasma secondary to drugs: A real-world pharmacovigilance study of the FDA adverse event reporting system (FAERS). *BMC Pharmacol. Toxicol.* **2025**, *26*, 73. [CrossRef]
- Maghfour, J.; Olayinka, J.; Hamzavi, I.H.; Mohammad, T.F. A focused review on the pathophysiology of post-inflammatory hyperpigmentation. *Pigment Cell Melanoma Res.* **2022**, *35*, 320–327. [CrossRef]
- Albahloul, A.M.; Alshehri, O.K.M.; Alrasheed, S.M.; Al Ali, M.A.; Al Sharif, A.O.R. Overview on post-inflammatory hyperpigmentation. *J. Pharm. Res. Int.* **2021**, *33*, 393–399. [CrossRef]
- Patel, A. Postinflammatory hyperpigmentation: Review of pathogenesis, prevention, and treatment. *Pigment Int.* **2014**, *1*, 59. [CrossRef]
- Lawrence, E.; Syed, H.A.; Al Aboud, K.M. Postinflammatory hyperpigmentation. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2025. Available online: <https://www.ncbi.nlm.nih.gov/books/NBK559150/> (accessed on 15 November 2025).

24. Dereure, O. Drug-induced skin pigmentation. Epidemiology, diagnosis and treatment. *Am. J. Clin. Dermatol.* **2001**, *2*, 253–262. [CrossRef] [PubMed]
25. Narayanan, A.; Chandrashekhar, L. Drug-induced pigmentation. *Pigment Int.* **2022**, *9*, 82–92. [CrossRef]
26. Tisack, A.; Mohammad, T.F. Drug-induced pigmentation: A review. *Drugs* **2024**, *84*, 1071–1091. [CrossRef]
27. Giménez García, R.M.; Carrasco Molina, S. Drug-induced hyperpigmentation: Review and case series. *J. Am. Board Fam. Med.* **2019**, *32*, 628–638. [CrossRef]
28. Camayo, T.V.; Lee, V.R.; Zhou, X.A. Drug-induced pigmentation. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2025. Available online: <https://www.ncbi.nlm.nih.gov/books/NBK542253/> (accessed on 16 November 2025).
29. Arni, C.; Preclaro, I. Drug-induced pigmentation. In *Pigmentation Disorders—Etiology and Recent Advances in Treatments*; IntechOpen: London, UK, 2023. [CrossRef]
30. Noroozi, S.; Fadaei, F.; Rahbar, M.; Tabarraei, M.; Mansouri, P.; Shirbeigi, L. Novel preventive and therapeutic strategies for ephelides (freckles) from a Persian medicine perspective: A narrative review. *J. Skin Stem Cell* **2022**, *9*, e123335. [CrossRef]
31. Plensdorf, S.; Livieratos, M.; Dada, N. Pigmentation disorders: Diagnosis and management. *Am. Fam. Physician* **2017**, *96*, 797–804.
32. Couteau, C.; Coiffard, L. Overview of skin whitening agents: Drugs and cosmetic products. *Cosmetics* **2016**, *3*, 27. [CrossRef]
33. Mohiuddin, A.K. Skin lightening & management of hyperpigmentation. *Pharm. Sci. Anal. Res. J.* **2019**, *2*, 180020.
34. Fabian, I.M.; Sinnathamby, E.S.; Flanagan, C.J.; Lindberg, A.; Tynes, B.; Kelkar, R.A.; Varrassi, G.; Ahmadzadeh, S.; Shekoohi, S.; Kaye, A.D. Topical hydroquinone for hyperpigmentation: A narrative review. *Cureus* **2023**, *15*, e48840. [CrossRef]
35. Burger, P.; Landreau, A.; Azoulay, S.; Michel, T.; Fernandez, X. Skin whitening cosmetics: Feedback and challenges in the development of natural skin lighteners. *Cosmetics* **2016**, *3*, 36. [CrossRef]
36. Hameed Gatea, A. Review on analysis of interesting whitening agents in cosmetics products. *IOP Conf. Ser. Mater. Sci. Eng.* **2020**, *928*, 052001. [CrossRef]
37. Phasha, V.; Senabe, J.; Ndzotoyi, P.; Okole, B.; Fouche, G.; Chuturgoon, A. Review on the use of Kojic Acid—A skin-lightening ingredient. *Cosmetics* **2022**, *9*, 64. [CrossRef]
38. Petrovici, A.-G.; Spennato, M.; Bitcan, I.; Péter, F.; Cotarcă, L.; Todea, A.; Ordodi, V.L. A comprehensive review of azelaic acid pharmacological properties, clinical applications, and innovative topical formulations. *Pharmaceuticals* **2025**, *18*, 1273. [CrossRef]
39. Liyanage, A.; Liyanage, G.; Sirimanna, G.; Schürer, N. Comparative study on depigmenting agents in skin of color. *J. Clin. Aesthet. Dermatol.* **2022**, *15*, 12–17.
40. Davis, E.C.; Callender, V.D. Postinflammatory hyperpigmentation: A review of the epidemiology, clinical features, and treatment options in skin of color. *J. Clin. Aesthet. Dermatol.* **2010**, *3*, 20–31.
41. Chambers, C. *Opinion on Kojic Acid*; Scientific Committee on Consumer Products: Brussels, Belgium, 2008; pp. 1–79.
42. Bergman, D.; Luke, J. Azelaic acid. *J. Dermatol. Nurses Assoc.* **2017**, *9*, 157–160. [CrossRef]
43. Gillbro, J.M.; Olsson, M.J. The melanogenesis and mechanisms of skin-lightening agents-existing and new approaches: Melanogenesis and skin-lightening agents. *Int. J. Cosmet. Sci.* **2011**, *33*, 210–221. [CrossRef]
44. Shin, J.W.; Park, K.C. Current clinical use of depigmenting agents. *Dermatol. Sin.* **2014**, *32*, 205–210. [CrossRef]
45. Ebanks, J.P.; Wickett, R.R.; Boissy, R.E. Mechanisms regulating skin pigmentation: The rise and fall of complexion coloration. *Int. J. Mol. Sci.* **2009**, *10*, 4066–4087. [CrossRef]
46. Fan, M.; Fan, X.; Lai, Y.; Chen, J.; Peng, Y.; Peng, Y.; Xiang, L.; Ma, Y. Protease-Activated Receptor 2 in inflammatory skin disease: Current evidence and future perspectives. *Front. Immunol.* **2024**, *15*, 1448952. [CrossRef] [PubMed]
47. Ito, Y.; Kanamaru, A.; Tada, A. Effects of methylophipogonanone B on melanosome transfer and dendrite retraction. *J. Dermatol. Sci.* **2006**, *42*, 68–70. [CrossRef]
48. Hakozi, T.; Minwalla, L.; Zhuang, J.; Chhoa, M.; Matsubara, A.; Miyamoto, K.; Greatens, A.; Hillebrand, G.G.; Bissett, D.L.; Boissy, R.E. The effect of niacinamide on reducing cutaneous pigmentation and suppression of melanosome transfer. *Br. J. Dermatol.* **2002**, *147*, 20–31. [CrossRef] [PubMed]
49. Solano, F.; Briganti, S.; Picardo, M.; Ghanem, G. Hypopigmenting agents: An updated review on biological, chemical and clinical aspects. *Pigment Cell Res.* **2006**, *19*, 550–571. [CrossRef] [PubMed]
50. Minwalla, L.; Zhao, Y.; Cornelius, J.; Babcock, G.F.; Wickett, R.R.; Le Poole, I.C.; Boissy, R.E. Inhibition of melanosome transfer from melanocytes to keratinocytes by lectins and neoglycoproteins in an in vitro model system. *Pigment Cell Res.* **2001**, *14*, 185–194. [CrossRef]
51. Zuo, A.-R.; Dong, H.-H.; Yu, Y.-Y.; Shu, Q.-L.; Zheng, L.-X.; Yu, X.-Y.; Cao, S.-W. The antityrosinase and antioxidant activities of flavonoids dominated by the number and location of phenolic hydroxyl groups. *Chin. Med.* **2018**, *13*, 51. [CrossRef]
52. Sharma, D.K.; Sharma, P. Augmented glutathione absorption from oral mucosa and its effect on skin pigmentation: A clinical review. *Clin. Cosmet. Investig. Dermatol.* **2022**, *15*, 1853–1862. [CrossRef]
53. Shimshak, S.J.E.; Tolaymat, L.M.; Haga, C.B.; Dawson, N.L.; Gillis, M.S.; Yin, M.; Kirsch, B.; Cooper, M.; Sluzevich, J.C. A review of oral therapies for the treatment of skin hyperpigmentation. *J. Cutan. Med. Surg.* **2022**, *26*, 169–175. [CrossRef]

54. Handog, E.B.; Datuin, M.S.L.; Singzon, I.A. An open-label, single-arm trial of the safety and efficacy of a novel preparation of glutathione as a skin-lightening agent in Filipino women. *Int. J. Dermatol.* **2016**, *55*, 153–157. [[CrossRef](#)]
55. Peng, X.; Ma, Y.; Yan, C.; Wei, X.; Zhang, L.; Jiang, H.; Ma, Y.; Zhang, S.; Xing, M.; Gao, Y. Mechanism, formulation, and efficacy evaluation of natural products for skin pigmentation treatment. *Pharmaceutics* **2024**, *16*, 1022. [[CrossRef](#)] [[PubMed](#)]
56. Singh, S.; Sharma, N.; Zahoor, I.; Behl, T.; Antil, A.; Gupta, S.; Anwer, M.K.; Mohan, S.; Bungau, S.G. Decrypting the potential of nanotechnology-based approaches as cutting-edge for management of hyperpigmentation disorder. *Molecules* **2022**, *28*, 220. [[CrossRef](#)] [[PubMed](#)]
57. Tangau, M.J.; Chong, Y.K.; Yeong, K.Y. Advances in cosmeceutical nanotechnology for hyperpigmentation treatment. *J. Nanopart. Res.* **2022**, *24*, 155. [[CrossRef](#)]
58. Chelliah, R.; Rubab, M.; Vijayalakshmi, S.; Karuvelan, M.; Barathikannan, K.; Oh, D.-H. Liposomes for drug delivery: Classification, therapeutic applications, and limitations. *Next Nanotechnol.* **2025**, *8*, 100209. [[CrossRef](#)]
59. Roselan, M.A.; Ashari, S.E.; Faujan, N.H.; Mohd Faudzi, S.M.; Mohamad, R. An improved nanoemulsion formulation containing kojic monooleate: Optimization, characterization and in vitro studies. *Molecules* **2020**, *25*, 2616. [[CrossRef](#)]
60. Duarah, S.; Durai, R.D.; Narayanan, V.B. Nanoparticle-in-gel system for delivery of vitamin C for topical application. *Drug Deliv. Transl. Res.* **2017**, *7*, 750–760. [[CrossRef](#)]
61. Madawi, E.A.; Al Jayoush, A.R.; Rawas-Qalaji, M.; Thu, H.E.; Khan, S.; Sohail, M.; Mahmood, A.; Hussain, Z. Polymeric nanoparticles as tunable nanocarriers for targeted delivery of drugs to skin tissues for treatment of topical skin diseases. *Pharmaceutics* **2023**, *15*, 657. [[CrossRef](#)]
62. Xiao, L.; Matsubayashi, K.; Miwa, N. Inhibitory effect of the water-soluble polymer-wrapped derivative of fullerene on UVA-induced melanogenesis via downregulation of tyrosinase expression in human melanocytes and skin tissues. *Arch. Dermatol. Res.* **2007**, *299*, 245–257. [[CrossRef](#)]
63. Ertam, I.; Mutlu, B.; Unal, I.; Alper, S.; Kivçak, B.; Ozer, O. Efficiency of ellagic acid and arbutin in melasma: A randomized, prospective, open-label study. *J. Dermatol.* **2008**, *35*, 570–574. [[CrossRef](#)]
64. Labouta, H.I.; Schneider, M. Interaction of inorganic nanoparticles with the skin barrier: Current status and critical review. *Nanomed. Nanotechnol. Biol. Med.* **2013**, *9*, 39–54. [[CrossRef](#)]
65. Al Mohammady, A.; Kadah, A.S.; Mahran, M.A.; Elsaie, M.L. Microneedling-assisted delivery of metformin versus tranexamic acid in treating melasma: A randomized controlled study. *Eur. J. Med. Res.* **2025**, *30*, 761. [[CrossRef](#)]
66. Pazyar, N.; Raeispour, M.; Yaghoobi, R.; Seyedtabib, M. Evaluation of the effectiveness of microneedling with tranexamic acid in comparison with microneedling with vitamin C in the treatment of melasma: A prospective and single-blind clinical trial. *Health Sci. Rep.* **2023**, *6*, e1636. [[CrossRef](#)]
67. Jutley, G.S.; Rajaratnam, R.; Halpern, J.; Salim, A.; Emmett, C. Systematic review of randomized controlled trials on interventions for melasma: An abridged Cochrane review. *J. Am. Acad. Dermatol.* **2014**, *70*, 369–373. [[CrossRef](#)]
68. Wang, T.; Wang, Y.; Wang, J.; Chen, H.; Qu, B.; Li, Z. Efficacy and safety of topical therapy with botanical products for Melasma: A systematic review and meta-analysis of randomized controlled trials. *Front. Med.* **2021**, *8*, 797890. [[CrossRef](#)]

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