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NARRATIVE REVIEW

Decoding Hyperpigmentation from Biological Mechanisms to Actives with Clinically Proven Topical Efficacy: A Narrative Review

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ABSTRACT

Hyperpigmentation disorders affect a large proportion of the population, significantly impacting their quality of life and carrying considerable social stigma. This growing global concern results in a strong demand for effective treatments. A rich body of literature proposes numerous active ingredients to solve hyperpigmentation concerns. At the same time, the complex regulation of skin pigmentation is much better understood with increased knowledge on the physiopathology of pigmentary disorders, beyond the sole melanogenesis, including the whole tissue environment of melanocytes. The abundance of mechanistic in vitro and in vivo scientific data makes it challenging for non-expert clinicians to identify the optimal care for patients. The aim of this review is to propose state-of-the-art of topical solutions with actives that have demonstrated conclusive clinical efficacy. It analyzes the different mechanisms involved, including the melanogenesis pathway and others addressing the melanocyte microenvironment. This review first examines the prevention of pigmentary disorders and the importance of a broad-spectrum photoprotection including the whole UV spectrum but also visible light in managing hyperpigmentation. The use of antioxidants to combat oxidative

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stress and complement photoprotection is also discussed. The following section reviews actives targeting the modulation of melanogenesis. It examines tyrosinase inhibitors, which are still widely used to manage hyperpigmentation problems, as well as new compounds targeting downstream pathways. Other clinically effective interventions include the normalization of epidermal homeostasis and the active restoration of the dermal fibroblastic microenvironment, together with anti-inflammatory agents and those aimed at reducing vascularization impact. Finally, this review highlights the value of combined approaches which have been shown to improve clinical efficacy. This suggests that future research should focus on well-tolerated, multifaceted therapies to effectively treat melanin hyperpigmentary disorders.

PLAIN LANGUAGE SUMMARY

Dark spots and uneven skin tone, known as hyperpigmentation, are a common skin concern affecting many people worldwide and can cause significant distress. As a result of growing demand for effective solutions, substantial research has focused on finding ingredients that can help. Our scientific understanding now shows that the process is complex and involves not only the pigment-producing cells (melanocytes) but also the surrounding skin environment. With numerous scientific studies available, it can be challenging for doctors to identify the best treatments for their patients. This review provides a comprehensive summary of different mechanisms involved in hyperpigmentation and gives a clear guide to topical active ingredients with clinical evidence. The review concludes that combining different approaches is the most effective way to treat hyperpigmentation. Future treatments should focus on using multiple ingredients that work together to deliver the best results safely.

Keywords: Hyperpigmentation; Melanogenesis; Pigmentary disorder; Topical actives

Key Summary Points
Hyperpigmented skin disorders affect half of the global population with impact on quality of life and strong therapeutic demand.
Hyperpigmentation arises from complex intricate mechanisms involving not only melanocytes but also their surrounding tissular and cellular microenvironment, including key contributions from keratinocytes, fibroblasts, endothelial cells, immune and inflammatory actors.
Scientific literature proposes numerous active ingredients but, as a result of the multiple biological targets and heterogeneous quality of data, identifying the optimal topical solution remains challenging.
This review provides a state-of-the-art overview of topical solutions with proven clinical efficacy, encompassing traditional anti-melanogenic actives and agents restoring epidermal homeostasis or targeting the underlying dermal and inflammatory triggers.
Multitargeted topical combinations are highlighted as the most effective approach to addressing the complex pathways of pigmentary disorders.

INTRODUCTION

According to a recent study on 48,000 people in 34 countries, 50% of participants reported pigmentation disorders, mostly hyperpigmentation such as solar lentigo (27%), post-inflammatory hyperpigmentation (PIH) (15%), and melasma (11%) [1]. In the USA, pigmentation disorders are the third most frequently cited skin disorders, with PIH followed by melasma [2–4]. This is a major issue for people with darker skin (Fitzpatrick III+) [4, 5] but also those in Southeast Asia [4, 6].

As recently shown, pigmentation disorders have a substantial negative impact on quality of life and are associated with significant stigmatization [1].

It is of critical importance to understand the mechanisms behind these melanin pigmentary disorders and to review the solutions available to manage them. Topical solutions, particularly sunscreens and depigmenting agents, are crucial for managing hyperpigmentation [7]. However, the vast array of options, each with varying efficacy, can overwhelm patients and physicians. This review discusses the main available active ingredients and their mode of action for modulating skin hyperpigmentation, alone or in combination.

Melanogenesis

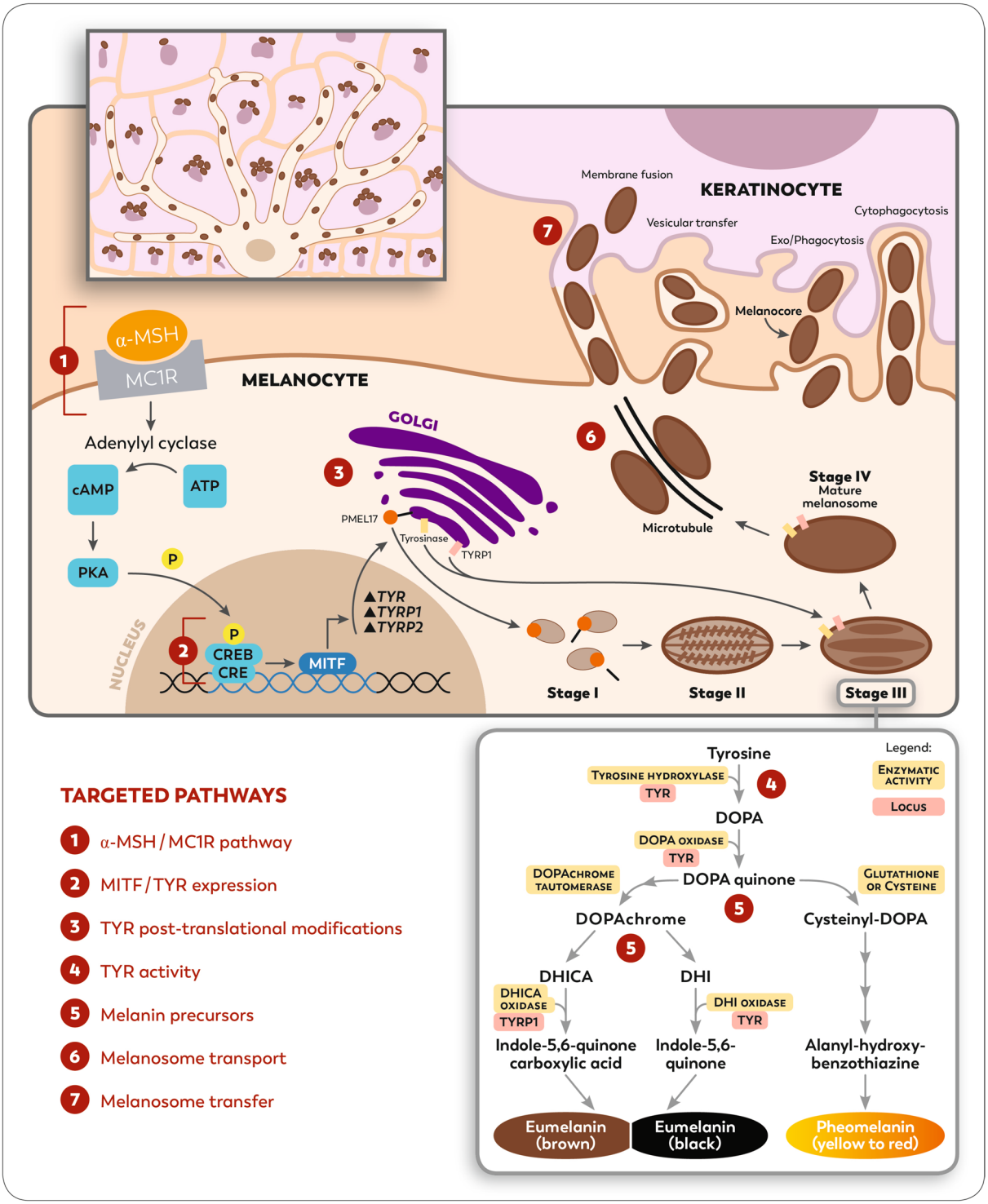
The color of the skin is a blend resulting from the skin chromophores red (oxyhemoglobin), blue (deoxygenated hemoglobin), yellow-orange (carotene, an exogenous pigment), and melanin. Melanin, however, is the primary determinant of skin color [8–10]. Two distinct melanin pigments are produced by melanocytes in the epidermis: pheomelanin, a yellow-red pigment; and eumelanin, a brown-black pigment [11–14]. These pigments in melanosome organelles are transferred through melanocyte dendrites to surrounding epidermal keratinocytes (Fig. 1) [11–15]. Skin color is primarily determined by the global quantity of eumelanin and pheomelanin pigments. Regardless of skin tone, the human epidermis contains a remarkably stable melanin composition of roughly 74% eumelanin and 26% pheomelanin. This ratio remains constant across all degrees of constitutive pigmentation, ranging from the lightest to the darkest complexions and covering the different Fitzpatrick phototypes [8, 9]. While eumelanin shows photoprotective capacity against ultraviolet (UV) [15], in contrast pheomelanin is weakly photoprotective and highly phototoxic, enhancing the UV-induced production of reactive oxygen species (ROS) and further damage of cells [16]. In addition to variations in the total amount of melanin [8, 9], the size, distribution, and fate of melanosomes within keratinocytes are key determinants in the diversity in skin pigmentation [11, 17, 18].

Hyperpigmentation Concerns

Skin hyperpigmentation is generally triggered or exacerbated by diverse factors including hormonal changes, nutritional status, but the major actor is sun exposure [17, 19]. However, hyperpigmented lesions show additional features compared to sun-induced pigmentation. The three most frequent hyperpigmented disorders include actinic (AL) or solar (SL) lentigines [20–24], PIH [25–27], and melasma [28–31], all sharing an increase in melanin content but each also being characterized by specific features (Fig. 2).

AL, also called age spots, are brownish pigmented macules with irregular borders and size of a few millimeters. They develop on photoexposed areas especially in individuals with Fitzpatrick II–IV skin usually after 35–40 years of age [20]. Besides the increase in melanin content, AL lesions are characterized by epidermal alterations such as proliferation/differentiation disbalance or mitochondrial dysfunction, dermal photoaging marks, and disorganization of the dermal extracellular matrix (ECM) [21–23]. In particular, AL lesions present an impairment of the cutaneous structure with a marked elongation of the dermal–epidermal junction (DEJ), an accumulation of melanin in the epidermis, especially in the rete ridges [21]. A subclinical chronic inflammation sustained by inflammatory mediators and immune cells is described in AL [24].

PIH is a dermal, epidermal, or mixed acquired skin hyperpigmentation that develops in inflammatory contexts such as lesional or healing skin. It is thus often associated with acne or inflammatory dermatoses or appears at sites of external injuries or dermatological procedures [25]. PIH commonly presents dark macules or patches at the site of the initial skin insult and more commonly affects individuals with darker skin tone. Exposure to solar light, even at low doses has been shown to be the triggering factor of PIH lesion [26].



PIH results from stimulation of melanocytes and overproduction of melanin in the epidermis in response to cytokines, chemokines released during inflammation. Inflammatory or trauma-induced damage to the basement membrane can also lead to melanin leakage and various other inflammatory cellular infiltrates in the dermis. The healing process following the

◂**Fig. 1** Melanogenesis and potential pathways to modulate melanogenesis. The process of melanogenesis involves a series of oxidative reactions catalyzed by key enzymes—tyrosinase and tyrosinase-related proteins (Tyrp1 and Tyrp2)—that tightly cooperate. Tyrosinase, a multifunctional metalloenzyme located in the membrane of melanosomes, catalyzes the initial rate-limiting steps of melanin synthesis, with the hydroxylation of L-tyrosine to L-dihydroxyphenylalanine (L-DOPA) and the oxidation of L-DOPA to DOPAquinone (DQ), which is the substrate for both eumelanin and pheomelanin synthesis. Tyrp1 and Tyrp2 are involved in the final catalytic reactions of eumelanogenesis and may also act as stabilizers of tyrosinase protein. The expression of melanogenic enzymes is regulated through various signaling pathways that converge to activate microphthalmia-associated transcription factor (MITF), a master transcription regulator in melanocytes. Tyrosinase activity is also modulated at the post-translational level by the binding of cofactors and copper ions, and the phosphorylation of serine residues. The intracellular level of reactive oxygen species (ROS) and the intramelanosomal pH also influence its enzymatic activity. The maturation of melanosomes (melanosome stage I to IV) and their transfer to keratinocytes are additional processes highly regulated during melanogenesis. The αMSH/MC1R pathway which is activated during UV exposure represents the major cause of melanogenesis activation. This figure summarizes the seven potential pathways to modulate melanogenesis

injury is accompanied by an increase in vascularization. Epidermal PIH may resolve better and faster than dermal PIH where melanin accumulates in long-lived melanophages [27].

Melasma is also a chronic acquired hypermelanosis which involves increased melanin levels in the epidermis and/or dermis [28–30]. It manifests as bilateral dark or grayish-brown macules, more particularly located on the face. These manifestations are associated with an increase of melanogenesis, hyperpigmented keratinocytes, senescent fibroblasts, vascularization and immune cells in particular mast cells as well as basement membrane disruption [32]. Melasma is a genetically based skin disorder with multiple factors being involved in its onset or exacerbation. The main extrinsic factor is the sun, particularly with the contribution of UV rays and visible light [30, 32, 33]. Other influencing factors include hormones, skin inflammation, and oxidative stress [28].

Collectively, these pigmentary disorders underscore the intricate and multifactorial pathophysiology of hyperpigmentation. Consequently, achieving effective clinical outcomes necessitates a multitargeted approach aimed at modulating the various actors and pathways contributing to its development.

This review aims to present the main available approaches, mostly topical medical and dermocosmetic ingredients, and their mode of action for modulating or reducing skin hyperpigmentation. Only active ingredients supported by published clinical trial data demonstrating significant improvement in hyperpigmentation (measured by validated clinical scores, colorimetry, or imaging) compared to vehicle or baseline are included in this review. Their use in combination will also be discussed.

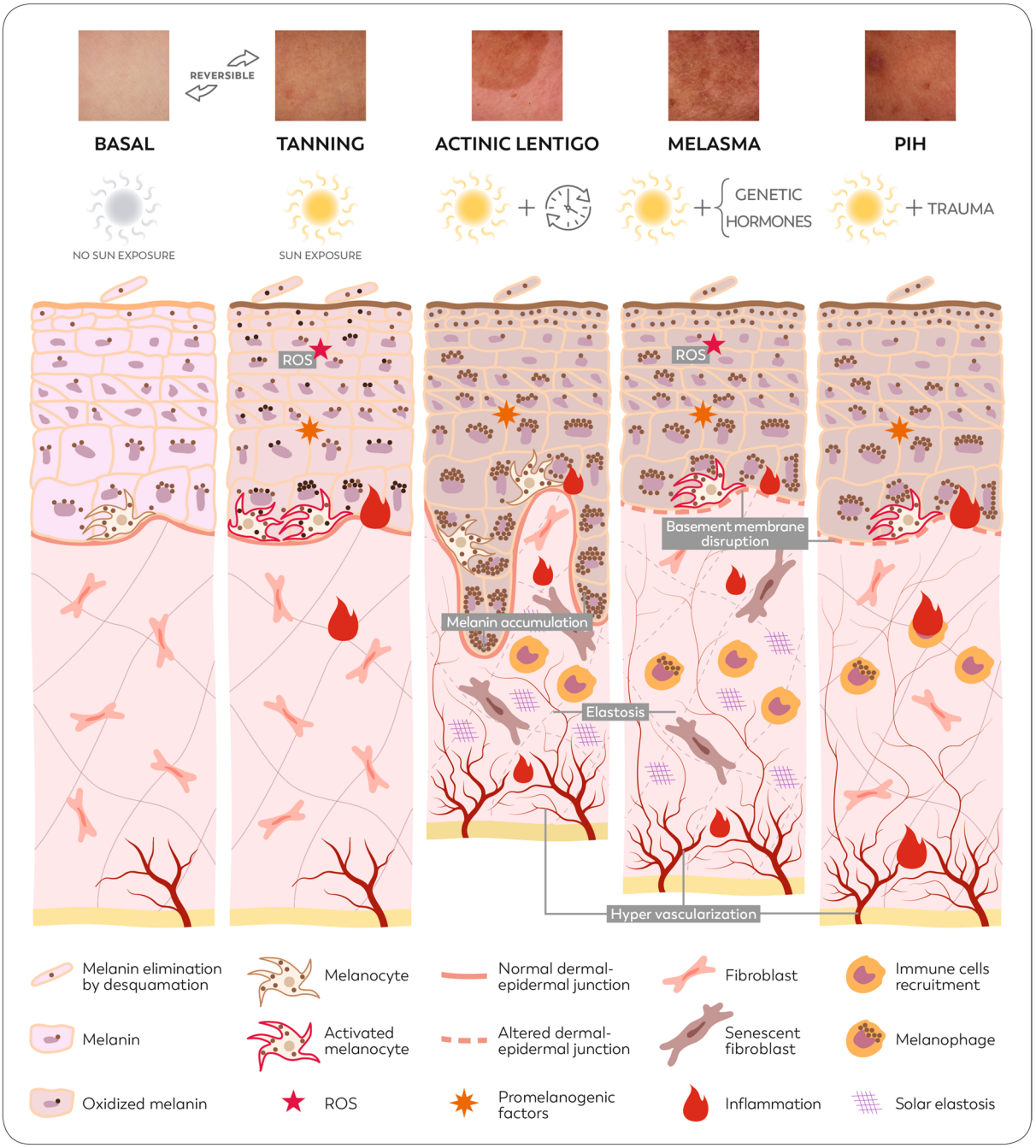
PREVENTIVE MEASURES OF SKIN HYPERPIGMENTATION

Prevention is the first strategy to manage hyperpigmentation by blocking the main inducing factors, i.e., UV and visible light (VL) solar radiation (Supplementary information, Sect. 2).

All UV rays, from UVB up to the longest UVA1 wavelengths, are involved in the induction of skin hyperpigmentation through different phases and mechanisms [34, 35]. Importantly, DNA damage, oxidative stress, and inflammatory mediators are key drivers for UV-induced hyperpigmentation. For VL, and especially high energy VL, one mechanism involves the Opsin-3 photoreceptor responsible for the activation of melanogenesis [36, 37].

Photoprotection with Sunscreens

To efficiently protect the skin, a combination of UVB and UVA filters is used to achieve a high level of UV photoprotection [38, 39]. In parallel to the mandatory high photoprotection during recreational sun exposures, it is important to consider a daily photoprotection in everyday life activities for all people



suffering from hyperpigmentary disorders [40]. The current European Union (EU) recommendation for broad-spectrum UV sunscreens is a UVA PF/SPF ratio of at least 1:3 and a critical wavelength > 370 nm [39, 41–43]. Recent guidelines from expert panels support the use of broad-spectrum sunscreens, even in people with darker skin tones, for the management of skin disorders such as melasma and PIH [25, 41, 44].

Recently, new UV filters have been developed to enable a more complete coverage of the full UV spectrum, such as bis-(diethylaminohydroxybenzoyl) benzoyl piperazine (BDBP) [45], phenylene bis-diphenyltriazine [46], or the UVA1 filter

◂**Fig. 2** Schematic representation of basal skin pigmentation, tanning, and pigmentary disorders. The natural color of the skin, i.e., constitutive pigmentation, is genetically controlled and results from melanin production by melanocytes, transfer to basal keratinocytes, and excess pigment elimination through epidermal turnover and desquamation. When exposed to sunlight, particularly ultraviolet (UV), the skin undergoes tanning, a temporary melanogenesis stimulation through epidermal and dermal paracrine signaling, inflammatory and oxidative stress. Individual susceptibility to tanning depends on genetic factors. However, chronic sun exposure and aging lead to more permanent conditions like actinic lentigo (AL). AL is characterized by a significant alteration of the cutaneous structure with elongation of the dermal–epidermal junction (DEJ), melanin accumulation particularly within the rete ridges, dermal impairments, and subclinical chronic inflammation. Melasma is another form of chronic hypermelanosis, manifesting as symmetrical dark patches on the face and characterized by melanocyte activation, hyperpigmented keratinocytes, dermal impairments, increased vascularization and inflammation/immune cells particularly mast cells. Dermal melanin within melanophages may be observed as a result of DEJ disruptions. While genetics play a foundational role, the development and worsening of melasma are triggered by a combination of factors such as sun exposure (UV and visible light) or hormonal changes. Post-inflammatory hyperpigmentation (PIH) is a dermal, epidermal, or mixed acquired skin hyperpigmentation following skin injuries, inflammatory dermatoses, or dermatological procedures, particularly in individuals with darker skin tone. These dark macules are driven by an inflammatory environment causing melanocyte activation, increase of melanin in the epidermis accompanied by capillary hyperplasia. Melanin can leak into the dermis through a compromised DEJ. Sunlight, even at low doses, can further trigger or worsen PIH lesions. Images source: SkinCam® Cross Polarized images provided by QIMA Newtone

methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate (MCE) with a peak of absorption at 385 nm [47] shown to significantly improve photoprotection against UV-induced hyperpigmentation [48, 49].

The proven contribution of visible light in skin hyperpigmentation and dyschromia has led to the addition of pigments (iron oxides) in formulations to protect against VL [41]. Therefore, broad-spectrum UV and VL sunscreens are shown to be more effective for melasma and PIH management [50–53].

In addition to the correct amount and frequency of sunscreen application [25], complementary preventive behaviors are mandatory [54]. However, there is still a lack of awareness regarding photoprotection in darker-skin populations who are highly susceptible to pigmentary disorders [41, 52].

Topical Antioxidants

UV radiation, specifically UVA rays, contributes significantly to the generation of oxidative stress in skin cells, causing molecular damage to lipids, proteins, and DNA, and contributing to hyperpigmentation through immediate melanin oxidation and delayed neomelanogenesis [35, 55, 56].

Although melanin pigment (mostly eumelanin) can scavenge free radicals, this is insufficient to counteract all the cutaneous consequences of ROS, as illustrated by an enhanced oxidative stress in melasma [57, 58]. Moreover, levels of endogenous antioxidants are significantly reduced during photoaging, increasing the skin's susceptibility to photodamage [55]. Altogether, these data support the use of antioxidants (AOX) to reduce the deleterious impact of ROS on skin and prevent hyperpigmentation.

AOX can reduce oxidative stress in sun-exposed skin cells, acting by directly scavenging ROS, inhibiting their production, and/or enhancing the intrinsic AOX pathways. The use of AOX could also prevent direct photooxidation of existing melanin in superficial skin cells [25, 59–61]. While oral antioxidants such as *Polypodium leucotomos* extract have demonstrated efficacy in photoprotection and may complement topical approaches [62, 63], systemic photoprotective strategies are not detailed in this review focusing on topical interventions. The most common ingredients with AOX properties used in topical formulations are presented in Table 1.

Overall, multiple clinical studies support the benefits of adding AOX in products targeting hyperpigmentation [55, 56, 64–67]. Both preventative studies showing reducing UV-induced pigmentation and therapeutic trials demonstrating improvement in melasma and

Table 1 Clinical application of most commonly used ingredients with antioxidant properties in topical formula

Ingredients	Clinical efficacy (topical application)	References
Vitamin C (ascorbic acid) and derivatives	Prevention of UV-induced pigmentation Treatment of melasma and age-associated skin hyperpigmentation	[64–68]
Vitamin E (tocopherols)	Treatment of melasma; better efficacy in association with vitamin C	[68, 68]
Resveratrol and analogues	Prevention of UV-induced pigmentation	[67, 95, 215, 216]
Ferulic acid	In association with other ingredients: treatment of melasma, or as an adjuvant to laser treatment of lentigines and melasma	[56, 66, 217]
Cysteamine	Treatment of melasma	[7, 67, 90]
Silymarin	Treatment of melasma	[27, 218]
Ellagic acid	In association with other ingredients: treatment of dark spots and melasma	[219, 220]
Carotenoids (beta-carotene, lycopene, lutein, etc.)	Treatment of melasma	[67]
Pomegranate extract	Skin lightening	[221]
Scutellaria baicalensis extract (baicalin)	In combination with resveratrol and vitamin E: improvement of radiance and hyperpigmentation	[216]

age-associated hyperpigmentation provide evidence for clinical relevance of topical antioxidants [55, 56, 66–68]. Additionally, sunscreens containing AOX were shown to have superior efficacy than sunscreens alone in reducing sunlight-induced pigmentation [69–71]. Remaining challenges reside in the strategy of formulation to overcome AOX intrinsic instability and reactivity [55, 60].

MELANOGENESIS MODULATION

Several medical or cosmetic strategies are used to limit melanin production (Fig. 1). These approaches most often inhibit key factors involved in melanin synthesis, more specifically the tyrosinase enzyme that mediates the first-rate limiting steps of melanogenesis.

Tyrosinase Inhibitors

Most tyrosinase inhibitors target the catalytic activity of the enzyme. Others inhibit its expression or post-translational modifications (Fig. 3).

Tyrosinase Catalytic Activity Inhibitors

Numerous synthetic or natural tyrosinase inhibitors are described in recent extensive reviews [72, 73]. These compounds are competitive, uncompetitive, mixed type, or non-competitive inhibitors of tyrosinase activity. They mainly act by binding directly to the enzyme or by interacting with copper molecules in its active site.

Hydroquinone, the gold standard, is the most widely used tyrosinase inhibitor in dermatology and is the reference compound in most skin lightening comparative studies [74, 75]. Despite being effective in blocking the conversion of

DOPA to melanin, hydroquinone monotherapy has moderate effectiveness on hyperpigmentation [76, 77] and is responsible for numerous side effects such as mild erythema, burning sensation, dryness, pruritus, and scaling, making it prohibited for use in cosmetics in a majority of countries [77–80]. Therefore, it is often used in combination with low potency steroids to reduce its adverse effects.

Other hydroquinone derivatives with less cytotoxic effect have been further identified, such as mequinol combined with tretinoin [6, 27, 74], or the over-the-counter medicines arbutin/deoxyarbutin [27, 74, 81]. The phenol resorcinol and its derivatives potently inhibit tyrosinase activity in vitro and have proven in vivo efficacy [73]. For example, isobutylamido-thiazolyl-resorcinol significantly improves melasma and PIH [7, 82–85]. 4-Butyl-resorcinol decreases melanin or pigmentation scores in patients with melasma [66], and use of phenylethyl resorcinol in a combination formulation improved melasma, lentigines, and signs of photoaging in subjects with hyperpigmentation problems [86, 87].

Other phenolic derivatives, monophenols and polyphenols, competitively inhibit tyrosinase by mimicking its substrate [73]. However, the oxidation of these compounds by tyrosinase can generate hydroxyl radicals and induce melanocyte cytotoxicity. This is the case for rhododendrol (RD or 4-(4-hydroxyphenyl)-2-butanol), which has been withdrawn from the Japanese market as a result of the appearance of leukoderma [88, 89].

Additional tyrosinase inhibitors with clinical evidence on melasma and/or PIH include azelaic acid [25, 27, 67, 90], kojic acid [27, 66, 90], cysteamine [7, 91–93], and several actives from licorice extracts such as glabridin, liquiritin, and isoliquiritin [27, 94], as well as resveratrol and some of its derivatives [73, 95]. Interestingly, some of them also display AOX properties (see Sect. "Topical Antioxidants") [95]. Cysteamine and glutathione could also promote the production of pheomelanin rather than eumelanin. Those lighter melanins can participate in the clinical efficacy of those compounds, but the well-demonstrated deleterious effects of pheomelanin raise concerns about the long-term safety of these approaches [16].

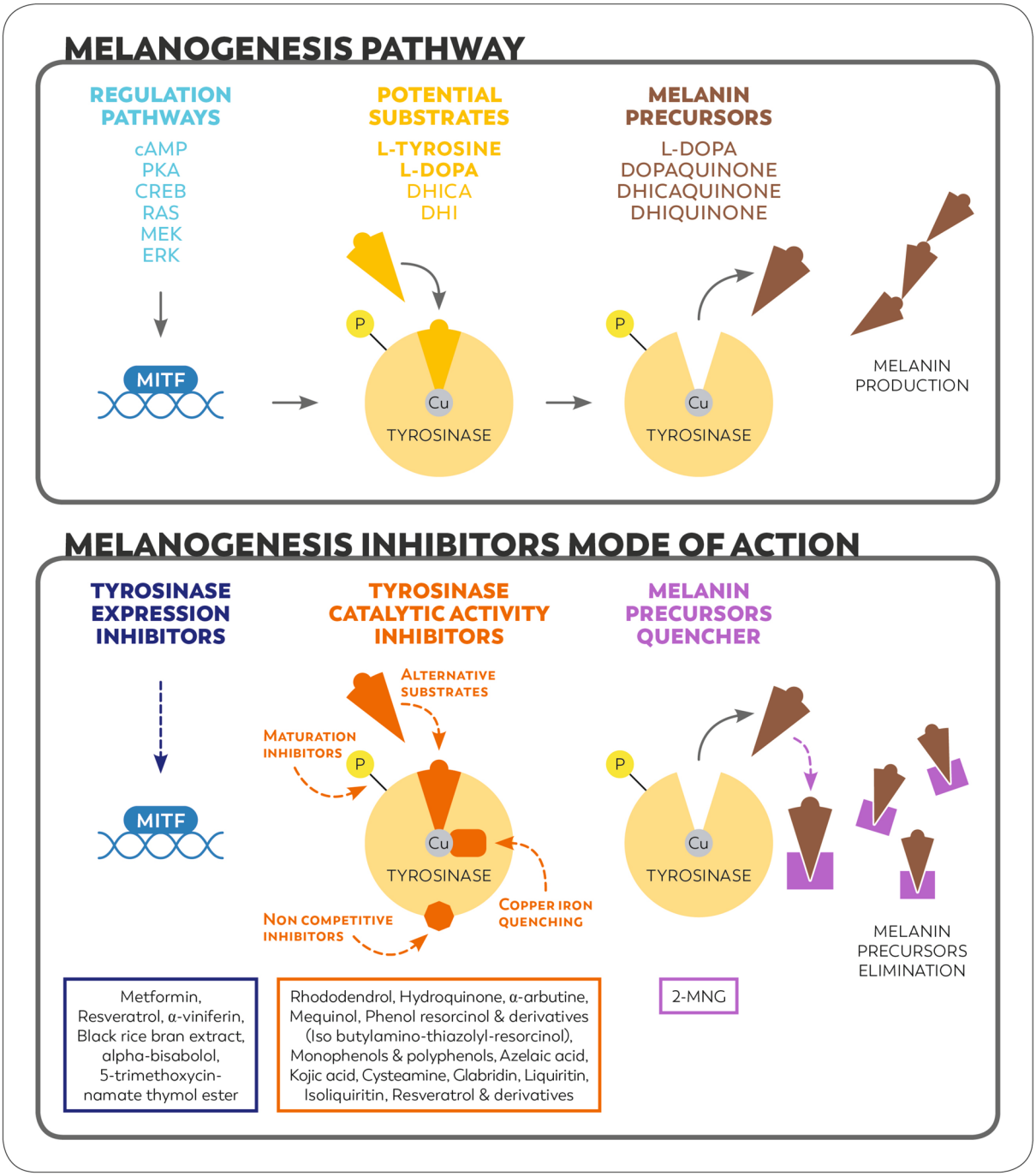
Some molecules inhibiting peroxidase activity are used as depigmenting agents. Methimazole, an oral antithyroid medication which is a potent peroxidase and tyrosinase inhibitor, has shown depigmentation effects when applied topically and caused significant skin lightening in patients with melasma [75, 78, 96, 97]. Topical methimazole, although not allowed in cosmetics, did not induce melanotoxicity or changes in thyroid functions [78, 98], and was proven to be a useful alternative treatment in some melasma cases [97].

Modulation of Tyrosinase Expression

Tyrosinase gene expression, together with Tyrp1 and Typr2, is induced by microphthalmia transcription factor (MITF), which is in turn regulated by signaling pathways, including cAMP/PKA/CREB, RAS/MEK/ERK, and β-catenin pathways. Therefore, inhibiting MITF expression and pathways modulates tyrosinase expression [11].

Metformin, an antidiabetic drug, inhibits the cAMP/CREB/MITF axis leading to the downregulation of the expression of tyrosinase, Tyrp1 and Tyrp2, and ultimately to the decrease of melanin production [99]. This led to its topical use as a dermatological ingredient to lessen melasma severity [100, 101]. Clinical evidence is still scarce.

Some natural ingredients were reported to target tyrosinase expression through MITF pathway, like resveratrol or α-viniferin, a resveratrol oligomer that improved facial melasma and freckles [102]. Alpha-viniferin has also shown anti-inflammatory activity [103]. A lotion containing black rice bran (*Oryza sativa* L. *indica*) extract with skin brightening properties could also act through this mechanism, in addition to its inhibitory effect on tyrosinase [104, 105]. Besides its AOX and anti-inflammatory actions [106], alpha-bisabolol, derived from chamomile, potentially exerts its skin depigmenting action by blocking CREB phosphorylation which resulted in decreased MITF, tyrosinase, and Tyrp1 expression [76, 107, 108]. In UV-induced skin pigmentation, a bisabolol-containing cream allowed significant lightening of skin without adverse reactions [108]. Another compound, 3,4,5-trimethoxycinnamate thymol ester, is



deemed to mainly act by decreasing the expression of tyrosinase and Tyrp1 but most probably through a cAMP-independent mechanism [109].

An anti-MITF small interfering RNA conjugated to a skin-penetrating peptide in a cream formulation was also successfully used for the treatment of patients with melasma, with an almost complete restoration of skin color on facial lesions after 12 weeks [110], but these agents need optimized topical delivery systems [111].

◂**Fig. 3** Melanogenesis pathways and relevant inhibitors. The figure schematizes the biological targets allowing inhibition of melanogenesis and the known modes of action of the main melanogenesis inhibitors. In the top section, melanogenesis pathways and targets for inhibition are summarized in 4 categories: i) Regulation pathways converging on MITF transcription factor expression. ii) Tyrosinase: tyrosinase, a copper-containing enzyme, catalyzes the conversion of initial substrates, mostly L-tyrosine and L-DOPA, but possibly DHI and DHICA, into melanin precursors. The "Cu" represents the copper ion, essential for its activity. The "P" indicates phosphorylation as a tyrosinase maturation and stabilization mechanism. iii) Melanin precursors: these are the intermediate molecules resulting from the conversion of initial substrates and necessary for melanin pigments formation. iv) Melanin production: progressive oxidation and polymerization of melanin precursors into melanin pigments. In the bottom section, the modes of action of the main melanogenesis inhibitors are summarized in 6 categories. The list of chemicals under each category provides examples of specific inhibitors. i) Tyrosinase expression inhibitors: these substances reduce the amount of tyrosinase produced by the cell. They act upstream by targeting MITF, the master regulator of tyrosinase expression. ii) Tyrosinase catalytic activity inhibitors: these compounds directly interfere with tyrosinase's ability to convert L-tyrosine to melanin. They employ different mechanisms: the alternative substrates compete for the tyrosinase active site, reducing the enzyme's effectiveness on its natural substrate. iii) Maturation inhibitors: these compounds prevent tyrosinase from reaching its fully functional, mature form. iv) Non-competitive inhibitors: these inhibitors bind to tyrosinase at a site different from the active site, altering the enzyme's shape and reducing its activity. v) Copper iron quenching: these substances bind to the copper ions that are essential for tyrosinase activity, inactivating the enzyme. vi) Melanin precursors quencher: this substance reacts with and neutralizes the intermediate melanin precursors (dopaquinone, DHICAquinone, and DHIquinone), preventing their further conversion into melanin

Tyrosinase Post-translational Modification

The main post-translational modification of tyrosinase is its glycosylation at asparagine residues [112]. Hence, *N*-acetyl glucosamine, a sugar derivative able to inhibit lipid carrier-dependent glycosylation of proteins, inactivates tyrosinase through the inhibition of its glycosylation [113]. It was incorporated in several cosmetic products [114] and successfully used as a standalone active alone or in combination to reduce facial spots and hyperpigmentation [27]. However, glycosylation inhibitor usage is often accompanied by cytotoxic effects, such as cell cycle arrest.

An alternative strategy to target tyrosinase activity is to indirectly inhibit its phosphorylation and subsequent interaction with Tyrp1. Two antisense oligonucleotides that specifically interact with the mRNAs of the protein kinase C-β, responsible for tyrosinase phosphorylation and thus its activation [115], decreased tyrosinase activity in cultured melanocytes and reduced hand pigmentation in volunteers after applying a care product containing these synthetic agents [116].

Other Targets in Melanogenesis Pathway

Besides tyrosinase and melanogenic enzymes, other targets in the melanogenesis pathway have been the subject of research for anti-melanogenic active ingredients (Fig. 3).

Inhibition of α-MSH Receptor

The UV-inducible melanocyte stimulating hormone (α-MSH) and its receptor MC1R, which activates the downstream expression of tyrosinase through MITF , are two targets of choice (Figs. 1 and 3). Glycinamide, a small α-MSH-mimicking peptide blocking MC1R receptor, inhibited melanin synthesis in melanocytes and reduced skin pigmentation in volunteers after topical application [117]. Another antagonist of MC1R, undecylenoyl phenylalanine, also induced significant lightening of pigmented lesions when applied twice daily at 2% in patients with melasma or SL [118, 119].

Capturing Melanin Intermediate Products

Recently, 2-mercaptonicotinoyl glycine (2-MNG) was described as a new inhibitor of melanin production through a novel mode of action. 2-MNG conjugates with some melanin precursors, preventing their integration into melanin polymers, leading to an inhibition of both

eumelanin and pheomelanin production, while preserving their ratio and melanocyte integrity [120]. In vivo, 2-MNG significantly inhibited the early skin darkening events following repeated UV exposures, and new melanin content, when compared to vehicle, with higher performance at 1% than at 0.5% [121, 122] and a significantly better performance than 4-butyl-resorcinol 2.5% [121]. In addition, 2-MNG was recently shown to be the first topical biological active to significantly and visibly reduce persistent, long-lasting pigmentation induced by high-energy visible (HEV) light, demonstrating a rapid and dose-dependent effect [123]. No side effects were reported.

MELANOSOME REGULATION

The maturation and transfer of melanosomes to keratinocytes are critical for the distribution of melanin in the epidermis (Fig. 1). Compounds inhibiting intracellular melanosome transport or activating melanosome degradation have been explored in recent years.

Melanosome Transport and Autophagy

Melanosome trafficking from the perinuclear area of melanocytes to peripheral dendrites, where pigments are transferred to keratinocytes, is tightly regulated by cytoskeleton-linked motor proteins, such as kinesin, the tripartite protein complex Rab27a/melanophilin/myosinVa, and small GTP-binding proteins [124].

Recent observations suggest that autophagy machinery proteins may be directly involved in melanogenesis regulation and melanosome trafficking on the cytoskeletal track [125]. Disrupting melanosome transport may also induce autophagy-mediated degradation of accumulating melanosomes, which can contribute to the decrease of melanin content in cells [126].

Several compounds have been shown to interfere with melanosome transport or to activate autophagy in cultured melanocytes and pigmented skin models (Supplementary information 4.1). However, clinical evidence showing that specific targeting of these pathways can improve hyperpigmentation is still missing.

Melanosome Transfer from Melanocytes to Keratinocytes

Four models are currently proposed to explain how melanin pigments might be transferred and processed from melanocytes to keratinocytes (Fig. 1) [127–129]: the direct membrane fusion between both cell types, the cytophagocytosis of melanocyte dendrite tips by keratinocytes, the release of vesicles containing melanosomes in the extracellular space and internalization by keratinocytes, and the coupled exocytosis/phagocytosis of melanocores (naked melanosomes deprived of their melanosomal membrane) by melanocytes and keratinocytes, respectively. Recent evidence indicates that the last two mechanisms could be predominant and might be targeted to modulate skin pigmentation [18, 127]. Furthermore, cell–cell recognition involving lectins and glycoproteins may also influence melanosome transfer and be a relevant target [129].

The transmembrane protease-activated receptor 2 (PAR-2), which is expressed on keratinocytes and has an important role in the formation of melanocyte dendrites and the phagocytosis of melanosomes by keratinocytes [129, 130], could also be specifically blocked by compounds to decrease epidermal pigmentation [131]. Accordingly, soymilk and soybean extracts with the ability to inhibit PAR-2 via the proteases soybean trypsin inhibitor (STI) and Bowman-Birk inhibitor (BBI) have demonstrated effectiveness in reducing skin pigmentation in human [66, 132–135]. The clinical effectiveness and favorable safety profile of soybean extract are supported by several trials [66, 114, 136] (Supplementary information 4.2).

Niacinamide (or nicotinamide) is a biologically active form of niacin (vitamin B_3) that has also been shown to inhibit melanosome transfer in a co-culture model of melanocytes and keratinocytes without impairing melanogenesis [137, 138]. Moreover, niacinamide may enhance the inhibition of melanosome transfer induced by lectins and neoglycoproteins [130, 138].

Nevertheless, numerous clinical studies with different topical niacinamide formulations, alone or in combination, found significant improvements in skin aging and hyperpigmentation [66, 130, 137–139]. A 4% topical niacinamide formulation was shown to be better tolerated than 4% hydroquinone cream, with almost comparable skin-lightening efficacy [140]. This product also has anti-inflammatory efficiency which could contribute to its efficacy [141]. It hence can constitute a valuable alternative option for melasma or PIH treatment [50, 76, 90, 130].

EPIDERMAL CELL TURNOVER

Retinoids are natural and synthetic vitamin A derivatives that modulate cellular differentiation and proliferation through the binding to nuclear retinoic acid receptors but also through the activation of kinase signaling pathways [142]. By this process, they strengthen the protective function of the epidermis [142–144].

It has been shown that tretinoin (retinoic acid) and its derivatives, isotretinoin, adapalene and tazarotene, may decrease pigmentation in vitro most probably via the induction of keratinocyte proliferation and epidermal turnover acceleration, rather than by acting directly on melanogenesis [145]. Retinoids may also exert their depigmenting effect by inhibiting oxidative stress and melanosome transfer to epidermal cells, as well as by remodeling dermal structure [25, 66] (see Sect. "Modulation of Dermal Structure"). Tretinoin and derivatives can be used as monotherapy or in combination in dermatological products for the treatment of melasma or PIH [27, 76, 90, 94]. Retinoid precursors, such as retinol (vitamin A) and retinaldehyde, which need to be metabolically converted into the active form of retinoic acid, are more often used in cosmeceuticals, but have lower potency than retinoic acid [66, 144, 146, 147]. Bakuchiol, a natural molecule with retinol-like activities, is also receiving growing interest (Supplementary information Sect. 5) [148–151].

Retinoids are commonly combined with other lightening agents and anti-inflammatory molecules, such as in Kligman-like formulas, to enhance the efficacy of the treatment [25, 66] (see Sect. "Combined Approaches").

TARGETING THE MICROENVIRONMENT OF MELANOCYTES

Besides melanocytes and keratinocytes, other players, such as dermal fibroblasts, immune, and endothelial cells, are involved in the development and relapse of hyperpigmentation [24, 152–154]. Melanophages, which are melanin-containing macrophages within the dermis, may also contribute to persistent pigmentation in melasma and PIH [154, 155]. Melanophages play a critical role in what is defined as dermal melanosis or pigmentary incontinence. These cells remain sequestered in the dermis for months to years, where the Tyndall effect translates deep-seated pigment into a clinically characteristic gray-blue hue [156]. Furthermore, as activated immune cells, melanophages may communicate and stimulate dermal T lymphocytes and secrete proinflammatory cytokines, potentially sustaining the chronic status of the hyperpigmented lesion [157, 158].

These various cells and their complex paracrine interplay may be relevant targets to potentiate anti-melanogenic strategies.

Anti-inflammatory Strategies

Skin inflammation, driven by a variety of inflammatory mediators such as interleukins, cytokines, chemokines, and prostaglandins, released by immune cells (macrophages, mast cells, lymphocytes), keratinocytes, dermal fibroblasts and sebocytes, exacerbates hyperpigmentation disorders [19, 153, 159–161]. Consequently, drugs with anti-inflammatory actions are investigated for therapeutic or adjuvant use.

Topical corticosteroids, potent anti-inflammatory agents, inhibit the synthesis of inflammatory mediators like prostaglandins, cytokines, endothelin-1 (EDN-1), and granulocyte macrophage colony-stimulating factor (GM-CSF) in various skin cells [162]. However, as a result of

weak depigmenting effects and potential side reactions like skin atrophy [6, 90], potent corticosteroids are usually not used as monotherapy for hyperpigmentation. They are preferentially incorporated at low concentrations in triple combination therapies for melasma, such as Kligman ones (containing dexamethasone or fluocinolone acetonide), to reduce irritation caused by other components. They are particularly crucial for PIH treatment by addressing subclinical inflammation and for decreasing PIH incidence after ablative fractional resurfacing [76].

Salicylic acid and its derivatives are the main nonsteroidal anti-inflammatory agents used in topical formulations, also capable of inhibiting melanin production and transport in melanocytes [163]. Niacinamide is also widely recognized for its anti-inflammatory properties [141]. Its clinical performance on pigmentation disorder is clinically proven (see Sect. "Melanosome Transfer from Melanocytes to Keratinocytes").

Phytoextracts offer alternative anti-inflammatory benefits. Aloe vera extract and aloesin, its major active, exhibit anti-inflammatory abilities, without the adverse effects of corticosteroids (Supplementary information 6.1) [114, 136, 164, 165].

Glycyrrhetinic acid, a triterpenoid derivative from licorice (*Glycyrrhiza glabra*) with anti-inflammatory and AOX properties [166, 167], has shown effectiveness in lightening hand SL in combination with 4-butyl-resorcinol [168]. Glabridin, another licorice compound, exhibits both anti-inflammatory and anti-tyrosinase activities contributing to its anti-pigmenting effect [167, 169] and effectiveness against melasma [170].

Inhibition of Vascularization/Endothelial Cells

Increased dermal vascularity (neovascularization/capillary hyperplasia) is implicated in melasma, PIH, and AL [30, 154, 160, 171]. It is driven by factors such as vascular endothelial growth factor (VEGF), transforming growth factor beta (TGFβ), EDN-1, fibroblast growth factor 2 (FGF-2) produced by mast cells, keratinocytes, and fibroblasts, stimulating endothelial cells [153, 154]. Endothelial cells, in turn, secrete EDN-1, SCF, and nitric oxide, promoting melanogenesis in melanocytes. Thus, endothelial cells are key targets for hyperpigmentation and prevention of melasma relapse [152]. Tranexamic acid (TXA), a lysine analogue and antifibrinolytic agent, inhibits the binding of plasminogen originating from endothelial cells to keratinocytes resulting in the diminution of melanocyte activators production (e.g., arachidonic acid, prostaglandins, leukotrienes, α-MSH) [6, 27, 90]. It also mitigates mast cell activity [160] and angiogenesis via VEGF and EDN-1 inhibition [172, 173].

TXA is extensively utilized for melasma treatment through various administration routes (systemic, topical, transepidermal, intradermal by intralesional microinjections or microneedling). Clinical evidence with TXA is scarcer and less compelling for PIH [173].

Several studies with oral TXA have demonstrated high response rates in melasma [6, 90, 173] and as adjuvant it can enhance the effectiveness of the topical hydroquinone or triple combination therapy [75, 174]. Topical TXA efficacy varies, some studies showing efficacy comparable to hydroquinone in treating melasma [7, 75] while other trials have found no significant difference compared to placebo [175]. This discrepancy likely reflects challenges for cutaneous penetration of TXA, leading to the development of enhanced delivery systems like liposomes to improve efficacy and tolerability [94]; however, clear demonstration of their efficacy in melasma has to be done [6].

Given the difficulty of targeting endothelial cells in the dermis, inhibiting downstream pathways activating melanocytes, like EDN-1/EDN receptor signaling [176–179], could be particularly relevant for treating melasma and solar lentigo as this signaling pathway is upregulated in these conditions [180]. *Matricaria chamomilla* extract, with a spiro ether active, proposed as an EDN-1 receptor antagonist, reduced in vitro melanin synthesis [179] and topically applied it prevented UVB-induced pigmentation in human skin and improved SL [179].

Modulation of Dermal Structure

Dermal fibroblasts play a pivotal role in the formation and maintenance of the skin's extracellular matrix (ECM). Beyond structural support, they mediate communication between melanocytes and keratinocytes and stimulate melanogenesis through soluble factors/signaling pathways, such as the SCF/cKit/MAPK pathway and Wnt/β-catenin pathway in melanocytes [22, 30, 153–155]. Deregulation of these pathways is frequently observed in melasma, post-inflammatory hyperpigmentation, and senile (actinic)lentigo [154, 155, 181–183]. Furthermore, the degradation of structural dermal proteins significantly contributes to these disorders. Matrix metalloproteinases (MMPs), alongside plasmin (derived from plasminogen released by fibroblasts and keratinocytes), are proteases that degrade collagen, elastin, and other ECM components, leading to dermal disorganization and destruction of the DEJ. Plasmin, in particular, can also enhance melanogenesis and exert proinflammatory and proangiogenic effects. These dermal alterations are closely linked to skin photoaging including the hyperpigmented lesions.

Topical retinoids and retinol improve the dermal ECM microenvironment by activating dermal fibroblasts. This activation primarily occurs through the stimulation of the TGFβ/CTGF pathway, which consequently enriches ECM deposition in aged human skin in vivo. Therefore, the beneficial effects of active compounds on the dermis and fibroblasts, combined with their impact on epidermal turnover (see Sect. "Epidermal Cell Turnover"), contribute to their efficacy in treating pigmentary disorders.

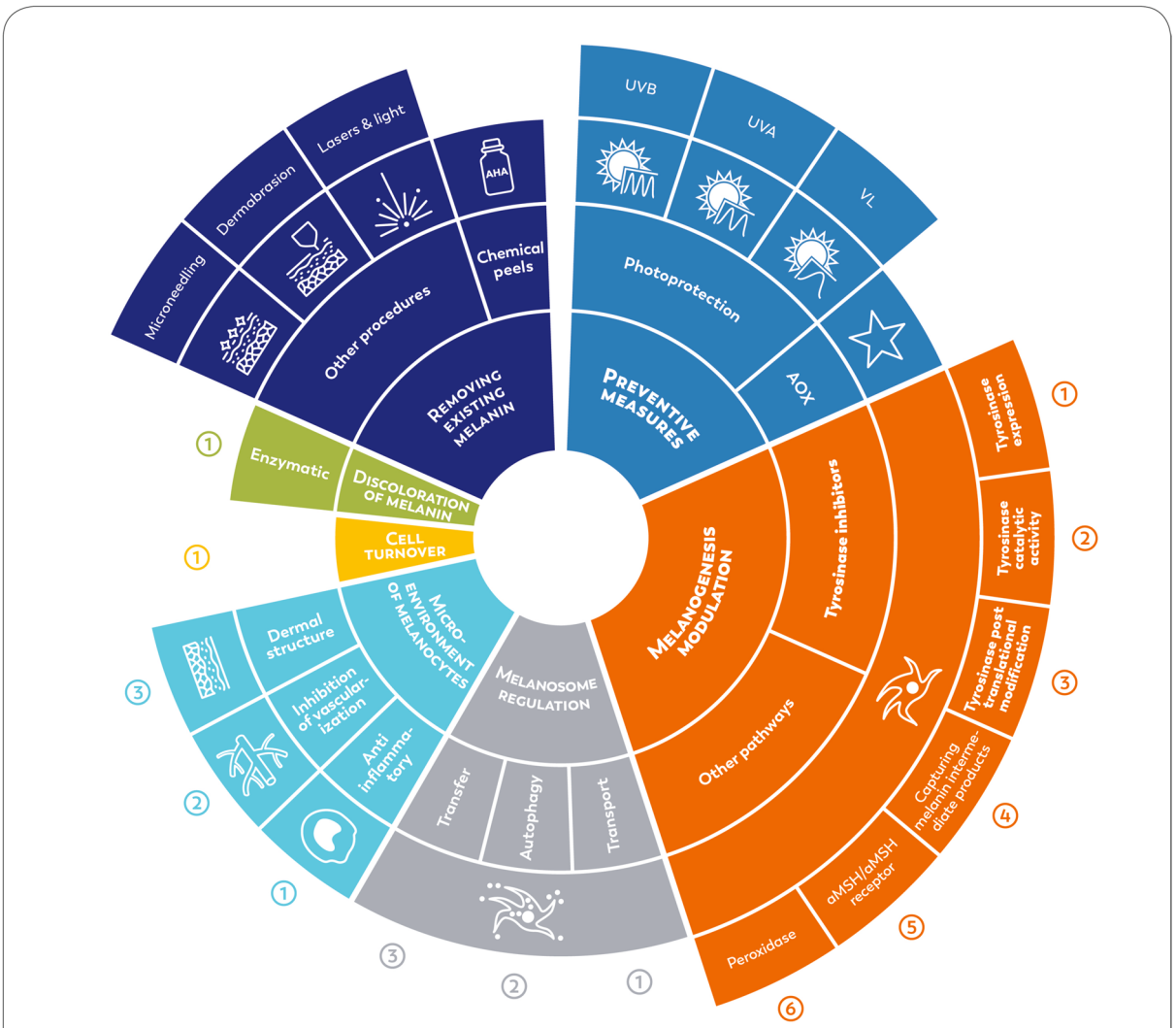
In melasma, the Wnt/β-catenin pathway is involved in the regulation of fibroblast-secreted factors that modulate melanocytes activity. Consequently, Wnt inhibitors such as Dickkopf agonist investigated in vitro are considered promising in hyperpigmentation treatment (Supplementary information 6.3) [30, 184, 185].

The monohydroxy fatty acid 10-hydroxystearic acid (HSA), a bio-derived PPARα agonist, has demonstrated efficacy in reducing pigmentation of facial age spots [186]. Its mechanism of action is hypothesized to involve the modulation of WNT-related fibroblast-secreted proteins, though further studies are needed to confirm this and its overall effectiveness in hyperpigmentation.

Another natural compound is glycyl-L-histidyl-L-lysine (GHK), a peptide found in human serum and various ECM proteins. Besides antioxidant (AOX) and anti-inflammatory effects, GHK exhibits potent tissue remodeling properties by stimulating collagen synthesis in fibroblasts and increasing keratinocyte proliferation [187, 188]. In patients with melasma, hydroporation with a GHK-containing formulation effectively reduced pigmentation and erythema, alongside inducing antiaging effects by stimulating ECM constituent production [188, 189]. Short peptides relatively stable in formulations can be designed or formulated to be skin-permeable.

ENZYMATIC DISCOLORATION OF MELANIN

Discoloration of melanin is an alternative method for skin lightening. Lignin peroxidase (LiP), an extracellular enzyme purified from the white-rot fungus *Phanerochaete chrysosporium*, has been shown to effectively degrade and decolorize melanin in vitro through an oxidative process [190, 191]. Recently developed, recombinant lignin peroxidase showed higher stability and in vitro performance [192]. To preserve and stabilize enzymes in formulation, technologies have been developed, among them encapsulation using liposome or nanoemulsion, addition of sugar or polyol as cosolute strengthening the hydration shell around the enzyme, or precise pH control matching the isoelectric point ensuring structural stability [193, 194]. Three studies showed the skin-lightening effect of a LiP-based cream, using a two-step protocol (first the enzyme product, second the activator H_2O_2), with no observable adverse effect [195]. This cream significantly and rapidly reduced skin pigmentation and was equally effective as 4% hydroquinone [136, 195]. Yet larger comparative



① **Metformin**
Resveratrol | α- viniferin | Black rice bran extract | Alpha-bisabolol | 3,4,5-trimethoxycynnamate thymol ester | Si RNA MITF

② **Hydroquinone**
Mequinol | Arbutin/deoxyarbutin | Phenol resorcinol | 4-butyl resorcinol | Iso butylamino-thiazolyl-resorcinol | Phenyl ethyl resorcinol | Azelaic acid | Kojic acid | Cysteamine | Glabidrin, liquiridin, isoliquiridrin

③ N-acetyl glucosamine | Anti-sense oligonucleotides PKC-β1, Tyrp1

④ 2-mercaptonicotinoyl glycine (2-MNG)

⑤ Glycinamide | Undecylenoyl phenylalanine

⑥ **Methimazole**

① Diterpenoide 16-kauren | 3-O-Glyceryl-2-O-hexyl ascorbate | Hesperidin/hesperetin | Bakuchiol | Salicylic acid | Rhamnazin

② **Tranexamic acid**
Ellagic acid | Resveratrol | Pterostilbene | 3-O-Glyceryl-2-O-hexyl ascorbate | 3,4,5-trimethoxycynnamate thymol ester | PTPD-12

③ Par-2 inhibitors (soymilk/soybean extracts) | Cytidine | Niacinamide (Vit B3)

① **Corticosteroids (usually in combination)**
Non steroid AI : Salicylic acid | Niacinamide (Vit B3) | Phytoextracts; flavonoids (aloe vera), Glechoma Hereracea, Glycyrrhetinic acid, Glabridin

② **Tranexamic acid (TXA)** (oral, intradermal)
TXA (topical) | EDN-1/EDN receptor pathway inhibitor: spiroether (matricaria chamomilla extract)

③ **Retinoid/retinol**
Wnt signaling pathway inhibitors: DDK1 agonist, Cardamonin (chalcone) | Chrysanthenium indicum extract | Glycyl-L-histidyl-L-lysine (GHK)

① **Retinoids (tretinoin, isotretinoin, adapalene, tazarotene)**
Retinol/retinol derivatives (retinaldehyde, bakuchiol)

① Lignin peroxidase (Phanerochaete chrysosporium)

◂**Fig. 4** Multilevel intervention strategies for the management of hyperpigmentation and relevant active ingredients. This figure summarizes the diverse strategies used to modulate/manage hyperpigmentation, targeting various stages of melanin production, transport, and distribution, as well as the melanocyte microenvironment and the removal of existing melanin. The graph combines the relevant active ingredients and measures on different pathways listed in the manuscript and the supplement file. The actives highlighted in color are dermatological references. Broad-spectrum photoprotection is indicated as a preventive or treatment support measure

clinical studies are necessary to confirm effectiveness for melasma and other pigmentary disorders.

REMOVING EXISTING MELANIN

To increase effectiveness and prevent recurrence, other strategies based on the removal of excess melanin can be used in second or third lines. Chemical peelings include superficial interventions for removing the outermost epidermal layers, and deeper interventions that reach the upper dermis and induce a wound healing response which may additionally improve aging signs. However, as a result of their invasiveness they must be used cautiously to avoid cutaneous reactions or risk of causing PIH, especially in patients with darker skin tone (Fitzpatrick phototype ≥ IV) [25, 27, 195–198]. Sun protection is also mandatory after these interventions [25, 199].

COMBINED APPROACHES

As multiple players are involved in hyperpigmentation concerns, some skin-lightening strategies aim to simultaneously target several skin cells and factors. The expectation is to improve the effectiveness of treatments while minimizing their adverse effects by reducing the concentration of each agent or the intensity of the procedures. Some are presented below to exemplify different multitargeting approaches.

Photoprotection Boosting

AOX compounds can be added to sunscreens to boost photoprotection [41]. Dermocosmetic products now often include several AOX [200], the most common being vitamins E and C [201].

The combination of skin-lightening agents with vitamins and UV filters has also been shown to improve skin hyperpigmentation [52], as shown in a study on melasma treatment comparing a cream containing 4% hydroquinone, 10% buffered glycolic acid, vitamins C and E, and UV filters with a UV-only sunscreen [202]. A skin-whitening serum combined with a SPF50+ sunscreen also allowed melasma improvement after 12 weeks of bidaily use [203].

Combined Skin-Lightening Agents

Combined skin-lightening formulations started in the 1970s with the Kligman formula combining hydroquinone with tretinoin and corticosteroids used primarily to reduce hydroquinone-induced skin reactions [27, 94]. Modified Kligman trio formulas using alternative retinoids and/or low-potency steroids have successfully been used to treat melasma and PIH for decades [7, 27, 74, 75, 204]. Currently, Triluma® (hydroquinone 4%, tretinoin 0.05%, fluocinolone acetonide 0.01%) is the only triple combination therapy approved in the USA for melasma [6, 205]. However, safety concerns with hydroquinone led to withdrawal of the Kligman formula in several countries [6, 27, 74, 77, 90]. Recently, it has been demonstrated that replacing hydroquinone with a potent cosmetic depigmenting agent, isobutylamido-thiazolyl-resorcinol, in the trio provides at least similar efficacy and better tolerance [206].

Other alternative multitargeted strategies have been developed to avoid hydroquinone-related safety issues.

Retinol and Antioxidant Combinations: A formulation combining retinol (0.5%), bakuchiol, *Ophiopogon japonicus* root extract, vitamin C (30%), vitamin E, and ubiquinone (coenzyme Q10) showed significant clinical improvement

in women with mild-to-moderate facial hyperpigmentation [207].

Retinaldehyde and Resorcinol Derivative Combinations: The combination of phenylethyl resorcinol (0.5%) and retinaldehyde (0.05%) with the antioxidant tocopheryl glucoside (0.1%) demonstrated efficacy in reducing and stabilizing solar lentigines [208].

Niacinamide's multimechanistic action (melanogenesis inhibition, melanosome transfer blockade, anti-inflammatory effects) makes it an ideal combination partner with tyrosinase inhibitors and anti-angiogenic agents.

Niacinamide and Resorcinol Derivative Combinations: Niacinamide (3%) combined with 4-hexylresorcinol (0.4%) demonstrated significantly better lightening of hyperpigmented spots compared to niacinamide alone [139].

Niacinamide and 2-MNG Combination: A topical regimen combining niacinamide (10%) and 2-mercaptonicotinoyl glycine (2-MNG, 0.5%) showed significant clinical efficacy in reducing facial dyschromia and post-inflammatory hyperpigmentation across diverse skin phototypes [209–212].

Other Niacinamide Combinations: A serum containing 5% niacinamide, 3% tranexamic acid, and 1% kojic acid demonstrated efficacy for facial dyschromia [213]. A 2% niacinamide, 2–3% TXA, 4% α-arbutin, and 4% ferment filtrate serum and a 4% niacinamide, 3% α-arbutin, 1% bisabolol, and 0.05% retinaldehyde cream were also effective in treating hyperpigmentation issues [130].

Skin-lightening products can further incorporate anti-inflammatory agents such as licorice extract or dipotassium glycyrrhizate, and/or actives that remodel and improve skin structure such as hyaluronic acid, glycolic acid, or proxylane [203, 213]. As an example of such a multipronged approach, the Neotone® formulation simultaneously targeting melanocytes, fibroblasts, and endothelial cells with the combination of five actives (niacinamide, licorice extract, diacetylboldine, a DKK1 agonist, and an inhibitor of EDN-1 synthesis) was found to be as effective as hydroquinone 4% cream in the management of facial melasma, while inducing fewer side effects [214].

Skin-lightening products can also be combined with chemical or physical exfoliating interventions to mutually enhance and prolong their depigmenting effects (Supplementary information 9).

SUMMARY AND CONCLUSION

Melanin hyperpigmented disorders affect a large population in the world and lead to negative impacts on quality of life. On the basis of the complex physiopathology of these pigmentary disorders, various treatment solutions are envisaged alone or in combination and summarized in Fig. 4.

Altogether, the present review highlights the development of treatment combinations mandatory for future products with high efficacy.

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Declarations

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Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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