Topical Agents for Melasma: A Perspective on Therapeutic Approaches and their Molecular Bases
Eleonora Da Pozzo and Claudia Martini*
Department of Pharmacy, University of Pisa, Italy

Abstract
Melasma is a common skin disease involving changes in normal skin pigmentation. It results from epidermal melanocyte hyperactivity that causes increased production and accumulation of melanin. The onset of the disease has been associated with sun exposure, drugs, genetic and hormonal factors. The primary focus of this review was to provide an updated overview of the main biological aspects behind skin pigmentation and melasma development.

As a second aim of this review, the main mechanisms by which different compounds could reduce melanogenesis were also discussed. Common hypo-pigmenting agents act by reducing the melanogenesis through several mechanisms; they can affect melanin transcription and glycosylation, inhibit tyrosinase (a pivotal enzyme in melanin synthesis), slow the melanosome transfer or increase the skin turnover. Although a number of skin-lightening agents were proposed for treatment of hyperpigmentary disorders, none of these has achieved satisfactory effects. In this light, the most recent therapeutic strategies for melasma, and emerging molecular targets to control skin pigmentation, such as MITF, Wnt and mTOR, were herein described.

Keywords: Melanin; Melanogenesis; Tyrosinase; Hyperpigmentation disorders; Hypo-pigmenting agents

Abbreviations: UV-R: UV Radiation; SCF: Stem Cell Factors; FGF: Fibroblast Growth Factor; PAH: Phenylalanine Hydroxylase; TH-1: Tyrosinase Hydroxylase 1; TRP-2: DOPA-Chrome Tautomerase; TRP-1: DHICA Oxidase; DHICA: 5,6-Dihydroxyindole; DHICA: 5,6-Dihydroxyindole-2-Carboxylic Acid; Indole-5,6-Quinone 1-Q; I-QCA: Indole-5,6-Quinone Carboxylic Acid; MSF: Melanocyte-Stimulating Hormone; TYR: Tyrosinase; MITF: Microphthalmia-Associated Transcription Factor; POMC: Proopiomelanocortin; MC1-R: Melanocortin 1 Receptor; PKC: Protein Kinase C; ET-1: Endothelin-1; Bfgf: Basic Fibroblast Growth Factor; NGF: Nerve Growth Factor; GM CSF: Granulocyte-Macrophage Colony-Stimulating Factor; LIF: Leukemia Inhibitory Factor; HGF: Hepatocyte Growth Factor; PKA: Protein Kinase A; CREB: Camp Response Element Binding Protein; CRE: Camp Response Element; ASP: Angiotensin Signalling Peptide; Pge: Prostaglandins; ETBR: ET-1 G Protein-Coupled Receptor; MAPK: Mitogen-Activated Protein Kinase; IL-1: Interleukin-1; PAR-2: Protease-Activated Receptor 2; Inos: Inducible Nitric Oxide Synthase

Skin Structures
The skin, in addition to provide a vast barrier against external physical threats, acts as a defence system against UV radiation (UV-R), through the high-molecular-weight brown pigment melanin [1,2]. The three skin’s layers are epidermis, dermis, and hypodermis [3].

The epidermis is the outermost layer, providing a waterproof barrier; it is a stratified epithelium devoid of blood or nerve supplies, and composed of several distinct cell populations, above all keratinocytes and melanocytes [4]. It is arranged in four layers, as follows (Table 1):

<table>
<thead>
<tr>
<th>Layer</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratum Basale</td>
<td>Basal layer of the epidermis, composed of rapidly dividing basal cells</td>
</tr>
<tr>
<td>Stratum Spinosum</td>
<td>Layer of cells with numerous intercellular bridges</td>
</tr>
<tr>
<td>Stratum Granulosum</td>
<td>Layer of cells with lamellar inclusions</td>
</tr>
<tr>
<td>Stratum Corneum</td>
<td>Outermost layer, composed of dead cells</td>
</tr>
</tbody>
</table>

The dermis is beneath the epidermis and forms the neural, vascular, lymphatic, and secretory apparatus of the skin. It contains connective tissue, fibroblasts (required for synthesis and degradation of the extracellular matrix), macrophages and mast cells (able to trigger allergic reactions by secreting bioactive mediators), hair follicles (providing a protective niche to several stem cell populations required during wound healing), nails, excretory and secretory glands [1,3,5].

The hypodermis is the deeper subcutaneous tissue. It contains fat and connective tissue; typical cells found in this layer are fibroblasts, adipose cells, and macrophages. It is used mainly for fat storage.

Melanocytes, Melanosomes and Melanogenesis
Normal human skin colour is mainly influenced by the production of the brown pigment melanin that also protects skin against ultraviolet light, and determines several aspects of the phenotypic appearance. The exogenous yellow pigment carotenoids and the endogenous red-oxygenated or blue-reduced haemoglobin contribute to skin colour, too [6]. However, skin and hair pigments depend mostly on size, number, composition and distribution of melanosomes, the melanocyte cytoplasmatic particles containing melanin. In addition, human pigmentation may be determined by the melanogenic activity inside melanocytes and by the melanin synthesis rate [6,7].

Melanocytes are dendritic cells, embryologically derived from the melanocyte precursor cells melanoblasts. The development of melanoblasts and their migration from the neural crest to peripheral sites are the first important steps of melanogenesis. Melanoblasts migrate from the neural crest throughout the embryo mesenchyme reaching specific target sites, mainly dermis (between the 10th and the 12th week of embryonic life), epidermis (between the 12th and the 14th week of development), and hair follicles, but also the eyes (retina pigment epithelium, iris and choroid), ears (vascular strias), and central nervous system (leptomeninges) [7,8].

During embryogenesis, the proper migration of neural crest-derived cells is greatly dependent on interactions between specific receptors and their extracellular ligands. For example, mast cell growth factor or stem cell factors (SCF) bind specific receptors on melanocytes and melanoblasts. Genetic mutations affecting the SCF pattern genes

*Corresponding author: Claudia Martini, Department of Pharmacy, University of Pisa, via Bonanno 6, 56126 Pisa, Italy, Tel: +39 050 2219509/522; Fax +39 050 2219608; E-mail: cmartini@farm.unipi.it
Received: October 27, 2014; Accepted: November 01, 2014; Published: November 04, 2014
Citation: Pozzo E, Martini C (2014) Topical Agents for Melasma: A Perspective on Therapeutic Approaches and Their Molecular Bases. Pigmentary Disorders 5:106. doi: 10.4172/JPD.S1-006
Copyright: © 2014 Pozzo E. This is an open-access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
The synthesis of melanin initiates with the transformation of L-phenylalanine into D-tyrosine and in turn to produce L-DOPA and DOPA-quinone, via phenylalanine hydroxylase (PAH), tyrosinase (TYR) and partly tyrosinase hydroxylase 1 (TH-1). From DOPA-quinone, the pathways are then divided into eumelanogenesis or pheomelanogenesis. The other melanogenic enzymes are TRP-2 (DOPA-chrome tautomerase) and TRP-1 (DHICA Oxidase) for eumelanogenesis. DHIC: 5,6-Dihydroxyindole; DHICA: 5,6-Dihydroxyindole-2-carboxylic acid; I-Q: Indole-5,6-quinone; I-QCA: Indole-5,6-quinone carboxylic acid) [13].

The initial elements of melanogenesis are tyrosine, an essential amino acid, and tyrosinase, a copper enzyme complex. Tyrosinase is a glycoprotein located in the membrane of the melanosome; it has an inner melanosomal domain containing the catalytic region, a short transmembrane domain and a cytoplasmic domain composed of approximately 30 amino acids [14]. Histidine residues are present in the catalytic portion of tyrosinase and bind copper ions required for tyrosinase activity [15]. Other two members of the tyrosinase-related enzyme family are involved in the melanogenesis: tyrosinase-related protein 1 (TRP-1), and DOPA-chrome tautomerase (TRP-2) [16].

Two types of melanin are synthesized within melanosomes, eumelanin and phaeomelanin; eumelanin is a dark brown-black insoluble polymer, whereas phaeomelanin is a light red-yellow sulphur-containing soluble polymer [17]. In the presence of molecular oxygen, tyrosinase oxidizes tyrosine into DOPA and this into DOPA-quinone. From then on, the content in eumelanin or phaeomelanin [18]. Indeed, in the absence of cytochrome P450, DOPA-quinone is converted into DOPA-chrome and then into DHI (dopa-5,6-dihydroxyindole), mostly, or DHICA (5,6-dihydroxyindole-2-carboxylic acid). This process is catalyzed by TRP-2. Finally, the dihydroxyindoles are oxidized into eumelanin by TRP-1 [18].

On the contrary, in the presence of cytochrome, DOPA-quinone quickly reacts with cytochrome to generate 5-S-cysteinyl-dopa and 2-S-cysteinyl-dopa, which are oxidized into intermediates to produce phaeomelanin (Figure 2).

Eumelanin absorbs and disperses ultraviolet light, attenuating its penetration on the skin and reducing the harmful effects of the sun. On the other hand, phaeomelanin has a great potential to generate free radicals in response to UV-R, which are capable of causing damage to DNA, and, in this manner, may contribute to the phototoxic effects of UV-R [19].

The second step of melanogenesis is the melanin distribution that uses the cytotoxic activity of melanocytes. Indeed, following the synthesis of melanosomes, filled melanosomes are introduced in the keratinocytes in the corresponding epidermal melanin unit, through the melanocyte dendritic extensions. Once inside keratinocytes, the melanosomes tend to spread through the cytoplasm, over the nucleus, to protect it from ultraviolet radiations [9,20,21].
Melasma

Figure 1: Integumentary System

Figure 2: Melanin synthesis
**Melanogenic Regulatory Proteins**

The melanocyte-keratinocyte complex responds quickly to a wide range of environmental stimuli, often in paracrine and/or autocrine manners. Thus, melanocytes respond to UV-R, signaling proteins, melanocyte-stimulating hormone (MSH), endothelins, growth factors, cytokines, etc. [1,13,22] (Figure 3).

The gene encoding the basic helix-loop-helix leucine zipper Microphthalmia-Associated Transcription Factor (MITF) [23,24] appears to be fundamental for the regulatory network of signalling pathways controlling the survival, proliferation and differentiation of melanocyte lineage [25]. Melanocyte development and pigmentation are affected by MITF via its transcriptional regulatory effect on tyrosinase, TRP-1 and TRP-2 [26], and on Rab27A, a protein important for melanosome transport [27].

UV radiation stimulates the melanocyte expression of proopiomelanocortin (POMC, the precursor of MSH) and its receptor melanocortin 1 receptor (MC1-R), TYR and TYRP1, protein kinase C (PKC), and other signalling factors [28,29], and increases also the production of endothelin-1 (ET-1) and POMC by keratinocytes [30,31] and those peptides can then act in a paracrine manner to stimulate melanocytes.

In addition, keratinocytes and fibroblasts produce cytokines, growth factors, and inflammatory mediators that can increase melanin production and/or stimulate melanin transfer to keratinocytes by melanocytes. α-MSH, ACTH, basic Fibroblast Growth Factor (bFGF), Nerve Growth Factor (NGF), endothelins, Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), stem cell factors, Leukemia Inhibitory Factor (LIF), and Hepatocyte Growth Factor (HGF) are keratinocyte-derived factors involved in the regulation of the proliferation and/or differentiation of melanocytes [32] (Figure 3).

The main factors that regulate the quantity and quality of the melanin produced by melanocytes include α-MSH, MC1-R, Agouti signalling peptide (ASP), ET-1, prostaglandins (PGEs), bFGF, SCF and HGF [1,6].

α-MSH is a tridecapeptide with a sequence identical to the first 13 amino acids of ACTH. The proteolytic cleavage of proopiomelanocortin, on the pituitary gland, is responsible for the origin of α-MSH [18]. Human keratinocytes and melanocytes are capable of synthesizing α-MSH at physiological quantities [6,19,31,33]. α-MSH and ACTH are produced in and released by keratinocytes and are involved in regulating melanogenesis and dendrite formation. They bind to a melanocyte-specific receptor, MC1-R [34], which activates adenylate cyclase through a G protein, which then elevates CAMP from adenosine triphosphate. Cyclic AMP exerts its effect in part through Protein Kinase A (PKA), which phosphorylates and activates the cAMP

---

**Figure 3:** Scheme of signalling pathways within the epidermal melanin unit and mechanisms by which keratinocyte-derived factors act on human melanocyte proliferation and differentiation. Based on and modified from references 1 and 23.
Response Element Binding Protein (CREB) that binds to the cAMP Response Element (CRE) present in the M promoter of the MITF gene [35,36]. The increase in MITF-M expression induces the up-regulation of TYR, TYRP1, and TRP-2 leading to melanin synthesis. Notably, it has been well established the activation of MC1-R influences the relative quantities of pheomelanin and eumelanin produced, and its activity loss is associated to red or yellow hair; variants of MC1-R have been associated with red hair inheritance, in which more yellow-redish pheomelanin pigment is produced and they present very small tanning capacity [19,37,38]. In 1994, the discovery of a peptide consisting of 131 amino acids acting as an inverse agonist at MC1 was reported, the ASP [39]. In mice, the agouti gene encodes a paracrine signalling molecule that causes hair follicle melanocytes to synthesizes the yellow pigment pheomelanin instead of the black or brown pigment eumelanin.

Endothelin-1 is a 21 amino acid peptide with vasoactive properties synthesized and secreted by keratinocytes after UV-R exposure [1]. Binding of ET-1 to its G protein-coupled receptor (ETBR) on melanocytes activates a cascade of signaling pathways, resulting in calcium mobilization, PKC activation, raise of cAMP levels, and activation of mitogen-activated protein kinase (MAPK). The ET-1 effect is the increase of melanocyte dendricity and the enhancement of melanocyte migration and melanisation [40]. Interestingly, UV-R stimulates keratinocytes to produce interleukin-1 (IL-1) that induce ET-1 expression in keratinocytes in an autocrine manner. These intracellar events in keratinocytes lead to increased TYR mRNA, protein, and enzymatic activity in neighboring melanocytes as well as to an increase in melanocyte number [41].

Prostaglandins PGE2 and PGF2α are known to be produced/ released from keratinocytes by the stimulation of proteinase-activated receptor 2 (PAR-2). PGE2 and PGF2α stimulate the cAMP-independent dendritogenesis, through EP1, EP3, and FP receptors [42].

SCF and FGF are expressed by keratinocytes and are involved in proliferation and melanogenesis/dendritogenesis of melanocytes [43-46].

HGF binds to its specific receptor, c-Met, activates MAPK, eliciting the up-regulation of proteins required for melanocyte proliferation [47-49].

GM-CSF binds to its specific receptor, GM-CSFR, activates the signal transducer and activator of transcription (STAT-1, STAT-3, and STAT-5) or MAPK, inducing the up-regulation of proteins required for the proliferation of melanocytes, and TYR, TYRP1 [50-53].

Finally, the molecular and cellular mechanisms involved in melanosome transfer to keratinocytes are not completely understood yet. Studies of the keratinocyte receptor PAR-2 suggested it controls the melanosome ingestion and phagocytosis by keratinocytes. Moreover, PAR-2 is induced by UV irradiation and inhibition of PAR-2 activation results in the prevention of UVB-induced tanning [54].

In summary, the epidermis has a complex network that secrete as well as responds to autocrine and paracrine factors produced by keratinocytes and melanocytes. It is likely that the melanocyte proliferation requires the cross talking of several signaling pathways (including the cAMP/PKA, PCK, and tyrosine kinase pathways), and the mechanisms by which various factors increase skin pigmentation are closely inter-related.

Melasma Pathogenesis

Up or down regulation of the interconnected network so far described is intrinsically involved in the alteration of melanocytic functions occurring in many epidermal pigmentation disorders [55]. In literature, it has been evidenced that in most hyperpigmentation syndromes multiple pathways regulating melanoblast differentiation/migration, melanogenesis and melanocyte proliferation are simultaneously affected.

Among skin pigmentation disorders, a typical melanogenesis dysfunction characterized melasma, a chronic acquired hypermelanosis of the skin [56,57]. Melasma common presentation consists of facial hyperpigmented macules, which become more evident after sun exposure. It may affect both sexes and all races, but it occurs more often in Asian or Hispanic people with intermediate phototypes. It is more common in adult women in childbearing age, but its onset can also be after menopause. The age of onset is usually between 30-55 years and men account for 10% of cases [58-60].

In melasma, the melanocytes are enlarged and highly dendritic, as in a hypermetabolic state, and an increase in melanin deposition in epidermis and dermis is evidenced [61,62].

There are numerous factors involved in the aetiology of the disease, including genetic influences, endocrinopathies, pregnancy, exposure to UV-R, distress, hormone therapy, drugs and cosmetics; among all these, it seems that genetic predisposition and exposure to sun radiation play the pivotal role.

During pregnancy, increased levels of estrogen, progesterone and MSH have been associated with melasma. In addition, oral contraceptives have been linked to skin hyperpigmentation; it has been speculated that increased levels of estrogens may stimulate the activity of melanocytes [63]. Indeed, melanocytes express estrogen receptors and estradiol stimulates melanogenesis enzymes, such as TYR, TRP1, and TRP2 [64]. Moreover, β-estradiol increases the expression of α-MSH and MC1-R in melanocytes [65]. In addition, a case report study demonstrated an increased expression of estrogen receptors on skin in two patients with melasma [66].

A strong α-MSH immunoreactivity on skin with melasma was suggested by immunohistochemical findings. A strong expression of α-MSH antigen in keratinocytes of melasma-affected skin suggested that α-MSH plays a key role in the hyperpigmentation [58,67]. Probably, persistent overexpression of α-MSH following UV exposure contributes to the development of melasma [67]. Nonetheless, the exact pathogenesis remains to be elucidated.

Other hypotheses on melasma pathogenesis include a) an up-regulation of genes modulating Wnt and prostaglandin pathways [68]; b) the involvement of non-coding RNA (H19 gene) [69]; c) the UV-mediated increase in inducible nitric oxide synthase (iNOS) levels, which can activate the AKT-NFkB pathway [70,71]. Finally, a genetic predisposition has been suggested in melasma development by reports of family occurrence [72].

Topical treatments for melasma and drugs affecting melanogenesis

Open clinical trials, randomized controlled and non-randomized trials about the interventions in the treatment of melasma evidenced that the conventional treatments for melasma include sunscreens, cosmetic camouflage, bleaching creams, acne creams, topical retinoids, chemical peels and laser therapy [73]. Furthermore, some treatments incorporate a combination approach; the most popular combination is a triple-combination cream consisting of hydroquinone, tretinoin, and steroid [74].
Melasma, the treatment of this skin disease is usually dissatisfactory, reported in Table 2.

The efficacy of hydroquinone depends on several factors, such as location of pigment and vehicle of administration.

Mequinol (4-hydroxyanisole, hydroquinone monomethyl ether) Mequinol is a derivative of hydroquinone. It is thought to be a substrate of tyrosinase, and acts as a competitive inhibitor of the enzyme function of melanin precursors. A recent review of randomized controlled trials are mostly lacking. Some of these compounds are reported earlier experimental evidence suggests possible benefits, controlled clinical trials are mostly lacking. Some of these compounds are reported in Table 3.

Many known substances can reduce the level of skin pigmentation, mostly having a tyrosinase-inhibiting effect that lead to reduced total melanin production (e.g. hydroquinone, kojic acid). Other drugs show an effect on the melanin transfer from melanocytes to keratinocytes, causing an overall lighter skin colour (e.g. nicotinamide and soybean). The increase in the desquamation of the skin is also commonly used to remove excessive melanin content within the skin (e.g. retinoic acid). Other agents act as inhibitors of the inflammation-induced melanogenic response mechanisms [75]. A recent review of randomized controlled trials on interventions for melasma evidenced that, although there was poor methodology, a lack of standardized outcome assessments and short duration of studies, the current limited evidence supports the efficacy of multiple interventions [76].

Although melasma can be difficult to treat and the prophylactic management is often the most effective means of prevention, some of the most important agents, commonly used against melasma, are reported in Table 2.

Despite the wide availability of classical agents currently used in melasma, the treatment of this skin disease is usually dissatisfactory, above all due to the great recurrence of lesions and due to the absence of a definitive whitening alternative.

In the light of unsuccessful action of current therapies, a number of agents, both synthetic and derived from natural sources, have been investigated for their potential role in reducing melanin pigmentation. Other agents either or combined with other products are currently investigated for their potential role in reducing melanin pigmentation. Some of these compounds are reported in Table 3.

Final Considerations

Skin-color is due to complex processes including tyrosinase reactions, formation of melanosomes in melanocytes, transfer and organization in the keratinocytes. Although the knowledge of melanocyte biology has made significant advancement, the pathogenic mechanisms underlying acquired hypopigmentation, such as melasma, have to be fully elucidated yet. However, the research has led to development of safer and enough effective skin-lightening drugs, mainly targeting the rate-limiting enzyme of melanogenesis,

\[\text{\textbf{DRUG (name)}} \quad \text{\textbf{Biochemical Effects}} \quad \text{Ref} \]

| Hydroquinone (HQ, 1,4-dihydroxybenzene) | HQ has been used for more than 50 years and is the standard drug for the treatment of facial hyperpigmentation, It acts by inhibition of tyrosinase, thus arrests the conversion of DOPA to melanin. Other proposed mechanisms of action are degradation of melanosomes and inhibition of DNA and RNA synthesis. | 7-79 |
| Retinoids | Retinoids reduce hyperpigmentation through many mechanisms, such as stimulation of keratinocyte turnover and reduction of melanosome transfer. Retinoids inhibit tyrosinase transcription, interfere with melanin synthesis and inhibit tyrosinase-related proteins 1 and 2. Tretinoin (retinoic acid, RA, vitamin A acid) is thought to have an effect on tyrosinase by inhibiting the enzyme's transcription, as well as on dopachrome conversion factor, with a resulting interruption of melanin synthesis. RA reduces hyperpigmentation also through the induction of skin desquamation. Tretinoin is a naphthoic acid derivative with retinoid activity, controlling cell proliferation/differentiation. It has also significant anti-inflammatory actions. | 81-84 |
| Azelaic acid (9-carbon dicarboxylic acid) | Azelaic acid is a compound derived from Pittyosporum ovale. It acts as a weak, reversible, competitive inhibitor of tyrosinase in vitro. Moreover, it has antiinflammatory and cytotoxic effects on melanocytes, via inhibition of mitochondrial oxidoreductase activity and DNA synthesis. | 85 |
| N-acetyl-4-S-cysteaminy1phenol (NACP) | NACP is a synthetic compound bearing phenol, catechol, and sulphur moieties. It acts as inhibiting the tyrosinase's activity as alternative substrate for it. It is more stable and causes less irritation than HQ. | 86 |
| Kojic acid (5-hydroxy-2-hydroxymethyl-4H-pyran-4-one) | Kojic acid is an antibiotic generated by many species of Aspergillus, Acetobacter and Penicillium. It inhibits tyrosinase through chelation of copper at the enzyme's active site. Moreover, it has NFκB activation-inhibitory effects in keratinocytes and is a potent antioxidant. | 87-92 |
| Topical steroids | It is well known that reversible hypopigmentation of normal skin is an untoward effect of prolonged potent steroid application, but the mechanism of this effect is still to clarify. Corticosteroids show inhibitory effects on the synthesis of prostaglandin and leukotriens and this action may partly explain their effects on melanogenesis. | 93-95 |
| Glycolic acid | Glycolic acid is an alpha-hydroxy acid that directly inhibits tyrosinase. In addition, it acts on epidermal remodeling and accelerated skin desquamation. | 96 |
| Ascorbic acid (Vitamin C) | Vitamin C has antioxidant properties and reduces melanogenesis by interacting with copper at the active site of tyrosinase. It also reduces DOPAQuinone by blocking dihydroxyindol-2-carboxylic acid oxidation. Because of its instability in aqueous solution, the magnesium ascorbyl-2-phosphate (MAP) ester has been used. Often acid ascorbic is in association with Iontophoresis in order to increase the penetration of vitamin C into the skin. | 97-100 |
| Liquorice derivatives | Liquorice is the root of the Glycyrrhiza glabra. Active drugs are glabridin, which inhibits tyrosinase in vitro, liquiritin, which disperse melanin, and isoliquiritin containing flavonoids. Liquorice extract has also anti-inflammatory properties in experimental studies. | 101, 102 |
| Soy | Soybean trypsin inhibitor reversibly inhibits the protease-activated receptor-2 pathway. Impaired activation of this receptor in keratinocytes, resulting in the accumulation of melanosomes within melanocytes. Inhibition of this receptor therefore blocks melanosome transfer between these cells, thus also blocking the dispersion of pigment to keratinocytes. | 103, 104 |
| Niacinamide (nicotinamide, vitamin B3) | Niacinamide reduces pigmentation by reversibly preventing the transfer of melanosomes from melanocytes to the keratinocytes, without effect on tyrosinase activity. | 105, 106 |
| N-Acetylglucosamine (NAG) | The carbohydrate NAG represents the monomeric unit of chitin. It acts by inhibiting the conversion of protorosinate to tyrosinase. NAG decreases melanin synthesis and downregulate the pigmentation-related gene expression. | 107 |
| Lignin peroxidase | Lignin peroxidase is a novel method of skin lightening and acts by targeting, enzymatically oxidizing and breaking down melanin in the skin. It acts with efficacy partly to hydroquinone. | 108 |

\textbf{Table 2: Classical agents commonly proposed in melasma treatment}
Diverse antioxidants and various mechanisms

Compounds with antioxidant properties exert hypopigmenting effects by interacting with copper at the active site of tyrosinase, or avoiding the oxidative polymerization of melanin intermediates, or inhibit the signaling process, enabling the stimulation of melanogenesis by ROS after sun exposure.

-o-Tocopherol (α-Toc) interferes with the membrane lipid peroxidation and increases intracellular glutathione content. It inhibits tyrosinase and melanogenesis in melanocytes. The alpha-tocopheryl ferulate, a compound consisting of alpha-tocopherol and ferulic acid, can absorb ultraviolet radiation was found to have significant effect in the retardation of melanogenesis by dual actions, including the downregulation of tyrosinase transcription (via ERK inhibition) and the upregulation of melanin degradation (via ubiquitin-dependent proteasomal degradation induction).

α-MSH can increase melanin synthesis by binding to 6(R)-L-erythro-5,6,7,8-tetrahydrobiopterin (6BH4), a competitive inhibitor of tyrosinase. 6BH4 analogues such as 6,7-(R,S)-dimethyl-tetrahydropterine and 6-(R,S)-tetrahydromonapterine have been studied as possible tyrosinase inhibitors, and it has been suggested that these compounds, like 6BH4, can act through an uncompetitive allosteric mechanism. It has been demonstrated that 6BH4 (and their analogues) also reduces α-dopaquinone non-enzymatically.

- α-MSH can increase melanin synthesis by dual actions, including the downregulation of tyrosinase transcription (via ERK inhibition) and the upregulation of melanin degradation (via ubiquitin-dependent proteasomal degradation induction).

β-MSH can increase melanin synthesis by binding to 6(R)-L-erythro-5,6,7,8-tetrahydrobiopterin (6BH4), a competitive inhibitor of tyrosinase. 6BH4 analogues such as 6,7-(R,S)-dimethyl-tetrahydropterine and 6-(R,S)-tetrahydromonapterine have been studied as possible tyrosinase inhibitors, and it has been suggested that these compounds, like 6BH4, can act through an uncompetitive allosteric mechanism. It has been demonstrated that 6BH4 (and their analogues) also reduces α-dopaquinone non-enzymatically.

For the inhibition of tyrosinase, the most frequently used is α-Lipoic acid (α-Toc), which prevents UV-induced oxidative damage, principally via the down-modulation of NF-κB and its downstream targets.
tyrosinase. Different hypopigmenting agents have been discussed based on a review of the literature. Moreover, other potential targets for control of human pigmentation have been described and new drugs under investigation were reported. Nevertheless, there are currently no guidelines for the management of melasma and the comparisons among outcomes are difficult.

**References**


12. Rouzaud F, Kadekaro AL, Abdel-Malek ZA, Hearing VJ (2005) MC1R and the anti-inflammatory effect involves interference with the arachidonic acid cascade, and that protection against oxidative stress performs a key role in modulating melanogenesis.


