Review Article

Future therapies in melasma: What lies ahead?

Rashmi Sarkar, Anuva Bansal, Pallavi Ailawadi

Department of Dermatology, Maulana Azad Medical College and Associated Lok Nayak Hospital, Delhi, India

Abstract

Melasma is a common, acquired, symmetrical hypermelanosis. It negatively impacts the patient's quality of life and responds poorly to treatment. Although earlier classified as epidermal and dermal, melasma is now thought to be a complex interaction between epidermal melanocytes, keratinocytes, dermal fibroblasts, mast cells, and vascular endothelial cells. Factors influencing melasma may include inflammation, reactive oxygen species, ultraviolet radiation, genetic factors, and hormones. With a better understanding of the pathogenesis of melasma and the realization that targeting melanin synthesis alone is not very effective, treatments focussing on newly implicated factors have been developed. These include agents targeting hyperactive melanocytes, melanosomal transfer to keratinocytes, defective skin barrier, the mast cells, vasculature, and estrogen receptors as well as drugs with anti-inflammatory and antioxidant activity. Many of these newer agents are botanicals with multimodal mechanisms of action that offer a better safety profile when compared with the conventional drugs. There has also been a focus on oral agents such as tranexamic acid, flutamide, and ascorbic acid. It has been suggested that the "triple therapy of the future" may be a combination of hydroquinone, an antiestrogen and a vascular endothelial growth factor inhibitor, as the "ideal" skin-lightening agent.

Key words: Future, melasma, pathogenesis, treatment

Correspondence:
Dr. Rashmi Sarkar,
Department of Dermatology,
Maulana Azad Medical
College, Bahadur Shah Zafar
Marg, Delhi - 110 002, India.
E-mail: rashmisarkar@gmail.com

Introduction

Melasma is a common, acquired, symmetrical hypermelanosis that presents as light to dark brown macules on the face usually over the forehead and malar areas.[1] Women with Fitzpatrick skin types III–V living in areas of increased ultraviolet (UV) light are frequently affected. Melasma is difficult to treat and negative impacts the quality of life.[2-6] The most commonly implicated etiological factors include genetic predisposition, exposure to UV radiation (UVR) and hormonal influences.[7]

Over the years the understanding of the pathophysiology of melasma has undergone a paradigm shift. Melasma was earlier classified on the basis of the localization of melanosomes as epidermal, dermal, and mixed.[1] However, *in vivo* reflectance confocal microscopy has revealed that the distribution of melanophages is heterogeneous, suggesting that all melasma is "mixed" with the dermis often showing solar elastosis and increased vascularity as well.[8,9] Thus, melasma is now thought to be due to a complex interaction between epidermal melanocytes, keratinocytes, dermal fibroblasts, and vascular endothelial cells, with hormonal and genetic factors and exposure to UVR contributing to the variability, dynamicity and the unyielding nature of this process [Figure 1].[9]

The recognition that all melasma is "mixed" has suggested several potential targets for its treatment. Novel agents acting at various levels, from classically targeting the melanogenesis pathway, to acting on hyperactive melanocytes, reducing

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inflammation and free radical production, and inhibiting melanosomal transfer to keratinocytes have been developed. Some newer drugs may act by restoring the skin barrier or hormonal levels, while others target the dermal vasculature and mast cells.

Melanogenesis and Its Regulation

Melanocytes residing in the skin produce melanin which is then transferred to the adjoining keratinocytes.[10,11] Melanogenesis is influenced by genetic factors, age, ethnicity, UVR, and drugs.[7] Melanin is synthesized inside melanosomes through a series of steps [Figure 2] catalyzed by tyrosinase, TYRP1, and TYRP2. The production of these enzymes is controlled by micropthalmia-associated transcription factor (MITF).[12,13]

The steps of this pathway are:

- Conversion of tyrosine to DOPA; this upregulates tyrosinase activity.[14,15]
- Tyrosinase then transforms the DOPA to dopaquinone, which then undergoes spontaneous conversion to 5,6 dihydoxyindole (DHI) and dihydroxyindole-2-carboxylic acid (DHICA).[16,17]
- Both DHI and DHICA are then converted to eumelanin. The activation of TYRP-2 leads to the formation of DHICA-eumelanin associated with a lighter skin phenotype.[17,18]
- Dopaquinone can also form pheomelanin in the presence of cysteine. A higher eumelanin: pheomelanin ratio contributes to a darker skin phenotype, and TYRP1 and TYRP2 have been found to increase this ratio.[16,19-21]

Melanogenesis is regulated by the tyrosine kinase receptor KIT, its ligand SCF (stem cell factor), as well as MITF and melanocortin-1 receptor (MC1R). The activation of MC1R induces a switch from the production of pheomelanin to eumelanin.[22-24] The SCF-KIT receptor tyrosine kinase pathway activates MITF and regulates melanin production through the induction of tyrosinase.[22]

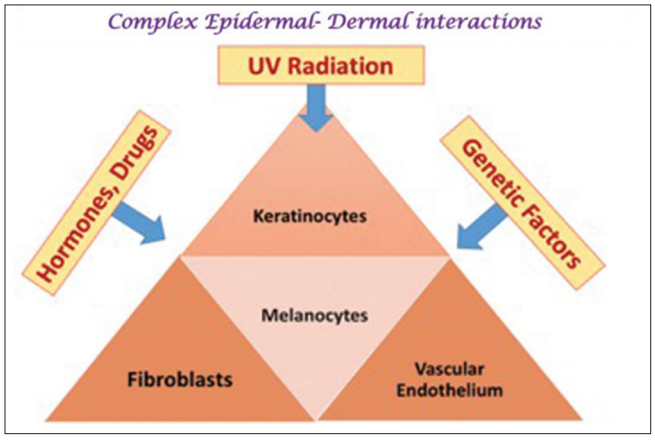

Figure 1 : Melasma – pathogenesis: A complex interaction among epidermal and dermal entities

Most conventional skin-lightening agents are inhibit melanogenesis and its regulation. However, newer therapies targeting other aspects of hyperpigmentation are now being developed.

Hyperactive Melanocytes

The genes involved in melanogenesis (tyrosinase, TYRP1, TYRP2, and MITF) are upregulated in the lesional skin of patients with melasma, and lesional melanocytes show an increased number of dendrites, mitochondria, golgi bodies, and rough endoplasmic reticulum. These findings suggest that heightened biological activity (rather than an increased number of cells) is responsible for the hyperpigmentation in melasma.[25,26] Thus, inhibiting the activity of melanocytes in addition to reducing melanin synthesis may be more effective in improving melasma.

Newer agents targeting melanogenesis and hyperactive melanocytes

Conventional skin-lightening agents such as hydroquinone (HQ) and azelaic acid exert their effects selectively in hyperactive melanocytes i.e. cells with upregulated tyrosinase activity.[27,28]

Newer agents specifically targeting hyperactive melanocytes

Linoleic acid (topical)

Linoleic acid selectively targets tyrosinase in hyperactive melanocytes and decreases UVB-induced pigmentation.[29] In a 6 week double-blind, randomized controlled trial (RCT), a combination linoleic acid with lincomycin and betamethasone valerate showed greater improvement than a combination of the latter two or the vehicle alone.[30]

Ascorbic acid (topical)

Ascorbic acid decreases the oxidation of dopaquinone and DHICA.[31] In addition, it decreases tyrosinase activity, reduces dermal damage, promotes collagen synthesis and has an antioxidant and photoprotective effects, thus reducing hyperpigmentation.[32] In a 16 week split-face study comparing 5% ascorbic acid (AsA) and 4% HQ cream improvement on the HQ side was seen in 93% of 16 women as compared to

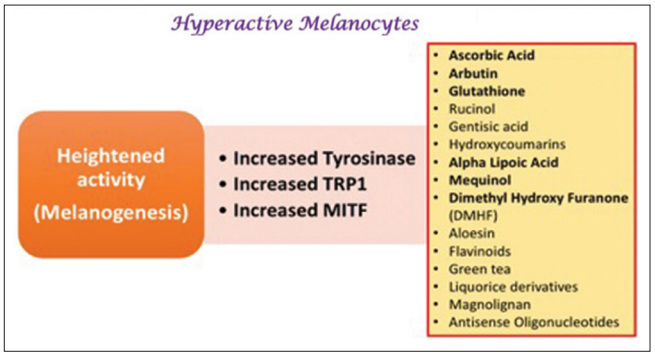

Figure 2: Pathway of melanogenesis and the role of the DHI:DHICA ratio

62.5% on the AsA side ($P < 0.05$). Side effects (SEs) were less frequent in AsA treated patients (6.2% vs 68.7%).[32]

N-acetyl-4-S-cysteaminylphenol (topical)

N-acetyl-4-S-cysteaminylphenol (NCAP) is effective in the treatment of hyperpigmentation[33] It is less irritant and more stable than HQ.[33,34] It inhibits tyrosinase in hyperactive melanocytes, interferes with the thiol system decreasing intracellular glutathione, and favors pheomelanin synthesis.[34] NCAP 4% produced significant improvement in 66% of 12 patients with melasma with complete resolution in 8%.[33,34]

Newer agents targeting melanogenesis

Arbutin and deoxyarbutin (topical)

Arbutin is a derivative of HQ. It inhibits tyrosinase and DHICA, and prevents melanosomal maturation. Its effect is dose-dependent and it has fewer SEs when compared with HQ.[33,34] In an 8 week study of 54 patients with melasma 2.51% arbutin was significantly more effective than placebo in improving melasma.[35] Deoxyarbutin, a synthetic derivative of arbutin, is also effective and safe.[33]

Aloesin (topical)

Aloesin is extracted from aloe vera. It competitively inhibits the conversion of tyrosine to DOPA and DOPA to dopachrome.[33] A dose-dependent skin-lightening effect was noted when aloesin was applied four times daily for 15 days on UV-irradiated human forearm skin.[36]

Rucinol (topical)

Rucinol (4-n-butylresorcinol) is a phenol derivative that inhibits tyrosinase and TYRP-1[37,38] In a randomized, double-blind, vehicle-controlled study 4-n-butylresorcinol 0.1% cream was shown to be effective in 20 patients with melasma.[38]

Flavonoids (topical)

Flavonoids are benzopyrene derivatives; they have anti-inflammatory and antioxidant properties and are competitive inhibitors of tyrosinase.[33,37] Hesperidin is a flavonoid that protects against UVR-induced free radical damage.[39]

Epigallocatechin gallate and ellagic acid (topical)

Epigallocatechin gallate is a phenolic compound extracted from green tea.[33,37] It inhibits melanogenesis and also has significant anti-inflammatory, antioxidant, and anticancer properties.[33] Ellagic acid is a polyphenol derivative found in green tea, strawberries, and pomegranate. It can inhibit tyrosinase and melanocyte proliferation.[40]

Gentisic acid (topical)

Gentisic acid is a compound extracted from gentian roots. It inhibits melanin synthesis.[37,41]

Hydroxycoumarins (topical)

Hydroxycoumarins are naturally occurring lactones that inhibit tyrosinase and also have antioxidant activity.[37] Umbelliferone (7-hydroxycoumarin) has, in addition, anti-inflammatory action.[33]

Cinnamic acid (topical)

Cinnamic acid is derived from ginseng. It inhibits tyrosinase [33,42] and is more potent than HQ.[43]

Antisense oligonucleotides (topical)

Antisense oligonucleotides act as skin-lightening agents by downregulating the production of enzymes involved in melanogenesis and decreasing the activity of DOPA oxidase.[37,44]

Role of Inflammation and Reactive Oxygen Species

Reactive oxygen species (ROS) may be produced by several environmental factors including UVR. ROS can cause oxidative damage to the skin by interacting with cellular lipids, proteins, DNA, and carbohydrates.[45,46] Excess ROS can activate tyrosinase and increase melanin synthesis and melasma is associated with a disruption of the oxidant–antioxidant balance.[33,47] Several interleukins and cytokines can stimulate melanocyte proliferation, upregulate melanin production, and enhance melanosome transfer.[48,49] Thus, drugs with an antioxidant and anti-inflammatory action are being investigated for their potential as therapeutic agents in melasma [Figure 3].[50]

Newer agents targeting ROS and inflammation

Liquorice extract (topical)

Liquorice extract derived from the root of Glycyrrhiza glabra inhibits melanin synthesis, causes melanin dispersion, and decreases ROS production.[33,37] It also has anti-inflammatory effects and can decrease UVB-induced hyperpigmentation in guinea pigs when used topically for 3 weeks.[51]

Proanthocyanidin (oral)

Proanthocyanidin extracted from grape seeds has significant antioxidant action and has been shown to be beneficial in melasma in several studies.[52,53] In a study of women with melasma, proanthocyanidin administered orally for 6 months resulted in significant skin-lightening in 10 of the 12 women (83%, $P < 0.01$).[53]

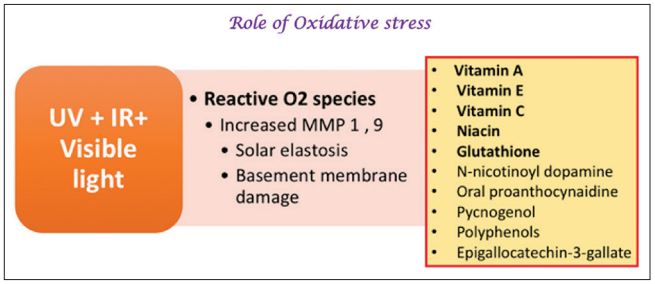

Figure 3: Role of drugs with antioxidant and anti-inflammatory activity

Acidified amino acid peels (topical)

Topical acidified amino acid peels with a pH similar to that of skin have significant antioxidant and tyrosinase inhibitory action and have fewer SEs as compared with glycolic acid.[37,54]

Orchid extract (topical)

Orchid extracts possess strong antioxidant activity. Orchid extract was as effective as 3% vitamin C in a study of 48 patients with melasma.[33,37]

Coffeeberry extract (topical)

Coffeeberry extract has antioxidant properties and it was found to significantly reduce hyperpigmentation and photodamage in a 6-week study of 40 patients with melasma.[33,37]

Mulberry extract (topical)

Derived from the plant *Mores alba*, mulberry extract is a free radical scavenger and inhibits tyrosinase.[33,47] The concentration producing 50% inhibition of tyrosinase activity is lower for mulberry extract than HQ and it markedly improved the Melasma Area and Severity Index (MASI) score in an RCT in 50 patients with melasma.[47]

Pycnogenol (oral)

Derived from the bark of *Pinus pinaster*, this agent has significant antioxidant and anti-inflammatory properties, and an oral formulation has been found to be beneficial in melasma.[33,55]

Other agents

Polypodium leucomatous extracts act by inhibition of UV induced ROS generation, including superoxide anions. AsA and alpha tocopherol are strong anti-inflammatory agents with a marked antioxidant mechanism.[33]

Melanosomal Transfer: Protease-Activated Receptor 2

Melanosomes are transferred from epidermal melanocytes to neighboring keratinocytes as part of the epidermal-melanin unit.[48] Drugs inhibiting the keratinocyte protease-activated receptor 2 (PAR-2) inhibit melanosomal transfer and have been shown to be effective in melasma.[33,48]

Newer agents targeting melanosomal transfer

Niacinamide (topical)

Niacinamide or vitamin B3, the active amide of niacin, interferes with melanosomal transfer to the surrounding keratinocytes by inhibiting PAR-2.[33,46]

Liquirtin (topical)

Liquirtin leads to a skin-lightening effect through dispersion of melanin. A 20% liquiritin cream was shown to be effective in melasma.[56]

Soymilk, soybean (topical)

Serine protease inhibitors (soy trypsin inhibitor (STI) and Bowman–Birk inhibitor (BBI)) found in soybeans have been shown to inhibit melanosome phagocytosis by keratinocytes via inhibition of PAR-2.[48,57] In a double-blind, study of a soy-containing moisturizer with a broad-spectrum sunscreen in 68 patients, significant improvements in fine wrinkles and pigmentary changes were demonstrated after 3 months of usage.[57]

The Defective Skin Barrier in Melasma

Impaired stratum corneum integrity has been demonstrated in melasma. A UVR-induced, as well well as a *de novo* downregulation of several lipid metabolism genes (such as peroxisome proliferator-activated receptor alpha) results in impaired production of free fatty acids leading to a disrupted epidermal barrier [Figure 4].[58-62]

Newer agents targeting the defective barrier

Soy (topical)

Topically applied, active soy moisturizer containing nondenatured serine protease inhibitors (STI and BBI) can decrease UVB-induced pigmentation by restoring the skin barrier.[57]

The Vascular Component

Increased synthesis of proangiogenic factors such as vascular endothelial growth factor (VEGF) results in the proliferation of the dermal vessels. VEGF may increase melanin synthesis through VEGF receptors located on melanocytes.[63,64] UVR-induced release of plasminogen from dermal vessels may also enhance melanogenesis.[65]

Newer agents targeting the vascular component

Tranexamic acid (oral)

Tranexamic acid (TXA) inhibits the plasmin/plasminogen pathway. This results in interference in melanocyte and keratinocyte interactions thus inhibiting melanin synthesis [Figure 5].[66] TXA also influences several other dermal changes associated with melasma such as erythema and reduces both epidermal and dermal pigmentation.[67] Several studies with oral TXA have demonstrated response rates of up to 89.7%, with visible lightening observed at around 2 months.[68-71] Padhi *et al*., observed faster improvement in melasma when a fluocinolone-based triple combination cream was used along with TXA.[72]

Role of Histamine and the Mast Cells

An increased number of mast cells has been noted in the lesional skin in melasma.[73] UVR induces histamine synthesis and this in turn stimulates proliferation of melanocytes through the H2 receptors. UVR also causes mast cell tryptase activation leading to extracellular matrix degradation and basement membrane disruption.[74,75] Mast cells can produce VEGF, transforming growth factor-beta (TGF-β), and fibroblast growth factor-2 all of which promote vascular proliferation thus contributing significantly to melasma.[76,77]

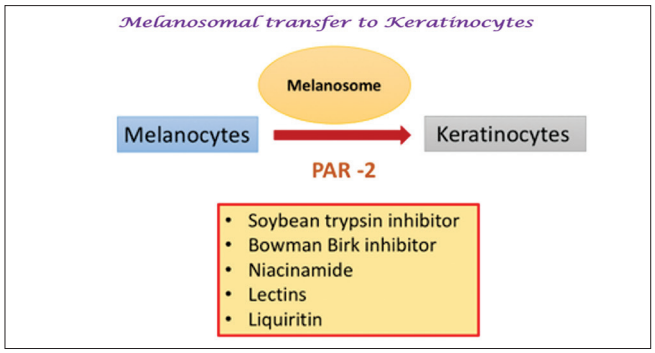

Figure 4: Role of a defective skin barrier in melisma

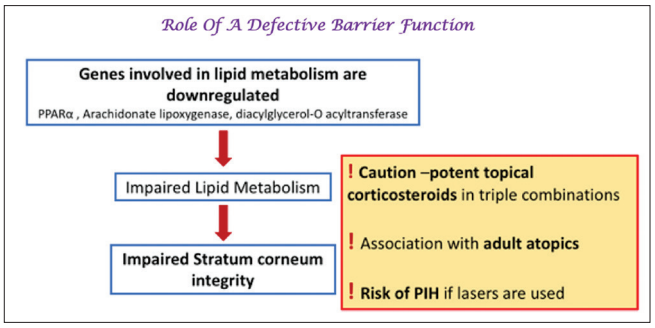

Figure 5: Role of vascular endothelium and mast cells – tranexamic acid inhibits the plasminogen pathway and decreases the activity of mast cells. Zinc primarily affects mast cell degranulation

Despite the significant role of mast cells and histamine in the pathogenesis of melasma, antihistamines have failed to demonstrate a significant benefit in the management of melasma.

Newer agents targeting mast cells

Tranexamic acid (oral)

TXA been shown to reduce the activity of mast cells. In a study of 25 women with melasma, oral TXA tablets were administered three times daily and a topical TXA agent was applied twice daily for 8 weeks. On histopathological analysis, mast cells were found to be decreased after treatment suggesting that the effect on mast cells may underly the therapeutic effect of TXA in melasma.[66]

Zinc (topical)

Zinc reduces histamine secretion through inhibition of mast cell degranulation and is also an antioxidant. A significant reduction in melasma was seen in 14 patients using 10% topical zinc sulfate after 3 months of therapy.[78,79]

Role of the Estrogen Receptor

Melasma is commonly seen among women in the reproductive age group especially during pregnancy or with oral contraceptive use.[80,81] Estrogens upregulate the synthesis of enzymes involved in melanin production such as tyrosinase, TRP-1, TRP-2, and MITF, and also upregulate estrogen receptors in the lesional skin.[82-86]

Thus, drugs inhibiting the effect of estrogen such as selective estrogen receptor modulators (eg., tamoxifen, raloxifene) or aromatase inhibitors (eg., anastrozole, letrozole or exemestane) may be efficacious in the treatment of melasma.[84,85] Furthermore, this research suggests that the "triple therapy of the future" could include a HQ, an antiestrogen, and a VEGF inhibitor.[87]

Newer agents targeting hormones

Topical flutamide

Flutamide is an antiandrogenic agent that can influence alpha-melanocyte-stimulating hormone and cyclic adenosine monophosphate which are key regulators of melanogenesis and in a randomized trial in 74 women with melasma both 4% HQ cream or 1% flutamide cream were found to equally effective in treating melasma.[88]

Newer Agents with Unique Mechanisms: Potential Targets of the future

Curcumin (topical)

Curcumin is a bioactive compound extracted from the rhizome of *Curcuma longa* and its use is well established in traditional Chinese medicine for the treatment of various skin diseases.[89-91] It inhibits UVB-induced production of ROS and expression of matrix metalloproteinase *in vitro* by blocking the activation of the UVB-induced mitogen-activated protein kinase, nuclear factor-κB and AP-1 transcription factor signal pathways.[92] Curcumin gel has been found to be useful in the repair of photodamaged skin and the associated pigmentary changes and solar elastosis.[93]

In view of its anti-inflammatory, free radical scavenging, UV-protective activities, curcumin in may serve as a novel skin-lightening agent of the future, both as a topical and an oral preparation.

Lignin peroxidase (topical)

Lignin peroxidase (LP), an enzyme derived from the fungus *Phanerochaete chrysosporium.* Since lignin is structurally similar to melanin, lignin-degrading enzymes can be utilized to decolorize melanin.[94,95] Lignin peroxidase is marketed as a formulation containing the active enzyme component and its activator (hydrogen peroxide) which causes the destruction of eumelanin. In 51 Asian patients, LP was found to be more efficacious than HQ 2% with significant results seen as early as 7 days.[96]

Platelet-rich plasma

TGF-β1 released from α-granules in platelets has been shown to cause significant inhibition of melanin synthesis through delayed extracellular signal-regulated kinase activation.[97] PRP therapy may also cause improvement in melasma by releasing platelet-derived growth factor, which causes an increase in skin volume as a result of angiogenesis and synthesis of collagen.[98] A greater than 80% reduction of melasma was seen in a 27-year-old

Table 1: Summary - newer drugs for melasma with level of evidence

Drug	Mechanism of action	Level of evidence	Grade of recommendation
Newer agents targeting hyperactive melanocytes			
Linoleic acid (topical)	Tyrosinase inhibition[29] Photoprotective[29]	2	#
NCAP (topical)	Tyrosinase inhibition[34] Favours pheomelanin synthesis[34]	4	#
Newer agents targeting melanogenesis			
Arbutin (topical)	Tyrosinase inhibition[33] DHICA inhibition[33] Prevents melanosomal maturation[33]	2	D
Aloesin (topical)	Tyrosinase inhibition[33]	2	#
Rucinol (topical)	Tyrosinase inhibition[37,38] TYRP-1 inhibition[37,38]	2	#
Flavonoids (topical)	Tyrosinase inhibition[33,37] Antioxidant action[33,43] Anti-inflammatory action[33,37]	*	#
Epigallocatechin (topical)	Tyrosinase inhibition[33] Anti-inflammatory action Antioxidants	1	#
Gentisic acid (topical)	Melanin synthesis inhibition[37]	*	#
Hydroxycoumarins (topical)	Tyrosinase inhibition[33,37] Anti-inflammatory action[33]	*	#
Cinnamic acid (topical)	Tyrosinase inhibition[33]	*	#
Antisense oligonucleotides (topical)	Dopa oxidase inhibition[37]	*	#
Newer agents targeting reactive oxygen species and inflammation			
Liquorice extract (topical)	Melanin dispersion[33] Inhibits melanin synthesis[33] Decreases free radical production[33] Anti-inflammatory effect[33]	2	#
Procyanidin (oral)	Antioxidant action[33]	1 (in combination with vitamins A, C, E)	#
Acidified amino acid peels	Tyrosinase inhibition[37] Antioxidant action[37]	*	#
Orchid extract (topical)	Antioxidant action[33]	2	#
Coffee-berry extract (topical)	Antioxidant action[33]	1	#
Mulberry extract (topical)	Tyrosinase inhibition[33] Free-radical scavenger[33]	1	#
Pycnogenol (oral)	Antioxidant[33] Anti-inflammatory[33]	2	#
Newer agents targeting melanosomal transfer			
Niacinamide (topical)	PAR-2 inhibition[33]	2	B
Soymilk (topical)	PAR-2 inhibition[47]	2	#
Liquirtin (topical)	Prevents melanin transfer[56] Melanin dispersion[56]	1	#
Newer agents targeting the defective barrier			
Soymilk (topical)	Restoration of the skin barrier[62]	2	#
Newer agents targeting the vascular component			
Tranexamic acid (oral)	Inhibits the plasmin/plasminogen pathway thus disrupting the melanocyte and keratinocyte interaction[66] Dermal changes associated with melasma such as erythema[67]	1-4	A
Newer agents targeting mast cells			
Tranexamic acid (oral)	Reduces the activity of mast cells[67]	1-4	A
Zinc (topical)	Inhibits mast cell degranulation[78]	2	#

Contd...

Table 1: Contd...

Drug	Mechanism of action	Level of evidence	Grade of recommendation
Newer agents targeting the hormones			
Topical flutamide	Antiandrogenic Decreases α-MSH, cAMP[89]	2	#

*Adequate human clinical trials not available to suggest level of evidence, #There is not enough evidence to recommend the use in melisma. Grading of recommendation as per OCEBM – levels of evidence (March 2009). Level of evidence as per OCEBM 2011 – 1: systematic review of randomized trials, 2: randomized trial, 3: nonrandomized controlled cohort/follow-up study, 4: case series; case–control; or historically controlled studies. OCEBM: Oxford Centre for Evidence-Based Medicine, DHICA: dihydroxyindole-2-carboxylic acid, PAR-2: protease-activated receptor-2, α-MSH: Alpha-melanocyte-stimulating hormone, cAMP: cyclic adenosine monophosphate, NCAP: N-acetyl-4-S-cysteaminylphenol, TYRP:-Tyrosine related protein

Table 2: Classification of agents, based on level of evidence

Level of evidence			
1	2	3	4
Epigallocatechin	Linoleic acid	-	NCAP
Procyanidin	Arbutin		
(in combination with vitamins A, C, E)	Aloesin		
Coffee berry extract	Rucinol		
Mulberry extract	Liquorice extract		
Liquirtin	Pycnogenol		
	Niacinamide		
	Soymilk		
	Zinc		
	Fluatmide		

NCAP: N-acetyl-4-S-cysteaminylphenol

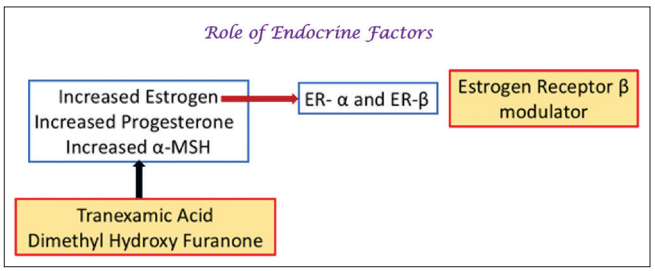

Figure 6: Summary of the various new drugs and their mechanism of action. 1–7 represent the mechanisms of development of melasma: 1 – hyperactive melanocytes and melanogenesis; 2 – melanosomal transfer to keratinocytes; 3 – inflammation and reactive oxygen species; 4 – skin barrier; 5 – dermal vasculature; 6 – mast cells and histamine; 7 – estrogen receptors. ER: estrogen receptors, NCAP: N-acetyl-4-S-cysteaminylphenol, TXA: tranexamic acid

woman treated with three sessions of PRP with no recurrence during follow-up.[99]

Microneedling

Microneedling is commonly used for enhancing the drug delivery of depigmenting agents in melasma. Microneedling under topical anesthesia (two sessions, 1 month apart) along with triple-combination cream applied at night was effective in reducing pigmentation in 22 patients with recalcitrant facial melasma.[100]

Newer sunscreens

Visible light (VL) and infrared light (IR) have been shown to play an important role in hyperpigmentation, especially in the darker skin types (III, IV, or V). VL may induce the production of ROS leading to DNA damage. IR light provokes the activation of the endothelin receptor B and the mitogen-activated protein kinase which facilitate melanogenesis. Sunscreens containing iron-oxide are effective against hyperpigmentation induced by VL. Other novel UV-VL sunscreens that allow absorption of the radiation in the VL spectrum, and systemic antioxidants such as vitamin A, C, and E, carotenoids and beta-carotene may provide additive protection. Nonorganic and organic filters that absorb or reflect IR are currently available and topical antioxidants may be able to offer some protection against IR-related damage. However, their clinical efficacy still remains to be determined.[101,102]

Conclusion

With improved understanding of the pathogenesis of melasma, novel therapeutic targets with the potential for development of newer therapies have now become available.

Melasma is no longer thought to be a static process but a complex epidermal–dermal dynamic interaction with various cell types, inflammation, oxidative stress, and photodamage all contributing significantly to this process. [Figure 6]. This implies that the earlier approach of targeting epidermal melanin alone is insufficient and newer drug classes that target other aspects of the pathogenesis of melasma such as hyperactive pendulous melanocytes, inflammation, free radicals, melanosomal transfer, dermal vasculature, hormone receptors, and the defective skin barrier may be effective [Tables 1and 2].

There are few studies of this ever-expanding list of drugs for melasma and it is imperative to investigate the efficacy and safety profile of these drugs in large scale trials. Despite encouraging results in limited studies most have been inferior to HQ and it is premature to recommend them as absolute alternatives to conventional drugs. It is likely that these newer drugs may play a role only as add-on or second-line drugs or for as maintenance therapy.

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Conflicts of interest
There are no conflicts of interest.

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Dr. J.K.Maniar,
Organising Chairperson
HIV Congress (2020)
69/2, Walkeshwar Road,
Mumbai 400 006, India.
Mobile : +91 - 98204 40613
Email : jkmaniar1944@outlook.com
www.hivcongress.com