

# Bleach peeling for melasma: an effective approach to treatment

## Abstract

Melasma is rare before puberty and most commonly occurs in women during their reproductive years. It not only has a notable effect on the appearance of a patient, but also it has a significant impact on his or her psychological wellbeing. Safe and effective treatment of melasma remains a substantial challenge, and it is difficult to find a way to manage the condition in the long term as it tends to reoccur. This article aims to give a comprehensive overview of the treating principles for melasma using tailored topical bleach peel protocols. The article will discuss relevant topical depigmenting agents that can be applied to effectively treat and manage melasma. Treatment protocols are based on more than 20 years of expertise and experience of a dermatologist specialised in treating this skin disease.

## Key words

► Melasma ► Skin pigmentation ► Skin ► Melanin ► Dermatology

**M**elasma is a common recalcitrant and resistant acquired dark skin colouration. It typically presents in women, post puberty, as characteristic brown patches predominantly on the face or other sun-exposed areas. The known aetiologies for melasma are various, ranging from ultraviolet (UV) exposure and drugs, to hormonal influences and genetics (Victor et al, 2004; Kang and Ortonne, 2009; 2010).

Most recently, the role of oestrogen in melasma has become clearer, as the G-protein coupled oestrogen receptor (GPER) has been shown to enhance melanin synthesis by increasing tyrosinase activity. Based on this finding, it was concluded that 'GPER is therefore a potential drug target for chloasma treatment' (Cohen, 2017; Sun et al, 2017).

Rostami Mogaddam et al (2015) also reported that 'there is a relationship between thyroid autoimmunity and melasma'. There was a significantly higher prevalence of thyroid dysfunction in women with

melasma compared with control groups ( $p=0.008$ ). This study suggested that there is a relationship between thyroid autoimmunity and melasma. The authors also later identified that 'there is a significant relationship between low levels of zinc and melasma' (Rostami Mogaddam et al, 2017).

## Clinical presentation

Clinically, melasma imposes as multiple configured patches located centrofacially, as well as on the neck and décolletage, and possibly on the lower arms and legs. It is diagnosed following expert clinical diagnosis, as well as investigation by a Wood's lamp. Epidermal melasma is fairly pigmented and shows a positive Wood's lamp result, whereas dermal melasma typically shows a grey-like colour and the test is negative (Rajaratnam et al, 2010; Ponka and Baddar, 2012).

Melasma shows histologically an increased melanin content either epidermally or dermally or in both levels (mixed type) (Rajaratnam et al, 2010). It is therefore a consequence of hyperfunctional melanocytes leading to excessive melanin deposition in the epidermis and dermis, or both. Additionally, in some cases, melasma presents with increased vascularity of dermal blood vessels (Rostami Mogaddam et al, 2017), as well as with typical signs of skin ageing, such as solar elastosis (Kim et al, 2007). Occasionally, perivascular lymphohistiocytic infiltrates may also occur (Grimes et al, 2005; Kim et al, 2007).

## Topical treatment principles

Various treatment concepts have been established and published (Ogbechie-Godec and Elbuluk, 2017). An interesting therapeutic approach to treating melasma is the use of topical treatment. Here, the strategy is to effectively downregulate melanogenesis by controlling the production of melanin on various levels (Briganti et al, 2003). Depigmentation can be achieved by regulating both melanin formation and the transcriptional control of the tyrosinase expression; reducing melanogenic mediators (alpha-Melanocyte-stimulating hormone); and increasing cell turnover.

A good example of a topical with transcription inhibition of tyrosinase is tretinoic acid—the carboxylic acid form of vitamin A, all-trans retinoic acid—as it acts on retinoid-activated transcription factors; interferes



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with melanocyte development and melanogenesis; stimulates the differentiation of melanocyte precursors; and removes differentiated melanocytes, thanks to its exfoliating capacity (Rafal et al, 1992; Bulengo-Ransby et al, 1993; Talwar et al, 1993; Kang et al, 2009). Derivatives, such as retinyl palmitate (the ester of retinol and palmitic acid) and retinol (vitamin A<sub>1</sub>, xerophthol), are frequently used in cosmeceuticals.

### Melanin synthesis

During melanin synthesis, the blocking of important enzymes involved in melanogenesis, such as tyrosinase and peroxidase, as well as the inhibition of reactive oxygen species (ROS) scavengers, is a common strategy. The gold standard treatment here is hydroquinone (HQ) (Jimbow et al, 1974; Yoshimura et al, 2006; Badreshia-Bansal and Draelos, 2007; Draelos, 2007).

HQ is well known for its suppressive effect on melanin synthesis. As its hydroxyphenolic compound is structurally similar to precursors of melanin, the mode of action is predominantly defined by being a competitive inhibitor of tyrosinase. HQ therefore affects the formation of melanin, as well as the degradation of melanosomes. Its efficacy is dose-dependent, as are its side effects. Typical side effects are mild irritation/contact dermatitis, confetti-like hypopigmentation or exogenous ochronosis (seen in South Africa where high concentrations of HQ of a non-pharmaceutical quality was used on a long-term scale). No malignancy has been related to topical HQ use (Draelos, 2007; Levitt, 2007; Nordlund et al, 2007; Bandyopadhyay, 2009).

Another active agent in this group is arbutin—a naturally occurring HQ b-d-gluconopyranoside, derived from leaves of various berries (e.g. bearberry, cranberry). It decreases the tyrosinase activity without affecting messenger RNA expression, inhibits 5,6-dihydroxyindole-2-carboxylic acid (DHICA) polymerase activity (pmel17/silver protein) and exerts an inhibitory effect on melanosome maturation. As with HQ, its efficacy is dose-dependent (Chakraborty et al, 1998; Boissy et al, 2005; Maeda and Fukuda, 1996; Hamed et al, 2006; Yoshimura et al, 2006).

Kojic acid (KA), 5-Hydroxy-2-Hydroxymethyl-4-Pyrone, is a natural substance produced by fungi or bacteria (acetobacter, aspergillus, penicillium). It inhibits free tyrosinase by chelating copper. KA is highly irritating, it has a limited skin penetration due to its hydrophilic nature, and its actions are dose-dependent.

ROS scavengers include azelaic acid (Baliña and Graupe, 1991), originally isolated from *Pityrosporum ovale*. Azelaic acid is known as an effective therapeutic agent for skin conditions, such as acne and rosacea. It also has the ability to inhibit melanin production.

Phenylethyl resorcinol is a potent non-irritant antioxidant with the potential to reduce melanin synthesis and to suppress inflammation by

inhibiting cox-II-tyrosinase and other inflammatory melanin-activating factors (Kim et al, 2017).

Vitamin C (ascorbic acid) interacts with copper ions at tyrosinase-active sites and inhibits the action of the enzyme tyrosinase—the main enzyme responsible for the conversion of tyrosine into melanin—thereby decreasing melanin formation (Kameyama et al, 1996; Ando et al, 2007).

One example of an agent with peroxidase inhibition properties is methimazole, an antithyroid agent belonging to the thionamide group, which exerts inhibitory action towards both mushroom tyrosinase and peroxidase oxidation of 5,6-dihydroxyindole (DHI) with the generation of hydrogen peroxide as a by-product (Kasraee, 2002; Kasraee et al, 2008).

### After melanogenesis

Once melanogenesis has taken place, melanosome transfer inhibition and melanin dispersion are the two major strategies to reduce unwanted pigmentation and melanin content, respectively. Acids such as the alpha hydroxy acid group of organic carboxylic compounds (e.g. glycolic or lactic acid), as well as beta hydroxy acids, exfoliate and peel the skin, result in thinning of stratum corneum and dispersion of melanin, and aid penetration of other compounds. Peeling with these AHAs results in thinning of the stratum corneum and dispersion of melanin, as well as the enhancement of the penetration of other agents.

AHAs are known for their antioxidant, anti-inflammatory and anticomedogenic effects to enhance overall skin quality. Glycolic and lactic acid can inhibit melanin production and, in combination with HQ, they are highly effective in treating melasma (Ditre et al, 1993; Garcia and Fulton, 1996; Tung et al, 2000; Usaki et al, 2003).

Niacinamide has anti-inflammatory properties and is able to decrease the transfer of melanosomes (Navarrete-Solís et al, 2011). Moreover, beta hydroxy acids, such as salicylic acid, loosen keratinocytes and in turn remove melanin (Grimes, 1999; Ahn et al, 2006).

### Bleach peeling for melasma: personal treatment approach

With the above in mind, combining depigmenting compounds with a different mode of action makes sense. The strategy here is to induce a controlled skin turnover and combine this with the controlled breakdown of unwanted hyperpigmentation. Any treatment has to be selected and customised individually.

Using skincare to ensure the skin is hydrated and protected against UV radiation is vital. To then control pigmentation, cosmeceuticals play a role (Zettersten et al, 1997; Kligman, 2000; Chen et al, 2005; Dureja et al, 2005; Choi and Berson, 2006; Gao et al, 2008). Cosmeceuticals contain biological actives to increase

**Table 1: Lightening and bleaching topicals for melasma**

Working agents	Action before melanogenesis	Action during melanogenesis	Action after melanogenesis
Tretinoin			
Hydroquinone			
Alpha-arbutin			
Kojic acid			
Azelaic acid			
Resorcinol			
Ascorbic acid			
Alpha and beta hydroxy acids			
Niacinamide			

skin hydration and moisture (Farwick et al, 2011), and offer protection (Farberg et al, 2016). They can also have anti-inflammatory effects or can enhance cell turnover (Ros et al, 1993; Gukasyan, 2002; Barrientos et al, 2008; Sundaram et al, 2009). Compounded topical prescription drugs have a bleaching capacity at therapeutic levels as standalone therapies or additionally by accompanying treatments before and after the procedure. Traditional topical drugs, such as HQ, tretinoin and corticosteroids, can be found in well-known prescription formulations, such as triple combination creams or Kligman's formula (Torok et al, 2005; Chan et al, 2008). The author's strategy is to formulate such magistral formulations as pre- and post-treatment care on an individual basis and on demand.

A typical dermatological melasma treatment is one using various topical agents known for their peeling or skin-lightening activity and potential. After taking various factors into consideration (e.g. characteristics and severity of the melasma, its duration, previous treatments, skin type, patient expectations and

considerations in regards to downtime), the author decides on which working agents to use and composes the respective topicals individually.

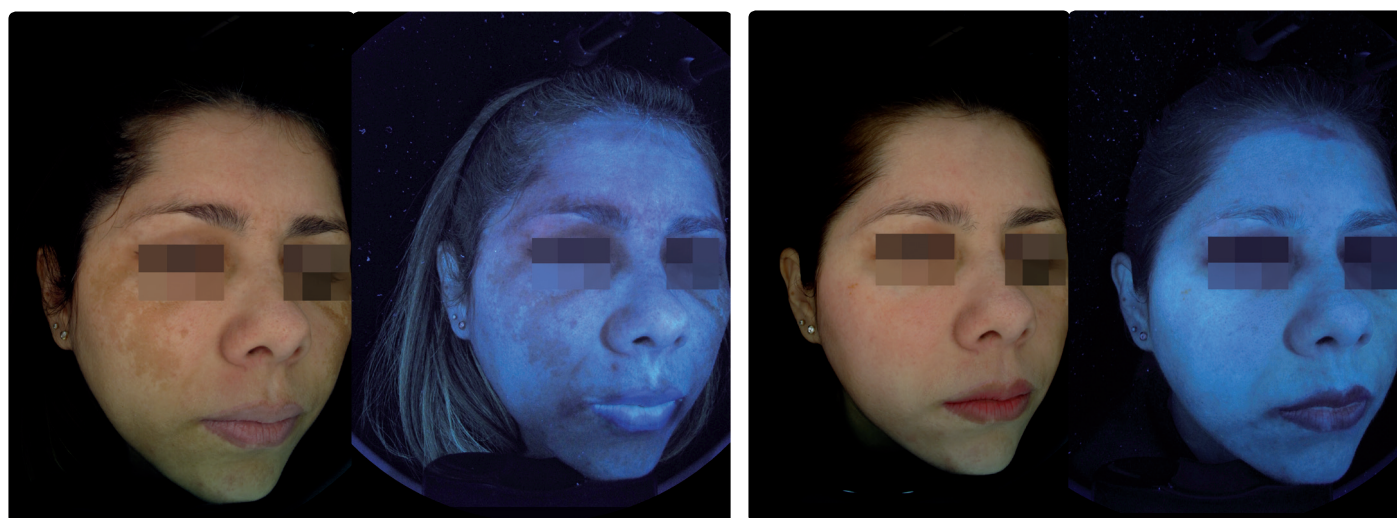
In principle, there are two strategic ways to choose topicals. In general, higher concentrations of certain agents, such as tretinoic acid, or peeling substances lead to more effective treatment results, but also result in a longer period of downtime. Other aspects are that one should try to avoid long-term exposure to HQ, for example, and consider having maintenance treatments using alternative agents.

A good example for a HQ-free treatment option are ready-to-use compositions, such as specialist combination peels. Typical working agents responsible for the bleach peel effect can include kojic acid, alpha-arbutin, azelaic acid, tyrosinase complex, vitamin C, niacinamide, retinyl palmitate and salicylic acid, such as in Dermamelan (Mesoestetic UK) (Table 1). The treatment involves a specific mask containing all the above working agents being applied to the affected area. The exposure to such a peel mask depends on all above named variables, such as severity of the melasma, skin type and skin condition. The clinical effect after one treatment is illustrated in Figure 1.

It is important to understand that one can achieve aesthetically pleasing results with such non-drug-containing combination peels already as a standalone treatment. The major advantage of such topical combination peels is that those treatments are very much suited to treat less severe cases and maintain the effect of additional medical treatments. However, many melasma cases may require stronger treatments.

Medical peels to treat melasma are typically based on the combination of various topicals regulated as cosmeceuticals and prescription drugs (Garcia and Fulton, 1996; Ghersetich et al, 2015). The aim is to combine the effect of a controlled deeper peeling

Figure 1. Melasma treatment of a 42-year-old woman before (first two) and after (second two) the application of Dermamelan (Mesoestetic UK)





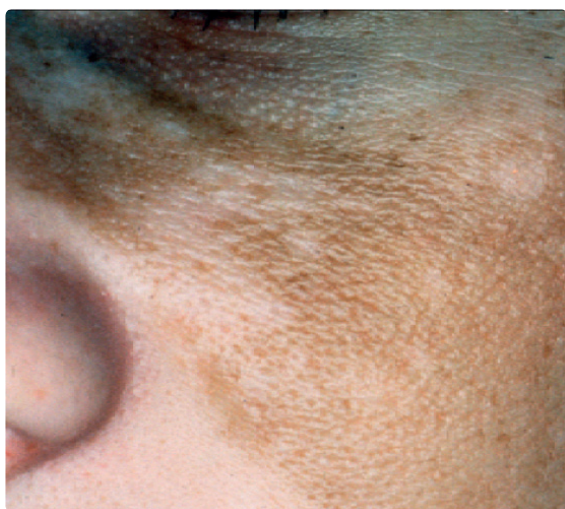


Figure 2a. Centropacial melasma before bleach peeling



Figure 2b. Centropacial melasma after bleach peeling

with the power of topical bleaching. Here, it makes sense to customise each patient's treatment protocol by combining various different agents with both strong peeling and bleaching capacity to peel the skin in a controlled way. Typical compounds included in such treatments are prescription drugs (e.g. HQ (1,4 dihydroxybenzol), tretinoin (trans-retinoic-acid)) with salicylic acid, lactic acid and ascorbic acid. By varying the working agents, their concentrations, the delivery agent (e.g. solution or mask), the exposure time and the number of layers applied, the overall therapeutic effect is adaptable to the patient individually. *Figures 2a and b* show the outcomes of such a personalised topical peeling protocol in combination with a skin-lightening treatment.

All topical treatments in melasma have to be carefully evaluated and planned individually for each and every patient. Patient selection is therefore key. Again, all agents have to be chosen individually. A distinct pre- and post-peel skincare plan has to be set up. The patient has to understand that every individual with a skin prone to melasma formation requires a tailored skin 'diet', meaning that one should be very careful in choosing their respected skincare, as many ingredients can increase the risk of aggravation or induction of this unwanted pigmentation. Cosmetics in general, such as perfume, can trigger or aggravate melasma, and eventually post-inflammatory hyperpigmentation can occur, especially after treatment (Verallo-Rowell, 2001). It goes without saying that any patient suffering from melasma needs to be individually instructed on their skincare regimen as well as the use of skin-type-adapted sun protection factor every day of the year.

Other triggering factors, such as potentially but not imperatively topical and oral hormones (Tamega et al, 2013; Çakmak et al, 2015; Snyder et al, 2017), also have to be identified. Additionally, 'coaching' our patients

is key to increase compliance. This has to be done by first evaluating different treatment options carefully and by consulting on realistic expectations of each procedure respectively. Then, the potential effect of the treatment has to be 'forecasted' in a realistic way, by simultaneously making patients understand that practitioners cannot heal melasma, but can manage this skin disease successfully, as many are suffering from this unwanted skin pigmentation, which can affect one's emotional wellbeing (Freitag et al, 2008).

### Limitations

Various topical treatment options described in the literature have been used in clinical practice over the decades. The author's personal experience performing dermatological topical treatments for melasma over more than 15 years shows that such treatments can be very effective and are safe to sustainably treat and manage melasma. However, data show that not only is there is limited evidence to support the efficacy of multiple interventions, but also studies have had poor methodology, have been too short in duration and have demonstrated a lack of standardised outcome assessments. As discussed in the Cochrane review published in 2014, 'randomised controlled trials on well-defined participants with long-term outcomes are needed' (Jutley et al, 2014) to find a consensus on how to treat melasma at best.

### Conclusion

Topical depigmentation protocols for melasma, based on the bleach peel principle, with various topicals, such as cosmeceuticals and compounded prescription drugs, acting before, during and after melanogenesis in a customised way represents an effective treatment approach to manage melasma successfully and safely on a long-term basis.

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## References

- Ahn HH, Kim IH. Whitening effect of salicylic acid peels in Asian patients. *Dermatol Surg*. 2006;32(3):372–375. <https://doi.org/10.1111/j.1524-4725.2006.32075.x>
- Ando H, Ryu A, Hashimoto A, Oka M, Ichihashi M. Linoleic acid and  $\alpha$ -linolenic acid lightens ultraviolet-induced hyperpigmentation of the skin. *Arch Dermatol Res*. 1998;290(7):375–381
- Ando H, Kondoh H, Ichihashi M, Hearing VJ. Approaches to identify inhibitors of melanin biosynthesis via the quality control of tyrosinase. *J Invest Dermatol*. 2007;127(4):751–761. <https://doi.org/10.1038/sj.jid.5700683>
- Badreshia-Bansal S, Draeos ZD. Insight into skin lightening cosmeceuticals for women of color. *J Drugs Dermatol*. 2007;6(1):32–39
- Baliña LM, Graupe K. The treatment of melasma. 20% azelaic acid versus 4% hydroquinone cream. *Int J Dermatol*. 1991;30(12):893–895
- Bandyopadhyay D. Topical treatment of melasma. *Indian J Dermatol*. 2009;54(4):303–309. <https://doi.org/10.4103/2F0019-5154.57602>
- Barrientos S, Stojadinovic O, Golinko MS, Brem H, Tomic-Canic M. Perspective article: growth factors and cytokines in wound healing. *Wound Repair Regen*. 2008;16(5):585–601. <https://doi.org/10.1111/j.1524-475X.2008.00410.x>
- Boissy RE, Visscher M, DeLong MA. DeoxyArbutin: a novel reversible tyrosinase inhibitor with effective in vivo skin lightening potency. *Exp Dermatol*. 2005;14(8):601–608. <https://doi.org/10.1111/j.0906-6705.2005.00337.x>
- Briganti S, Camera E, Picardo M. Chemical and instrumental approaches to treat hyperpigmentation. *Pigment Cell Res*. 2003;16(2):101–110
- Bulengo-Ransby SM, Griffiths C, Kimbrough-Green CK et al. Topical tretinoin (retinoic acid) therapy for hyperpigmented lesions caused by inflammation of the skin in black patients. *N Engl J Med*. 1993;328(20):1438–1443. <https://doi.org/10.1056/NEJM199305203282002>
- Çakmak SK, Özcan N, Kılıç A et al. Etiopathogenetic factors, thyroid functions and thyroid autoimmunity in melasma patients. *Postepy Dermatol Alergol*. 2015;32(5):327–330. <https://dx.doi.org/10.5114%2Fpdia.2015.54742>
- Chakraborty AK, Funasaka Y, Komoto M, Ichihashi M. Effect of arbutin on melanogenic proteins in human melanocytes. *Pigment Cell Res*. 1998;11(4):206–212. [doi:10.1111/j.1600-0749.1998.tb00731.x](https://doi.org/10.1111/j.1600-0749.1998.tb00731.x)
- Chan R, Park KC, Lee MH et al. A randomized controlled trial of the efficacy and safety of a fixed triple combination (fluocinolone acetonide 0.01%, HQ 4%, tretinoin 0.05%) compared with HQ 4% cream in Asian patients with moderate to severe melasma. *Br J Dermatol*. 2008;159(3):697–703. <https://doi.org/10.1111/j.1365-2133.2008.08717.x>
- Chen Z, Seo JY, Kim YK et al. Heat modulation of tropoelastin, fibrillin-1, and matrix metalloproteinase-12 in human skin in vivo. *J Invest Dermatol*. 2005;124(1):70–78. <https://doi.org/10.1111/j.0022-202X.2004.23550.x>
- Choi CM, Berson DS. Cosmeceuticals. *Semin Cutan Med Surg*. 2006;25(3):163–168. <https://doi.org/10.1016/j.sder.2006.06.010>
- Cohen PR. Melasma treatment: a novel approach using a topical agent that contains an anti-estrogen and a vascular endothelial growth factor inhibitor. *Med Hypotheses*. 2017;101:1–5. <https://doi.org/10.1016/j.mehy.2017.01.020>
- Ditre CM, Griffin TD, Murphy GF, Van Scott EJ. Improvement of photodamaged skin with alpha-hydroxy acid (AHA): a clinical, histological, and ultra-structural study. *Dermatology Congress*, 18–21 May 1993, Vienna, Austria
- Draeos ZD. Skin lightening preparations and the hydroquinone controversy. *Dermatol Ther*. 2007;20(5):308–313. <https://doi.org/10.1111/j.1529-8019.2007.00144.x>
- Dureja H, Kaushik D, Gupta M, Kumar V, Lather V. Cosmeceuticals: an emerging concept. *Indian J Pharmacol*. 2005;37(3):155–159
- Farberg AS, Rigel AC, Rigel DS. Online survey of US dermatologists sunscreen opinions: perceptions, recommendation factors, and self-usage. *J Drugs Dermatol*. 2016;15(9):1121–1123
- Farwick M, Gauglitz G, Pavicic T et al. Fifty-kDa hyaluronic acid upregulates some epidermal genes without changing TNF- $\alpha$  expression in reconstituted epidermis. *Skin Pharmacol Physiol*. 2011;24(4):210–217. <https://doi.org/10.1159/000324296>
- Freitag FM, Cestari TF, Leopoldo LR, Paludo P, Boza JC. Effect of melasma on quality of life in a sample of women living in southern Brazil. *J Eur Acad Dermatol Venereol*. 2008;22(6):655–662. <https://doi.org/10.1111/j.1468-3083.2011.04430.x>
- Ghersetich I, Tripo L, Garzitto A, Lotti TM. Chemical peelings. In: Katsambas AD, Lotti TM, Dessinioti C, D'Erme AM, eds. *European handbook of dermatological treatments*. 3rd edn. Heidelberg: Springer; 2015. 1115–1128
- Gao XH, Zhang L, Wei H, Chen HD. Efficacy and safety of innovative cosmeceuticals. *Clin Dermatol*. 2008;26(4):367–374. <https://doi.org/10.1016/j.clindermatol.2008.01.013>
- Garcia A, Fulton J Jr. The combination of glycolic acid and hydroquinone or kojic acid for the treatment of melasma and related conditions. *Dermatol Surg*. 1996;22(5):443–447
- Grimes PE. The safety and efficacy of salicylic acid chemical peels in darker racial-ethnic groups. *Dermatol Surg*. 1999;25(1):18–22
- Grimes PE, Yamada N, Bhawan J. Light microscopic, immunohistochemical, and ultrastructural alterations in patients with melasma. *Am J Dermatopathol*. 2005;27(2):96–101
- Gukasyan GS. Study of the kinetics of oxidation of monophenols

## CPD reflective questions

- ▶ Is hydroquinone the best treatment for patients presenting with melasma?
- ▶ How can the bleach-peeling principle be applied to the management of melasma?
- ▶ What are some of the typical side effects that can arise from skin peeling in melasma patients?
- ▶ How would you go about customising a topical treatment protocol for a melasma patient?

## Key points

- ▶ Melasma can be classified into three broad categories: epidermal, dermal or mixed
- ▶ The prescription drug hydroquinone (HQ) is one of the most effective inhibitors of melanogenesis
- ▶ HQ-free topicals can help to prevent the reoccurrence of melasma and typically consist of several bleach-peeling compounds
- ▶ These topicals are an effective therapeutic tool in melasma management

- by tyrosinase. The effect of reducers. *Biochemistry (Moscow)*. 2002;67(2):277–280
- Hamed SH, Sriwiriyanont P, deLong MA, Visscher MO, Wickett RR, Boissy RE. Comparative efficacy and safety of deoxyarbutin, a new tyrosinase-inhibiting agent. *J Cosmet Sci*. 2006;57(4):291–308
- Jimbrow K, Obata H, Pathak MA, Fitzpatrick TB et al. Mechanism of depigmentation by hydroquinone. *J Invest Dermatol*. 1974;62(4):436–449
- Jutley GS, Rajaratnam R, Halpern J, Salim A, Emmett C. Systematic review of randomized controlled trials on interventions for melasma: an abridged Cochrane review. *J Am Acad Dermatol*. 2014;70(2):369–373. <https://doi.org/10.1016/j.jaad.2013.07.044>
- Kameyama K, Sakai C, Kondoh S et al. Inhibitory effect of magnesium L-ascorbyl-2-phosphate (VC-PMG) on melanogenesis in vitro and in vivo. *J Am Acad Dermatol*. 1996;34(1):29–33
- Kang HY, Ortonne J-P. Melasma update. *Actas Dermosifiliogr*. 2009;100(Suppl 2):110–113
- Kang HY, Ortonne J-P. What should be considered in treatment of melasma. *Ann Dermatol*. 2010;22(4):373–378. <https://doi.org/10.5021%2Fad.2010.22.4.373>
- Kang HY, Valerio L, Bahadoran P, Ortonne JP. The role of topical retinoids in the treatment of pigmentary disorders: an evidence-based review. *Am J Clin Dermatol*. 2009;10(4):251–260. <https://doi.org/10.2165/00128071-200910040-00005>
- Kasraee B. Depigmentation of brown Guinea pig skin by topical application of methimazole. *J Invest Dermatol*. 2002;118(1):205–207. <https://doi.org/10.1046/j.0022-202X.2001.01621.x>
- Kasraee B, Safaee Ardekani GH et al. Safety of topical methimazole for the treatment of melasma. Transdermal absorption, the effect on thyroid function and cutaneous adverse effects. *Skin Pharmacol Physiol*. 2008;21(6):300–305. <https://doi.org/10.1159/000148222>
- Kligman A. Cosmeceuticals: do we need a new category? In: Elsnér P, Maiback H, eds. *Cosmeceuticals*. New York (NY): Marcel Dekker; 2000. 1–8
- Kim EH, Kim YC, Lee ES, Kang HY. The vascular characteristics of melasma. *J Dermatol Sci*. 2007;46(2):111–116. <https://doi.org/10.1016/j.jdermsci.2007.01.009>
- Kim BS, Na YG, Choi JH et al. The improvement of skin whitening of phenylethyl resorcinol by nanostructured lipid carriers. *Nanomaterials*. 2017;7(9):pii:E241. <https://doi.org/10.3390/nano7090241>
- Levitt J. The safety of hydroquinone: a dermatologist's response to the 2006 Federal Register. *J Am Acad Dermatol*. 2007;57(5):854–872. <https://doi.org/10.1016/j.jaad.2007.02.020>
- Maeda K, Fukuda M. Arbutin: mechanism of its depigmenting action in human melanocyte culture. *J Pharmacol Exp Ther*. 1996;276(2):765–769
- Navarrete-Solís, Castanedo-Cázares JP, Torres-Álvarez B. A double-blind, randomized clinical trial of niacinamide 4% versus hydroquinone 4% in the treatment of melasma. *Dermatol Res Pract*. 2011;2011:379173. <https://doi.org/10.1155/2011/379173>
- Nordlund J, Grimes PE, Ortonne JP. The safety of hydroquinone. *J Europ Acad Dermatol Venerol*. 2007;20(7):781–787. <https://doi.org/10.1111/j.1468-3083.2006.01670.x>
- Ogbechie-Godec OA, Elbuluk N. Melasma: an up-to-date comprehensive review. *Dermatol Ther*. 2017;7(3):305–318. <https://doi.org/10.1007/s13555-017-0194-1>
- Ponka D, Baddar F. Wood lamp examination. *Can Fam Physician*. 2012; 58(9): 976
- Rafal ES, Griffiths CE, Ditre CM et al. Topical tretinoin (retinoic acid) treatment for liver spots associated with photodamage. *N Engl J Med*. 1992;326(6):368–374. <https://doi.org/10.1056/NEJM19920603260603>
- Rajaratnam R, Halpern J, Salim A, Emmett C. Interventions for melasma. *Cochrane Database Syst Rev*. 2010. <https://doi.org/10.1002/14651858.CD003583.pub2>
- Ros JR, Rodríguez-López JN, García-Cánovas F. Effect of L-ascorbic acid on the monophenolase activity of tyrosinase. *Biochem J*. 1993;295(1):309–312
- Rostami Mogaddam M, Iranparvar Alamdari M, Maleki N, Safavi Ardabili N, Abedkouhi S. Evaluation of autoimmune thyroid disease in melasma. *J Cosmet Dermatol*. 2015;14(2):167–171. <https://doi.org/10.1111/jocd.12138>
- Rostami Mogaddam M, Safavi Ardabili N, Iranparvar Alamdari M, Maleki N, Aghabalaie Danesh M. Evaluation of the serum zinc level in adult patients with melasma: is there a relationship with serum zinc deficiency and melasma? *J Cosmet Dermatol*. 2017. <https://doi.org/10.1111/jocd.12392>
- Snyder A, Schiechert RA, Zaiac MN. Melasma associated with topical estrogen cream. *J Clin Aesthet Dermatol*. 2017;10(2):57–58
- Sun M, Xie HF, Tang Y et al. G protein-coupled estrogen receptor enhances melanogenesis via cAMP-protein kinase (PKA) by upregulating microphthalmia-related transcription factor-tyrosinase in melanoma. *J Steroid Biochem Mol Biol*. 2017;165(Pt B):236–246. <https://doi.org/10.1016/j.jsbmb.2016.06.012>
- Sundaram H, Mehta RC, Norine JA et al. Topically applied physiologically balanced growth factors: a new paradigm of skin rejuvenation. *J Drugs Dermatol*. 2009; 8(5 Suppl Skin Rejuvenation):4–13
- Talwar HS, Griffiths CEM, Fisher GJ et al. Differential regulation of tyrosinase activity in skin of white and black individuals in vivo by topical retinoic acid. *J Invest Dermatol*. 1993;100(6):800–805
- Tamega AA, Miot LDB, Bonfietti C, Gige TC, Marques MEA, Miot HA. Clinical patterns and epidemiological characteristics of facial melasma in Brazilian women. *J Eur Acad Dermatol Venerol*. 2013;27(2):151–156. doi:10.1111/j.1468-3083.2011.04430.x
- Torok H, Taylor S, Baumann L et al. A large 12-month extension study of an 8-week trial to evaluate the safety and efficacy of triple combination (TC) cream in melasma patients previously treated with TC cream or one of its dyads. *J Drugs Dermatol*. 2005;4(5):592–597
- Tung RC, Bergfeld WF, Vidimos AT, Remzi BK. Alpha-hydroxy acid-based cosmetic procedures. Guidelines for patient management. *Am J Clin Dermatol*. 2000;1(2):81–88
- Usuki A, Ohashi A, Sato H, Ochiai Y, Ichihashi M, Funasaka Y. The inhibitory effect of glycolic acid and lactic acid on melanin synthesis in melanoma cells. *Exp Dermatol*. 2003;12(Suppl 2):43–50
- Verallo-Rowell VM. Skin in the tropics: sunscreen and hyperpigmentation. Philippines: Anvil Publishing Inc; 2001.
- Victor FC, Gelber J, Rao B et al. Melasma: a review. *J Cutan Med Surg* 2004;8(2):97–102. <https://doi.org/10.1177/120347540400800204>
- Yoshimura K, Sato K, Aiba-Kojima E et al. Repeated treatment protocols for melasma and acquired dermal melanocytosis. *Dermatol Surg*. 2006;32(3):365–371. <https://doi.org/10.1111/j.1524-4725.2006.032074.x>
- Zettersten EM, Ghadially R, Feingold KR, Crumrine D, Elias PM. Optimal ratios of topical stratum corneum lipids improve barrier recovery in chronologically aged skin. *J Am Acad Dermatol*. 1997;37(3):403–408