Vehicles and Formulas:

Hyperpigmentation and Melasma Review

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Melasma is a common chronic hyperpigmentation skin disorder that typically presents with symmetrically distributed light to dark brown spots. Melasma is commonly found on sun exposed areas such as the face and is more common in female patients and those with darker skin tones.[1-3] A recent cross sectional study found an overall prevalence of 0.18% with the highest reported prevalence in Asian and Hispanic patients and in the 41-55 year age group.[4] Melasma can be triggered by UV radiation, inflammation, hormonal changes (such as pregnancy), underlying disorders such as thyroid disorders, or certain medications such as antineoplastic agents, hormonal medications, or antimicrobial agents among others. Genetic predisposition and certain polymorphisms may also play a role in the development of melasma.[5] The pathophysiology of melasma is varied, but some major causative factors resulting in increased melanin production include:

- Increased number of melanocortin-1 receptors on the melanocyte surface,
- Induction of protein kinase A and tyrosine kinase leading to cAMP phosphorylation and melanocyte hyperactivation and hypervascularization via vascular endothelial growth factor
- Fibroblast growth factor-2 induced melanogenesis.[5]

A variety of methods can be employed to help improve and prevent melasma including topical medications, oral treatments, procedures (such as laser therapy or microneedling), or combinations thereof. The goals of treatment include management of photodamage, decreasing inflammation, improving vascularity, and, of course, reducing pigmentation hot spots and creating a more even skin tone. Generally, topical management of melasma is considered first line management and UV protection/sunscreen is important during all treatments.[2]

Common topical agents include hydroquinone, corticosteroids, retinoids, tranexamic acid, niacinamide, kojic acid, ascorbic acid, azelaic acid, or chemical peels (glycolic acid, salicylic acid etc).[2] In this review, we will also discuss emerging treatments such as topical methimazole, glutathione, and metformin.

Hydroquinone is most commonly used between 2-5%, though concentrations of up to 10% and even beyond are sometimes compounded.[4] Hydroquinone lightens skin by decreasing formation of melanosomes and increasing degradation of melanosomes. Hydroquinone has the potential to cause permanent bleaching via necrosis of whole melanocytes. Hydroquinone concentrations ranging from 2 to 5% applied once daily have demonstrated efficacy in many studies, with the effects usually becoming evident by 5 to 7 weeks and sometimes earlier.[5,6] Though higher concentrations including 10%, 12% or even higher concentrations are sometimes compounded, very limited data exists regarding the safety and efficacy of these high concentrations. In vitro data suggests hydroquinone may have some cytotoxic activity at higher doses. Long term application of hydroquinone, especially at high concentrations may be associated with increased serious adverse effects such as ochronosis, a condition characterized by blue-black pigmentation.[25] Ochronosis is more common with application of higher concentrations of hydroquinone (concentrations greater than 4%) and

in patients with darker skin types. One systematic review found that ochronosis associated with hydroquinone, while rare, was also more likely to occur in patients using for longer than 1 year with the median duration of use in patients with ochronosis being 5 years.[26] Though hydroquinone is a common and effective agent for management of hyperpigmentation, some experts in the US recommend using it for no longer than 6 months at a time to decrease the risk of adverse effects.[27] Though use of hydroquinone remains common in some countries and especially in the US, it should be noted that the European Union banned hydroquinone from cosmetics in 2001 due to concerns of rare adverse skin events such as ochronosis.[28]

Retinoids are a common topical treatment for a wide variety of skin conditions including photoaging, acne, and hyperpigmentation among others. Topical retinoids are recommended by the American Academy of Dermatology for treatment of acne and are also beneficial for hyperpigmentation associated with acne as well as general melasma. Commercially available retinoids include tretinoin (in concentrations ranging from 0.01-0.1%), adapalene (in concentrations ranging from 0.1-0.3%), tazarotene (in concentrations ranging from 0.045-0.1%) and trifarotene (at 0.005%).[30] Retinoids are thought to improve hyperpigmentation via anti-inflammatory effects, suppression of toll-like receptors, and reduction of release of cytokines. Retinoids also inhibit the transfer of melanosomes to keratinocytes and increase the rate of epidermal cell turnover.[30] Limited comparison studies, mainly on acne, have evaluated the impact of retinoids on post inflammatory hyperpigmentation (PIH) as well. One study of tazarotene 0.1% vs adapalene 0.3% over 16 weeks found improvement in acne lesions and PIH in both groups, however, tazarotene was significantly more effective than adapalene at decreasing PIH, though slightly more poorly tolerated.[31] Tretinoin used in combination with other agents, usually between 0.01-0.05%, or used as a single agent, up to 0.1%, has been shown in placebo controlled studies to decrease pigmentation.[9,10] Studies on trifarotene are limited, but one recent study evaluating trifarotene 0.005% found significant reduction in acne-induced hyperpigmentation in all skin types compared to placebo. Animal trials suggest that trifarotene may have superior depigmentation effects as compared to adapalene and tretinoin, but further human trials are needed to corroborate these results.[32] Data suggests that retinoids as a class are efficacious for management of melasma and hyperpigmentation especially related to acne. Some limited data suggests tazarotene may be slightly more efficacious and adapalene may be the best tolerated of the retinoids.[33]

In addition to synthetic retinoids, retinol (vitamin A alcohol) has also been studied for utility for hyperpigmentation.[47] Though exact numbers are difficult to come by, some studies estimate that retinol is approximately 20 times less potent than retinoic acid (tretinoin).[48,49] Studies of retinol for hyperpigmentation generally evaluate much higher concentrations than those seen for synthetic retinoids. One study of hydroquinone 4% (applied twice daily) and retinol 1% (applied once daily, mixed with the hydroquinone cream in the evenings) found significant improvement in overall photodamage and hyperpigmentation by the 4th week of treatment.[50] Another study of retinol 0.5% in combination with 30% of a vitamin C derivative (tetrahexyldecyl ascorbate) found statistically significant improvements in skin brightness, lines, evenness of skin tone, and overall photodamage.[51] Though head-to-head data is limited, some sources note an inverse relationship between retinoid efficacy and tolerability with more efficacious products (like tazarotene) having worse tolerability profiles as compared to weaker retinoids or retinol.[52]

Corticosteroids, such as fluocinolone, also play a role in skin lightening. They are primarily used in combination with other agents, both for their own effect on hyperpigmentation related to inflammation and to decrease irritation sometimes associated with other active ingredients that are also being used to treat hyperpigmentation.[6] The mechanism of skin lightening is not well understood, though it may be related to inhibition of inflammatory markers such as prostaglandins which can play a role in melanogenesis. Studies

evaluating hydroquinone 4%, tretinoin 0.05%, fluocinolone acetonide 0.01% combination cream (commercially available as Tri-Luma) have demonstrated benefit by week 8 with continued benefit at the 6-month follow-up.[11] Even after 12 months most patients continued to tolerate the cream without adverse effects.[12] Studies looking at corticosteroids alone for prevention of PIH have demonstrated benefit as well. One study looking at clobetasol 0.05% used short term for 2 days found significantly reduced post procedural PIH in the clobetasol group as compared to placebo.[34]

Tranexamic acid is another option gaining popularity for dermatological use. The mechanism of action may be multimodal, but one proposed mechanism is inhibition of plasmin which plays a role in the release of a growth factor that can stimulate melanocyte growth.[14] The anti-inflammatory activity (via its ability to suppress prostaglandin E2 production thereby reducing tyrosinase activity) of tranexamic acid may also play a role.[35] Studies evaluating oral 500mg per day dosing over just 8 to 12 weeks have seen benefit in the management of patients with refractory melasma.[14,15] Topical 5% tranexamic acid alone, favored for a lower likelihood of systemic effects, applied twice daily over a period of 12 weeks faired as well as hydroquinone 2% in a skin lightening study without as many adverse events as the hydroquinone group.[15] A study comparing azelaic acid 20% to tranexamic acid 5% found comparable efficacy for the management of acne-related PIH, but the tranexamic acid group had significantly fewer adverse effects in the first month of treatment.[43] Tranexamic acid has also been evaluated in combination. One trial of tranexamic acid 3%, niacinamide 5%, and ascorbic acid 2% in a hyaluronic acid containing cream applied twice daily found significant improvement in facial hyperpigmentation over an 8-week period.[35] Another combination trial evaluated tranexamic acid 3% in combination with 1% kojic acid and 5% niacinamide applied twice daily over a 12-week period. An average of 81% reduction in PIH was noted along with improvement of melasma and hyperpigmentation by 60%.[36] Tranexamic acid has also been studied orally as an adjunct to fluocinolone/hydroquinone/tretinoin combination creams. One randomized controlled trial investigated tranexamic acid 250mg orally twice daily in combination with fluocinolone/hydroquinone/tretinoin cream vs the cream alone. This study used the Melasma Area and Severity Index (MASI) to measure impact and found at 4 weeks, patients in the combination treatment group demonstrated 39.9% improvement in MASI score compared to just 25.7% in the cream alone group. This superiority persisted at the 8-week mark as well with patients in the combination group noting a 76.5% improvement compared to just a 45.9% improvement in the cream alone group.[37] These studies, while limited, demonstrate the utility of tranexamic acid both on its own and as an adjunct to existing therapies for the management of hyperpigmentation.

In addition to being studied in combination with tranexamic acid, niacinamide has also been studied on its own for treatment of melasma. Niacinamide is a B-vitamin with anti-inflammatory properties that may work to help decrease incidence of melasma by decreasing transfer of melanosomes.[16] A study comparing niacinamide 4% cream with hydroquinone 4% cream over a period of 8 weeks found that while patients treated with hydroquinone 4% did see more significant improvement, 44% of patients in the niacinamide group still reported excellent improvement and the incidence of adverse effects was greatly decreased.[16] Similarly, other studies investigating 2% niacinamide have also observed a reduction in area of hyperpigmentation after as little as 4 weeks of treatment.[17] Another study evaluating niacinamide 4% in combination with N-acetyl glucosamine 2% over a period of 8 weeks also found significant benefit with a low incidence of adverse effects.[24]

Other vitamins have also been evaluated for potential efficacy for melasma and hyperpigmentation. Ascorbic acid is thought to exert this effect via its antioxidant properties in addition to its ability to inhibit tyrosinase, an enzyme responsible for the conversion of tyrosine into melanin.[38] Ascorbic acid has been investigated at a wide range of concentrations (from 2-30% in combination products or as a solo agent) for melasma and

photoaging.[38,39] One split-face study had patients apply ascorbic acid 5% and hydroquinone 4% cream once daily at night one on each side of the face. Over a period of 16 weeks patients had less benefit with ascorbic acid than with hydroquinone, though 62.5% of patients using the ascorbic acid cream still reported good or excellent results. Additionally, the ascorbic acid has an adverse effect rate in the 6% range as opposed to almost 69% of patients who used the hydroquinone.[18] Though studies on ascorbic acid suggest benefit for hyperpigmentation, further data is needed to compare efficacy and safety of various strengths to determine ideal concentration for use for this indication.

Azelaic acid is another popular option in the management of hyperpigmentation. Like ascorbic acid, azelaic acid is thought to improve hyperpigmentation due to its ability to inhibit tyrosinase. Azelaic acid has been studied for various dermatological conditions in a wide array of concentrations ranging from 5-20%, with most studies for hyperpigmentation evaluating 15% or 20% concentrations.[40] Azelaic acid has demonstrated benefit as compared to hydroquinone in a series of head-to-head trials. One double-blind randomized study spanning 24 weeks comparing hydroquinone 4% to azelaic acid 20% applied twice daily found no significant difference in improvement between the two groups, with significantly fewer side effects in the azelaic acid group.[20] A similar study of 20% azelaic acid vs 2% hydroquinone applied twice daily over 24 weeks found significantly more improvement in the azelaic acid group (73%) as compared to the hydroquinone 2% group (19%).[21] In addition to comparative studies, azelaic acid has been evaluated in combination with hydroquinone as well. A study evaluating 20% azelaic acid in combination with 5% hydroquinone vs hydroquinone alone did find faster onset of action and improved efficacy with the combination, though, this improved benefit was at the expense of tolerability, with significantly more patients reporting adverse effects (stinging, dryness, itching, and erythema) in the combination treatment group.[40,41] Lower concentrations of azelaic acid have also demonstrated benefit for hyperpigmentation. One study of azelaic acid 15% for management of acne induced post-inflammatory erythema and PIH found twice daily azelaic acid to be significantly superior to placebo.[42]

Kojic acid is yet another common topical agent that works via inhibition of tyrosinase in addition to its action as an antioxidant. It is commonly used in concentrations of 1 to 4%, however, kojic acid may be better tolerated at lower concentrations such as 1 or 2%.[44,45] Though studies have demonstrated efficacy, kojic acid has a higher incidence of irritation than some other options that also inhibit tyrosinase, such as ascorbic acid.[6] One double-blind study spanning 12 weeks evaluating kojic acid 2% combined with hydroquinone 2% and glycolic acid 10% compared to hydroquinone and glycolic acid without kojic acid found the kojic acid containing combination to be significantly superior to the hydroquinone/glycolic acid alone combination. Of those receiving the three-agent combination 60% reported a 50% or better improvement in melasma compared to just 47.5% of the hydroquinone/glycolic acid alone group.[23] Another preliminary study on kojic acid 3% applied to patients with hyperpigmentation as a result of acne found 75% of patients tested demonstrated increased skin brightness.[46]

Emerging agents for topical management of melasma include methimazole. Methimazole has been demonstrated to decrease melanin synthesis without melanocytotic effects in in vitro studies.[53] A recent double blind randomized trial comparing 5% methimazole to 2% hydroquinone applied once daily at night in patients with melasma found methimazole to be more effective with a more significant decrease in MASI score by the end of the study. The researchers also noted that the topical methimazole did not impact serum TSH levels, suggesting minimal systemic absorption.[54] Another single-blind patient controlled trial in which patients applied 5% methimazole to one side of the face and 4% kojic acid to the other found both groups saw significant improvement in MASI score, there was a non-statistically significant trend toward greater patient satisfaction with the methimazole treatment.[55] Another randomized controlled trial compared methimazole 5% to hydroquinone 4%. Treatments were applied once daily for 8 weeks, both groups had decreases in MASI score,

and though the hydroquinone group had a larger decrease, there was also a higher relapse rate after discontinuation at the 12 week follow up.[56]

Glutathione, though it has a long history for skin lightening via alternative routes of administration, such as the intravenous and oral routes, has recently been studied for potential efficacy via the topical route as well.[57] One study evaluated topical glutathione 2% compared to 500mg oral glutathione daily. Improvement was more significant in the oral glutathione treatment groups as compared to the topical, but both treatments were superior to placebo for reduction of MASI score.[58] Another double-blind, placebo-controlled clinical trial evaluated 2% glutathione lotion. Participants applied glutathione 2% to half of their face, and placebo to the other half twice daily for 10 weeks. The melanin skin index was significantly lower in the glutathione treated group at 10 weeks. Additionally, improved skin smoothness and moisture content in the skin was noted in the treatment group.[59] Further head-to-head trials of topical glutathione compared to more commonly used agents for hyperpigmentation are needed, but current data on the efficacy and tolerability of topical glutathione is promising.

Another agent with limited data to support use is melatonin. Melatonin may improve hyperpigmentation via its antioxidant effect resulting in decreased UV induced free radicals. Currently data on topical melatonin for this condition is limited, one study had patients apply melatonin 5% cream twice daily for 90 days and found a 31% decrease in MASI score compared to a 37% decrease noted in patients applying hydroquinone 4%.[60] Studies on oral use have also noted benefit, with one randomized double-blind placebo-controlled trial of melatonin 5mg finding significant improvement in MASI score in the melatonin group as compared to placebo over an 8 week period.[61] Comparative data on topical melatonin vs hydroquinone is promising, but further studies are needed to investigate the potential utility of melatonin for topical management of melasma.

Metformin is another ingredient that has been garnering interest in the dermatology space. One study of metformin 30% lotion applied twice daily over 8 weeks found similar decrease in MASI score as patients who received Kligman's Formula (combination tretinoin/hydroquinone and a steroid).[62] Another trial compared metformin 30% cream vs hydroquinone 4%, applied once daily at night for 12 weeks. Patients in the metformin group noted a more significant decrease in MASI score (80.6%) compared to the hydroquinone group (58.1%).[63] Another randomized, double-blind clinical trial of metformin 15% applied twice daily for 12 weeks. The study found a downward trend with MASI scores in the metformin group, though, it failed to reach the level of statistical significance by the end of the study. This study also evaluated relevant lab markers including blood glucose and did not note a significant difference between metformin and placebo treatment.[64] Additional trials to determine the most effective concentration of metformin for topical use are needed.

Lastly, chemical peels are another treatment sometimes used for the management of melasma. A chemical peel causes destruction of part of the epidermis and sometimes the dermis (depending on agent and concentration used) leading to the removal of superficial lesions.[22] Peels can generally be divided into superficial, medium, and deep peels:

Peel Depth	Peel	Considerations for Use
Superficial (Epidermis)	Glycolic Acid 30-50% Lactic Acid 10-30% Salicylic Acid 30% Trichloroacetic Acid 10-30% Tretinoin 1%	• Typically applied every 2-4 weeks in 4-6 treatments. • Glycolic and lactic acid solution applications are generally followed by application of a neutralizer (sodium bicarbonate solution) 1-2 minutes after application • Exfoliation occurs over several days, re-epithelialization complete within 7-10 days
Medium (Epidermis and papillary dermis)	Glycolic Acid 70% Salicylic Acid >30% Trichloroacetic Acid 30-50% Jessner's Solution (Salicylic 14%, Resorcinol 14%, Lactic acid 14%)	• May need to be applied only once to begin seeing benefit • Increased risk of pain compared to superficial peels • Erythema is expected after application, peaking at 4-5 days post treatment, exfoliation is complete at 10-14 days post application
Deep (Epidermis and mid reticular dermis)	Trichloroacetic Acid >50% Phenol Peels (50-55%)	• May need to be applied only once to begin seeing benefit • Inflammation can be severe and re-epithelialization may take more than 14 days • Less commonly used due to serious risk of adverse effects

Information from Solymani et al [65], Sumita et al. [66], and Lee et al. [67]

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Peel protocols can vary depending on area of application and goal of treatment. Patients with darker skin types, especially Fitzpatrick skin phototypes ≥4, are typically recommended not to receive medium or greater depth peels due to the risk of post-inflammatory hyperpigmentation.[67] Some patients are directed to apply pretreatments with agents such as retinoids or hydroquinone prior to the peel to minimize the risk of PIH.[65]

In summary, there are a wide variety of options for the management of hyperpigmentation with many of these options having high quality supporting data in the form of head-to-head trials or placebo-controlled trials. Combination treatments may be the key to both faster results and fewer side effects.

Vehicle	Water Activity	Utility for Hyperpigmentation Formulas
Nourivan Antiox	>0.6	A smooth white oil in water cream base that already contains antioxidants for the stabilization of oxidation prone ingredients such as hydroquinone or kojic acid. Nourivan Antiox can tolerate high API load of common ingredients used for hyperpigmentation such as azelaic acid and is robust enough to serve as a vehicle for some peel formulations as well.
Cleoderm	>0.6	A smooth white cream base containing plant based anti-inflammatory and peptide ingredients. Cleoderm has been demonstrated to be noncomedogenic in clinical testing. Cleoderm also has limited BUD data to support use with some ingredients used for hyperpigmentation treatment such as hydroquinone. Cleoderm can tolerate high API load of common ingredients used for hyperpigmentation such as azelaic acid and is robust enough to serve as a vehicle for peel formulations as well.
Versatile Anhydrous	<0.6	A smooth, white, anhydrous cream base allowing for extended BUD per USP <795> due to its nonaqueous nature. Versatile Anhydrous contains antioxidants and has demonstrated compatibility in benchtop tests with ingredients prone to oxidation such as hydroquinone or kojic acid.

Formula ID	Formula Name
FA-22920	Hydroquinone 4% - Tretinoin 0.05% - Hydrocortisone 1% Cream (Nourivan™ Antiox)
FA-21780	Hydroquinone 4% - Tretinoin 0.05% - Fluocinolone Acetonide 0.01% Cream (Nourivan™ Antiox)
FA-21048	Hydroquinone 4% - Tretinoin 0.05% - Hydrocortisone 1% - Kojic Acid 4% Cream (Nourivan™ Antiox)
FA-23674	Hydroquinone 6% Cream (Cleoderm)(BUD Study)
FA-23586	Azelaic Acid 25% - Niacinamide 4% Cream (Versatile™ Anhydrous Cream)
FA-23029	Azelaic Acid 15% - Niacinamide 4% Cream (Cleoderm™)
FA-23592	Niacinamide 5% - Tranexamic Acid 3% - Kojic Acid 1% Cream (Versatile™ Anhydrous Cream)
FA-22747	Tranexamic Acid 5% Cream (Cleoderm™)
FA-23084	Hydroquinone 4% - Tazarotene 0.1% Cream (Cleoderm™)
FA-21925	Tazarotene 0.1% - Niacinamide 3% - Vitamin E Acetate 1% Cream (Cleoderm™)
FA-23632	Kojic Acid 4% Cream (Versatile™ Anhydrous Cream)
FA-23595	Ascorbic Acid 20% - Niacinamide 4% - Kojic Acid 4% - Tretinoin 0.25% Cream (Versatile™ Anhydrous Cream)
FA-23483	Adapalene 0.3% Cream (Cleoderm)(BUD Study)
FA-23080	Glycolic Acid 30% Cream (Cleoderm™)
FA-20926	Salicylic Acid 30% Topical Solution (PEG)
FA-12128	Trichloroacetic Acid 35% (w/v) Topical Solution
FA-10942	Lactic Acid 14% - Salicylic Acid 14% - Resorcinol 14% Topical Solution

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