Active Ingredient Summary Table
Hyperpigmentation

Active Pharmaceutical Ingredient	Mechanism of Action (MoA)	Dosing	Studies
Adapalene	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[1]	0.1-0.3% applied once daily at night	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[2]
Ascorbic Acid	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[3]	2-30% once or twice daily depending on use alone or in combination	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[4]
Azelaic Acid	Azelaic acid is thought to improve hyperpigmentation due to its ability to inhibit tyrosinase[5]	5-20% typically applied twice daily	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.[6] 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%).[7]
Cysteamine	Cysteamine inhibits tyrosinase enzyme activity and decreases melanocyte hyperactivity[8]	5% cream applied and left on for 15 minutes before washing off	One study comparing cysteamine 5% to hydroquinone 4% and ascorbic acid 3% in combination for PIH found similar efficacy between both treatments[8]

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Fluocinolone Acetonide	Corticosteroids 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[9]	Studied at low concentrations (0.01%) in combination with other agents, applied once daily	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[10]
Glutathione	Glutathione's impact on hyperpigmentation may be multimodal, but the main benefit is likely related to inhibition of tyrosinase[11]	Studied topically, orally, and via injection. Studies on topical use have evaluated 2% applied twice daily	A 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[12]
Glycolic Acid	Glycolic acid is thought to treat hyperpigmentation via its anti-inflammatory, antioxidant, and keratolytic effects.[13]	For repeated daily use, lower concentrations such as 10% are sometimes used in combination products. When used as a peel concentrations between 30-70% are used depending on peel depth	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[14]
Hydroquinone	Hydroquinone lightens skin by decreasing formation of melanosomes and increasing degradation of melanosomes[15,16]	Used once daily alone or in combination typically at concentrations between 2-5%	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[15,16]
Kojic Acid	Kojic inhibits tyrosinase and also has antioxidant properties[17,18]	Typically 1-4% applied once or twice daily as a solo agent or in combination	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

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			melasma compared to just 47.5% of the hydroquinone/glycolic acid alone group.[14] 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[19]
Lactic Acid	Lactic acid is thought to treat hyperpigmentation via its anti-inflammatory, antioxidant, and keratolytic effects.[13]	Typically used in peel products at concentrations ranging from 10-88% either alone or in combination (such as in Jessner's solution)	One study comparing lactic acid 60% vs glycolic acid 40% peel applied every 4 weeks for a total of six sessions found lactic acid to be more effective than glycolic acid.[20] One study evaluated Jessner's solution vs Salicylic acid 30% applied every other week for a total of 3 sessions for acne induced hyperpigmentation. The treatments were found to be equally effective.[21]
Metformin HCl	Metformin HCl can decrease intracellular cyclic adenosine monophosphate (cAMP) which in turn inhibits melanogenesis[22]	Applied 15-30% twice daily	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).[23] 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%).[24]
Methimazole	Methimazole has been demonstrated to decrease melanin synthesis without melanocytotic effects in in vitro studies[25]	Studied at 5% applied once daily	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[26]
Melatonin	Melatonin may improve hyperpigmentation via its antioxidant effect resulting in decreased UV induced free radicals	Limited data on oral use (5mg dose) and topical use (5% cream applied twice daily)	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%.[27]

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Niacinamide	Niacinamide is a B-vitamin with anti-inflammatory properties that may work to help decrease incidence of melasma by decreasing transfer of melanosomes[28]	Typically used at 2-5% concentrations applied once or twice daily alone or in combination	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[28]
Retinol	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[1]	Typically used at 0.5-1% concentrations applied once daily at night alone or in combination	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[29]
Salicylic Acid	Used topically as a peeling agent/keratolytic	30% is the most common concentration for peel products	One study evaluated Jessner's solution vs Salicylic acid 30% applied every other week for a total of 3 sessions for acne induced hyperpigmentation. The treatments were found to be equally effective.[21]
Tazarotene	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[1]	Applied once daily at night in concentrations from 0.045-0.1%	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[2]
Tranexamic Acid	One proposed mechanism is inhibition of plasmin which plays a role in the release of a growth	Studied orally (500mg per day) and topically (3-5% applied twice daily) alone or in combination	Topical 5% tranexamic acid 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[31]

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	factor that can stimulate melanocyte growth[30]		
Tretinoin	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[1]	0.01-0.05% topically applied once daily at night	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[10]
Trichloroacetic Acid	Used topically as a peel	Concentrations range from 10->50% depending on peel depth	Studies have found trichloroacetic acid peels as low as 15% in combination with other acids such as glycolic acid 70% or as a solo agent at 35% to be effective for reducing melanin index.[32,33]
Trifarotene	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[1]		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[34]

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