Received: 21 June 2022 | Accepted: 11 July 2022

DOI: 10.1111/jocd.15242

JCD Journal of Cosmetic Dermatology WILEY


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Melasma is a common malady affecting all races with a higher incidence in Hispanics, Middle Eastern, Asians, and African origin females (Fitzpatrick skin phototypes III–V). Women are affected much more often than men. Melasma remains a significant cause of cosmetic morbidity and psychosocial embarrassment affecting quality of life necessitating effective and reliable treatment. Unfortunately, treatment remains unsatisfactory due to limited efficacy, adverse effects, and relapses after stopping treatment. Although chemical peels, laser and light therapies and dermabrasion may have utility, the evidence available for their efficacy is limited and they often cause post-inflammatory hyperpigmentation, particularly in individuals with darker skin types. Medical therapies remain mainstay in the management of melasma. The triple combination, hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01% (Triluma, Galderma, Ft. Worth Texas, often modified incorporating different corticosteroids) remains the only US FDA-approved treatment for melasma and is the gold standard due its demonstrated efficacy across ethnicities. Oral tranexamic acid alone or in combination with other modalities has also shown significant efficacy. Several cosmeceuticals and botanical extracts used as skin lightening agents have been demonstrated to be useful. Physical sunscreens containing zinc oxide, iron oxide, titanium dioxide, and silicones provide photoprotective and camouflage effect. We propose that a multimodality approach to the treatment of melasma is the most effective treatment approach. This review is focused on the medical therapies for melasma.

chemical peels, cosmeceuticals, hydroquinone, natural ingredients, tranexamic acid

Melasma (Greek- Melas; Black) is a common acquired skin hyperpigmentation primarily affecting sun-exposed areas of forehead, cheeks, nose, upper lip, and chin, and occasionally the neck and forearms. Its exact prevalence in general population is understudied but accounts for 5–6 million people in US alone, 0.25%–4% of dermatology clinic attendees in Southeast Asia and it is one of the common pigmentary disorders among Indians.[1] Melasma affects all races but individuals of Hispanic, Latin American, Middle Eastern,

Asia and African origin (Fitzpatrick skin phototypes III–V) predominate.[2] Women are affected much more often than men who comprise 10%–20% of cases mostly in their 3rd and 4th decade of life with mean age of 30 years at onset.[3–5] Variable presentations are reported based on clinical examination, histology, and intensification of pigment under long wave ultraviolet light (Wood's light) (Table 1). The diagnostic significance of "Fitzpatrick macule," a confetti-like macule of regularly pigmented skin observed in about 89% clinical photographs of large hyperpigmented patch of melasma cases compared with 1% cases of poikiloderma of Civatte and 6% of solar lentigenosis cases has been highlighted recently.[6]

Melasma remains a significant cause of cosmetic morbidity and psychosocial embarrassment affecting quality of life.[3,4] However, treatment remains unsatisfactory for most individuals due to limited efficacy and adverse effects of available therapies, and frequent relapses after stopping treatment. This paper presents an overview of hydroquinone, often used as first-line therapy and non-hydroquinone medical treatment options in patients with melasma.

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A high incidence of up to 70% in family members favors genetic predisposition to develop melasma. Other frequently implicated etiologic factors include pregnancy, oral contraceptives, endocrine dysfunction, hormone replacement treatments, thyroid disorders, drugs, cosmetic contact sensitivity, light exposure including both sun and artificial light and stress.[7,8] Pigmentation is usually confined to the epidermis, but dermal factors have been implicated for its recurrent and refractory nature. Ultraviolet (UV) irradiation induced increased proliferation on dermal vasculature proliferation and upregulation of dermal proangiogenic factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and interleukin (IL)-8) have been implicated in the pathogenesis of melasma.[9,10] Interaction between VEGF receptors on epidermal keratinocytes and dermal proangiogenic factors leads to release of mediators such as arachidonic acid metabolites and plasminogen from proliferated vessels, which enhance melanogenesis in melasma.[11,12] Plasmin also converts extracellular matrix-bound VEGF into freely diffusible forms and plays an important role in angiogenesis and melanogenesis.

Recently, the role of mast cells in the pathogenesis of melasma has been also highlighted. They are related to various histological changes and their increased number observed in melasma lesions is attributed to repetitive UV irradiation. The mast cell tryptase degrades type IV collagen that might be the cause of weak basement membrane observed in melasma. Solar elastosis is another histological feature of melasma, and elastin content in UV-exposed skin correlates with mast cell counts suggesting their role in this process. Interestingly, in experimental mast cell-deficient mouse models, solar elastosis was not observed even after repeated UV irradiation.[13] The mast cells can also induce vascular proliferation by secreting various dermal proangiogenic factors like VEGF, FGF-2, TGF-B enhancing melanogenesis in melasma.

Recently, the effect of visible light in inducing pigmentation and the role of UV radiation on keratinocyte–melanocyte interaction, dermal inflammation, and fibroblast activation through a complex interaction and interplay between increased melanocyte proliferation, fibroblast activation, stem cell factor, prostaglandin synthesis, inducible nitric oxide synthesis and melanogenesis has been elucidated.[11,12]

for maximum benefit. Newer peels like phytic acid peels and amino fruit acid peel are developed to overcome the drawbacks of conventional peels. Phytic acid peels have low pH and do not need neutralization. They are applied on face overnight and used once every week and clinical effect is observed usually after 5–6 sessions.[17] Recently introduced 10% tretinoin peel mask has shown significant therapeutic benefit in 20 patients with melasma.[32] Ilknur et al.[33] in a single-blinded, randomized study found amino fruit acid peels were superior to glycolic acid peels in melasma treatment after 12 sessions. These carboxylated acidified amino acid peels have an alka-

Non-hydroquinone-based therapies for melasma

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| Tyrosinase inhibitors | Competitive | Arbutin (α or β Arbutin), Deoxyarbutin, Aleosin, Azelaic acid, Kojic acid, Gentisic acid, Mequinol, Flavonoids |
| | Non-Competitive | Glabridin, Liqourice extract, Mulberry extract, N-acetyl glucosamine (Chitin), Hydroxystilbenes (resveratrol, genitol), |
| Melanosome transfer Inhibitors | | Niacinamide (Vit B3), Soy extract (Soyabean trypsin inhibitor), Retinoic acid |
| Melanosome maturation inhibition | | Arbutin, Deoxyarbutin |
| Antioxidants | | Vitamin E (α-Tocoferol acetate), Vitamin C (Sodium ascorbyl phosphate, Ascorbyl Palmitate, Ascorbyl Glucoside) |
| Epidermal turnover enhancers | | Retinoic acid, α-hydroxy acids, Salicylic acid, Linoleic acid |
| Plasmin inhibitor | | Tranexamic acid |
| α-MSH induced melanin reduction | | β-carotene |
| Protease activator receptor-2 inhibitor | | Soyabean trypsin inhibitor |
| By interaction with copper | | Kojic acid, Ascorbic acid |

Hydroquinone (1,4 dihydroxybenzene), a hydroxyphenolic compound, has been used extensively as a standalone or in combination with other agents for topical treatment of melasma. It inhibits conversion of DOPA to melanin by inhibiting the activity of tyrosinase possibly interacting with copper at the active end of the enzyme.[41] It is also said to alter melanosome formation, increase their degradation, destroy melanocytes, and inhibit DNA and RNA synthesis. It is used topically as a 2% to 5% cream or alcohol-based solution and has been found effective even in monotherapy. The pigmentation decreases evidently in a dose-dependent manner by 5–7 weeks of treatment that needs to be continued at least for 3 months to a year.[8,42–45] Hydroquinone 4% has resulted in complete or partial clearance of melasma in 95% patients versus 67% patients in the placebo group at 12 weeks without significant adverse effects.[46] Although azelaic acid 20% produced a more favorable response than hydroquinone 2% resulting in excellent or good overall improvement (73.8% vs. 19.4%), hydroquinone 4% was as effective as azelaic acid 20% over 24 weeks without causing itching and burning noted with the latter.[47–49] It was equally effective as monotherapy in 4% concentration and in a combination with glycolic acid (20%–30%) peel leading to significant improvement in a split face study comprising 21 Hispanic women.[50] Hydroquinone 4% showed a 77% improvement over a 3-month period when compared with a 67% improvement from a skin whitening cream containing *uva ursi* extract, fermented *Aspergillus*, rice extract and grapefruit extract.[51] Pruritus was the major adverse effect from hydroquinone. A twice-daily application of 4% hydroquinone was superior to placebo and improved melasma in 38% and 77% patients versus 10% and 67% patients in placebo group in two separate studies.[46,51] Apparently, a 4% concentration is particularly useful when used as monotherapy. However, nearly 25% patients may experience a dose- and duration-dependent irritation from transient inflammatory reaction with higher concentrations, especially during initial 2 weeks of topical therapy.[43,44,52] Mild itching, burning sensation, erythema, irritant and allergic contact dermatitis, transient hypopigmentation, nail discoloration, and post-inflammatory hyperpigmentation are reported more often with 4% than 2% formulations. Prolonged use and higher concentration is also associated with exogenous ochronosis, a difficult-to-treat, gray-blue-black pigmentation over treated areas.[46,51] However, these adverse events may also be associated with other substances added to the hydroquinone formulation.[41,53] Another concern is its propensity for rapid oxidation resulting in unstable formulations, discoloration, decreased efficacy, and actual depigmentation from melanotoxic hydroxybenzoquinone and *p*-benzoquinone, the byproducts of its oxidation.[17] The risk of possible bone marrow toxicity, development of renal adenomas or carcinogenic effect of topical hydroquinone therapy in humans is considered insignificant since it bypasses its metabolism in liver.[41,54] There was also no significant risk for premature death or malignancy among workers exposed to the compound during industrial production than normal population.[41] Nevertheless, its use in over-the-counter cosmetics in USA, Australian, European, Japanese, and Indian markets is not allowed while Poland and West African country Ghana have totally banned it.

Currently, hydroquinone is often used in combination with other agents such as retinoids, topical corticosteroids, kojic acid, and/or glycolic acid for added effect. It is also used along with chemical peels.

### 5.2.1 | Triple combination treatments

The triple combination of hydroquinone with a retinoid and a corticosteroid remains the most studied modality to treat melasma because of improved tolerability and efficacy. The original triple combination developed by Kligman–Willis in 1975 consisted of hydroquinone 5%, tretinoin 0.1%, and dexamethasone 0.1%.[55] Overall, it has been noted that hydroquinone 10% is more effective but highly irritating, tretinoin 0.2% is irritating without being more effective while tretinoin 0.05% is less irritating but takes a long time

Classification of chemical peels

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|---|---|---|---|
| Very superficial peels | | Glycolic acid 30%–50%<br>Trichloroacetic acid (TCA)10%<br>Jessner's solution (1–3 coats)<br>Salicylic acid 20%–30%<br>Lactic acid 50%<br>Tretinoin 1%–5% | Stratum corneum |
| Superficial peels | | Glycolic acid—50%–70%<br>TCA 10%–30%<br>Jessner's solution[a] (4–7 coats) | Epidermis extending to papillary dermis |
| Medium peels | | Glycolic acid 70%<br>TCA 35%–50%<br>Phenol 88%<br>Pyruvic acid | Upper reticular dermis |
| Deep peels | | Baker Gordon phenol formula[b] | Mid reticular dermis |
| Classic peels | Mono peels | Glycolic acid<br>Trichloroacetic acid<br>Salicylic acid<br>Retinoic acid<br>Phenol | – |
| | Combination peels | Jessners peel<br>Modified Jessners peel (lactic acid, salicylic acid and citric acid)<br>Baker-Gordon peel (phenol, croton oil, septisol and water)<br>Salicylic - mandelic acid | - |
| Newer peels | Mono peels | Mandelic acid<br>Pyruvic acid<br>Lactic acid<br>Ferulic acid<br>Jasmonic acid<br>Tartaric acid<br>Malic acid | - |
| | Combination peels | Salicylic-mandelic acid peel<br>VI peel (TCA 10%–12%, salicylic acid 10%–12%, tretinoin 0.1%–0.4%, phenol 10%–12%, and vitamin C 4% in mineral blend)<br>Phytic acid<br>Lipohydroxy acid<br>Polyhydroxy acid<br>Black peel | - |

[a]Jessner's solution: salicylic acid 14%, lactic acid 14%, resorcinol 14% in 95% ethanol.

[b]Baker Gordon phenol formula: 3 ml phenol, 2 ml water, 8 drops of hexachlorophene (septisol), and 3 drops of croton oil yielding 48.5% phenol and 2.2% croton oil.

to be effective, and dexamethasone can be increased up to 0.2% to enhance activity without significant difference in irritancy potential.[45,55] Several modifications using different corticosteroids (hydrocortisone 0.1%, mometasone 0.1%, fluticasone 0.1%, betamethasone valerate, flucinolone acetonide 0.01%) have been in use since then. The fluorinated corticosteroids are apparently more effective than non-fluorinated steroids. A formulation of hydroquinone 4%, tretinoin 0.05%, and flucinolone acetonide 0.01% (HTF, Triluma®) remains the only US FDA approved triple combination for melasma therapy. Studies across ethnicities have documented its superior efficacy even in moderate to severe melasma and improved quality of life compared with hydroquinone monotherapy or other combination therapies. This triple combination was more effective than hydroquinone 4% alone from 4 weeks onwards in a comparative study in 120 Brazilian patients with moderate-to-severe melasma.[45] A complete clearance of pigmentation in 35% and >75% improvement occurred in 73% at 8 weeks compared with 5% and 49% patients, respectively, in hydroquinone-only group without a significant difference in adverse effects in both the groups. Chan et al.[56] also demonstrated a superior effect of HTF triple combination compared with hydroquinone 4% cream alone in a multicenter randomized study of 206 Southeast Asian patients. Nearly 70% of 125 patients with moderate to severe melasma achieved complete clearance in triple combination group as compared to 44% of 129 patients in hydroquinone group. Similar observations on its efficacy and safety have been made in 1290 Latin American patients

(including 23% Hispanics) in a phase IV community-based study (PIGMENT trial).[57] A statistically significant reduction in degree of melasma was observed and nearly 49% patients improved from moderate or severe (99%) at first visit to absent or mild melasma at 8 weeks. The adverse events were mild in 68%, moderate in 25%, and severe in 6.9% only. Sequential treatment with triple combination cream and IPL was more efficacious than sequential treatment with an inactive (control) cream and IPL in a 10-week split-face study by Goldman et al.[58] They treated 56 patients having moderate to severe melasma with triple combination cream on one side of the face and an inactive control cream on the other side of the face. Patients also had two IPL treatments 2 and 6 weeks after suspending topical treatment one day before IPL treatments. Melasma severity was significantly less with triple combination cream and IPL compared with control cream and IPL at 6 weeks and end of 10-week study period.

The triple combination therapy has also proven impact on improving quality of life in patients with melasma. A statistically significant reduction in MASI and MelasQoL scores observed after 4 and 8 weeks of treatment with HTF triple combination in 135 of 300 patients (mean age 42 years) with skin phototypes I through V in a Brazilian multicenter study.[59] Similarly, HTF triple combination was superior in improving quality of life in comparative clinical trial for efficacy and safety, and effect on MelasQoL when compared with hydroquinone 4% and tretinoin 0.05% in studies of melasma patients from Latin America, Mexico, and Hispanic women with a range of Fitzpatrick skin types I through VI.[60–62] Triple combination therapy was overall the best topical treatment for melasma in a recent Cochrane review.[63] Its efficacy has been attributed to synergistic effect of individual components and time taken for its beneficial effect with a twice-daily application is roughly three weeks. Tretinoin prevents oxidation of hydroquinone and improves epidermal penetration of other agents while topical corticosteroid decreases cellular metabolism, inhibits melanin synthesis, and reduces irritation from the other two components.[55] Nevertheless, adverse effects such as erythema, burning, pruritus and irritation, dryness and desquamation are not uncommon and other corticosteroid-induced cutaneous adverse effects may occur from its unsupervised prolonged use. Another problem is of post-inflammatory hyperpigmentation from irritant reaction noted in few patients with darker skin. A less frequent application may ameliorate irritation in such patients.

### 5.2.2 | Dual combination treatments

Dual combination treatments tested for melasma include hydroquinone plus retinoic acid or hydroquinone (4%) plus glycolic acid (5–10%) with moderate improvement and generally tolerable irritant effects.[13,64,65] A combination of hydroquinone 4%, glycolic acid 10%, antioxidants and sunscreen showed reduction in melasma pigmentation after 12 weeks of treatment that was more significant than seen with antioxidants/sunscreen alone in a comparative study.[66] A combination of hydroquinone and kojic acid or glycolic acid demonstrated a significant decrease in degree of melasma in a study of 39 patients.[67] However, addition of glycolic acid peel did not improve the efficacy of similar regimen of hydroquinone 4% and glycolic acid 10% over 7 months in a Brazilian study.[68]

Mequinol (4-hydroxyanisole, monomethyl ether of hydroquinone), a derivative of hydroquinone with a similar mechanism of action is used as 2% concentration in combination with tretinoin (0.01%) for treating melasma. It was superior in efficacy to hydroquinone 3% and tolerated well in a randomized, parallel-group, double-blind study of 216 patients with solar lentigines/hyperpigmented lesions.[69] Keeling et al.[70] achieved moderate improvement in one and complete clearance with the combination in four males with melasma at 12 weeks with effect lasting up to 16 weeks. The combination is usually safe and well tolerated but caused mild erythema, irritation/burning, stinging/tingling, desquamation, pruritus, and hypopigmentation in another open-label study using twice-daily application of mequinol/tretinoin and sunscreen with SPF ≥25 for 24 weeks to treat solar lentigines and related hyperpigmented lesions.[71] Experimentally, mequinol was effective in treating melasma and showed less irritant potential than hydroquinone and adverse effects were less than those from monobenzyl ether of hydroquinone.[72,73] Although licensed for monotherapy in Europe and Brazil or in combination with tretinoin in United States and Canada, hydroquinone and not mequinol remains preferred first-line therapy for melasma world over.[74] Few large controlled clinical studies for mequinol in the management of melasma will perhaps resolve issues related to its efficacy and safety for a wider acceptance.

Topical corticosteroids, retinoids, and alpha hydroxy acids (glycolic acid, kojic acid, azelaic acid), several plant extract-based therapies

hypertrichosis, acneiform eruptions, telangiectasias, rosacea, and perioral dermatitis.[16,76] Moreover, the short-lived beneficial effect prompts repeated and prolonged treatment without supervision causing marked skin atrophy and other adverse changes. The mechanism for their skin lightening effect remains poorly understood and is often attributed to their direct anti-metabolic effect on melanin synthesis, alteration of melanocyte function without being melanotoxic and/or inhibition of synthesis of inflammatory mediators such as leukotriene and prostaglandins.[76] Topical use of a potent or super potent corticosteroid alone has demonstrated good therapeutic effect.[77] Corticosteroids such as hydrocortisone, dexamethasone, mometasone furoate, fluocinolone acetonide, and fluticasone remain preferred in (triple) combination therapy of melasma. Once daily futicasone (0.05%) topical application was as effective as betamethasone (0.12%) twice daily or mometasone furoate without hypothalamic-pituitary-adrenal axis suppression and caused less skin atrophy than mometasone furoate and fluocinolone acetonide in the triple combination.[78,79] Topical corticosteroids as monotherapy for melasma are usually not preferred for their atrophogenic potential and other adverse effects, although fluticasone is less atrophogenic than others. However, they are beneficial when used with caution to reduce irritation from other topical agents or when pigmented cosmetic dermatitis is suspected.

Tretinoin (0.05%–0.1%) remains a common retinoid used effectively to treat melasma even as monotherapy but needs at least 24 weeks for apparent clinical improvement.[80] It inhibits tyrosinase transcription and related proteins 1 and 2 (TRP-1 and TRP-2) to decrease post-transcriptional levels of tyrosinase and TRP-1and interrupts melanin synthesis after UVB exposure.[13,81–84] Additionally, it also decreases melanosome transfer by accelerating keratinocyte turnover and desquamation.[83] When used in combination, it improves penetration of other active ingredients like hydroquinone and antagonizes atrophogenic effect of corticosteroid.[13] Topical tretinoin lead to 68% improvement in 38 patents over a 40-week treatment period.[85] However, 88% patients experienced burning, itching, erythema, and scaling from continuous therapy. Tretinoin (10%) peeling mask was effective in a study of 20 women with Fitzpatrick skin type II-VI and tretinoin 1% peel was as effective as 70% glycolic acid peel.[32,86] Topical adapalene, isotretinoin and tazarotene are other retinoids used in melasma.[82,83,87] Adapalene is well tolerated and equally effective among retinoids in long-term melasma treatment. Retinol causes less irritation but its comparative efficacy is lower than tretinoin or tazarotene.[41]

Kojic acid (5-hydroxy-2-hydrxymethyl-4-pyrne), a metabolite of *Aspergillus orzae* and certain species of *Acetobacter* and *Penicillium*, inhibits free tyrosinase by chelating copper at the enzyme's active site and exhibits antioxidant effects. It is available in 1–4% concentration and has efficacy almost equal to other therapies. Addition of hydroquinone 2% or glycolic acid (5%–10%) has an augmenting effect. Its combination with hydroquinone 2% was superior in efficacy than kojic acid used alone or its combination with betamethasone valerate 0.1% or glycolic acid 5%, or a combination of betamethasone valerate 0.1% and hydroquinone 2%.[6,88] A combination of kojic acid 2%, glycolic acid 10%, and hydroquinone 2% was more effective in melasma than the same combination without kojic acid in a spilt-face study.[89] The combination of kojic acid 2% and glycolic acid 5% had efficacy equal to that of hydroquinone 2% and glycolic acid 5% in a split-face study to treat melasma.[49] It makes a useful option in patients responding poorly to hydroquinone and glycolic acid or who are intolerant to other first-line therapies. However, it is potentially an irritant and a contact sensitizer and known to cause paradoxical pigmented contact dermatitis.[90]

Azelaic acid, a dicarboxylic acid, produced by *Pityrosporum* sp., is responsible for hypopigmentation in tinea versicolor. It has antiproliferative and selective cytotoxic effect on abnormally hyperactive melanocytes by its inhibitory effect on tyrosinase and mitochondrial oxidoreductase enzymes with minimal effects on normally pigmented skin. Azelaic acid (15%–20%) is effective in melasma and post-inflammatory hyperpigmentation as monotherapy and was equally effective as hydroquinone 4% but superior to hydroquinone 2% while its combination with tretinoin 0.05% and glycolic acid 15%–20% showed synergistic effect.[47,48,91,92] A combination of azelaic acid 20% and glycolic acid 15%–20% was as effective as hydroquinone 4% in moderate to severe melasma and other facial hypermelanoses in patients with skin of color.[91] It makes a safe choice in hydroquinone intolerant patients. However, mild and transient itching and burning may occur while acneiform eruptions and telangiectasias, hypertrichosis, vitiligo, and asthma are extremely rare occurrences.[92]

Arbutin, a d-glucopyranoside derivative of hydroquinone, derived from bearberry leaves is widely used for its skin lightening and depigmenting effect. It hydrolyses to hydroquinone in vivo and competitively inhibits enzyme tyrosinase and 5,6-dihydroxyindole-2-carboxylic acid polymerase activity in vitro in a dose-dependent manner.[93] Deoxyarbutin and α-arbutin, the synthetic derivatives of arbutin, are more stable and show better efficacy than the natural one. The inhibitory effect of arbutin on tyrosinase activity equals to that of hydroquinone and deoxyarbutin in an in vitro study but is less effective than kojic acid.[41,49]

less toxic in vitro to melanocytes than hydroquinone. A significant skin lightening and improvement in solar lentigines was observed following topical deoxyarbutin treatment for 12 weeks in patients with either light or dark skin tones.[93] However, good clinical studies are lacking for its efficacy and safety in patients with melasma.

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The efficacy of Tranexamic acid (TA) (Trans-4-Aminomethylcyclohexanecarboxylic acid) in treating melasma has immensely renewed interest for this mode of therapy in recent years. This synthetic derivative of the amino acid lysine is a plasmin inhibitor and antifibrinolytic agent used primarily to prevent and treat blood loss in menstrual disorders and surgeries with high risk of blood loss such as cardiac, liver, vascular, and orthopedic procedures.[94,95] It exerts its effect by reversibly blocking lysine binding sites on plasminogen molecules thus inhibiting plasminogen activator from converting plasminogen to plasmin. It has no effect on coagulation parameters in recommended antifibrinolytic doses of 0.5–1.5 g given three times daily or up to 2.0–4.5 g/day. It is given intravenously as 10 mg/kg immediately before surgery or in 6–8 hourly doses one day prior to surgery. The peak plasma concentrations are reached within 3 h after oral administration and its absorption is not hampered by food. Approximately 3% of the drug is bound weakly to plasma protein, the plasminogen. Almost 45% of the dose is recovered in the urine in first 3 hours and 90% of the intravenous administered drug is eliminated mostly in one day. The drug can cross the blood–brain barrier and the placenta but excretion into breast milk is minimal.

### 6.6.1 | Tranexamic acid in melasma

Sadako[96] incidentally observed that severity of melasma reduced significantly after 2–3 weeks of TA in a patient under treatment for urticaria. It has been reported effective when used alone or in combination with other modalities to treat melasma topically (liposome formulations), intradermally (by microinjection), transepidermally (by mesotherapy), orally, or intravenously with comparable efficacy.[15,97–104] Although intravenous TA has been advocated for the "whitening of skin" in Taiwan since 2007, the usual recommended intravenous dose (500 mg every 2–4 weeks administered directly or with normal saline infusion) is potentially risky and considered too low for skin whitening effect.[103] Further, there are no clinical studies to justify such use.

### 6.6.2 | Topical tranexamic acid

Topical TA 2% or 5% in liposomal formulations has been found effective with clinical effect observed in 2–3 months.[105–107] Although no significant difference was noted between 5% TA versus vehicle in a 12-week randomized controlled split-face study, topical 3% tranexamic acid was as effective as topical hydroquinone 3% and 0.01% dexamethasone combination cream in another similar trial.[105,106] It was also effective as topical emulsion in melasma and freckles applied for 5–18 weeks.[107]

### 6.6.3 | Intralesional tranexamic acid

TA is not commercially available for intralesional use but prepared as 4 mg/ml solution from 100 mg/ml commercial injectable solution for mesotherapy (transepidermally by microneedling or intradermal by localized microinjections) to treat melasma in both genders.[15,102] Lee et al.[99] reported significant decrease in MASI score in 8–12 weeks from baseline in 100 patients with melasma but injection site erythema and pain were major limiting factors. Although the results were not statistically significant, the improvement in baseline MASI score was better with drug administration by microneedling than microinjections (44.4% vs. 35.7%) in a comparative study comprising two groups of 30 patients each.[98] However, TA by microinjection was superior to topical TA in a small study comparing the two routes of administration.[108] Similarly, an overall efficacy with comparable reduction in MASI score was noted in patients receiving intradermal or oral TA in a recent study.[102] These results suggest that the efficacy of TA is perhaps independent of its route of administration. Nevertheless, direct injection to the affected sites is minimally invasive, offers the advantage of delivering adequate amount of medication directly at the affected skin, and allows use of lower than oral dose. However, pain and discomfort during injection procedure and turn around period of 2–3 days are real drawbacks. The use of TA by ionotophoresis chemical enhancer and constant electric current may have the advantage of being without pain and discomfort but requires further clinical evaluation.[109]

### 6.6.4 | Oral tranexamic acid

Oral TA in doses varying between 500 mg/day and 2.25 g/day for up to 6 months have been used alone or as adjuvant with almost equal efficacy (Table 5). Hajime et al.[110] in a study showed 33 of 40 patients aged 24–60 had their melasma reduced in severity with 1–1.5 g daily oral TA in 10 weeks. Zhu et al.[111] compared oral 250 mg TA, vitamin C (0.2 g) and vitamin E (0.02 g), all given thrice daily to treat 128 patients with melasma and vitamins C and E only in 30 controls for a period of 6–8 weeks. They observed statically significant reduction in melasma in the treatment group. Similar results were obtained by Liu et al.[112] in a study comprising 176 patients and 70 controls. The treatment group who received oral TA 250mg three times daily, and vitamin C (0.3 g/d), and vitamin E (0.1 g/d) in controls given for 2 months showed more improvement with about 24% patients showing 90% improvement and 40% patients having 60% improvement compared with the control group. Thirty-three percent of the 256 melasma patients of Wu et al.[113] showed improvement in the first month from oral TA 250 mg given twice daily and 33% improved further after

Clinical studies using oral tranexamic acid in the treatment of melasma

| | | | acid | | | | | |
|---|---|---|---|---|---|---|---|---|
| [15] | 66/66 | 18-52 | 250 mg once daily (Group-A) Topical sunscreen | 500 mg twice daily (Group-B) Topical sunscreen | 4 months | MASI ↓60.1% (Group-A) versus 78.09% (Group-B) | Mild gastrointestinal upset in both groups; oligomenorrhoea in 3 cases in Group-B (self-limiting) | Although, 500 mg twice daily showed early clinical response and overall better efficacy both in per-protocol and intention-to-treat analysis, 250 mg once daily was also effective and can be a choice to maintain remission. |
| [99] | 12/0 | 30–69 | 1.5 g/day + Vitamin B, C, E | No control | 5 months | 11/12 patients had obvious result | Not mentioned | Effect onset mostly in 4 weeks |
| [102] | 130/130 | 17–55 | 500 mg/day+ topical hydroquinone and sunscreen | Topical hydroquinone and sunscreen | 3 months | mMASI ↓ 82.3% versus 40.8% $p < 0.05$ | Oligomenorrhea 14.7% Belching 9.2% Abdominal cramp 6.9% | – |
| [104] | 39/41 | 18–55 | 250 mg twice daily | Intradermal TXA | 3 months | 64%>75%↓ 36% 50%–75%↓ | Mild gastrointestinal upset in 2 cases; oligomenorrhoea in 6 cases (self-limiting) | Both were equally effective |
| [106] | 24/27 | 32–50 | 500 mg/day + IPL-Nd:Yag | IPL- Nd:Yag | 6 months | mMASI ↓ 43.8% versus 23.6% $p < 0.005$ | No significant adverse effect | – |
| [112] | 40/0 | 24–60 | 1–1.5 g/day | No control | 10 weeks | 33/40 patients had decrease severity | Not mentioned | – |
| [113] | 128/30 | 30–49 | 750 mg/day + Vitamin C, E | Vitamin C, E | 6–8 weeks | 20% >95% ↓ 30% >60% ↓33% 20–60%↓ $p < 0.001$ | Gastrointestinal upset in few cases | Observed increase duration of TXA more effective than increased dose. No change in clotting profile |
| [114] | 176/70 | 25–57 | 750 mg/day + Vitamin C, E | Vitamin C, E | 2 months | 24% >90% ↓ 40% >60% ↓ $p < 0.01$ | 5% gastrointestinal upset in both group | No change in clotting profile |
| [115] | 256/0 | 21–65 | 500 mg/day | No control | 6 months | 10.5% >90% ↓ 18.8% >60% ↓ 51.6% 30%↓ | Gastrointestinal upset in 4.3%, oligo- menorrhea in 3.5% | 33% response in 1st month, 33% in 2nd month. No change in clotting profile |
| [116] | 99/100 | >15 | 2.25 g/day | Placebo | 8 weeks | 76.8% improved versus 27% placebo ($p < 0.001$) | Transient chest discomfort in one case | – |

is a key antioxidant and significantly decreased levels of plasma glutathione have been reported in patients with melasma as compared to controls.[120–122] Its efficacy in treating melasma is attributed to inhibition of tyrosinase enzyme by chelation of copper ions, transfer of tyrosinase to premelanosomes for melanin synthesis, shifting of the process of melanogenesis from eumelanin to pheomelanin, and inherent antioxidant effect in free radicals and peroxides quenching, preventing tyrosinase activation and melanin formation.[123]

### 7.1.1 | Glutathione in melasma

Glutathione has been used topically (cream, face wash, soap, lotion, and glutathione-based chemical peels), intradermally as mesotherapy solution, and orally alone or in combination with alpha lipoic acid, pyruvic acid, N-acetyl cysteine, vitamin C, vitamin E, grape seed extract and other antioxidants, or intravenously as skin lightening agent in patients with melasma. While loading glutathione into the hyaluronic acid microneedles for transdermal delivery enhanced efficacy, its use for mesotherapy remains under reported.[124,125] Its topical use is also limited because of its foul odor, poor permeability, and absorption.

Most of the orally administered glutathione is absorbed within the gut luminal cells and there is only a transient increase in blood levels, finally gets eliminated via renal excretion. Sublingual administration has better bioavailability than orally administration drug and is considered safe by US FDA. However, sulfurous taste remains a major drawback for its acceptability in general. The usual recommended oral dose is 20–40 mg/kg/d (maximum 1–2 g/d) given in two divided doses with a maintenance dose of 500 mg/d and significant response occurs within 3–6 months in dark brown skin, in 6–12 months in very dark skin and in 2 years or more in black skin.[126]

The intravenous administered glutathione (600–1200 mg, given once or twice in a week) has a half-life of 10 min and gets oxidized immediately into its three constituent amino acids (glutamate, glycine, and cysteine).[127] Intravenously, it is usually given in a dose of 900 mg weekly or can be repeated 2–3 times a week. The skin whitening effect usually occurs as early as 2–3 weeks.[128] However, intravenous use of glutathione as skin whitening agent remains under-evaluated and is banned by US FDA because of commonly reported adverse effects such as skin rashes, abdominal pain that may be severe, thyroid, and renal function derangement, Stevens–Johnson syndrome, and toxic epidermal necrolysis.

The results of its efficacy to treat melasma remain variable.[128–131] Wahab et al.[128] in a double-blind randomized controlled study involving 46 subjects found glutathione an effective skin-lightening agent and a combination of topical and oral glutathione was superior than either route used alone. Another randomized, double-blind, placebo-controlled clinical trial comprising 124 Asian females demonstrated significant skin-lightening and reduction in size of facial pigmentation after oral supplementation with combination of l-cystine and l-glutathione.[129] While benefits of skin lightening with 500 mg/d orally administered glutathione given for 4 weeks were limited to certain age groups and body areas in 60 healthy Asian subjects, no significant improvement occurred in 16 patients receiving glutathione and any improvement seen in two separate randomized controlled trials was short lasting.[130–132]

Table 6[43,133–170] lists some naturally occurring depigmenting agents and flavonoids such as vitamin C, vitamin E, rucinol, glucosamine, niacinamide, extracts of soybean (soy), safflower (linoleic acid), licorice, mulberry and grapes (hydroxylstilbene compound resveratrol), coffee berry, orchid, green tea leaves (epigallocatechin-3-gallate), eucalyptus and strawberry (ellagic acid), *Silybum marianum* (sylimarin), *Pinus pinaster* (pycnogenol) *Boswellia serrata* (boswellic acids), citrus fruits (bioflavonoid hesperidin), grape seis i lyfb64.9 (p)-17.4 (y)-5 (f)-17.11.9 espt)

Clinical studies for cosmeceuticals and botanicals in the treatment of melasma

| | | | | | | |
|---|---|---|---|---|---|---|
| [155] | Oral proanthocyanidin (grape seed extract) x 6 months | Efficacy study | Colorimetry Focal macule size | 12 women | Maximum improvement occurred after 6 months and none thereafter | Antioxidant properties, reduces melanin biosynthesis, reduces UV-induced hyperpigmentation |
| [156] | Oral procyanidin with vitamins A, C, E x 8 weeks | Efficacy study | – | – | Effective | – |
| [166] | Oral ginseng (3 g) | Open-label, prospective clinical study | Reduction in MASI, Improved MELAS QoL scores, PGA | 25 women | MASI decreased and MELAS QoL improved in 74% patients | Inhibition of key enzymes of melanogenesis.<br>Nausea, mild gastrointestinal discomfort. |
| [151] | Topical *N*-acetyl glucosamine, applied twice daily x 8 weeks | Randomized, double-blinded, placebo-controlled split-face clinical trial. | Reduction in MASI score | 50 women | improves facial hyperpigmentation | – |
| [154] | Topical Niacinamide 4% versus hydroquinone 4% | Spilt-face randomized trial | Reduction in MASI score | 27 subjects | Both sides responded equally to treatment with progressive reduction in pigmentation | – |
| [157] | Topical dioic acid 1% versus HQ 2% crème applied twice daily x 12 weeks | Open label comparative study | Reduction in MASI score | 96 women | Equal therapeutic efficacy | Reduces tyrosinase mRNA expression |
| [158] | Topical Cysteamine 5% Cream versus placebo cream | Open label comparative study | Reduction in MASI score | 25 subjects | Significant reduction in cysteamine treated groups as compared to placebo group | – |
| [159] | Topical 75% mulberry (*Morus alba*) extract oil versus placebo versus placebo, applied for 8 weeks | Randomized, single-blind, placebo-controlled trial | Reduction in MASI, Improved MELAS QoL scores | 50 subjects | MASI and MELASQoL scores improved significantly in the mulberry group | Tyrosinase inhibition, superoxide scavenging properties.<br>Mild itching. |
| [160] | Topical Lignin Peroxidase cream applied for 8 weeks | Efficacy study | Reduction in MASI score | 31 women | significant reduction in MASI scores | – |
| [161] | Topical Zinc sulfate versus HQ 4% cream | Randomized controlled trial | Reduction in MASI score | – | Better reduction in MASI scores from Zinc sulfate versus HQ | – |
| [162] | Topical Flutamide1% cream versus HQ 4% cream | Randomized controlled trial | Reduction in MASI score | 74 women | Flutamide showed higher reduction in MASI score versus HQ | – |
| [163] | Topical methimazole applied for 8 weeks | Case report | Reduction in MASI score | 2 HQ resistant cases | Significant improvement noted in both cases | – |
| [164] | Total soy (*Glycine soja*) extract applied for 3months | Efficacy study | Reduction in hyperpigmentation | 16 women | 12% reduction in 14 of 16 treated women | – |

(Continues)

### 7.2.2 | Vitamin E

Vitamin E (Alpha-tocopherol), a major lipophilic antioxidant in the tissues, membranes, and plasma, includes four molecules each of tocopherols and tocotrienols occurring naturally. Alpha-tocopherol is the most abundant vitamin E derivative in humans.[142] It has photoprotective effects and cause depigmentation by tyrosinase inhibition, increased intracellular glutathione content and interfering with lipid peroxidation of melanocyte membranes.[143] Alpha-tocopheryl ferulate, a compound of α-tocopherol and ferulic acid, can absorb ultraviolet radiation and reportedly showed significant effect in retardation of melanogenesis.[144] Topical α-tocopherol 5% or less is mostly used in cosmeceuticals in combination with vitamin C for lightening effect. A significant improvement in melasma and pigmented contact dermatitis lesions was observed with topical vitamins E and C in a double-blind study and results were better with combination compared with either vitamin used alone.[145] Allergic or irritant reactions from topical use are infrequent.

### 7.2.3 | Polypodium leucotomos

Extract of *Polypodium leucotomos*, a tropical fern with anti-inflammatory, antioxidant, and photoprotective properties, has been tried in the oral treatment of melasma with variable results. Nestor et al.[146] in their randomized placebo control study reported significant reduction in MASI scores and melasma quality of life (MelasQoL) scale with oral *P. leucotomos* compared with placebo given twice daily for 12 weeks. However, Ahmed et al.[147] in a double-blind controlled study reported no significant reduction in MASI score or improvement in MelasQoL scale from its combination with a sunscreen versus sunscreen alone in 40 Hispanic women with moderate to severe melasma randomized to get *P. leucotomos* 240 mg or placebo three timed daily.

### 7.2.4 | Topical rucinol

Rucinol (4-n-butylresorcinol), a phenolic derivative, inhibits tyrosinase and tyrosinase-related protein (TRP-1). A significant improvement in melasma was seen on treated side in a double-blind randomized split-face study on 23 Korean women after 8 weeks of treatment with twice-daily application of rucinol 0.1% cream as compared to vehicle-treated side.[148] Huh et al.[149] in a double-blind split-face randomized controlled trial conducted on 32 women with melasma also reported significant improvement in melasma with rucinol 0.3% serum applied twice daily for 12 weeks on treated side as compared to vehicle-treated side. The adverse effects of stinging, burning, erythema, dryness, peeling, and desquamation were mild.

### 7.2.5 | Cysteamine

Cysteamine, a natural aminothiol biological compound found in mammalian tissues and human milk, provides powerful synergistic effects for skin depigmentation *without the concerns for adverse effects associated with triple combination therapy*.[171] It is part of the vitamin B3 family and works as antioxidant and inhibits melanosomal transfer. Available as Cyspera® (cysteamine + isobionic-amide complex) 5% cream for topical use and has been found very safe with very low risk of adverse effects. Initial results are visible after 6 weeks of daily use of Cyspera/cysteamine cream applied for 15 min to the affected skin. Rarely, mild skin irritation (warm sensation, mild redness on immediate application and dryness) may occur temporarily. Its three-product system includes: (1) *Cyspera® Intensive™* comprises a dual chamber technology that keeps the cysteamine+isobionic-amide complex and alpha hydroxyl acid (AHA) separate until use. The immediate antioxidant effect of isobionic-amide with AHA after application causes instant pigment reduction effect. (2) *Cyspera® Neutralize™* has AHA and L-Arginine - Lactobionic Acid complex to neutralize the odor of cysteamine and re-balance the epidermis before application of Cyspera® Boost™. The L-Arginine complex stops the Isobionic-Amid Complex™ - AHA reaction and the mild-surfactant gently removes any residue, helps soothe skin, and promote healthy skin barrier. The Lactobionic Acid complex neutralizes and balances the skin pH. (3) *Cyspera® Boost™* features Isobionic-Amide Complex™ and retinol which works synergistically with Cyspera® Intensive™ to even skin tone, improve complexion and provide natural skin glow. The retinol has an anti-inflammatory effect and leads to a visual pigment reduction by increased skin shedding and non-pigmented skin layers after application of Cyspera® Intensive™.

Although cysteamine formulations have shown significant decrease in MASI score after 4 months of application compared with placebo and even in a case resistant to Kligman's triple combination therapy, it was not found superior to 4% hydroquinonein or tranexamic acid mesotherapy in comparative trials.[155,172–174] However, a recent systematic review suggests that insufficient sample size, lack of long-term follow-up, and efficacy in cases with epidermal melasma only remain major limitations of clinical studies to draw a meaningful conclusion for the cysteamine's role in treating melasma that often remains unsatisfactorily treated.[175]

### 7.2.6 | Sunscreens and camouflage makeup

It is well established now that both UV radiation and visible light play a significant role in the pathogenesis of melasma. Several studies have demonstrated the benefit of concomitant photoprotection and sunscreens of at least SPF 15 should be prescribed to all patients with melasma (Table 7). The sunscreens effectively reduce pigmentation following sun exposure, significantly increase the efficacy of topical therapy, and prevent relapses of melasma.[176–178] Physical sunscreens containing zinc oxide, iron oxide, titanium dioxide, and silicones (dimethicone, cyclomethicone) are not only photoprotective for the whole spectrum but also provide immediate whitening camouflage effect and are preferred. However, a blend of physical and organic sunscreens can be used for persons who do not find inorganic salts cosmetically elegant because of their high

concentrations. As UVA can penetrate through clouds and window panes, the chosen sunscreen needs to be applied daily irrespective of time/season.

As prescribed treatment takes time to make a visible difference, a cosmetic camouflage should be prescribed in the meantime. A cosmetic camouflage is basically a makeup available in several shades and hues to match with the skin tone and color to conceal skin discoloration and improve appearance. The presence of 25% more pigment and fillers with optical properties differentiate them from foundations. They should be easy-to-blend, non-irritating, and provide smooth coverage.

## |

Patient education about melasma, identification and avoidance of precipitating factors, long-term prognosis, treatment strategies including preventative measures such as adequate sun protection are imperative for a successful treatment and prolonged remission. Additionally, the patient must be counseled for treatment adherence, use of broad-brimmed hats and avoidance of sun exposure during peak radiation times, frequent use of soaps, astringents, toners or other products with irritant potential, over-the-counter products, and to maintain adequate skin hydration by use of emollients and moisturizing creams.

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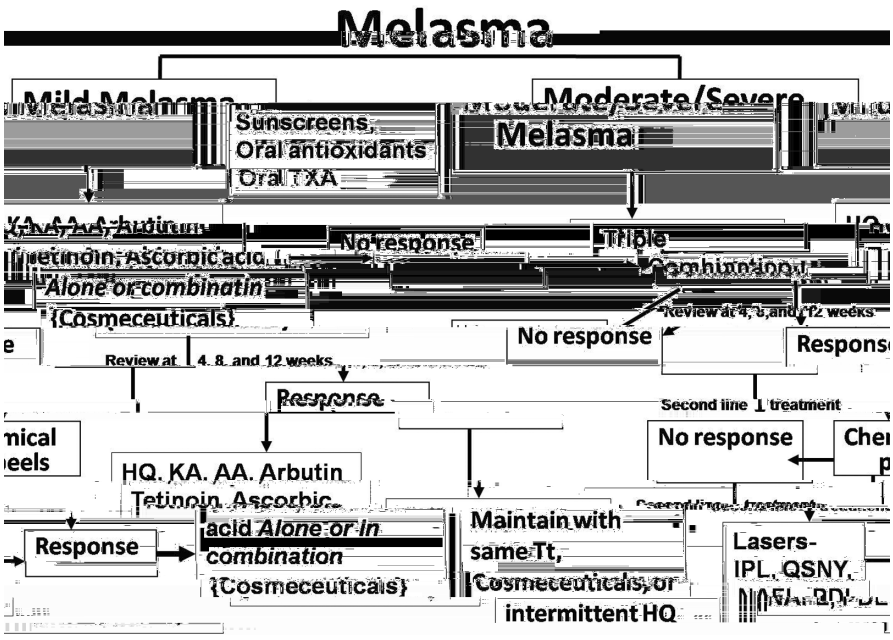


Treatment algorithm for melasma. Before actual treatment, other causes of facial pigmentation such as post-inflammatory hyperpigmentation, lichen planus pigmentosus, lichen planus actinicus, pigmented cosmetic dermatitis, facial acanthosis nigricans, nevus of Ota, Hori nevus, frictional melanosis, drug-induced pigmentation, photosensitivity disorders, and secondary ochronosis must be excluded. If possible, assessment for melasma should be made both clinically and with Wood's lamp. Advise photoprotection to all patients by physical barriers and prescribe a broad-spectrum sunscreen specially containing titanium oxide/zinc oxide. Consider chemical peels and lasers for resistant cases only. Abbreviations: AA, Azelaic acid; HQ, hydroquinone; IPL, Intense pulse light; KA, Kojic acid; NAFL, Non-ablative fractional laser; PDL, Pulsed dye laser; QSNY, Q-switched Nd:YAG laser; TXA, tranexamic acid.

plasma (PRP) therapy alone or in combination with topical TA or IPL in small studies or that of needling (microneedling, mesoneedling, radiofrequency microneedling) to increase the delivery of topical medications or to induce epidermal thickness for protection against UV radiation remains limited for lack of controlled clinical trials.[179,180]

Pregnancy remains the most common trigger for melasma (mask of pregnancy) and it is mostly treatment-resistant. However, melasma in pregnancy may be transient lasting until parturition and improve significantly thereafter. The treatment during pregnancy is thus usually deferred until delivery/lactation. Nevertheless, physical sunscreen can be prescribed for regular use in the meantime.

Since relapses are common after discontinuation of the treatment, it is imperative to maintain remission and prevent relapse with continuous use of medical therapy that is safe and effective along with adequate sun protection. Relapses are usually treated on similar lines. A recent study has suggested that TA 500 mg twice daily can be used as initial therapy to achieve early clearance of melasma and follow-up treatment with TA 250 mg or a lesser dose once daily can be used safely to maintain prolonged remission.[15] Several treatment algorithms have been proposed for mild as well as moderate to severe melasma.[74,181] The suggested treatment algorithm (Figure 2) is simple, easy to follow and can be a quick reference guide in routine office practice. Nevertheless, a multimodality approach such as using a topical formulation, sunscreen, oral TA, and *Polypodium leucotomos* in combination or in a sequential manner with IPL and/or PDL to treat the vascular component then a low fluence 1927 nm laser will perhaps provide an effective treatment approach.

Vikram K Mahajan involved in conception, writing and revising the manuscript. Anant Patil, Martin Kassir, Nellie Konnikov, Michael H. Gold, Mitchel P Goldman, Hassan Galadari, and Leszek Blicharz involved in review and revising the manuscript. Mohamad Goldust involved in conception, writing, review, and revising the manuscript. We confirm that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met and that each author believes that the manuscript represents honest work.

Open Access funding enabled and organized by Projekt DEAL.

None.

No ethical approval was required as this research did not involve human subjects or animals.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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