Shah S, Shah RM, Patel S, Patel S, Doshi S, Lio P. Integrative approaches to hyperpigmentation therapy. *Journal of Integrative Dermatology*. Published online December 22, 2022.

Review Article

Integrative approaches to hyperpigmentation therapy

Sareena Shah[1], Rohan M. Shah, BA[2], Shrey Patel, BS[3], Shiv Patel, BA[2], Sahil Doshi, BA[2], Peter Lio, MD[2] [a]

[1] University of Missouri-Kansas City School of Medicine, Kansas City, MO, USA, [2] Northwestern University Feinberg School of Medicine, Chicago, IL, USA, [3] University of Miami Miller School of Medicine, Miami, FL, USA

Keywords: hyperpigmentation, complementary, alternative, therapeutics, naturopathic

Journal of Integrative Dermatology

Hyperpigmentation involves darkening of skin due to increased production of melanin and encompasses a wide range of dermatologic conditions, including melasma, post-inflammatory hyperpigmentation, maturational hyperpigmentation, and periorbital melanosis. The etiologies of hyperpigmentation may be inherited, acquired, or congenital.

There are multiple approaches for treating hyperpigmentation, including conventional therapeutics and complementary and alternative medicines (CAMs). There is a growing body of literature investigating the uses of these alternative therapies in patients with hyperpigmentation, which can be broadly organized into three major groups: 1) minimally invasive treatments, 2) plant-based therapies, and 3) natural antioxidants. CAMs offer relatively low-risk and readily available treatment options for patients seeking to manage hyperpigmentation. The use of these alternative therapies has gained substantial traction in recent years. These therapies may be especially beneficial for patients who have not achieved favorable clinical outcomes using conventional treatments alone. A greater understanding of the various integrative approaches available for treating hyperpigmentation can allow providers to make the most informed recommendations and help ensure the best health outcomes for patients.

INTRODUCTION

Hyperpigmentation is characterized by darkening of the skin following an increased production of melanin, or melanogenesis, in the dermis or epidermis.[1] Melanin production is initiated by the activation of both the α-melanocyte-stimulating hormone (α -MSH) and adrenocorticotropic hormone (ACTH), which stimulate the chemical breakdown of tyrosine.[2] In melanocytes, L-tyrosine yields dopa with the assistance of the enzyme tyrosinase, and dopa is subsequently converted to either eumelanin or pheomelanin. Melanin production in melanocytes is transferred to keratinocytes apparent in the skin and hair.[3] Tyrosinase is the rate limiting enzyme in the melanogenic pathway and is a common target for therapeutics seeking to reduce hyperpigmentation.[4] Along with the modulation of tyrosinase transcription and activity, depigmenting agents can affect the related enzymes peroxidase, tyrosinase related protein-1 (TYRP-1), and tyrosinase related protein-2 (TYRP-2).

Hyperpigmentation encompasses a broad range of conditions including melasma, post-inflammatory hyperpigmentation, maturational hyperpigmentation, and periorbital melanosis.[2] Facial hyperpigmentation can be inherited, acquired, or congenital, and is more prevalent in persons of color.[5] Conventional therapies for hyperpigmentation include topical medications such as hydroquinone, corticosteroids, chemical peels, laser therapy, and topical vitamin C application.[6] Complementary and alternative medicine (CAM) provides a set of interesting adjunct therapies that may be useful for patients with concerns of adverse effects from conventional treatments, individuals who have struggled to achieve satisfactory results with typical therapies, persons with chronic disease, and within certain cultural traditions.[7]

In recent years, there has been a growing body of literature evaluating the efficacy of alternative therapies in mediating hyperpigmentation. This narrative review evaluates the current literature studying alternative medicine in hyperpigmentation patients, grouping findings into the following themes: 1) minimally invasive procedures, 2) plant-based therapies, and 3) natural antioxidants.

[a] **Corresponding Author:**
Peter A. Lio, MD
Address: 363 W. Erie Street, Suite #350, Chicago, IL 60654
Fax: 312-995-1956
Tel: 312-995-1955
E-mail: peterlio@gmail.com

MINIMALLY INVASIVE PROCEDURES

Chemical peels and laser therapies remain in the conventional cannon, so we will look outside of those modalities here, discussing minimally invasive procedures that have gained popularity in recent years. It is possible to administer medications via intradermal injections, and mesotherapy has been used for hyperpigmentation. Microneedling, also known as percutaneous collagen induction therapy, and acupuncture present two non-pharmaceutical options for complementary therapy. Primary studies included in this article have been categorized in Table 1.

MESOTHERAPY

Mesotherapy has gained popularity in recent years, particularly in the West, and is characterized by the intradermal or subcutaneous microinjection of medications and/or vitamins.[26] In patients with hyperpigmentation, mesotherapy may promote the lightening of the skin by delivering therapeutic agents, with the most commonly described being tranexamic acid (TXA).[27]

Studies evaluating the effectiveness of mesotherapy have found similar and potentially improved outcomes when compared to topical lightening agents,[8,10,12,14] laser therapy,[11] and oral medications.[9,13]

A randomized controlled trial (RCT) by Badran et al compared two dosages of intradermal tranexamic acid injections (4 and 10 mg/mL) with topical tranexamic acid cream in a cohort of 60 women with melasma, finding that the highest percentage reduction in melasma area and severity index (MASI) scores was in 10 mg/mL intradermal injections (62.7%), followed by 4 mg/mL injections (39.1%) and 4.2% topical TXA cream.[8] In a study by Steiner et al, 18 women with melasma were similarly administered either topical or injected TXA.[14] Patients were studied over 12 weeks and instructed to administer either TA 3% topical cream twice a day or received weekly intradermal injections. Patients were evaluated with self-assessments of progress, photographic evaluation, MASI scores, and colorimetry. Subjective assessments – photographic evaluations and self-assessment – were significantly superior in intradermal TXA; however, mMASI scores and colorimetry showed similar improvement between groups.

An RCT by El Hadidi et al found that oral and transdermal TXA were similarly effective in reducing modified melasma area and severity index (mMASI) and melanin index scores.[9] Their study administered one of two concentrations of intradermal TXA (4 mg/mL and 100 mg/mL) or oral TXA (250 mg twice daily for 8 weeks) in a group of 45 women with melasma. Notably, only patients given oral TXA saw improved erythema index scores. Similarly, Sharma et al performed an RCT (N = 100) comparing oral TXA (250 mg twice daily) with intradermal TXA (4 mg/mL every 4 weeks), finding that both methods were similarly effective at reducing MASI scores.[13]

In an RCT performed by Karrabi et al (N = 54), patients received either 5% cysteamine cream or TXA mesotherapy.[10] The group administered 5% cysteamine cream was instructed to apply 30 minutes before sleeping every night for 4 consecutive months. The TXA mesotherapy group were given 0.05 mL (4 mg/mL) injections by a physician every 4 weeks until 2 months. mMASI scores significantly improved by the second and third visits for both groups, though the improvement rates were not significantly different for each cohort. Though there were no substantial differences in clinical outcomes, complications were noted less frequently in the cysteamine group.

An RCT by Saki et al (N = 37) recently compared three monthly sessions of TXA intradermal injections with topical 2% hydroquinone once per night for three months via a split-face design.[12] Their study demonstrated that both treatments led to decreased melanin values and that TXA injection was superior for up to 20 weeks (P = 0.013), though further decreases thereafter were not significantly different (P = 0.17). Mokhtari et al compared laser therapy + 4% topical hydroquinone vs. intradermal TXA + 4% topical hydroquinone in a split-face design (N = 27).[11] In their study, both groups saw significant improvements in mMASI scores, and there was no significant difference between treatments.

Studies have shown that the side effects of mesotherapy are typically short-lasting, and include edema, erythema, irritation, and bruising.[27] With positive results demonstrated in the literature, mesotherapy may be a good alternative for patients who have low adherence with topical treatments, and for those whose first-line therapies were ineffective. Future research is needed to better understand the optimal concentrations of medications delivered and quantify the potential benefits of combining mesotherapy with other treatment modalities.

MICRONEEDLING

Microneedling is an aesthetic treatment option in dermatology with a variety of applications, including the management of melasma, acne scarring, dyschromia, enlarged pores, and skin rejuvenation.[28] Microneedling is the delivery of fine, sterile needles into the skin, typically using roller-type devices, mechanized pen devices, or stamping.[29] The procedure produces controlled microinjuries in the skin without substantially damaging the epidermis, resulting in increased collagen and elastin deposition.[30] Microneedling may also improve the transdermal delivery of medications by depositing drugs directly into the vascularized dermis, bypassing the stratum corneum.[31]

Several studies have investigated microneedling as an adjunct therapy alongside topical agents, including tranexamic acid,[15,17,20–22] topical platelet rich plasma,[18] and vitamin C.[19] The current findings suggest that microneedling may yield equal or improved results when compared with using only topical treatments. Though there is limited research regarding microneedling as a monotherapy, early research has demonstrated the potential for clinical benefits when used on its own.[16] However, there is evidence that microneedling is more effective in conjunction with topical agents than when used as monotherapy.[20] Mild side effects have been associated with microneedling, including erythema, edema, pain, and temporary irritation of the skin.[32]

Table 1. Minimally Invasive Therapies

	Study Reference	Study Design	Description of Sample	Key Findings
Mesotherapy				
	Badran et al. (2021)[8]	RCT	Women with melasma (N = 60) were given either 1) intradermal TXA (4 mg/mL) injections, 2) 10 mg/mL intradermal TXA injections, or 3) TXA cream	The percentage of MASI score reduction was highest in 10 mg/mL intradermal injections (62.7%), followed by 4 mg/mL injections (39.1%, and TXA cream (4.2%).
	El Hadidi et al. (2021)[9]	RCT	Women with melasma (N = 45) were given 1) intradermal TXA (4 mg/mL) injections, 2) 100 mg/mL intradermal TXA injections, or 3) oral TXA (250 mg twice daily for 8 weeks)	All treatments saw significant reduction in mMASI and Melanin Index scores ($P < 0.05$). Only patients given oral TXA saw significant improvement in Erythema Index. Overall, both oral and transdermal TXA were similarly effective.
	Karrabi et al. (2021)[10]	RCT	All subjects presenting with melasma (N = 54) received either 1) 5% cysteamine cream nightly for 4 months or 2) TXA mesotherapy	Both cysteamine and mesotherapy were effective at treating melasma, though neither was significantly better.
	Mokhtari et al. (2021)[11]	Split-Face Study	Patients (N = 27) were randomized to receive laser therapy + 4% topical hydroquinone or intradermal TXA + topical 4% hydroquinone in a split-face design	Both groups saw significant improvements in mMASI scores. There was no difference in the improvement between the treatments.
	Saki et al. (2018)[12]	Split-Face Study	Patients (N = 37) were randomized to receive monthly sessions of TXA intradermal injections and topical 2% hydroquinone in a split-face design	A reduction in melanin value was observed in both treatments, though the TXA injection showed better results up to 20 weeks.
	Sharma et al. (2017)[13]	RCT	Consecutive patients (N = 100) were split into two	Both methods of administration were similarly effective at reducing Melasma Area and Severity Index scores.

			groups, receiving either 1) oral TXA (250 mg twice daily) or 2) intradermal TXA microinjections (4 mg/mL every 4 weeks)	
	Steiner et al. (2009)[14]	RCT	Women with melasma (N = 18) were divided into two groups administered 1) topical TXA and 2) injected TXA	Subjective clinical evaluation found greater improvements with injected TXA; however, in objective evaluation, both treatments were similarly effective.
Microneedling				
	Budamakuntla et al. (2013)[15]	RCT	Patients (N = 60) were given either 1) localized microinjections of TXA or 2) TXA with microneedling	A 35.72% improvement in MASI scores was observed in mesotherapy patients, compared with 44.41% in microneedling. There were no adverse effects observed.
	Cassiano et al. (2019)[16]	Non-Randomized Comparative Study	Women with melasma (N = 20) were given either 1) microneedling therapy or 2) no treatment and results were assessed after 7 days	Only the microneedling group saw significant improvements in mMASI scores ($P < 0.01$), calorimetry ($P < 0.01$), and quality of life parameters ($P = 0.02$).
	Ebrahim et al. (2020)[17]	Split-Face Study	Female patients (N = 56) with bilateral symmetrical melasma were given intradermal TXA on one side, and TXA with microneedling on the other	Clinical outcomes, as measured by mMASI score, were significantly reduced in both treatments, though there was no difference between the two. Patient satisfaction was higher in those with TXA and microneedling.
	Hofny et al. (2019)[18]	Split-Face Study	Egyptian melasma patients (N = 23) were given autologous PRP through microneedling on the right side of the face and mesotherapy on the left side of the face	After treatment, both mMASI and MASI scores significantly decreased, though there was no difference between microneedling and mesotherapy.
	Ismail et al. (2019)[19]	Cohort Study	Female melasma patients (N = 30) were treated with 6 sessions of	All patients saw improvement. Mean MASI scores significantly decreased by the end of the treatment ($P < 0.0001$).

			microneedling and topical vitamin C every 2 weeks	
	Salch et al. (2019)[20]	RCT	Patients (N = 42) were given either 1) microneedling and TXA or 2) solely microneedling	Microneedling alone improved MASI scores, reduced epidermal hyperpigmentation and dermal melanophages, and decreased melanoma antigen recognized by T cells-1-positive cells. Microneedling with topical TXA showed significantly improved results in all outcomes.
	Xu et al. (2017)[21]	Split-Face Study	Women with melasma (N = 28) were given a combination of microneedling and topical TXA on one side of their face, and only topical TXA on the other	At 12 weeks, a significant decrease in brown spots was observed in patients treated with TXA and microneedling. Melanin Index scores decreased in both groups, though there was a significantly greater change in patients treated with microneedling. Photographs noted >25% improvement in 25 patients who received combined therapy, and only 10 who did not. Patient satisfaction was higher in those who also received microneedling.
	Zaky et al. (2021)[22]	Split-Face Study	Melasma patients (N = 50) were given topically applied TXA after microneedling and topical hydroquinone (4%) alone	Both treatments showed significant improvements in MASI scores (P < 0.0001). Patient satisfaction was similar.
Acupuncture				
	Chen (2007)[23]	RCT	Chloasma patients were divided into 1) control group receiving simple acupuncture (N = 46) and 2) treatment group receiving acupuncture and light therapy (N = 50)	The overall effectiveness rate was higher in the acupuncture + light therapy group (98.0%) than acupuncture alone (89.1%), though few patients reached total clearance in either group.
	Feng et al. (2010)[24]	RCT	Women with chloasma (N = 60) were treated with either 1) acupuncture and herbal medicine or 2) vitamins C and E.	The total effectiveness rate of the acupuncture/herbal therapy (93.3%) was better than the control group (76.7%) at 3 months (P < 0.01).
	Rerksuppaphol et. al (2016)[25]	RCT	Women with melasma were given either 1) facial acupuncture (N = 20) or 2) facial/body acupuncture (N = 21)	Facial acupuncture, with and without body acupuncture, decreased melasma areas. A total 66.7% of facial/body acupuncture patients improved skin pigmentation, compared with 80% of those who had facial acupuncture (N = 20) [P = 0.482].

With little to no recovery time and few drawbacks, microneedling is an attractive option for patients with hyperpigmentation. The current evidence indicates that microneedling may improve patient outcomes when combined with conventional therapies, presenting a viable complementary option.

ACUPUNCTURE

Acupuncture is a component of traditional Chinese medicine that has been practiced for thousands of years and can be described as the insertion of dry needles at specific sites to promote healing.[33,34] Proposed mechanisms for how facial acupuncture can improve skin pigmentation and texture include increasing blood flow and muscle tone, balancing *qi*, and balancing internal *Zang Fu* organs.[35]

A study by Feng et al compared a combined acupuncture and herbal remedy treatment with a control group treated with vitamin C and E in a cohort of 60 women with chloasma.[24] They found that the total effectiveness rate of the acupuncture/herbal therapy (93.3%) was better than the control group (76.7%) at 3 months ($P < 0.01$). A randomized trial by Chen compared acupuncture as a monotherapy for chloasma with combined acupuncture and intensive pulse light irradiation therapy in a sample of 96 cases.[23] The overall effectiveness rate was higher in the acupuncture + light therapy group (98.0%) than acupuncture alone (89.1%), though few patients reached total clearance in both groups. A comparative study designed by Rerksuppaphol et al ($N = 41$) compared the effects of using only facial acupuncture and combined facial/body acupuncture on improving hyperpigmentation.[25] Regimens consisted of twice-weekly sessions over an 8-week period. Facial acupuncture, both with and without body acupuncture, successfully decreased melasma areas: 66.7% of patients who received facial/body acupuncture ($N = 21$) improved skin pigmentation, compared with 80% in those who had facial acupuncture alone ($N = 20$) [$P = 0.482$].

It is important to note that these studies are greatly limited by the lack of comparison with true placebo and control groups, making it difficult to determine the comparative effectiveness of acupuncture. Acupuncture may be a viable complementary therapy for patients seeking a multimodal approach to managing hyperpigmentation. However, high-quality evidence regarding its effectiveness is lacking, and further research is necessary for stronger affirmatory conclusions to be made. There remains little research comparing acupuncture-only regimens with other forms of hyperpigmentation therapy.

PLANT-BASED MEDICINES AND NATURAL ANTIOXIDANTS

Over the past decades, several botanical agents from a variety of geographies have been reported in the literature as having benefits in treating hyperpigmentation.[36–39] Though plant-based therapies act through a variety of mechanisms, anti-inflammatory activity, suppression of reactive oxygen species (ROS) formation, and inhibition of tyrosinase activity are the most commonly reported as mechanisms of action.[36,40] Mulberry and soy are two compounds that have been found to provide both pharmaceutical efficacy and safety in the treatment of hyperpigmentation disorders.[6] A variety of additional plant-based therapies have also been identified for the treatment of melasma and hyperpigmentation disorders.[36] The utilization of botanicals into skin care products and medications can offer a favorable side effect profile while also providing non-synthetic modalities of treatment for patients who prefer naturally-derived treatments.[41–44]

Many factors have been identified in the pathogenesis of hyperpigmentation, with recent research identifying oxidative stress as having an important role.[45] Consequently, various topical and oral antioxidant treatments have been found to be effective in managing hyperpigmentation. Though certain antioxidants, such as vitamin C, are well-described in the literature, there remains a wide variety of less commonly used natural antioxidants that may have benefits in improving hyperpigmentation. These include amino fruit acids, azelaic acid, carotenoids, cysteamine, ginseng powder, grape seed extract, green tea, kojic acid, niacinamide, parsley, oolong and black tea, polypodium leucotomos extract, pomegranate extract, silymarin, turmeric, and zinc.

AMINO FRUIT ACIDS

Amino fruit acids (AFAs) are potent antioxidants derived from natural acidic amino acids and have been found to have anti-photoaging effects and benefits against photopigmentation.[88] A split-face RCT by Ilknur et al compared glycolic acid and amino fruit acid peels in a cohort of 30 women, finding that both improved melasma, though the AFA peel was better tolerated and less irritating.[47] Aside from this study, the literature on AFAs for treating hyperpigmentation is sparse.

AZELAIC ACID

Azelaic acid is a naturally occurring saturated dicarboxylic acid, which is typically administered topically as a 15%-20% gel, foam, or cream.[89] It has been found to be effective in treating various dermatological conditions, including comedonal and inflammatory acne and hyperpigmentary disorders. Azelaic acid has long been studied for its effects on pigmentation, with studies finding it to be a well-tolerated and effective treatment, including in patients with darker skin types.[48,49]

CAROTENOIDS

Carotenoids are naturally occurring pigments with a variety of effects on human health, and can be found in most fruits, vegetables, plants, photosynthetic bacteria, and algae.[90] Humans cannot synthesize carotenoids, which can only be ingested via food products or supplementation. There is evidence that carotenoids may provide health benefits, though further research is needed in many disciplines.

Table 2. Plant-Based Treatments and Antioxidants

	Treatment	Description of Ingredient	Studies Evaluating Use for Hyperpigmentation
Plant-Based Treatments			
	Mulberry Extract	Extract from mulberry plant with anti-tyrosinase properties decrease melanin production and melanocyte activity	41,42
	Soybean	Soybeans, widely grown for food consumption, decreases activation of protease-activated receptor 2 found on keratinocytes, reducing melanosome transfer and depigmentation	36,46
Antioxidants			
	Amino Fruit Acids	Potent antioxidant with anti-photoaging effects	47
	Azelaic Acid	Topical antiseptic with anti-inflammatory properties	48,49
	Carotenoids	Naturally occurring pigments found in food; cannot be produced endogenously in humans, and may inhibit melanin production	50,51
	Cysteamine	Aminothiol and antioxidant that can be endogenously biosynthesized by degrading coenzyme A; has antimelanoma, antimutagenic, and anticarcinogenic properties	52–55
	Ginseng Powder	Used in food and medicine for thousands of years in East Asian cultures; active ingredient ginsenoside Rb1, is involved in pathways of human collagen synthesis, and inhibits cell apoptosis and melanogenesis	56–58
	Grape Seed Extract	Commonly used as a medicinal tool; rich in proanthocynidins, making it a tyrosinase inhibitor	59,60
	Green Tea	Contains large amounts of plant polyphenols; has antioxidant, antimelanogenic, anti-inflammatory, and anti-wrinkle properties	61
	Kojic Acid	A fine, white powder and well recognized tyrosinase inhibitor	62–66
	Niacinamide	Form of vitamin B3 with anti-inflammatory properties	67–69
	Oolong and Black Tea	Rich with theasinensin A, a major group of catechin dimers that may decrease melanin formation and secretion	70
	Parsley	Plant species commonly harvested as an herb; antioxidant and anti-inflammatory effects coupled with low risk for adverse events make it a potential candidate for treating pigmentation	71
	Polypodium Leucotomos Extract	Extract derived from tropical fern leaves; known to protect against the harmful effects of UV-exposure, and may provide adjunct benefits in reducing pigmentation	72
	Pomegranate Extract	Extract from pomegranates; high levels of punicalagins, namely ellagic acid, give anti-tyrosinase properties	73–76
	Silymarin	Commonly known as milk thistle; polyphenolic flavonoid with antioxidant and anti-inflammatory properties	77–79
	Turmeric	Commonly used as a spice; active ingredient curcumin may inhibit tyrosinase and melanin production	75,80,81
	Zinc	Essential micronutrient; potential tyrosinase inhibitor with antioxidant and anti-inflammatory effects	82–87

An open clinical trial studied the topical application of a beta-carotene lotion in a sample of 31 adults with melasma who applied the product twice daily.[50] Beta-carotene, an agonist of vitamin A, has been proposed as a potential therapeutic agent for hyperpigmentation since it reduces melanin production by saturating nuclear receptors of melanocytes and/or binding proteins. In the study, 26 patients completed an 8-week regimen, while 9 individuals continued for another 16 weeks to complete 24 weeks. In the 8-week group, one case had grade-I pigmentation, while 13 were grade-II and 12 grade-III. The grade-I pigmentation case made a complete recovery. One grade-II case recovered completely, 10 improved to grade-I, and 2 did not change. Ten grade-III individuals improved to grade-II, one to grade-I, and one did not change. The 9 cases that completed a 24-week regimen (2 grade-II and 7 grade-III) all improved by one grade. Adverse effects were uncommon and mild.

A randomized trial by Teo et al evaluated the oral administration of the product Crystal Tomato®, which contained carotenoid-rich tomato powder and L-Cysteine.[51] Subjects consumed either the product or placebo, taking one tablet

per morning in conjunction with a lightening cream containing tyrosinase inhibitors (such as niacinamide, alpha arbutin, and kojic palmitate), antioxidants, and mild exfoliating acids. Subjects were also instructed to utilize a prescribed sunblock prior to exposure. A total of 44 patients were included, with median mMASI scores significantly decreasing in both the oral carotenoid treatment and placebo groups. There was no significant difference in the mMASI improvement between groups. In both cohorts, the erythema score significantly improved, though this was more pronounced in the group treated with oral supplementation (P = 0.02). Adverse reactions were rare, and not attributed to the oral supplementation.

Current literature indicates that carotenoids may be useful for adjunct therapy alongside traditional methods, albeit with a limited impact. Future investigations on the effectiveness of adding a carotenoid regimen are needed, with the literature currently being sparse and limited by small studies.

CYSTEAMINE

Cysteamine is an aminothiol and antioxidant that can be endogenously biosynthesized in mammals, including humans, via the degradation of coenzyme A.[91] Cysteamine has an excellent safety profile and has been found to demonstrate antimelanoma, antimutagenic, and anticarcinogenic properties.[92] In recent years, topically administered cysteamine has been well-documented in several studies to be a powerful depigmenting agent that may be comparable to conventional therapies including hydroquinone and tranexamic acid mesotherapy.[93]

A double-blinded RCT by Nguyen et al compared cysteamine and hydroquinone creams in a cohort of 20 patients over 16 weeks.[52] The mMASI score was used as a primary outcome measure, along with standard digital photography. Upon completion of the study, 5 cysteamine and 9 hydroquinone patients remained. There was no significant difference in mMASI reduction (P = 0.3); however, the study is limited by its small sample.

Lima et al similarly compared topical 5% cysteamine and 4% hydroquinone in a quasi-randomized, multicenter, evaluator-blinded clinical trial.[53] Their study included a total of 40 women with facial melasma, who applied topical cysteamine or hydroquinone each night for 120 days. Upon study completion, the mean reduction of mMASI scores was higher in the hydroquinone group (41% vs. 24%; P = 0.015). Melasma quality of life scores progressively improved in both groups, though better in hydroquinone patients (P = 0.018). Photographic assessments did not significantly differ, with both groups yielding 74% improvement, and calorimetric evaluation showed similar progressive depigmentation in both cohorts (P>0.160). Neither group experienced any major adverse events, leading the study to conclude cysteamine was an effective and well-tolerated treatment, albeit potentially inferior to hydroquinone.

In an RCT by Sepaskhah et al, 5% cysteamine and 4% hydroquinone/3% ascorbic acid cream (HC) were compared in a cohort of 65 patients over a course of 4 months.[54] Both mMASI scores at baseline (6.69 for cysteamine group, 6.26 for HC) and 4 months (4.47 in cysteamine vs. 3.87 for HC) were not statistically different (P > 0.05). However, there was a more pronounced reduction in mMASI for HC patients (P < 0.001). Similarly, there was a greater change in melanin index for the HC group (P = 0.002), though both treatments saw significant improvements.

Recently, an RCT performed by Karrabi et al (N = 50) demonstrated superior results of 5% cysteamine cream compared with a modified Kligman's formula (4% hydroquinone, 0.05% retinoic acid and 0.1% betamethasone).[55] Both products were applied once daily for 4 months, though the cysteamine was only left for 15 minutes of exposure, while the modified Kligman's formula was given for overnight exposure. After 2 and 4 months, cysteamine yielded approximately 9% greater reduction in mMASI scores than Kligman's formula (P = 0.005 and 0.001).

An important advantage of cysteamine is its tolerability and safety, which makes it among the most favorable hyperpigmentation treatments. In the near future, it is very possible that cysteamine may be viewed alongside currently used therapies such as hydroquinone as a standard modality for hyperpigmentation. While some studies showed slightly inferior results compared to hydroquinone, cysteamine clearly reduced hyperpigmentation and may be considered an alternative to hydroquinone.

GINSENG POWDER

Korean red ginseng powder has been used both in food and as a medicine in Eastern Asian cultures for thousands of years, being known to contain significant amounts of various bioactive compounds including ginsenosides, which exhibit antioxidant, antitumor, antihypertensive, and antidiabetic effects, among others.[94] The dominant ginsenoside in ginseng roots, ginsenoside Rb1, is involved in pathways of human collagen synthesis and inhibiting cell apoptosis, and has been found to inhibit melanogenesis in cell models in a dose-dependent manner.[56,57]

An uncontrolled study by Song et al examined the oral administration of 3 g of Korean red ginseng in a sample of 25 women over a 24-week period.[58] After the treatment period ended, the MASI score decreased from 8.8 to 5.6 and the melasma quality of life scale was improved in 91% of patients (p<0.05). The average pigmentation level decreased from 184.3 to 159.7, while erythema levels decreased to 216.4 from 253.6 (p<0.05). Patient and investigator rated global improvement scales were better at 24 weeks for 74% of patients. Adverse effects were rare, with only one patient experiencing nausea and mild gastrointestinal discomfort that ceased after ending use of the ginseng powder.

Korean red ginseng powder appears to be a viable adjunct therapy, as it carries little risk for adverse effects and has been demonstrated to improve hyperpigmentation. To better quantify the utility of ginseng powder, further controlled studies are needed.

GRAPE SEED EXTRACT

Grape seed extract (GSE) is available as a nutritional tool across the world, including in the United States, with re-

ported benefits in combating a variety of conditions, including diabetes, inflammation, cardiac disease, infections, and ulcers.[95] GSE is rich in proanthocyanidins, which have powerful antioxidant properties.[96] GSE has been found to have a lightening ability, as it inhibits tyrosinase and melanogenesis.[97]

An RCT by Sharif et al studied the skin-improving effects of muscat hamburg, a red *Vitis vinifera* grape variety commonly found in North America, Europe, and Asia that has been used in traditional medicine for centuries.[59] A stable water-in-oil emulsion was created containing 2% muscat hamburg grape seed extract. The formula was compared with a placebo, as both were administered using an occlusive patch for 8 weeks during the winter season in young, adult Pakistani men (N = 110). Subjects used the formula on the left cheek and placebo on the right, applying the products twice daily. The study found significant improvements on melanin, elasticity, and sebum content when using the M. hamburg formula; however, the placebo had similar effects on erythema and skin moisture. No patients experienced hypersensitivity, and the study provided evidence for the safety of grape-based creams on conditions such as hyperpigmentation.

Yamakoshi et al evaluated the effects of orally administered GSE on chloasma within a cohort of 12 Japanese women over the span of one year.[60] Their study administered proanthocyanidin-rich GSE to 12 women for 6 months between August 2001 and January 2002, and 11 of the initial 12 women for 5 further months between March and July 2002. After 6 months of using GSE, chloasma was improved or slightly improved in 10 women (83%), and 5 of 11 women (54%) following 5 months of intake. Clinical chloasma was improved at 12 months, as measured by the L* value, melanin-index, and size measurements. The study found maximal improvement after 6 months, while the further therapy was believed to be useful for preventing the chloasma from worsening. Notably, the chloasma worsened in several women during month 1 and between months 6 and 7 of the study, when the subjects were not taking GSE. No patients experienced adverse effects. The study is limited by its small sample size, but is instructive nonetheless.

It is important to note that the current literature investigating GSE as a therapy for hyperpigmentation is sparse, with future investigations being needed to better identify its applications. As it stands, early evidence suggests that GSE can be a valuable complementary tool, with little risk for side effects.

GREEN TEA

Green tea has a large store of plant polyphenols that have various health benefits, including protective effects against photoaging that stem from antioxidant, anti-inflammatory, antimelanogenic, and antiwrinkle properties.[98] These effects of green tea make it a potential candidate for treating hyperpigmentation. A randomized study by Syed et al examined the effectiveness of green tea in a cohort of 60 patients administered 100 g of either 2% analog of green tea extract or placebo in a hydrophilic cream for 12 weeks.[61] Both cohorts significantly improved; however, the green tea extract yielded significantly higher reduction in mean lesion count when compared with placebo. Though the research is limited, early findings indicate that green tea extract can be a suitable and low-cost adjunct therapy for patients seeking a natural therapy.

KOJIC ACID

In the past several years, kojic acid, which has antioxidant and anti-inflammatory properties, has become increasingly popular as a treatment for hyperpigmentation.[99] Kojic acid is a well-known tyrosinase inhibitor, allowing it to suppress melanin production and making it useful for skin lightening.[100] Esters synthesized from kojic acid have also demonstrated depigmenting properties with a lower cytotoxic effect, making them potential alternatives for hyperpigmentation therapies.[101]

Recently, Desai et al performed a clinical trial evaluating a formula containing 3% TXA, 1% kojic acid, and 5% niacinamide in a group of 55 Brazilian women with hyperpigmentation.[62] The serum was applied twice daily over a 12-week period. At the end of the study, a significant decrease in melanin index was observed in lesions with post inflammatory hyperpigmentation (36 subjects) and melasma (48 patients).

Garcia et al compared a 5% glycolic acid/2% kojic acid formula with a 5% glycolic acid/2% hydroquinone mixture in a cohort of 39 patients, finding both products effectively reduced hyperpigmentation.[63] This was measured by a clinical investigator using ultraviolet light photography and Wood's light examination. The study found that 51% of patients responded equally to the formulas, while 28% had greater pigment reduction using kojic acid versus 21% experiencing greater pigment reduction using hydroquinone. The results were not statistically different, and the kojic acid formula was more irritating. In contrary, Gajjala et al demonstrated that kojic acid was inferior to hydroquinone cream in a split-face study performed with a cohort of 50 Indian women.[64] Patients were studied over 3 months, and severity was determined using color, size, and clinical symptoms of lesions. Statistical differences were noted after 3 months, with positive responses of 30% for kojic acid and 58% for hydroquinone. Similarly, Monteiro et al found that hydroquinone was a superior treatment, comparing a once-daily application of 0.75% kojic acid/2.5% vitamin C cream with 4% hydroquinone over 12 weeks.[65] The treatments were alternately allocated to a cohort of 60 patients, and clinical response was measured using MASI scores.

An RCT by Deo et al compared the efficacies of different combinations of 1% kojic acid, 2% hydroquinone, and 0.1% betamethasone valerate in reducing pigmentation levels, measured using MASI scores.[66] Eighty patients were included in their study and randomized to receive either 1) only 1% kojic acid, 2) 1% kojic acid and 2% hydroquinone, 3) 1% kojic acid and 0.1% betamethasone valerate, and 4) 1% kojic acid, 2% hydroquinone, and 0.1% betamethasone valerate. Treatments were applied once daily over 12 weeks. At the end of the study, 1% kojic acid and 2% hydroquinone was most effective, followed by the combination of all three ingredients.

Kojic acid is a well-studied ingredient for hyperpigmentation treatments and can be safely used both independently and in conjunction with hydroquinone. Current findings suggest that using kojic acid with hydroquinone yields the best patient outcomes and should be recommended as a combined therapy.

MULBERRY EXTRACT

Extract from the mulberry plant, *Morus alba*, is often utilized as a natural whitening agent for patients with melasma.[102] Mulberry plant extract has been shown to have antioxidant and anti-tyrosinase properties when applied topically, resulting in decreased melanin production and melanocyte activity.[103] A randomized, single-blind, placebo-controlled trial by Alvin et. al. demonstrated a 29% improvement in melasma area and severity score over an 8 week period of using 75% mulberry in coconut oil base ($P < 0.05$), compared to a lesser improvement of 2% using a placebo of virgin coconut base, further emphasizing its clinical utility.[102] A total of 50 patients (49 female) with melasma were recruited into the study and instructed to apply the topical oil twice daily to areas of hyperpigmentation. Subjects were also given SPF 30 sunblock to apply to the entire face each morning 30 minutes after applying the topical treatments and were advised to use unscented soap and limit unnecessary sun exposure.

NIACINAMIDE

Niacinamide is a form of vitamin B3 that has been demonstrated to have benefits in various aspects of dermatologic health, including in managing rosacea,[104] psoriasis,[105] and acne.[106] It may also be useful for managing cutaneous hyperpigmentation, as an early *in vitro* study by Hakozaki et al found that niacinamide suppresses melanosome transfer.[107] The study found that niacinamide application yielded a 35-68% inhibition of melanosome transfer in cell cultures, and reduced pigmentation in a pigmented reconstructed epidermis.

In a split-face study by Navarrete-Solis et al, 27 melasma patients received 4% niacinamide cream and 4% hydroquinone cream over an 8-week study period.[67] Patients were also recommended to apply sunscreen. Upon completion of the study, all patients showed improvement in both treatments, and calorimetric measures yielded no significant differences between both sides. The average MASI score decrease was 70% for hydroquinone and 62% for niacinamide. Side effects were observed in 18% of niacinamide and 29% for hydroquinone. In all, the study concluded that niacinamide was a safe and effective treatment for managing hyperpigmentation. A study by Lee et al investigated the effectiveness of a niacinamide and TXA formula on reducing facial pigmentation in 42 Korean women.[68] Patients used either 2% niacinamide + 2% TXA cream or a control twice-daily over an 8-week period, after which pigmentation was measured. The study found that the formulation was significantly more likely ($P < 0.05$) to reduce pigmentation, as measured using a physician's assessment of clinical photographs and chromameter measurements.

Castanedo-Cazares et al performed a randomized, double-blind, placebo-controlled trial to assess the efficacy of 4% niacinamide and 0.05% emulsions of desonide for managing axillary hyperpigmentation.[69] A total of 24 women were included in the study, and randomly received either of the two treatments or a placebo. Subjects were evaluated at baseline and after 9 weeks. After the study period was completed, both treatments showed significant calorimetric improvement when compared with the placebo. However, desonide was more effective than niacinamide, with desonide showing an improvement in 30% of cases, while niacinamide showed an improvement in 24% of cases.

In all, niacinamide presents a viable therapeutic agent for reducing hyperpigmentation and has been shown to yield clinically significant improvement. Niacinamide is widely available in over-the-counter products and can be recommended for hyperpigmentation treatment.

OOLONG AND BLACK TEA

Oolong and black tea are rich with theasinensin A (TSA), which are a major group of catechin dimers that have been found to decrease melanin formation and secretion in cell models.[70] TSA has been shown to inhibit the expression of tyrosinase, and other proteins in the melanocortin 1 receptor pathway, making it a candidate for treating skin pigmentation. Clinical studies to identify the effectiveness of oolong and black tea are needed.

PARSLEY

Parsley has been found to exhibit a wide variety of medicinal properties, including anti-inflammatory and antioxidant activities.[108] It has been used as a natural skin lightener in traditional medicine and carries little risk for adverse effects, making it a potential candidate as a therapeutic agent for hyperpigmentation. An RCT performed by Khosraven et al divided a cohort of 54 women into two, even cohorts to compare the effectiveness of topical application of parsley with hydroquinone cream.[71] The case treatment was brewed by participants by filtering a mixture of hot water and parsley. Both case and control therapies were administered over an 8-week period. In the study, the severity of melasma significantly decreased in both groups, with no statistical differences between the two treatments in an independent t-test ($P = 0.858$). The study indicates that parsley may be an effective agent for treating hyperpigmentation, and can be a readily available, cost-effective adjunct option for patients.

POLYPODIUM LEUCOTOMOS EXTRACT

Polypodium leucotomos extract (PLE) is derived from tropical fern leaves and has potent antioxidant and anti-inflammatory properties.[109] Several studies have identified its dermatological applications. The current literature indicates that PLE can protect against the harmful effects of UV-exposure and provide adjunct benefits in treating both

melasma and post-inflammatory hyperpigmentation.[110] Notably, a double-blind RCT performed by Goh et al found that orally administered PLE improved and accelerated clinical outcomes when used in combination with hydroquinone and sunscreen, making it potentially suitable as a complementary treatment.[72] The study recruited 40 healthy Asian adults with melasma and randomized subjects to receive either PLE or a placebo. At 4, 8, and 12 weeks of therapy, significant differences from baseline modified melasma area and severity index scores were identified ($p \leq 0.01$). At 8 and 12 weeks, mMASI scores were significantly lower in the PLE group than those receiving the placebo ($p \leq 0.05$). Upon study completion, significant improvements in clinical photograph observation and slight improvements in melanin and erythema indices were noted, with no significant differences between treatments. The Melasma Quality of Life score showed greater improvement in the PLE group, and no significant side effects occurred. Further research is needed to better understand the role of PLE as an adjunct option, but it may be capable of accelerating improvements when used alongside conventional therapies.

POMEGRANATE EXTRACT

Pomegranate extract (PE) has demonstrated benefits in skin lightening, as it is rich with polyphenols, namely punicalagins and its bioactive metabolite ellagic acid, which directly inhibit melanin production.[111,112] Yoshimura et al demonstrated that the inhibitory activity of PE containing 90% ellagic acid against mushroom tyrosinase *in vitro* was comparable to the known whitening agent arbutin, and that oral administration in guinea pigs yielded similar skin whitening effects as L-ascorbic acid.[73] In the epidermis of UV-irradiated guinea pigs, PE decreased the number of DOPA-positive melanocytes, while L-ascorbic acid did not.

A recent study by Kanlayavattanakul et al evaluated pomegranate peel extract in both cellular models and human volunteers.[74] The major phenolic compound in the PE was sinapic acid, followed by ellagic and gallic acids and 4 other phenols. In B16F10 melanoma cells, an inhibitory effect on tyrosinase and TRP-2 was observed, supporting the ability for PE to treat hyperpigmentation by suppressing melanogenesis. The extract was found to have antioxidant and proliferative properties towards dermal fibroblasts, and an inhibitory effect on MMP-2 was noted. Using the PE, a stable serum and mask was developed and tested on 30 Thai volunteers over the course of 28 consecutive days of treatment. The study was randomized, double-blind, placebo-controlled, and split-face, with results being measured using an automated computerized pigment measuring system. The study found greater facial skin lightening using the serum and mask ($P < 0.005$), suggesting that phenolic-rich PE can be a safe therapy for hyperpigmentation. Similarly, a double-blind, placebo controlled RCT by Kasai et al found that orally administered, ellagic-acid rich PE improved UV-induced skin pigmentation in female subjects aged 30-49.[113]

Wang et al recently tested the whitening and anti-photoaging properties of a pomegranate, osmanthus, and olive extract mixture using a 2D human culture and 3D pigmented, full-thickness skin model treated with both UVB and UVA.[76] Pomegranate extract reduced tyrosinase activity and melanin content in melanocytes ($P < 0.05$). In the 3D model, pomegranate extract, punicalagin, and the mixture inhibited melanin production and pre-melanosomal protein expression ($P < 0.001$). The mixture also repaired the effects of UV exposure on collagen I expression and elastin ($P < 0.01$), decreased lipid peroxidation ($P < 0.001$), and redacted protein carbonylation ($P < 0.05$).

Ultimately, pomegranate extract has been demonstrated to have skin lightening and anti-photoaging properties when topically or orally administered. Pomegranate extract is a valuable adjunct therapy and can be recommended to patients seeking natural treatment for hyperpigmentation.

SILYMARIN

Silymarin (SM), commonly known as milk thistle, is a natural polyphenolic flavonoid with potent antioxidant and anti-inflammatory properties.[114] These effects have made silymarin of interest in treating hyperpigmentation, with few studies being conducted to evaluate its effectiveness.

An RCT performed at Medical City Hospital in Baghdad studied the use of silymarin to manage melasma in a cohort of 96 patients, who were randomized to receive either 7 mg/mL SM cream, 14 mg/mL SM cream, or placebo applied topically twice daily.[77] All patients demonstrated significant improvement in pigmentation and lesion size reduction from the first week, with a 100% satisfaction rate and no observed side effects.

A study by Nofal et al compared topical SM in concentrations of 0.7% and 1.4% with 4% hydroquinone in a group of 42 women divided into 3 equal cohorts.[78] Treatments were administered for 3 months, after which MASI scores were found to be significantly reduced in all groups. There were no significant differences in the responses to therapy between groups. Silymarin patients were observed to have no side effects, while hydroquinone had significant adverse effects. Similarly, Ibrahim et al compared topical 1.4% SM with low fluence Q switched ND:YAG 1064-nm laser therapy in a group of 50 women divided evenly between the two treatments.[79] Upon completion of a 3-month therapy duration, the mMASI was significantly reduced in all patients. There was no significant difference between the two treatments. No side effects were identified in SM patients.

The current literature, though limited by the number of studies available, indicates that silymarin can be a powerful tool in managing hyperpigmentation, comparable with standard therapies. Silymarin does not carry high risk for adverse side effects, potentially making it a less irritative option that patients can utilize. Future research should examine the combined effectiveness of SM with standard treatments.

SOYBEAN

Glycine max, commonly known as soybean, has exhibited ability to reduce pigmentation, leading to its incorporation into numerous skincare products.[36] Naturally occurring

serine protease inhibitors found in soybean extract have been found to decrease activation of protease-activated receptor 2 found on keratinocytes through *in vivo* and *in vitro* experiments, resulting in reduced melanosome transfer and depigmentation.[36,46] In the study by Paine et al, an *in vitro* analysis was performed by treating keratinocyte-melanocyte cocultures with two soybean-derived serine protease inhibitors for a total 72 hours. Additionally, the authors performed an *in vivo* experiment by topically treating dark-skinned Yucatan microswine with the inhibitors. Image analysis, staining, and histology were used to evaluate effects on pigmentation. Both *in vitro* and *in vivo* results showed that soybean and soybean derivatives promoted skin lightening through the inhibition of the protease-activated receptor 2 pathway. While basic science data suggest that soybean extracts may reduce pigmentation, there are no human studies confirming the efficacy of soybean extracts on reducing hyperpigmentation.

TURMERIC

Turmeric is a commonly used spice that has been long recognized for its medicinal properties, which stem from the principal compound curcumin.[115] Notably, curcumin does not provide health benefits if ingested by itself, as it is poorly absorbed and rapidly eliminated. Instead, curcumin can be beneficial when combined with other components that increase its bioavailability.

The antioxidant and anti-inflammatory properties of turmeric have made it a viable option for managing hyperpigmentation. In a study by Park et al, aromatic (ar)-turmerone, a major bioactive compound in turmeric, was found to inhibit alpha-melanocyte stimulating hormone (α-MSH) and 3-isobuty-1-methxlzanthine (IBMX) induced melanin synthesis and tyrosinase expression.[80] In stimulated B16F10 cells, ar-turmerone also inhibited TRP-1 and TRP-2, and demonstrated greater suppression of melanogenesis than curcumin. Similarly, Panich et al found that extract from the turmeric plant (Curcuma aromatica) suppressed UVA-mediated melanin production at noncytotoxic concentrations.[81] The extract had antioxidant properties and protected against the depletion of catalase, glutathione peroxidase, and intracellular glutathione. The effects were dose-dependent.

Swanson et al performed two clinical studies evaluating the effects of turmeric extract in cream formulations on facial hyperpigmentation and wrinkles.[75] The first study subjected a cohort of Caucasian women to a 10-week, randomized, split-face treatment, comparing turmeric extract + niacinamide in cream formulation with niacinamide alone. The second study was performed in Beijing, China, and evaluated a cream formulation containing only turmeric extract in Asian women. In the first study, the turmeric extract + niacinamide combination was significantly more successful at reducing fine lines and wrinkles at 4 weeks ($P = 0.004$), directionally better at 8 weeks ($P = 0.125$), and significantly better overall ($P = 0.009$). In the second study, the turmeric extract-containing formula reduced hyperpigmentation by 14.16% ($P < 0.0001$) at 4 weeks and 14.91% ($P < 0.0001$) at 8 week. These studies provide evidence that turmeric extract can be leveraged in topical creams to reduce hyperpigmentation, fine lines, and wrinkles.

ZINC

Zinc is an essential micronutrient with an important role in preserving skin health; however, deficiency is common, with an estimated prevalence in a third of the world's population.[116] Several studies have examined the utility of zinc in managing hyperpigmentation.

An early study by Sharquie et al treated 28 patients with a 10% zinc sulfate solution, which was applied twice daily for 2 months.[82] Severity was measured with MASI scores, and patients applied sunscreen (SPF>30) prior to sun exposure during the study and for 3 months following. The study found a significant improvement in average MASI (4.70 vs. 9.45; $P < 0.0005$), with no reported side effects aside from mild stinging. Patients mostly maintained improvement after 3 months of ceasing therapy.

An RCT by Iraji et al compared 10% zinc sulfate with 4% hydroquinone cream, which is considered to be the standard treatment for hyperpigmentation.[83] A sample of 72 women with moderate to severe melasma were divided into two groups, with one being treated with 10% zinc sulfate and the other hydroquinone cream twice daily. At 2 months of therapy, both groups saw reduction in MASI scores; however, it was significantly more pronounced in the hydroquinone group. At 6 months follow-up, only the hydroquinone group saw continued decreases in MASI scores. Yousefi et al similarly compared 10% zinc sulfate with 4% hydroquinone in a sample of 82 women, with melasma severity being evaluated at 2 and 5 months.[84] Similar to the previous study, the MASI scores were significantly decreased in both groups, though there was a greater decrease in patients treated with hydroquinone ($P < 0.001$). Irritation was observed in 30.9% of the hydroquinone group, while postinflammatory pigmentation was found in 5.2% of zinc-treated patients.

Zinc oxide has been commonly used in sunscreens often recommended for patients with hyperpigmentation, being used in the form of nanoparticles so that the sunscreen cannot be visible on the skin.[85] However, recent research indicates that it may be optimal for patients with hyperpigmentation to use tinted sunscreens, which are made using different formulas and often include iron oxides and pigmentary titanium dioxide. Unlike sunscreens that are not visible on the skin, tinted sunscreens protect against visible light along with UV radiation. Tinted sunscreens are available in many different shades to accommodate different skin phenotypes.

Recent research has evaluated whether there is a relationship between low serum zinc levels and melasma; however, the current findings are sparse and contradictory.[86,87] Further research is needed to better understand the possible association.

The current literature on zinc as a hyperpigmentation therapy indicates that, though it may provide clinical benefits, more conventional treatments provide more favorable results. There remains little research investigating the

combined use of zinc with other hyperpigmentation treatments.

CONCLUSIONS

Complementary and alternative treatments can provide relatively low-risk, readily available therapies for patients with hyperpigmentation. Particularly in patients who struggle with topical treatments, adjunct therapies can improve clinical outcomes and promote both self-concept and quality of life. In recent years, alternative treatments have gained more traction, underscoring the need for future high-quality randomized control trials to quantify the effectiveness of the many available agents. With further research, providers can leverage complementary therapies and make more informed recommendations to patients; however, early studies have shown to be promising.

CONFLICTS OF INTEREST

SS, RMS, SP, SP, SD report no conflicts of interest. PAL reports research grants/funding from the National Eczema Association, AOBiome, Regeneron/Sanofi Genzyme, and AbbVie; is on the speaker's bureau for Regeneron/Sanofi Genzyme, Pfizer, Incyte, Eli Lilly, LEO, Galderma, and L'Oreal; reports consulting/advisory boards for Almirall, ASLAN Pharmaceuticals, Dermavant, Regeneron/Sanofi Genzyme, Pfizer, LEO Pharmaceuticals, AbbVie, Eli Lilly, Micreos, L'Oreal, Pierre-Fabre, Johnson & Johnson, Level Ex, KPAway, Unilever, Menlo Therapeutics, Theraplex, IntraDerm, Exeltis, AOBiome, Realm Therapeutics, Altus Labs, Galderma, Verrica, Amyris, Bodewell, Burt's Bees, My-Or Diagnostics, and Kimberly-Clark. In addition, Dr. Lio has a patent pending for a Theraplex product with royalties paid and is a Board member and Scientific Advisory Committee Member of the National Eczema Association.

FUNDING DISCLOSURES

N/A

Submitted: May 24, 2022 PST, Accepted: November 25, 2022 PST

REFERENCES

1. Rigopoulos D, Gregoriou S, Katsambas A. Hyperpigmentation and melasma. *J Cosmet Dermatol*. 2007;6(3):195-202. doi:10.1111/j.1473-2165.2007.00321.x

2. Vashi NA, Wirya SA, Inyang M, Kundu RV. Facial Hyperpigmentation in Skin of Color: Special Considerations and Treatment. *Am J Clin Dermatol*. 2017;18(2):215-230. doi:10.1007/s40257-016-0239-8

3. D'Mello SAN, Finlay GJ, Baguley BC, Askarian-Amiri ME. Signaling Pathways in Melanogenesis. *Int J Mol Sci*. 2016;17(7):1144. doi:10.3390/ijms17071144

4. Ebanks JP, Wickett RR, Boissy RE. Mechanisms regulating skin pigmentation: the rise and fall of complexion coloration. *Int J Mol Sci*. 2009;10(9):4066-4087. doi:10.3390/ijms10094066

5. Vashi NA, Kundu RV. Facial hyperpigmentation: causes and treatment. *Br J Dermatol*. 2013;169:41-56. doi:10.1111/bjd.12536

6. Sarkar R, Arora P, Garg KV. Cosmeceuticals for Hyperpigmentation: What is Available? *J Cutan Aesthet Surg*. 2013;6(1):4. doi:10.4103/0974-2077.110089

7. Dastgheib L, Farahangiz S, Adelpour Z, Salehi A. The Prevalence of Complementary and Alternative Medicine Use Among Dermatology Outpatients in Shiraz, Iran. *J Evid Based Complementary Altern Med*. 2017;22(4):731-735. doi:10.1177/2156587217705054

8. Badran AY, Ali AU, Gomaa AS. Efficacy of topical versus intradermal injection of Tranexamic Acid In Egyptian melasma Patients: A randomised clinical trial. *Australas J Dermatol*. 2021;62(3):e373-e379. doi:10.1111/ajd.13575

9. El Hadidi H, Mosaad R, Ragab N. The efficacy of oral vs different dilutions of intradermal tranexamic acid microinjections in melasma-A randomized clinical trial. *Dermatol Ther*. 2021;34(3):e14924.

10. Karrabi M, Mansournia MA, Sharestanaki E, Abdollahnejad Y, Sahebkar M. Clinical evaluation of efficacy and tolerability of cysteamine 5% cream in comparison with tranexamic acid mesotherapy in subjects with melasma: a single-blind, randomized clinical trial study. *Arch Dermatol Res*. 2021;313(7):539-547. doi:10.1007/s00403-020-02133-7

11. Mokhtari F, Bahrami B, Faghihi G, Asilian A, Iraji F. Fractional Erbium:YAG Laser (2940 nm) plus Topical Hydroquinone Compared to Intradermal Tranexamic Acid plus Topical Hydroquinone for the Treatment of Refractory Melasma: A Randomized Controlled Trial. *J Dermatolog Treat*. Published online August 13, 2021:1-21.

12. Saki N, Darayesh M, Heiran A. Comparing the efficacy of topical hydroquinone 2% versus intradermal tranexamic acid microinjections in treating melasma: a split-face controlled trial. *J Dermatolog Treat*. 2018;29(4):405-410. doi:10.1080/09546634.2017.1392476

13. Sharma R, Mahajan VK, Mehta KS, Chauhan PS, Rawat R, Shiny TN. Therapeutic efficacy and safety of oral tranexamic acid and that of tranexamic acid local infiltration with microinjections in patients with melasma: a comparative study. *Clin Exp Dermatol*. 2017;42(7):728-734. doi:10.1111/ced.13164

14. Steiner D, Feola C, Bialeski N, et al. Study evaluating the efficacy of topical and injected tranexamic acid in treatment of melasma. *Surgical and Cosmetic Dermatology*. 2009;1:174-177.

15. Budamakuntla L, Loganathan E, Suresh D, et al. A Randomised, Open-label, Comparative Study of Tranexamic Acid Microinjections and Tranexamic Acid with Microneedling in Patients with Melasma. *J Cutan Aesthet Surg*. 2013;6(3):139. doi:10.4103/0974-2077.118403

16. Cassiano D, Espósito AC, Hassun K, Lima E de A, Bagatin E, Miot H. Early clinical and histological changes induced by microneedling in facial melasma: A pilot study. *Indian J Dermatol Venereol Leprol*. 2019;85(6):638. doi:10.4103/ijdvl.ijdvl_44_19

17. Ebrahim HM, Said Abdelshafy A, Khattab F, Gharib K. Tranexamic Acid for Melasma Treatment: A Split-Face Study. *Dermatol Surg*. 2020;46(11):e102-e107. doi:10.1097/dss.0000000000002449

18. Hofny ERM, Abdel-Motaleb AA, Ghazally A, Ahmed AM, Hussein MRA. Platelet-rich plasma is a useful therapeutic option in melasma. *J Dermatolog Treat*. 2019;30(4):396-401. doi:10.1080/09546634.2018.1524821

19. Ismail ESA, Patsatsi A, Abd el-Maged WM, Nada EEA el-Aziz. Efficacy of microneedling with topical vitamin C in the treatment of melasma. *J Cosmet Dermatol*. 2019;18(5):1342-1347. doi:10.1111/jocd.12878

20. Saleh F, Abdel-Azim E, Ragaie M, Guendy M. Topical tranexamic acid with microneedling versus microneedling alone in treatment of melasma: clinical, histopathologic, and immunohistochemical study. *J Egypt Womens Dermatol Soc*. 2019;16(2):89. doi:10.4103/jewd.jewd_25_19

21. Xu Y, Ma R, Juliandri J, et al. Efficacy of functional microarray of microneedles combined with topical tranexamic acid for melasma: A randomized, self-controlled, split-face study. *Medicine*. 2017;96(19):e6897. doi:10.1097/md.0000000000006897

22. Zaky M, Obaid Z, Khalil E, Elsaie ML. Microneedling-Assisted Topical Tranexamic Acid Solution versus 4% Hydroquinone for Treating Melasma: A Split-Face randomized study. *Authorea Preprints*. Published online March 27, 2021. doi:10.22541/au.161684931.19413802/v1

23. Chen W. Fifty cases of chloasma treated by acupuncture plus intensive pulse light irradiation. *J Tradit Chin Med*. 2007;27(4):265-267.

24. Feng X jing, Fu J ying, Liu F. Clinical observation on the combined use of acupuncture and herbal medicine for treatment of chloasma. *J Tradit Chin Med*. 2010;30(1):15-17. doi:10.1016/s0254-6272(10)60004-0

25. Rerksuppaphol L, Charoenpong T, Rerksuppaphol S. Randomized clinical trial of facial acupuncture with or without body acupuncture for treatment of melasma. *Complement Ther Clin Pract*. 2016;22:1-7. doi:10.1016/j.ctcp.2015.10.004

26. Vedamurthy M. Mesotherapy. *Indian J Dermatol Venereol Leprol*. 2007;73(1):60. doi:10.4103/0378-6323.30661

27. Khalili M, Amiri R, Iranmanesh B, Zartab H, Aflatoonian M. Safety and efficacy of mesotherapy in the treatment of melasma: A review article. *J Cosmet Dermatol*. 2022;21(1):118-129. doi:10.1111/jocd.14644

28. Alster TS, Graham PM. Microneedling: A Review and Practical Guide. *Dermatol Surg*. 2018;44(3):397-404. doi:10.1097/dss.0000000000001248

29. Singh A, Yadav S. Microneedling: Advances and widening horizons. *Indian Dermatol Online J*. 2016;7(4):244. doi:10.4103/2229-5178.185468

30. Aust MC, Fernandes D, Kolokythas P, Kaplan HM, Vogt PM. Percutaneous collagen induction therapy: an alternative treatment for scars, wrinkles, and skin laxity. *Plast Reconstr Surg*. 2008;121(4):1421-1429. doi:10.1097/01.prs.0000304612.72899.02

31. Waghule T, Singhvi G, Dubey SK, et al. Microneedles: A smart approach and increasing potential for transdermal drug delivery system. *Biomed Pharmacother*. 2019;109:1249-1258. doi:10.1016/j.biopha.2018.10.078

32. Gowda A, Healey B, Ezaldein H, Merati M. A Systematic Review Examining the Potential Adverse Effects of Microneedling. *J Clin Aesthet Dermatol*. 2021;14(1):45-54.

33. Acar HV. Acupuncture and related techniques during perioperative period: A literature review. *Complement Ther Med*. 2016;29:48-55. doi:10.1016/j.ctim.2016.09.013

34. Tait P, Brooks L, Harstall C. Acupuncture: Evidence from Systematic Reviews and Meta-analyses. *Health Technol Assess*. 2002;Series A.

35. Yun Y, Kim S, Kim M, Kim K, Park JS, Choi I. Effect of facial cosmetic acupuncture on facial elasticity: an open-label, single-arm pilot study. *Evid Based Complement Alternat Med*. 2013;2013(424313):1-5. doi:10.1155/2013/424313

36. Fisk WA, Agbai O, Lev-Tov HA, Sivamani RK. The use of botanically derived agents for hyperpigmentation: a systematic review. *J Am Acad Dermatol*. 2014;70(2):352-365. doi:10.1016/j.jaad.2013.09.048

37. Hu S, Wolfe S, Laughter M, Sadeghpour M. The Use of Botanical Extracts in East Asia for Treatment of Hyperpigmentation: An Evidenced-Based Review. *J Drugs Dermatol*. 2020;19(7):758-763. doi:10.36849/jdd.2020.4776

38. Ye Y, Chou GX, Mu DD, et al. Screening of Chinese herbal medicines for antityrosinase activity in a cell free system and B16 cells. *J Ethnopharmacol*. 2010;129(3):387-390. doi:10.1016/j.jep.2010.04.009

39. Kamagaju L, Bizuru E, Minani V, et al. An ethnobotanical survey of medicinal plants used in Rwanda for voluntary depigmentation. *J Ethnopharmacol*. 2013;150(2):708-717. doi:10.1016/j.jep.2013.09.031

40. Zaidi KU, Ali SA, Ali A, Naaz I. Natural Tyrosinase Inhibitors: Role of Herbals in the Treatment of Hyperpigmentary Disorders. *Mini Rev Med Chem*. 2019;19(10):796-808. doi:10.2174/1389557519666190116101039

41. Woolery-Lloyd H, Friedman A. Optimizing patient care with "natural" products: treatment of hyperpigmentation. *J Drugs Dermatol*. 2009;8(6 Suppl):s10-13.

42. Pourang A, Hendricks AJ, Shi VY. Managing dermatology patients who prefer "all natural" treatments. *Clin Dermatol*. 2020;38(3):348-353. doi:10.1016/j.clindermatol.2019.10.025

43. Zhang Q, Tu Y, Gu H, et al. A cream of herbal mixture to improve melasma. *J Cosmet Dermatol*. 2019;18(6):1721-1728. doi:10.1111/jocd.12938

44. Hollinger JC, Angra K, Halder RM. Are Natural Ingredients Effective in the Management of Hyperpigmentation? A Systematic Review. *J Clin Aesthet Dermatol*. 2018;11(2):28-37.

45. Choubey V, Sarkar R, Garg V, Kaushik S, Ghunawat S, Sonthalia S. Role of oxidative stress in melasma: a prospective study on serum and blood markers of oxidative stress in melasma patients. *Int J Dermatol*. 2017;56(9):939-943. doi:10.1111/ijd.13695

46. Paine C, Sharlow E, Liebel F, Eisinger M, Shapiro S, Seiberg M. An alternative approach to depigmentation by soybean extracts via inhibition of the PAR-2 pathway. *J Invest Dermatol*. 2001;116(4):587-595. doi:10.1046/j.1523-1747.2001.01291.x

47. İlknur T, Biçak MÜ, Demirtaşoğlu M, Özkan Ş. Glycolic acid peels versus amino fruit acid peels in the treatment of melasma. *Dermatol Surg*. 2010;36(4):490-495. doi:10.1111/j.1524-4725.2010.01481.x

48. Lowe NJ, Rizk D, Grimes P, Billips M, Pincus S. Azelaic acid 20% cream in the treatment of facial hyperpigmentation in darker-skinned patients. *Clin Ther*. 1998;20(5):945-959. doi:10.1016/s0149-2918(98)80076-3

49. Kakita LS, Lowe NJ. Azelaic acid and glycolic acid combination therapy for facial hyperpigmentation in darker-skinned patients: a clinical comparison with hydroquinone. *Clin Ther*. 1998;20(5):960-970. doi:10.1016/s0149-2918(98)80077-5

50. Kar HK. Efficacy of beta-carotene topical application in melasma--an open clinical trial. *Indian J Dermatol Venereol Leprol*. 2003;69(2):92-94.

51. Teo WL, Gan EG, Jinghan A, et al. Double Blind Placebo Controlled Trial to Evaluate of the Effectiveness of a Dietary Supplement Rich in Carotenoids as Adjunct to Topical Lightening Cream for the Treatment of Melasma: A Pilot Study. *J Pigment Disord*. 2015;02(02). doi:10.4172/2376-0427.1000164

52. Nguyen J, Remyn L, Chung IY, et al. Evaluation of the efficacy of cysteamine cream compared to hydroquinone in the treatment of melasma: A randomised, double-blinded trial. *Australas J Dermatol*. 2021;62(1):e41-e46. doi:10.1111/ajd.13432

53. Lima PB, Dias JAF, Cassiano D, et al. A comparative study of topical 5% cysteamine versus 4% hydroquinone in the treatment of facial melasma in women. *Int J Dermatol*. 2020;59(12):1531-1536. doi:10.1111/ijd.15146

54. Sepaskhah M, Karimi F, Bagheri Z, Kasraee B. Comparison of the efficacy of cysteamine 5% cream and hydroquinone 4%/ascorbic acid 3% combination cream in the treatment of epidermal melasma. *J Cosmet Dermatol*. 2022;21(7):2871-2878. doi:10.1111/jocd.15048

55. Karrabi M, David J, Sahebkar M. Clinical evaluation of efficacy, safety and tolerability of cysteamine 5% cream in comparison with modified Kligman's formula in subjects with epidermal melasma: A randomized, double-blind clinical trial study. *Skin Res Technol*. 2021;27(1):24-31. doi:10.1111/srt.12901

56. Wang L, Lu AP, Yu ZL, et al. The melanogenesis-inhibitory effect and the percutaneous formulation of ginsenoside Rb1. *AAPS PharmSciTech*. 2014;15(5):1252-1262. doi:10.1208/s12249-014-0138-3

57. Kim K. Effect of ginseng and ginsenosides on melanogenesis and their mechanism of action. *J Ginseng Res*. 2015;39(1):1-6. doi:10.1016/j.jgr.2014.10.006

58. Song M, Mun JH, Ko HC, Kim BS, Kim MB. Korean red ginseng powder in the treatment of melasma: an uncontrolled observational study. *J Ginseng Res*. 2011;35(2):170-175. doi:10.5142/jgr.2011.35.2.170

59. Sharif A, Akhtar N, Khan MS, et al. Formulation and evaluation on human skin of a water-in-oil emulsion containing Muscat hamburg black grape seed extract. *Int J Cosmet Sci*. 2015;37(2):253-258. doi:10.1111/ics.12184

60. Yamakoshi J, Sano A, Tokutake S, et al. Oral intake of proanthocyanidin-rich extract from grape seeds improves chloasma. *Phytother Res*. 2004;18(11):895-899. doi:10.1002/ptr.1537

61. Management of melasma with 2% analogue of green tea extract in a hydrophilic cream: A placebo-controlled, double-blind study. *J Am Acad Dermatol*. 2009;60(3, Supplement 1):AB160. doi:10.1016/j.jaad.2008.11.702

62. Desai S, Ayres E, Bak H, et al. Effect of a Tranexamic Acid, Kojic Acid, and Niacinamide Containing Serum on Facial Dyschromia: A Clinical Evaluation. *J Drugs Dermatol*. 2019;18(5):454-459.

63. Garcia A, Fulton JE 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. doi:10.1111/j.1524-4725.1996.tb00345.x

64. Gajjala S, Ali SY, Lakshmi Chowdary N, Harshini D. The comparative study of Hydroquinone and kojic acid in treatment of Melasma in Shadan Institute of Medical Science Teaching Hospital and Research Centre , Himayathsagar road , Hyderabad (Telangana State). *J Med Dent Sci*. Published online 2016. https://www.semanticscholar.org/paper/7c59730b9510b194d03cfe22c2e2ae9ec8f177eb

65. Monteiro RC, Kishore BN, Bhat RM, Sukumar D, Martis J, Ganesh HK. A Comparative Study of the Efficacy of 4% Hydroquinone vs 0.75% Kojic Acid Cream in the Treatment of Facial Melasma. *Indian J Dermatol*. 2013;58(2):157. doi:10.4103/0019-5154.108070

66. Deo KS, Dash KN, Sharma YK, Virmani NC, Oberai C. Kojic Acid vis-a-vis its Combinations with Hydroquinone and Betamethasone Valerate in Melasma: A Randomized, Single Blind, Comparative Study of Efficacy and Safety. *Indian J Dermatol*. 2013;58(4):281-285. doi:10.4103/0019-5154.113940

67. Navarrete-Solís J, Castanedo-Cázares JP, Torres-Álvarez B, et al. A Double-Blind, Randomized Clinical Trial of Niacinamide 4% versus Hydroquinone 4% in the Treatment of Melasma. *Dermatol Res Pract*. 2011;2011(379173):1-5. doi:10.1155/2011/379173

68. Lee DH, Oh IY, Koo KT, et al. Reduction in facial hyperpigmentation after treatment with a combination of topical niacinamide and tranexamic acid: a randomized, double-blind, vehicle-controlled trial. *Skin Res Technol*. 2014;20(2):208-212. doi:10.1111/srt.12107

69. Castanedo-Cazares JP, Lárraga-Piñones G, Ehnis-Pérez A, et al. Topical niacinamide 4% and desonide 0.05% for treatment of axillary hyperpigmentation: a randomized, double-blind, placebo-controlled study. *Clin Cosmet Investig Dermatol*. 2013;6:29-36. doi:10.2147/ccid.s39246

70. Lim HY, Kim E, Park SH, et al. Antimelanogenesis Effects of Theasinensin A. *Int J Mol Sci*. 2021;22(14):7453. doi:10.3390/ijms22147453

71. Khosravan S, Alami A, Mohammadzadeh-Moghadam H, Ramezani V. The Effect of Topical Use of Petroselinum Crispum (Parsley) Versus That of Hydroquinone Cream on Reduction of Epidermal Melasma: A Randomized Clinical Trial. *Holist Nurs Pract*. 2017;31(1):16-20. doi:10.1097/hnp.0000000000000186

72. Goh CL, Chuah SY, Tien S, Thng G, Vitale MA, Delgado-Rubin A. Double-blind, Placebo-controlled Trial to Evaluate the Effectiveness of Polypodium Leucotomos Extract in the Treatment of Melasma in Asian Skin: A Pilot Study. *J Clin Aesthet Dermatol*. 2018;11(3):14-19.

73. Yoshimura M, Watanabe Y, Kasai K, Yamakoshi J, Koga T. Inhibitory effect of an ellagic acid-rich pomegranate extract on tyrosinase activity and ultraviolet-induced pigmentation. *Biosci Biotechnol Biochem*. 2005;69(12):2368-2373. doi:10.1271/bbb.69.2368

74. Kanlayavattanakul M, Chongnativisit W, Chaikul P, Lourith N. Phenolic-rich Pomegranate Peel Extract: In Vitro, Cellular, and In Vivo Activities for Skin Hyperpigmentation Treatment. *Planta Med*. 2020;86(11):749-759. doi:10.1055/a-1170-7785

75. Topical turmeric extract in a moisturizing cream formula reduces the appearance of facial spots and fine lines and wrinkles on human facial skin. *J Am Acad Dermatol*. 2010;62(3, Supplement 1):AB19. doi:10.1016/j.jaad.2009.11.118

76. Wang X, Heraud S, Thépot A, Dos Santos M, Luo Z. The Whitening Properties of the Mixture Composed of Pomegranate, Osmanthus and Olive and the Protective Effects Against Ultraviolet Deleterious Effects. *Clin Cosmet Investig Dermatol*. 2021;14:561-573. doi:10.2147/ccid.s302997

77. Altaei T. The treatment of melasma by silymarin cream. *BMC Dermatol*. 2012;12(1). doi:10.1186/1471-5945-12-18

78. Nofal A, Ibrahim AM, Nofal E, Gamal N, Osman S. Topical silymarin versus hydroquinone in the treatment of melasma: A comparative study. *J Cosmet Dermatol*. 2018;18(1):263-270. doi:10.1111/jocd.12769

79. Ibrahim SMA, Farag AS, Ali MS, El-Gendy WMAF. Efficacy and Safety of Topical Silymarin Versus Low Fluence 1064-nm Q Switched Nd:YAG Laser in the Treatment of Melasma: A Comparative Randomized Trial. *Lasers Surg Med*. 2021;53(10):1341-1347. doi:10.1002/lsm.23440

80. Park SY, Jin ML, Kim YH, Kim Y, Lee SJ. Aromatic-turmerone inhibits α-MSH and IBMX-induced melanogenesis by inactivating CREB and MITF signaling pathways. *Arch Dermatol Res*. 2011;303(10):737-744. doi:10.1007/s00403-011-1155-7

81. Panich U, Kongtaphan K, Onkoksoong T, et al. Modulation of antioxidant defense by Alpinia galanga and Curcuma aromatica extracts correlates with their inhibition of UVA-induced melanogenesis. *Cell Biol Toxicol*. 2010;26(2):103-116. doi:10.1007/s10565-009-9121-2

82. Sharquie KE, Al-Mashhadani SA, Salman HA. Topical 10% zinc sulfate solution for treatment of melasma. *Dermatol Surg*. 2008;34(10):1346-1349.

83. Iraji F, Tagmirriahi N, Gavidnia K. Comparison between the efficacy of 10% zinc sulfate solution with 4% hydroquinone cream on improvement of melasma. *Adv Biomed Res*. 2012;1:39. doi:10.4103/2277-9175.100134

84. Yousefi A, Khani Khoozani Z, Zakerzadeh Forooshani S, Omrani N, Moini AM, Eskandari Y. Is topical zinc effective in the treatment of melasma? A double-blind randomized comparative study. *Dermatol Surg*. 2014;40(1):33-37. doi:10.1111/dsu.12296

85. Lyons AB, Trullas C, Kohli I, Hamzavi IH, Lim HW. Photoprotection beyond ultraviolet radiation: A review of tinted sunscreens. *J Am Acad Dermatol*. 2021;84(5):1393-1397. doi:10.1016/j.jaad.2020.04.079

86. Rostami Mogaddam M, Safavi Ardabili N, Iranparvar Alamdari M, Maleki N, Aghabalaei 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*. 2018;17(3):417-422. doi:10.1111/jocd.12392

87. Sastrini Sekarnesia I, Sitohang IBS, Agustin T, Wisnu W, Hoemardani ASD. A comparison of serum zinc levels in melasma and non-melasma patients: a preliminary study of thyroid dysfunction. *Acta Dermatovenerol Alp Pannonica Adriat*. 2020;29(2):59-62. doi:10.15570/actaapa.2020.14

88. Klein M. Amino fruit acids: the new cosmeceutical. *Cosmet Dermatol*. 2000;13(9):25-29.

89. Fitton A, Goa KL. Azelaic acid. A review of its pharmacological properties and therapeutic efficacy in acne and hyperpigmentary skin disorders. *Drugs*. 1991;41(5):780-798. doi:10.2165/00003495-199141050-00007

90. Eggersdorfer M, Wyss A. Carotenoids in human nutrition and health. *Arch Biochem Biophys*. 2018;652:18-26. doi:10.1016/j.abb.2018.06.001

91. Besouw M, Masereeuw R, van den Heuvel L, Levtchenko E. Cysteamine: an old drug with new potential. *Drug Discov Today*. 2013;18(15-16):785-792. doi:10.1016/j.drudis.2013.02.003

92. Kasraee B, Mansouri P, Farshi S. Significant therapeutic response to cysteamine cream in a melasma patient resistant to Kligman's formula. *J Cosmet Dermatol*. 2019;18(1):293-295. doi:10.1111/jocd.12837

93. Desai S, Hartman C, Grimes P, Shah S. Topical Stabilized Cysteamine as a New Treatment for Hyperpigmentation Disorders: Melasma, Post-Inflammatory Hyperpigmentation, and Lentigines. *J Drugs Dermatol*. 2021;20(12):1276-1279. doi:10.36849/jdd.6367

94. Lee H, Shahbaz HM, Ha N, Kim JU, Lee SJ, Park J. Development of ginseng powder using high hydrostatic pressure treatment combined with UV-TiO2 photocatalysis. *J Ginseng Res*. 2020;44(1):154-160. doi:10.1016/j.jgr.2018.11.004

95. Rauf A, Imran M, Abu-Izneid T, et al. Proanthocyanidins: A comprehensive review. *Biomed Pharmacother*. 2019;116:108999. doi:10.1016/j.biopha.2019.108999

96. Sochorova L, Prusova B, Cebova M, et al. Health Effects of Grape Seed and Skin Extracts and Their Influence on Biochemical Markers. *Molecules*. 2020;25(22):5311. doi:10.3390/molecules25225311

97. Yamakoshi J, Otsuka F, Sano A, et al. Lightening effect on ultraviolet-induced pigmentation of guinea pig skin by oral administration of a proanthocyanidin-rich extract from grape seeds. *Pigment Cell Res*. 2003;16(6):629-638. doi:10.1046/j.1600-0749.2003.00093.x

98. Roh E, Kim JE, Kwon JY, et al. Molecular mechanisms of green tea polyphenols with protective effects against skin photoaging. *Crit Rev Food Sci Nutr*. 2017;57(8):1631-1637. doi:10.1080/10408398.2014.1003365

99. Zachary CM, Wang JV, Saedi N. Kojic Acid for Melasma: Popular Ingredient in Skincare Products. *Skinmed*. 2020;18(5):271-273.

100. Saeedi M, Eslamifar M, Khezri K. Kojic acid applications in cosmetic and pharmaceutical preparations. *Biomed Pharmacother*. 2019;110:582-593. doi:10.1016/j.biopha.2018.12.006

101. Lajis AFB, Hamid M, Ariff AB. Depigmenting effect of Kojic acid esters in hyperpigmented B16F1 melanoma cells. *J Biomed Biotechnol*. 2012;2012:952452. doi:10.1155/2012/952452

102. Alvin G, Catambay N, Vergara A, Jamora MJ. A comparative study of the safety and efficacy of 75% mulberry (Morus alba) extract oil versus placebo as a topical treatment for melasma: a randomized, single-blind, placebo-controlled trial. *J Drugs Dermatol*. 2011;10(9):1025-1031.

103. Chang LW, Juang LJ, Wang BS, et al. Antioxidant and antityrosinase activity of mulberry (Morus alba L.) twigs and root bark. *Food Chem Toxicol*. 2011;49(4):785-790. doi:10.1016/j.fct.2010.11.045

104. Draelos ZD, Ertel K, Berge C. Niacinamide-containing facial moisturizer improves skin barrier and benefits subjects with rosacea. *Cutis*. 2005;76(2):135-141.

105. Namazi MR. Nicotinamide: a potential addition to the anti-psoriatic weaponry. *FASEB J*. 2003;17(11):1377-1379. doi:10.1096/fj.03-0002hyp

106. Walocko FM, Eber AE, Keri JE, Al-Harbi MA, Nouri K. The role of nicotinamide in acne treatment. *Dermatol Ther*. 2017;30(5):e12481. doi:10.1111/dth.12481

107. Hakozaki T, Minwalla L, Zhuang J, et al. The effect of niacinamide on reducing cutaneous pigmentation and suppression of melanosome transfer. *Br J Dermatol*. 2002;147(1):20-31. doi:10.1046/j.1365-2133.2002.04834.x

108. Farzaei MH, Abbasabadi Z, Ardekani MRS, Rahimi R, Farzaei F. Parsley: a review of ethnopharmacology, phytochemistry and biological activities. *J Tradit Chin Med*. 2013;33(6):815-826. doi:10.1016/s0254-6272(14)60018-2

109. Segars K, McCarver V, Miller RA. Dermatologic Applications of Polypodium leucotomos: A Literature Review. *J Clin Aesthet Dermatol*. 2021;14(2):50-60.

110. Nestor M, Bucay V, Callender V, Cohen JL, Sadick N, Waldorf H. Polypodium leucotomos as an Adjunct Treatment of Pigmentary Disorders. *J Clin Aesthet Dermatol*. 2014;7(3):13-17.

111. Rana J, Diwakar G, Saito L, Scholten JD, Mulder T. Inhibition of melanin content by Punicalagins in the super fruit pomegranate (Punica granatum). *J Cosmet Sci*. 2013;64(6):445-453.

112. Hering NA, Luettig J, Jebautzke B, Schulzke JD, Rosenthal R. The Punicalagin Metabolites Ellagic Acid and Urolithin A Exert Different Strengthening and Anti-Inflammatory Effects on Tight Junction-Mediated Intestinal Barrier Function In Vitro. *Front Pharmacol*. 2021;12:610164. doi:10.3389/fphar.2021.610164

113. Kasai K, Yoshimura M, Koga T, Arii M, Kawasaki S. Effects of oral administration of ellagic acid-rich pomegranate extract on ultraviolet-induced pigmentation in the human skin. *J Nutr Sci Vitaminol*. 2006;52(5):383-388. doi:10.3177/jnsv.52.383

114. Camini FC, Costa DC. Silymarin: not just another antioxidant. *J Basic Clin Physiol Pharmacol*. 2020;31(4). doi:10.1515/jbcpp-2019-0206

115. Hewlings SJ, Kalman DS. Curcumin: A Review of Its Effects on Human Health. *Foods*. 2017;6(10):92. doi:10.3390/foods6100092

116. Gupta M, Mahajan VK, Mehta KS, Chauhan PS. Zinc therapy in dermatology: a review. *Dermatol Res Pract*. 2014;2014:709152. doi:10.1155/2014/709152