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The Therapeutic Use of Antioxidants for Melasma

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ABSTRACT

Melasma is a chronic dermatologic condition with an incompletely understood pathogenesis and well-demonstrated impact on patient quality of life. Melasma is a common cause for seeking dermatologic care, and with no universally efficacious therapy or cure, combination treatment is the best approach for many cases. Numerous studies have demonstrated the role of oxidative stress in patients with melasma, prompting investigation into several antioxidants for melasma therapy. In this review, we discuss the well-defined role of oxidative stress in melasma and the therapeutic efficacy of various antioxidants for patients suffering from melasma. We focus our discussion on studies investigating the role of vitamin C, azelaic acid, cysteamine, glutathione, carotenoids, and numerous other antioxidants in disorders of hyperpigmentation. There is promising evidence for the use of these antioxidants, as topical, oral, and intravenous preparations, both in isolation and in conjunction with other melasma therapies.

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INTRODUCTION

Melasma is a chronic and acquired skin disorder of hyperpigmentation that presents with symmetric hypermelanosis of sun exposed areas, especially the face. Disease prevalence, ranging from 1 to 50%, varies with gender, ethnicity, skin phenotype, and sun exposure.[1]

The pathogenesis of melasma is incompletely understood, which poses a challenge for disease management. Causative factors include genetics, ultraviolet (UV) radiation, cosmetics, pregnancy, hormonal therapy, phototoxic drugs, and various medications.[1,2]

Melasma is evaluated by Melasma Area and Severity Index (MASI) score, modified MASI (mMASI) score, Melasma Quality of Life Scale (MelasQoL), colorimetry, and mexametry.

With a well demonstrated impact on quality of life, melasma is a common cause for seeking dermatologic care. There is no universally efficacious therapy, so combination treatment is preferred. Therapies include topical hypopigmenting agents, laser treatment, microneedling, chemical peels, radiofrequency, and oral medications.[1] Furthermore, it is critical for patients to avoid exacerbating factors.

The skin, a protective organ critical in homeostasis, is the site of numerous biochemical processes, including the generation of free radicals, namely reactive oxygen and nitrogen species. Reactive oxygen species (ROS) are necessary for biological signaling processes, but, in excess, ROS can damage biomolecules.[3] There is clear evidence of oxidative stress in melasma.[4,5]

Antioxidant Therapy in Melasma

Vitamin C

Vitamin C, or ascorbic acid, is a potent antioxidant with a myriad of research on its role in numerous diseases. It is a ROS scavenger and can regenerate various other antioxidants. Vitamin C and magnesium ascorbyl phosphate (MAP), a vitamin C derivative, have been investigated for their role in treating melasma.

Oral vitamin C supplementation has been studied for treatment of hyperpigmentation disorders. Hayakawa et al investigated the role of oral vitamins C and E, both alone and in combination, in patients with chloasma and pigmented contact dermatitis. The combination group had the most significant response, but all experienced significant reductions in skin luminosity differences between hyperpigmented and normal skin areas.[6] Similarly, Handog et al found oral combination therapy with vitamins A, C, E, and procyanidin effective for treating Filipino women with melasma.[7]

Vitamin C cream has been investigated as a topical remedy for melasma, by both direct skin and ultrasound application. In a comparison of hydroquinone and ascorbic acid cream for melasma, there was significantly greater subjective

improvement with hydroquinone but a lower incidence of side effects with ascorbic acid.[8] Additionally, a combination of MAP cream and fluorescent pulsed light was effective, well-tolerated, and safe for refractory melasma in Asian patients.[9] Likewise, a comparison of MAP liposomal cream and a chemical peel using trichloroacetic acid (TCA) suggested MAP liposomal cream was superior.[10]

Vitamin C serums, peels, and gels have also been explored. In a study, patients who used C'ensil, a serum containing ascorbic acid, experienced a significant decrease in pigmentation and improved quality of life after therapy.[11] Kim et al investigated a chemical peel containing vitamin C and found significant improvement in hyperpigmentation for patients with melasma.[12] Hakozaki et al studied a skin-lightening gel containing ascorbyl glucoside and niacinamide. Patients receiving ultrasound radiation and gel had significantly reduced facial hyperpigmentation compared with those receiving gel alone.[13] Many others have also demonstrated the beneficial role of ultrasonic application of vitamin C.[14-16] Various studies revealed the benefits of topical vitamin C administered with TCA peels.[17-19]

Others have studied the efficacy of vitamin C iontophoresis.[20-25] Additionally, microneedling and mesotherapy with vitamin C have been investigated for their potential role in melasma therapy.[26-28]

Azelaic Acid

Azelaic acid (AzA), a dicarboxylic acid, competitively inhibits tyrosinase, the key enzyme of melanogenesis, and reversibly inhibits various respiratory chain enzymes and mitochondrial oxidoreductase activity.[29,30]

Lowe et al assessed the safety, tolerability, and efficacy of AzA cream compared to its vehicle for treatment of hyperpigmentation. AzA treated patients had significantly greater decreases in pigmentary intensity and significantly greater global improvement, but they reported more burning and stinging.[31] Many have compared AzA to hydroquinone, the gold standard melasma topical agent. Findings are inconsistent, with some concluding AzA to have better outcomes,[32,33] while others found no significant difference.[34]

Others have studied AzA in conjunction with various melasma therapies. Sarkar et al evaluated sequential therapy of topical steroids plus AzA cream versus AzA alone in Indian patients. Over 90% of all patients had good to excellent responses to treatment.[35] Researchers have reported a therapeutic benefit from a combination therapy consisting of glycolic acid (GA) peels and AzA cream for patients with melasma.[36,37] Combination therapies with AzA have included salicylic acid, hydroquinone, methylprednisolone aceponate, resorcinol, phytic acid, tacrolimus, zinc oxide, and tazarotene.[38-40] A recent publication investigated nanotechnology as a tool for optimizing AzA for hyperpigmentation.[41]

Cysteamine

Cysteamine is an amino thiol prescribed to reduce intralysosomal cystine accumulation in patients with cystinosis. At low concentrations, cysteamine promotes intracellular transport of L-cysteine, which is used to synthesize glutathione, a powerful antioxidant.[42]

Two trials demonstrated the efficacy of cysteamine cream for melasma treatment.[43,44] Mansouri et al compared cysteamine cream with placebo. MASI scores were significantly lower in patients receiving cysteamine.[43] Farshi et al conducted a similar study to evaluate melanin content; findings further supported the therapeutic benefit of cysteamine for facial hyperpigmentation.[44]

Glutathione/ N-acetyl-cystine

Glutathione, an endogenous peptide, plays a critical role in protection from oxidative stress.[45] N-acetyl-cysteine (NAC), a cysteine prodrug, is a precursor for glutathione that has greater bioavailability than cysteine itself through parenteral administration.

In a study of healthy students, subjects were orally administered glutathione capsules or placebo. Those receiving glutathione had decreased melanin indices in sun-exposed areas and developed significantly less UV spots.[46] Handog et al used a glutathione-containing lozenge for buccal mucosal absorption and found a significant decrease in melanin indices.[47] A study of healthy women found topical oxidized glutathione safe and effective for skin-whitening and improving skin condition.[48]

Various studies investigated combined therapies containing glutathione; however, it is difficult to draw conclusions about glutathione alone, when it is used with other therapies.[28,49,50]

Carotenoids

Carotenoids, namely beta-carotene, lycopene, lutein, and zeaxanthin, are naturally occurring pigments in photosynthetic organisms. Carotenoids decrease oxidative stress by quenching singlet oxygen species and other ROS scavenging properties.[51]

Teo et al evaluated the effectiveness of a carotenoid-rich oral supplement with a topical lightening cream. There was a greater, yet insignificant, decrease in mMASI score in the oral supplement group.[52] In a similar study, patients received either a nutri-concentrate capsule (containing lycopene and beta-carotene) and sunscreen or sunscreen only. The supplement group showed a greater decrease in MASI score.[53] Although not in melasma patients, Juturu et al found oral supplementation with lutein and zeaxanthin promoted skin lightening.[54]

One study found topical application of beta-carotene effective and safe for melasma.[55]

Curcuma longa

Curcuma longa, commonly known as turmeric, is a spice and herbal supplement with antioxidant, anti-inflammatory, antimicrobial, and antineoplastic properties.[56] Studies have investigated turmeric, curcumin (the active ingredient of turmeric), and aromatic (ar)-turmerone (a naturally occurring turmeric oil) in hyperpigmentation disorders.

Swanson et al conducted a double-blind, split-face study of non-melasma patients and found topical cream containing turmeric extract to reduce hyperpigmented spots.[57] Park et al studied the anti-melanogenic effect of ar-tumerone and determined that it reduces gene expression of tyrosinase-related proteins 1 and 2 and downregulates tyrosinase activity. Although ar-tumerone was found to be more effective, curcumin also significantly inhibited melanin synthesis and tyrosinase activity.[58]

Ellagic Acid

Ellagic acid is a natural antioxidant that activates antioxidant enzymes and suppresses genes responsible for inflammation and disturbance of biochemical systems.[59] Ellagic acid also suppresses melanogenesis by inhibiting tyrosinase activity.[60] Ertam et al conducted a randomized, open-label study comparing the effectiveness of plant extracts containing ellagic acid, gels containing synthetic ellagic acid, and arbutin, a well-established whitening agent. A significant difference in pigment density occurred in all patients using arbutin and natural ellagic acid, and in most who used synthetic ellagic acid.[61]

Kojic Acid

Kojic acid, a natural metabolite from fungi, has many cosmetic and pharmaceutical functions.[62] It is used for antioxidant, antiproliferative, anti-inflammatory, antimicrobial, antiviral, and radioprotective therapy. Kojic acid also has tyrosinase inhibitory activity, so it restricts melanin formation and limits hyperpigmentation.[62]

Kojic acid has been added to creams, serums, and gels in concentrations ranging from 0.75 to 2%. In a split-face study of Chinese women with melasma, patients applied kojic acid gel containing GA and hydroquinone to one side of the face and the same application without kojic acid to the other. Patients had an insignificantly greater improvement on the kojic acid side.[63] In another combination therapy study, Deo et al investigated four creams with various combinations of kojic acid, hydroquinone, and betamethasone valerate. Kojic acid, in synergy with hydroquinone, was considered superior to other creams as a depigmenting agent.[64]

Tranexamic acid is a useful topical agent for decreasing pigmentation in patients with melasma. It functions by inhibiting the release of inflammatory mediators critical for melanogenesis. In a study by Desai et al, patients applied a topical serum containing tranexamic acid, kojic acid, and niacinamide and had significant improvement in hyperpigmentation and melasma.[65]

Other studies found kojic acid to be less beneficial and more irritating than alternative therapies.[66,67]

Resveratrol

Resveratrol is a plant-synthesized polyphenol phytoalexin with numerous uses in dermatology due to its antioxidant, antiaging, anti-inflammatory, and antimicrobial properties. Resveratrol is a modulator of tyrosinase activity and influences melanogenic genes, making it a useful skin-lightening agent.[68]

Ryu et al investigated the safety and whitening ability of resveratryl triacetate, a resveratrol prodrug. In their artificial tanning and hyperpigmentation models, there were significant improvements in skin whitening in the test group, compared with controls.[69]

Others have studied resveratrol in conjunction 4-n-butyl-resorcinol, which is reported to inhibit tyrosinase. Kim et al concluded this combination of compounds had a synergistic hypopigmentary effect in vitro.[70] Kwon et al found that the melanin index of lesional skin was significantly decreased, and mean investigator's global assessment score was significantly improved.[71]

Others studied a hybrid compound of esterified resveratrol with GA. This compound decreased melanin levels in vitro,[72] and in vivo, resulted in significant depigmentation, compared with a control.[73]

Additional antioxidants

Other antioxidants under investigation for their role in antioxidant therapy include the following: vitamin E, melatonin, niacinomide, polypodium leucotomos, pycogenol, grape seed extract, amino fruit acids, phytic acid, zinc, silymarin, Korean red ginseng powder, plant extracts including orchid extract, and petroselinum crispum. Like the previously mentioned therapies, there is conflicting evidence surrounding the use of these compounds for treatment of hyperpigmentation.

CONCLUSIONS

With a poorly understood pathogenesis and well-demonstrated impact on quality of life, melasma is a frequently investigated dermatologic condition. Therapeutic efficacy of various drugs has been studied, and combined therapy is often recommended for this disorder of skin hyperpigmentation. Scientific evidence supports the role of antioxidants as a reasonable therapeutic option for patients suffering from skin hyperpigmentation.

DISCLOSURES

The authors have no conflicts of interest.

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