Review Article

A Review of Oral Therapies for the Treatment of Skin Hyperpigmentation

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Abstract

This review article examines evidence supporting the use of oral therapies in treating idiopathic, actinic, and metabolically induced skin hyperpigmentation. A thorough review of the literature regarding oral treatments for hyperpigmentation was systematically conducted through PubMed. Keywords used in the primary search include "Hyperpigmentation," "Melanosis" or "Melasma," "Lightening," "Oral," and "Therapeutics." The search was limited to the English language, and no timeframe restrictions were implemented. Numerous orally administered therapies have been proposed for the treatment of skin hyperpigmentation. There is an abundant body of literature demonstrating the efficacy of orally administered tranexamic acid, glutathione, isotretinoin, and proanthocyanidin. It is reasonable to expect that the most effective oral therapies will address known underlying causes of hyperpigmentation such as thyroid disease, diabetes, and hormonal imbalance. Improvement due to oral therapy of otherwise unresponsive skin hyperpigmentation or hyperpigmentation of unknown cause is less predictable. This review is limited by the strength of evidence contained within the available studies. Clinical studies investigating the treatments discussed within this article are limited in number, at times lack blinding in the study design, and are based on small sample sizes. Based on existing research, the most promising oral remedies for hyperpigmentation appear to be tranexamic acid, glutathione, isotretinoin, and proanthocyanidin. Additional studies to better establish safety and efficacy are necessary.

Keywords

oral, treatment, hyperpigmentation, melasma

Introduction

Hyperpigmentation is a common complaint of dermatology patients, which is caused by excessive production of melanin in the skin. It may be viewed as cosmetically undesirable and has the potential to produce significant psychosocial distress. There are 2 important types of melanin: pheomelanin (yellow-red pigment) and eumelanin (black-brown pigment). The type and concentration of melanin pigment determines skin coloration.

Hyperpigmentation usually occurs secondary to chronic sun exposure due to excess production of both eumelanin and pheomelanin. Other melanin-related causes of hyperpigmentation include systemic disorders like adrenal insufficiency, Addison's disease, Cushing syndrome, and acromegaly.[1] In contrast, non-melanin-related pigmentation disorders may result from medication use or post-inflammatory hyperpigmentation, such as acne, atopic dermatitis, and Riehl's melanosis.[2,3] Common medications associated with hyperpigmentation include minocycline, amiodarone, and hydroxychloroquine.[2] Hormonally driven hyperpigmentation, or melasma, is another notable systemic cause frequently associated with pregnancy.

The degree of hyperpigmentation can be assessed by several tools. Mexameter is used to quantify melanin and hemoglobin (erythema) indices through reflectance. VISIA is another useful software tool that quantitatively evaluates skin discoloration, evenness, and pores. Hyperpigmentation is often described by a melasma area and severity index

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(MASI) or modified MASI (mMASI), a method that removes the homogeneity component of classic MASI, producing a more consistent scoring system.

While most scientific studies have examined the skin lightening effects of topical agents, a growing number have begun to review the benefits of oral therapies in decreasing tyrosinase production and efficacy, regulating inflammatory mediators of hyperpigmentation, and inhibiting keratinocyte uptake of melanin. We examine clinical evidence supporting the use of oral treatments including glutathione, tranexamic acid, isotretinoin, proanthocyanidin, polypodium leucotomos, and glycyrrhizin.

Material and Methods

A thorough review of the literature regarding oral treatments for hyperpigmentation was systematically conducted through PubMed. Keywords used in the primary search include "Hyperpigmentation," "Melanosis" or "Melasma," "Lightening," "Oral," and "Therapeutics." The search was limited to the English language, and no timeframe restrictions were implemented.

Results

Glutathione

Glutathione is an important water-soluble thiol tri-peptide antioxidant synthesized in plants, animals, fungi, and some bacteria from the amino acids glutamate, cysteine, and glycine. Glutathione is thought to work to inhibit melanin synthesis by interrupting the activity of tyrosinase through binding and chelating copper, interfering with the transfer of tyrosinase to premelanosomes, as well as quenching the free radicals and peroxides that contribute to tyrosinase activation.[4] In addition, glutathione increases cysteine levels, which shift melanogenesis from eumelanin to pheomelanin synthesis, thus leading to lightening of the skin.[5,6]

Oral glutathione is in the "generally regarded as safe" category of the Food and Drug Administration and is usually marketed as a food or dietary supplement.[6] In a randomized, double-blinded, placebo-controlled study, the efficacy of orally administered glutathione (500 mg daily for 4 weeks) was investigated in 60 young healthy subjects of Thai descent determined by Mexameter and use of VISIA.[7] The primary outcome was the melanin index determined by Mexameter at 6 sites—bilateral face, bilateral extensor surfaces of forearms, and bilateral upper inner arms. Facial solar lentigines were assessed using VISIA. Those who received oral glutathione demonstrated a statistically significant reduction of melanin indices at all 6 sites compared to baseline as determined by Mexameter. When compared to placebo, the skin-lightening effect of glutathione was statistically significant on the right side of the face and left forearm.[7] With respect to the VISIA analysis, individuals receiving glutathione developed statistically fewer lentigines than the placebo group after baseline adjustment. Overall, oral glutathione dosed at 500 mg daily for 4 weeks significantly reduced the melanin indices and ultraviolet (UV) spots in sun-exposed areas supporting its impact on new melanogenesis.

Weschawalit et al conducted a randomized, double-blinded, placebo-controlled, parallel, 3-arm study to evaluate whether reduced glutathione (GSH) and oxidized glutathione (GSSG) maintained its skin-lightening effect when dosed at 250 mg per day compared to previous studies at dosing of 500 mg daily.[8] While both GSH and GSSG exist physiologically, the effect on melanogenesis between the 2 forms had not been previously investigated. Sixty females were treated with GSH 250 mg daily, GSSG 250 mg daily, or placebo for 12 weeks. Melanin index of all sites for both GSSG and GSH treatment were lower than the placebo group, though the difference was not statistically different. There was no statistical difference with regard to the efficacy of skin lightening between the reduced and oxidized forms of glutathione.[8]

The oral bioavailability of glutathione is controversial.[9,10] To address questions regarding the bioavailability of oral formulations, the skin-lightening efficacy of glutathione was also evaluated using a novel preparation of glutathione containing lozenges in an open-label study performed in 30 Filipino women.[11] This route of administration enables glutathione absorption directly into systemic circulation, thus bypassing the gastrointestinal tract. Subjects were administered dissolvable lozenges, containing 500 mg glutathione, once daily for 8 weeks. At week 8 of the study, 100% of subjects exhibited a statistically significant decrease in melanin index from baseline.[8] No serious adverse side effects were reported in this study, although 1 study participant dropped out due to complaints of soreness in the gums due to the lozenge. There has also been novel research supporting the use of a proliposomal glutathione formulation to enhance both bioavailability and duration of action.[12]

Side effects associated with oral glutathione use include flatulence, pruritus, macular erythema, transient red spots on the skin, and tiredness.[7,8,11]

Tranexamic Acid

Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine and can be used to prevent bleeding by inhibiting activation of plasminogen to plasmin. The skin-whitening effects of tranexamic acid are also attributed to this antiplasmin activity, which depletes the keratinocyte pool of arachidonic acid involved in UV-induced melanogenesis.[5] In addition, TXA has been postulated to reduce erythema through inhibition of angiogenesis and basic fibroblast growth factor induced neovascularization.[13]

Oral TXA therapy alone for melasma. Over the past 5 years, a large and growing body of literature has demonstrated

the efficacy and safety of oral TXA in the treatment of skin hyperpigmentation, particularly in the setting of melasma.[14] Nagaraju et al explored the efficacy and immunohistopathologic features of oral TXA for refractory melasma. This prospective study concluded that TXA has an inhibitory effect on melanin synthesis and melanocyte proliferation in addition to anti-inflammatory qualities exhibited notably through a reduction in the number of mast cells, vascularity, inflammation, and edema within melasma lesions.[13] In a 16 -week, prospective, open-label study of 35 subjects in Beijing, China, receiving oral compound TXA 3 times per day, Li et al observed improvement in VISIA photos in 85% of subjects after 4 weeks, 97% after 8 and 12 weeks, and 100% after 16 weeks.[15] A study conducted in Hangzhou, China, administered 250 mg of TXA twice daily for 6 months to 74 women. Improvement of melasma was assessed independently by 2 physicians every 4 weeks and graded into 1 of 4 levels: excellent, good, fair, and poor. At 6 months, 65% patients demonstrated excellent or good improvement.[16] Lee et al conducted a retrospective study of 561 patients in Singapore, which showed lightening of lesional skin within 2 months in 89.7% of patients after 250 mg TXA twice daily as measured by the Physician Global Assessment scale.[17] A retrospective analysis of case records of 25 Singaporean patients demonstrated a mean reduction of 69% in MASI score after 250 mg TXA twice daily for 3.7 ± 0.33 months.[18] Common side effects observed in these studies included gastrointestinal irritation, such as nausea, abdominal pain, and diarrhea, as well as menstrual irregularities, the most notable being hypomenorrhea.[15-18]

While much of the research regarding the use of oral TXA has been conducted in Asia, a recent randomized, placebo-controlled, double-blinded study conducted at the University of Texas Southwestern investigated the effects of oral TXA on moderate to severe melasma.[19] The study enrolled 44 women, predominantly of Hispanic background, who received 250 mg TXA or placebo twice daily in conjunction with sunscreen for 3 months, followed by an additional 3 months of sunscreen alone. At 3 months, a 49% reduction in mMASI score was demonstrated in the TXA group (n = 22) compared with 18% in the control group (n = 22). Three months after TXA discontinuation, treatment group participants still exhibited a 26% reduction in mMASI score versus 19% in the placebo group. Similar results were observed for the melanin index scores at 3 months, which decreased significantly more from baseline in patients taking TXA than placebo. Subjects with severe melasma demonstrated greater improvement than those with moderate melasma; however, this comparative improvement was not sustained once treatment with TXA was discontinued.[19]

Oral TXA use combined with topical therapeutic regimens for melasma. An open-label, randomized, comparative trial conducted in India evaluated 40 patients treated with either 250 mg of TXA twice daily used in conjunction with triple combination cream containing fluocinolone acetonide 0.01%, tretinoin 0.05%, and hydroquinone 2% applied once daily for 9 weeks, or triple combination cream alone. This study revealed a statistically significant difference in melasma severity index at 4 and 8 weeks favoring TXA used in conjunction with triple combination cream.[20] A case series of 22 women in Seoul, South Korea, demonstrated significant decrease of the mean melanin index score for lesional skin after 8 weeks of a TXA compound tablet dosed 250 mg 3 times a day in conjunction with twice daily application of a 2% TXA and 2% niacinamide topical agent.[21] Shihab et al conducted a randomized, controlled, double-blind study of 50 Indonesian females with moderate or severe melasma which showed participants treated with 500 mg/day TXA and 4% hydroquinone cream had a more significant reduction in mMASI at 3 and 6 months than those treated only with 4% hydroquinone.[22] In a prospective, randomized controlled trial conducted in Nepal, 130 melasma patients were treated with 500 mg TXA daily in conjunction with routine topical hydroquinone and sunscreen for 3 months. When compared with those treated solely with routine topical measures, patients who also received oral TXA demonstrated a significantly lower mean MASI score at both 8 and 12 weeks.[23]

Oral TXA combined with laser therapy for melasma. A randomized, prospective clinical trial involving 48 women aged between 18 and 55 years conducted in Seoul, South Korea showed better results with 750 mg of oral TXA daily for 8 weeks combined with 2 sessions of Q-switched neodymium: yttrium aluminum garnet (QS-Nd:YAG) laser treatment than with laser alone.[24] Furthermore, a retrospective review of 51 healthy Korean women determined that those receiving oral TXA, dosed at 500 mg/day, in addition to intense pulsed light (IPL) and low QS-Nd: YAG laser exhibited a greater reduction in modified MASI score than those treated with IPL and laser alone.[25]

Oral TXA therapy for other hyperpigmentation disorders. Oral TXA has also been explored for the treatment of Riehl's melanosis. In a prospective pilot study, Kwon et al administered 250 mg TXA per day in combination with 4% hydroquinone cream and QS-Nd:YAG laser treatments to 8 patients with recalcitrant Riehl's melanosis. All 8 patients received a grade of "almost clear" or "marked improvement" with significant mean reductions in melanin and erythema indexes.[26] This study supports the therapeutic use of oral TXA for hyperpigmentation disorders beyond melasma, warranting research of more extensive applications of TXA.

Oral TXA—risks of use. The use of TXA to lighten skin is considered off-label by the Food and Drug Administration. The biggest concern with oral TXA use has been its potential to cause thrombosis. While there have been cases of

thrombosis reported following treatment with oral TXA, those individuals affected have generally had relevant comorbidities, such as clotting disorders, history of pulmonary emboli, prolonged immobility, hormone therapy, drug interactions, active bleeding, cancer, and surgery.[14] Available data do not suggest TXA increases thromboembolic risk in otherwise healthy individuals.[26-31] In addition, dosage of TXA for skin hyperpigmentation in studies to date has ranged from 500 mg to 1500 mg daily, with an average dose of 250 mg twice daily.[14] In contrast, labeled dosing for menorrhagia is from 3.9 to 4 g daily for up to 5 days during menstruation.[14] A prospective clinical trial analyzed the therapeutic effect of different oral TXA doses for melasma at 500 mg, 750 mg, 1000 mg, and 1500 mg per day over 2 years with clinical assessment at 4 weeks, 8 weeks, 6 months, 1 year, and 2 years. No significant differences in the MASI, melanin index, or adverse events were determined between the 4 doses.[32]

Common adverse effects include gastrointestinal discomfort such as bloating, nausea, diarrhea, and vomiting, in addition to hypomenorrhea, headache, nasal and sinus discomfort, musculoskeletal pain, and fatigue.[14,17]

Isotretinoin

Isotretinoin is a synthetic vitamin A derivative known for having both immunological and anti-inflammatory effects. Vitamin A is an essential fat-soluble micronutrient involved in vision, immunity, and cell differentiation. The main sources of vitamin A are liver, eggs, and butter.[33] The oral form of isotretinoin has been widely used for treating severe, cystic acne, which is unresponsive to conventional therapy. In recent years, oral isotretinoin has been used in disorders other than acne including its use to improve appearance of hyperpigmentation and photoaged skin. Although the exact mechanism by which isotretinoin improves hyperpigmentation is not known, the effects on photoaged skin are thought to work through several mechanisms including collagen synthesis, increasing dermal vascularization, cell differentiation, and stabilizing extracellular matrix.[34]

To date, most of the literature supporting the use of isotretinoin for treatment of hyperpigmentation consists of case reports for various hyperpigmentation disorders including: prurigo pigmentosa, erythema dyschromicum persistans, post-inflammatory hyperpigmentation from acne vulgaris, malignant acanthosis nigricans, Kyrle's disease, and minocycline-induced hyperpigmentation.[35-40]

A single prospective pilot study evaluated 32 patients with lichen planus pigmentosus (LPP). These patients were treated with low-dose (20 mg/day) oral isotretinoin daily for 6 months and subsequently graded as mild (≤25%), moderate (26% to 50%), or good (>50%) based on the degree of improvement in their hyperpigmentation. Out of the 27 patients that completed the study, treatment outcome was good in 7 patients, moderate in 15, and mild in 2. Three patients had no response to treatment.[41]

Hernandez-Perez conducted a study evaluating cutaneous aging outcomes in patients undergoing surgical rejuvenation procedures who received low dose oral isotretinoin (10, 20 mg three times per week for 2 months) to those undergoing the same rejuvenation procedures who did not receive oral isotretinoin. This study found that those who also used oral isotretinoin noted statistically significant improvement in cutaneous aging, including reduction in pigmented lesions, and mottled hyperpigmentation compared to those who received surgical rejuvenation procedures alone. They reported minimal side effects in their treatment group with less than 10% of patients reporting cheilitis with use of isotretinoin.[42]

Oral isotretinoin is a well-known teratogen and is frequently associated with mild adverse effects including xerosis, cheilitis, transient transaminitis, and dyslipidemia.[41-43] Due to these adverse effects, close patient observation, including clinical evaluation and counseling, routine laboratory monitoring, and strict contraceptive management is recommended.

Proanthocyanidin

Proanthocyanidin is a flavonoid found in a variety of plants including apples, cinnamon, and grapes. Flavonoids are a group of organic compounds thought to provide health benefits through cell signaling pathways and antioxidant effects and are often used to explain some of the health benefits associated with fruit- and vegetable-rich diets. In recent years, it has been shown that flavonoids possess inhibitory effects on tyrosinase. Cocoa beans are thought to contain the highest concentration of proanthocyanidin. This plant metabolite has both antioxidant and anti-inflammatory properties and has recently been posited to play a protective role in alleviating signs of UV damage. Proanthocyanidins from grape seeds have also been found to effectively inhibit UV-induced melanogenesis of human melanocytes in vitro.[44]

In 1 study, proanthocyanidin-rich grape seed extract was orally administered to 12 Japanese women with melasma for 6 months.[45] The study demonstrated improvement of melasma in 10 out of the 12 women with the maximal effect observed at 6 months.

In another study, a significant decrease in pigmentation of solar lentigines was demonstrated following 12 weeks of supplementation with the maritime pine bark extract, Pycnogenol, which contains between 65% to 75% proanthocyanidins.[46]

A randomized, double-blind, placebo-controlled trial assessed the efficacy of oral procyanidin, a member of the proanthocyanidin family, in conjunction with vitamin A, C, and E for the treatment of melasma. Over a course of 8 weeks, 60 Filipino women with bilateral melasma were

twice daily orally administered a supplement containing 24 mg procyanidin, 6 mg β-carotene, 60 mg ascorbic acid, and 15 IU of D-α-tocopherol acetate. The average melanin index, as determined by mexametry, decreased significantly by weeks 4 and 8 in subjects treated with the supplement ($P < .0001$). The supplement was well tolerated with no serious adverse side effects; however, one participant dropped out due to the development of a metallic taste.[47]

Polypodium leucotomos. Another notable flavonoid source is *Polypodium leucotomos* (PLE), a tropical fern that grows in central and South America. The extracts of PLE are thought to offer photoprotective benefits via its antioxidant, chemoprotective, and anti-inflammatory properties. PLE enhances the neutralization of superoxide anions, lipid peroxides, and hydroxyl radicals by endogenous antioxidant systems after UV radiation exposure. These attributes support use of PLE in the treatment of UV-induced hyperpigmentation conditions such as melasma.[48] A study conducted through the Henry Ford Hospital in Michigan investigated the impact of oral PLE on ultraviolet B (UVB) response. Results demonstrated that 24 hours after irradiation by Minimal Erythema Dose (MED), there was a decrease in UVB-induced change in subjects treated with oral PLE (240 mg administered 2 hours and 1 hour prior to MED). This response was evident by clinical assessment, colorimetry, and histology.[49] A randomized trial by Ahmed et al did not show significant improvement in 40 Hispanic women with melasma when comparing oral administration of PLE to placebo.[50]

Glycyrrhizin

Glycyrrhizin is a flavonoid derived from licorice and has a broad range of therapeutic uses. In addition to its anti-inflammatory and antiviral effects, glycyrrhizin has been demonstrated to have protective effects against hydrogen peroxide (H_2O_2) induced cytotoxicity within melanocytes. Glycyrrhizin works by upregulating the nuclear factor E2-related factor 2 (Nrf2), which is integral to the antioxidative stress mechanisms of melanocytes, as well as by inducing the expression of heme oxygenase in macrophages.[51] While this compound has largely been used to treat hepatitis and allergic diseases, use in the treatment of hyperpigmentation disorders has recently been explored.[51] Wang et al explored the treatment of Riehl's melanosis in 3 Chinese patients with a triple combination therapy of 30% salicylic acid chemical peels once every 2 weeks, 150 mg oral glycyrrhizin compound daily, and 100 mg vitamin C daily. All patients demonstrated improvement over the course of 4-6 months, as assessed through VISIA, and experienced no adverse effects.[52] A prospective pilot study in China also assessed the efficacy of oral glycyrrhizin for Riehl's melanosis but in conjunction with oral TXA. Patients ($n = 10$) were treated with 500 mg TXA and 150 mg Glycyrrhizin daily for 3 months, with 3 successive months of treatment with 500 mg TXA alone. All 10 patients exhibited a significant reduction in melanin index at 3 and 6 months, with a further significant reduction at 6 months compared to 3 months, suggesting oral TXA alone is an effective treatment for Riehl's melanosis.[53] At this point in time, studies exploring the role of oral glycyrrhizin in the treatment of hyperpigmentation are limited to combined therapeutic regimens; more extensive studies must be performed before clinical conclusions regarding its use can be made.

Discussion

Numerous orally administered therapies have been proposed for the treatment of skin hyperpigmentation, many of which target the tyrosinase pathway or have direct or indirect anti-inflammatory effects. It is reasonable to expect that the most effective oral therapies will address known underlying causes of hyperpigmentation such as thyroid disease, diabetes, malnutrition, and hormonal imbalance.[1] Improvement of otherwise unresponsive skin hyperpigmentation or hyperpigmentation of unknown cause to oral therapy is less predictable. This review is limited by the strength of evidence contained within the available studies. Clinical studies investigating the treatments discussed within this article are limited in number, at times lack blinding in the study design, and are based on small sample sizes. Based on existing research, the most promising remedies appear to be tranexamic acid, glutathione, isotretinoin, and proanthocyanidin.

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The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Please be aware that one of the contributing authors has a personal blog which contains content similar to this review article. This blog can be accessed at: https://clearifirx.com/blog/oral-therapies-hyperpigmentation.

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