# Optimizing Patient Care With "Natural" Products: Treatment of Hyperpigmentation

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## ABSTRACT

Patients with skin of color suffer from different cutaneous issues when compared with skin of light complexion, and therefore management of the former must be representative of these variations. The most common pigmentary complaints in patients with skin of color are post-inflammatory hyperpigmentation, melasma and sun-induced hyperpigmentation. Often, patients with darker skin will turn to naturally occurring ingredients over synthetic analogues both to satisfy cultural preferences and to limit potential adverse effects that have been tied to synthetics. Science-based natural products can offer an attractive adjunct to conventional therapies that treat melasma, post-inflammatory hyperpigmentaion, and other dyschromias. Increasing data on the biological effects and the efficacy of natural therapies support the use of these complementary therapies in treating hyperpigmentation.

## INTRODUCTION

Patients with skin of medium-to-dark complexion suffer from different cutaneous issues when compared with skin of light complexion, and therefore management of the former must be representative of these variations. There are clearly well-established structural and functional differences between darker and lighter complected skin. Most differences between light and darkly pigmented skin are related to melanosome distribution and packaging.[1] The most common pigmentary complaints in patients with medium-to-dark-colored skin are post-inflammatory hyperpigmentation, melasma and sun-induced hyperpigmentation.[2] Often, patients with darker skin will turn to natural ingredients over chemical products both to satisfy cultural preferences and to limit potential adverse effects that have been tied to synthetics. The purpose of this article is to evaluate natural ingredients with known biological action and potential benefit for patients with medium-to-dark complected skin through a review of the published literature.

### Evaluation of Topical Therapies In Vivo: Open Label and Animal Studies

*Arbutin/ Aleosin*

Arbutin is found in bearberry (*Arctostaphylos uva-ursi*, Sprengel) and certain pear trees. It functions as a glycosylated hydroquinone, and has demonstrated tyrosinase inhibition in vitro.[3] It is currently available in 1-3% formulations, although there are few well-controlled studies available to determine its efficacy.

Aloesin is a glycosylated chromone derived from the Aloe vera plant that similarly inhibits tyrosinase. Aloesin and a few chemically related chromones have been shown to have a stronger inhibitory effect on tyrosinase than do arbutin and kojic acid in vitro.[4]

One clinical study evaluated the combination of aloesin with arbutin in preventing UV-induced tanning on the inner forearm. Vehicle, aloesin alone, arbutin alone or the combination of aloesin and arbutin were administered topically four times a day for up to 15 days and compared. Aloesin suppressed pigment production by 34 %, arbutin by 43% and the combination by 63 %.[5] Unfortunately, peer-reviewed data on these products are limited.

*Fatty Acids*

Alpha linolenic acid, a polyunsaturated omega-3 fat, is found in such sources as soybeans, flaxseed, hempseed, pumpkin seed, ocean-dwelling microalgae and cold-water fish. Linoleic acid, a polyunsaturated omega-6 fat, is naturally found in nuts, seeds and vegetable oils (e.g., safflower and sunflower seed oils). Related fats include: gamma linolenic acid (GLA), found in borage, black currant and evening primrose; dihomogammalinolenic acid (DGLA), found in mother's milk; and arachidonic acid (AA), which is found in meat. Oleic acid, a monounsaturated omega-9 fat, is found in such sources as olive, almond, peanut, pecan, cashew and macadamia nut oils.

In one study, ultraviolet B (UVB)-induced hyperpigmentation in guinea pig skin was evaluated following the application of linoleic acid, alpha-linolenic acid and oleic acid. It was demonstrated that topical linoleic acid is most efficacious.[6] Researchers have since encapsulated the linoleic acids in liposomes to enhance cutaneous penetration. A second study evaluated UV-stimulated hyperpigmentation on both human upper-arm skin and guinea pig skin. Four distinct areas on the human inner upper arm were exposed to UVB radiation five-to seven times a week for two consecutive weeks in order to stimulate significant pigmentation; subsequently, test samples were applied twice daily for two months with the degree of pigmentation assessed once every week. This experi-

ment was repeated on the guinea pig population. In the guinea pig group, application of liposomal linoleic acid application lightened UVB induced pigmentation the greatest. Similar results were witnessed in the human subjects.[7]

## Evaluation of Topical Therapies In Vivo

*Soy*

There has been much research interest in soy's biological mechanism of action. Soy interferes with melanin transfer by inhibiting the protease-activated receptor-2 (PAR2) pathway. PAR2 is a G-protein-coupled receptor that regulates the ingestion of melanosomes by keratinocytes. Both trypsin and UVB cleave peptide chains at the carboxyl side of the amino acids lysine and arginine, allowing for binding of its ligand SLIGRL (serine-leucine-isoleucine-glycine-arginine-leucine), the PAR2-specific activating peptide. Binding results in phagocytosis of melanosomes and ultimately increased melanosome transfer.[8] Soymilk-derived proteins (soybean trypsin inhibitor [STI] and Bowman-Birk inhibitor [BBI]) inhibit PAR2 activation. Specifically, STI and BBI inhibit trypsin and chymotrypsin activities and prevent the peptide cleavage required for PAR2 activation.[9]

One 12-week blinded controlled trial evaluated patients aged 30–61 years with Fitzpatrick skin types 1–3 for photo-aging, mottled hyperpigmentation, lentigines, blotchiness and rough skin. Subjective and objective assessments with colorimetry and photography were recorded before and after application of a soy-containing moisturizer. A significant improvement in mottled pigmentation, blotchiness, dullness, fine lines, overall texture, overall skin tone overall appearance was demonstrated as compared to the vehicle.[10]

*Licorice Extract*

Glabridin, a primary active ingredient in licorice extract derived from *Glycyrrhiza glabra*, is the active agent in many botanicals, one believed to provide anti-inflammatory effects via inhibition of superoxide anion production and cyclooxygenase activity. It has also been shown to have bleaching properties and inhibits UVB-induced hyperpigmentation.[11] In one in vivo study, 0.5% glabridin inhibited UVB-induced pigmentation and erythema in guinea pig skin.[11]

Licochalcone A, derived from *Glycyrrhiza inflata*, is primarily known for its anti-inflammatory properties.[12] Liquiritin extract is a flavonoid in licorice that, along with other components, imparts a natural yellow color. In addition, liquiritin also has clinically established bleaching properties. In a study of 20 women aged 18 to 40 years with a clinical diagnosis of bilateral and symmetrical idiopathic epidermal melasma, liquiritin cream was applied to one side of the face and a vehicle cream on the other side twice daily for 4 weeks. Sixteen of the active-group participants (80%) were rated as exhibiting an "excellent" response, with no discernible differences between the normal skin and previously pigmented areas. In contrast, only 10% of those participants (2 patients) treated with placebo vehicle showed any reduction in pigmentary intensity.[13]

*N-acetylglucosamine*

N-acetylglucosamine is a monosaccharide derivative of glucose found in chitin, the structural biopolymer that forms the outer coverings of insects and crustaceans. N-acetylglucosamine inhibits the conversion of protyrosinase to tyrosinase.[14] In an 8-week, double-blind, placebo-controlled, randomized, split-face clinical trial, 2% N-acetylglucosamine reduced the appearance of facial hyperpigmentation. A combination of 2% N-acetylglucosamine with 4% niacinamide demonstrated even greater improvement.[15]

*Niacinamide*

Niacinamide is the biologically active amide of vitamin B3. Like soy, it inhibits the transfer of melanosomes to keratinocytes. In a clinical study, 3.5% niacinamide/retinyl palmitate demonstrated significantly decreased hyperpigmentation and increased skin lightness compared with vehicle alone after four weeks of use in Asian women, suggesting it has some efficacy in treating hyperpigmentation.[16]

*Vitamin C*

Magnesium-L-ascorbyl-2-phosphate (VC-PMG) is a stable derivative of ascorbic acid. Vitamin C has received considerable attention both for its anti-photoaging effects as well as efficacy in treating hyperpigmentation. In one study, topical VC-PMG used on patients with melasma or solar lentigines demonstrated a significant lightening effect in 19 of 34 participants.[17] However, problems with product stability and cutaneous absorption have limited its use. Although efforts to overcome these impediments have been pursued. For example, in a randomized, double-blind, placebo-controlled study it was shown that, with iontophoresis, penetration can be increased; therefore, significantly decreased pigmentation was seen as compared to placebo.[18]

## Systemic Agents

*Proanthocyanidins*

A French scientist working in Canada, Jacques Masquelier, was the first to identify and characterize these bioflavonoid compounds as 85% OPCs (oligomeric proanthocyanidins), other compounds and water. Masquelier developed a process to extract these compounds from pine bark (in 1951) and from grape seeds (1970). He used the term "pycnogenol" to refer to this whole family of OPCs.

Pycnogenol OPCs contains monomeric phenolic compounds (catechin, epicatechin, and taxifolin) and condensed flavonoids.[19] There is extensive evidence supporting the antioxidant and anti-inflammatory activities of pycnogenol.[20,21] In a clinical study, oral pycnogenol (25 mgTID) demonstrated improvement of hyperpigmentation in an open label 30-day trial including 30 women with melasma.[22]

**TABLE 1.**

| Overview of Natural Topical Therapies to Treat Hyperpigmentation | | | |
|---|---|---|---|
| **In Vitro Studies** | **Animal Studies** | **Open Label Studies** | **Blinded Controlled Trials** |
| Paper mulberry | Linoleic Acid | Arbutin | Soy |
| *Angelica dahurica* | Alpha-linolenic Acid | Aloesin | Liquiritin |
| *Vitex negundo* Linn. | Oleic Acid | Linoleic Acid | N-acetylglucosamine |
| Emblica | | Glabridin | Niacinamide |
| Ellagic acid | | | Vitamin C |
| Helix aspera | | | |
| Gentisic Acid | | | |
| *Morus alba* L. extract | | | |

**TABLE 2.**

| Oral Agents |
|---|
| Pine Tree Bark Extract |
| Grape Seed Extract |
| Polypodium leucotomos |

*Grape seed extract*

As noted above, grape seed and skin contain multiple active components including flavonoids, polyphenols, anthocyanins, proanthocyanidins, procyanidines, and the stilbene derivative, resveratrol. Grape seed extract, in particular, has been reported to possess a broad spectrum of pharmacological and therapeutic effects such as antioxidative, anti-inflammatory and anti-microbial activities.[23] Oral administration of grape seed extract has been shown to reduce UV-induced pigmentation in guinea pig skin.[24]

*Polypodium leucotomos*

Polypodium leucotomos is a type of fern native to the tropical and subtropical regions of the Americas and has a long history of use as a folk remedy. It functions as an antioxidant has been shown to provide systemic photoprotection. It was clinically shown to significantly decrease UV-induced erythema and generation of cyclobutane pyrimidine dimers.[25]

## DISCUSSION

Treating hyperpigmentation is a challenge in patients with moderate-to-dark-complected skin. Natural products offer an attractive adjunct to conventional therapies that treat melasma, post-inflammatory hyperpigmentaion and other dyschromias. These naturally derived and formulated products may be used in combination, or for maintenance once improvement has been achieved. Similarly, oral photoprotectants are useful adjuncts in treating hyperpigmentation. Increasing data on the biological effects and the efficacy of natural therapies support the use of these complementary therapies in treating hyperpigmentation.

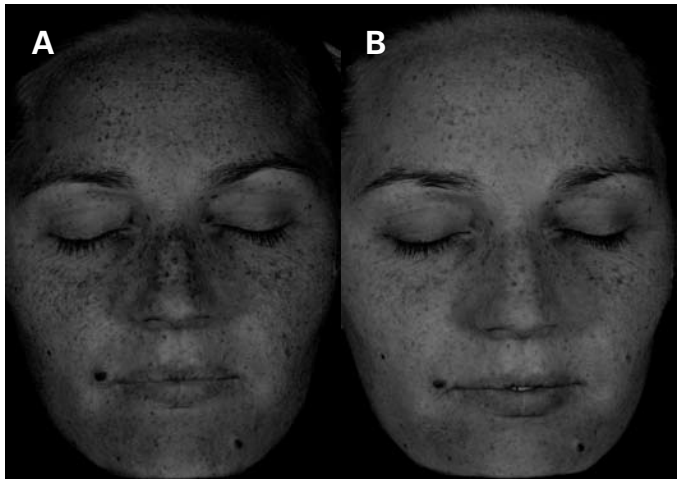


**FIGURE 1a-1b. 1a)** Baseline before treatment. **1b)** After 12 weeks of Total Soy with sunscreen

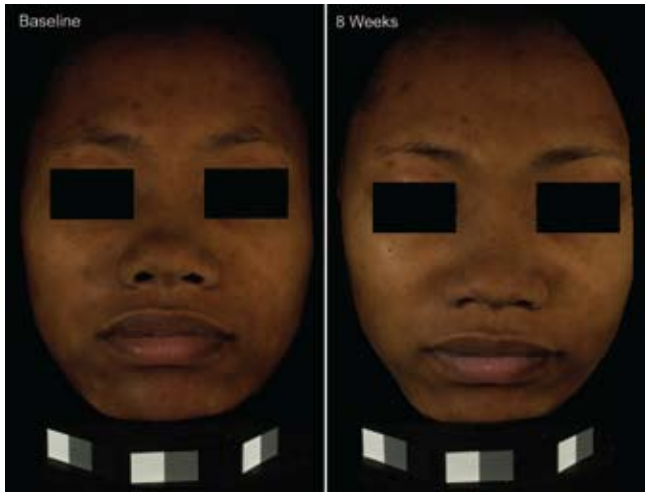


**FIGURE 2.** Cross polarized images. Subject shows reduction in pigmentation intensity and improvement of skin tone after 8 weeks of Total Soy with sunscreen

## DISCLOSURES

Dr. Woolery-Lloyd has served as an advisory board member for Johnson and Johnson and Galderma. She has served on the speaker's bureau for Stiefel and Johnson and Johnson. She has also served as an investigator for Dermik, Galderma, Medicis, Allergan, and Johnson and Johnson.

Dr. Friedman has no relevant disclosures.

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