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The Role of Natural Products in Skincare

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The Role of "Natural" Products in Skincare

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Statement of Need

Natural ingredients* have long been a part of over-the-counter treatment of cutaneous conditions, from dry skin, to inflammation, to signs of aging. The popularity of natural, over-the-counter treatments has increased as clinical trials and other research has recently become available and as patients are increasingly more receptive to healthy, natural skin care options. As a result, dermatologists and dermatology residents are required to be well-informed regarding natural, over-the-counter products and options for their patients. This includes identifying available products, and understanding natural ingredient composition, as well as the benefits and side-effects of product use.

The goal of the supplement to the *JDD* is to disseminate key scientific information to the dermatologic community in a timely manner. In particular, the supplement aims to disseminate the proceedings from a "Natural Products in Skincare" symposium at ODAC 2009.

Educational Objectives

After attending this symposium, dermatologists and dermatology residents will be able to:

- Distinguish the various natural, over-the-counter product elements and their uses
- Differentiate between the multiple natural, over-the-counter products available and their particular uses and qualities
- Illustrate the appropriate uses of natural, over-the-counter products for patients with various skin considerations, such as sensitive skin
- Relate the results of current clinical studies of natural over-the-counter product elements to clinical recommendations
- Predict and communicate the effects of natural, over-the-counter products based on clinical trials and other research

Target Audience

This CME enduring material has been designed to meet the educational needs of Dermatology Physicians and Dermatology Residents.

Accreditation Statement

This activity has been planned and implemented in accordance with the essential areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Core Medical Publishing and the *Journal of Drugs in Dermatology*. Core Medical Publishing is accredited by the ACCME to provide Continuing Medical Education (CME) for physicians.

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DISCLOSURES

Any real or apparent conflicts of interest have been addressed through a peer-review process, as required by ACCME.

Dr. Baumann has served as an advisory board member for Stiefel, Philosophy, Vichy, Proctor and Gamble, Borba, Topix and Medicis. She has served on the speaker's bureau for La Roche Posay. She has also served as an investigator for Dermik, Galderma, Medicis, Allergan, Johnson and Johnson, Unilever, Dermworx and Avon.

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.

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**Natural ingredients are operationally defined as naturally occurring compounds that closely resemble those found in nature.*

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Introduction

The use of "natural" products in cosmetic dermatology has grown in recent years. Both patients and physicians increasingly seek alternatives to treat various conditions, including photoaging and dyschromias. The approach to treating photoaging frequently involves the use of a comprehensive skin care regimen to address the various manifestations of photoaging. Natural therapies that improve hydration, reduce unwanted pigmentation, reduce inflammation and minimize oxidative stress are most beneficial and are frequently used in skin care designed to treat photoaging. This supplement aims to review these agents and provide the data to support these effects in the skin.

In addition to the treatment of photoaging, novel therapies to treat hyperpigmentation have garnered significant interest. This trend stems from recent concerns with hydroquinone. Although hydroquinone remains the gold standard in the treatment of hyperpigmentation, this therapy has several unwanted side effects, including irritation and the rare but significant risk of ochronosis with long term use. For these reasons, natural agents are increasingly being investigated as alternative therapies. The aim in treating hyperpigmentation with natural products is to identify agents that match the clinical efficacy of hydroquinone without the associated side effects and limitations on use. This remains a challenging task, but various therapies have demonstrated remarkable efficacy in both open label and well controlled clinical trials.

Overall, scientific data to support the use of natural products continues to grow. As the trend towards natural and organic products increases so will the need for a greater understanding of the mechanisms and efficacy of these types of therapies. This supplement aims to provide an overview of the natural products that are frequently utilized in cosmetic dermatology. The review will cover the origins of these natural agents in addition to scientific data that support their use in cosmetic dermatology.

Heather Woolery-Lloyd

"Natural" Ingredients in Cosmetic Dermatology

Leslie Baumann MD, Heather Woolery-Lloyd MD, Adam Friedman MD[b]
[a]Cosmetic Medicine and Research Institute, University of Miami School of Medicine, Miami Beach, FL
[b]Division of Dermatology, Albert Einstein College of Medicine, New York, NY

ABSTRACT

Recently, both clinical and bench research has begun to provide scientific validation for the use of certain botanical ingredients. Related findings regarding proposed biological mechanisms of action have translated into clinical practice. Botanical compounds for which dermatologic and cosmetic applications have emerged include: olive oil, chamomile, colloidal oatmeal, oat kernal extract, feverfew, acai berry, coffee berry, curcumin, green tea, pomegranate, licorice, paper mulberry, arbutin, and soy. Many of these botanical sources offer biologically active components that require further in vitro and in vivo investigation in order for us to properly educate ourselves, and our patients, regarding over-the-counter products based on these ingredients.

INTRODUCTION

As the lay public increasingly embraces complementary and alternative medicine, so too has the use of herbal therapies in cosmetic dermatology been welcomed in the United States (U.S.). Botanicals with longstanding and historical uses in traditional or folk medicine are especially popular in our modern armamentarium of over-the-counter (OTC) cosmetic products. Recently, both clinical and bench research has begun to provide scientific validation of these herbal ingredients and investigations into the biological mechanisms of action have translated into a variety of clinical applications.

Hydrating Ingredients

Olive Oil

Ancient Greek mythology attributes the therapeutic potential of the olive tree *Olea europaea* L. to the goddess of wisdom, Athena, who is said to have planted the very first tree at the Acropolis and imbued the tree with the powers of light, healing and nourishment. Today, olive leaf extract is incorporated into a number of lotions and moisturizers to combat skin damage caused by ultraviolet (UV) radiation and to assist in wound healing. Olive leaf is used in topical preparations to stimulate blood flow, in much the same way that capsicum (a pepper extract) is used. Capsicum, however, directly stimulates the nerve endings in the skin, while olive leaf extract acts directly on the muscle, increasing perfusion to relieve muscular aches and pains. Conversely, the polyphenolic oleuropein contained in the extract vasoconstricts superficial veins in the skin, helping to promote a smooth and clear complexion.[1] The oleanolic acid and flavonoids in the extract are believed to stimulate certain components in the cutaneous connective tissue, promoting regular growth and balance and, thereby, improving skin health.

Anti-inflammatory Ingredients

Chamomile

German chamomile, one of the 12 most commonly used medicinal herbs, has been recognized for its therapeutic and soothing properties since the age of Hippocrates. Chamomile is included in skin formulations as an emollient and to provide anti-inflammatory action for sensitive skin.[2] Since it is part of the ragweed family, and therefore could cause allergic contact dermatitis, it should be used with caution.

Colloidal Oatmeal

Oatmeal was used for skin health and beauty as early as 2000 B.C. in Arabia (today comprising Yemen, Oman, Saudi Arabia and Jordan) and Egypt to soothe and protect dry, itchy, inflamed skin. Colloidal oatmeal has a high polysaccharide content and forms a gelatinous hydrocolloid in water, which leaves a protective film on the skin that physically retards water loss. Additionally, this film helps to repair and maintain the epidermal barrier.[3] The oat lipids add to oatmeal's moisturizing, barrier-enhancing properties, and oat proteins have the ability to buffer both acids and bases that aid in barrier maintenance and repair. Furthermore, oatmeal saponins help to solubilize dirt, oil and sebaceous secretions.

Colloidal oatmeal is one of few natural ingredients cited as possessing efficacy by the U.S. Food and Drug Admininstration (FDA) in the *Skin Protectant Drug Products for Over-the-Counter Use* monograph (21 CFR Part 347). It is labeled to provide skin relief and protection for insect bites, rashes caused by poison ivy and similar plants, and eczema. A variety of colloidal oatmeal bath products for both the geriatric and pediatric populations have been commercially available for several decades,[4] including oatmeal soap, body washes and now oat-containing moisturizers, which are increasingly popular for dry and inflamed skin.

Avenanthramide Extract

Avenanthramides are the main polyphenolic antioxidants in oat grains (*Avena sativa*). They are shown to offer antierythrogenic and anti-inflammatory effects with oral administration.[5] Recently, a formulation containing a proprietary standardized avenanthramide fraction isolated from oats has been introduced for

inclusion into topical products. It is referred to as Avena Sativa Kernel Extract and is intended to enhance the overall benefits of colloidal oats.[6]

Feverfew

Feverfew (*Chrysanthemum parthenium)* is a flowering plant from the daisy family whose leaves have been used medicinally for thousands of years. Its namesake is derived from its traditional use as a fever reducer. The efficacy of oral feverfew in treating migraine was attributed to parthenolides, a group of compounds believed to beneficially modulate serotonin while, at the same time, known as skin irritants. Therefore, research has been conducted to purify feverfew by removing parthenolides while preserving its antioxidant and anti-irritant properties. Feverfew PFE™ is a non-steroidal anti-inflammatory that inhibits numerous inflammatory pathways associated with cutaneous irritation. It has exhibited an ability to inhibit activated macrophage pro-inflammatory cytokine release, neutrophil chemotaxis, keratinocyte expression of inflammatory adhesion molecules as well as IL-8 release, and NF-κB, a transcription factor implicated in UVR-induced photodamage.[7,8]

Antioxidants/Anti-aging

Acai Berry

The Brazilian acai (açaí) berry is considered to be nutrient-dense. With the symmetry of a grape and the size of a giant blueberry, the acai fruit tastes a bit like wild raspberry with a hint of grape. Acai berries grow on the Amazon Heart of Palm tree and have been prized for hundreds of years by indigenous Brazilian people for its health properties. Its pulp is used in wines, liqueurs, flavorings, colorants and on its own as a juice. Acai berries are high in essential fatty acids: 60% oleic acid (omega-9) and 12% linoleic acid (omega- 6). Acai also contains phytosterols.[9]

Specifically, the acai berry is a dense source of a particular class of flavonoids called anthocyanins. Acai berry's oxygen radical absorbance capacity (ORAC) antioxidant value is said to be higher than that of other edible berries. Acai is currently being tested not only for its health properties, but also as a radiocontrast agent for nuclear magnetic resonance imaging (MRI) of the gastrointestinal tract.[10] Unfortunately, topical products only contain a modest amount of acai, secondary to the risk of staining with high concentration.

Coffee Berry

The coffee plant (*Coffea arabica)* is cultivated worldwide and is, of course, the source of the eponymous, universally popular beverage. *C. arabica* originates from Ethiopia and is thought to have been introduced into Arabia before the 1400s, into Java before 1700, and into the West Indies and the Americas in the 1700s. Coffee berry is the unripe stage of the coffee bean that is eventually roasted for consumption. In proprietary research, coffee berry extract demonstrated 10 to 15 times the antioxidant capacity as green tea by ORAC measurement.[11,12] Its major polyphenolic components include: chlorogenic acid, quinic acid, ferulic acid and condensed proanthocyanidins.[13]

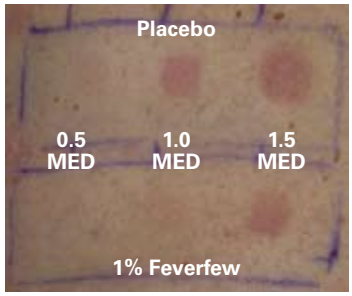

FIGURE 1. Topically applied feverfew reduces UV-induced erythema

Curcumin/Tumeric

Turmeric (*Curcuma longa*, Zingiberaceae) is best known as a spice used predominantly in Asian cuisine. Turmeric has long been used as an anti-inflammatory agent in Traditional Chinese Medicine (TCM) and Ayurvedic medicine,[14] specifically, in Ayurvedic medicine to treat sprains and edema due to injury.

Curcumin (diferuloylmethane), the key biologically-active component of turmeric, has shown potency against acute inflammation,[14] and has exhibited wound-healing, anti-carcinogenic, anti-inflammatory and antioxidative properties.[15] Its anti-carcinogenic characteristics are particularly well-documented, as are its previously noted antioxidative and anti-lipid peroxidation activity.[15] Antibacterial, antiparasitic and anti-HIV (Human Immunodeficiency Virus) activity have also reportedly exhibited by turmeric or curcumin.

In various animal models, topical application of curcumin has been shown to inhibit initiation and promotion of tumorigenesis.[16] In addition, very low doses of topically applied curcumin have been found to mediate 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced oxidation of DNA bases in the epidermis and tumor promotion in the skin. Pretreatment with curcumin has exhibited the same inhibitory effects on TPA-mediated dermatitis. Finally, topical curcumin is considered one of the only safe therapies for radiation exposure, and it is believed to possess great potential as a therapeutic agent for wound repair, specifically in reducing healing delays caused by radiation.[17] Cosmetics containing curcumin are available globally, particularly in India.

Green Tea

Green tea is a well-established herbal preparation that is believed to enhance immunity. It exhibits antibacterial, antiviral and anti-carcinogenic properties, and the Chinese have used this natural antioxidant for centuries. Green tea is produced via the steaming and drying of the fresh leaves of the tea plant *Cammelia sinensis*—a process that preserves its polyphenolic components.

Green tea contains a variety of polyphenols that have been shown to confer significant photoprotection in addition to serving as antioxidants. The most studied of these are (-)-epigallocatechin-3-gallate (ECGC) and (-)-epicatechin-3-gallate (ECG). First, ECGC inhibits the generation of intracellular hydrogen peroxide, one of the most active DNA-damaging reactive oxygen species. In addition, ECGC inhibits the formation of cyclobutane pyrimidine dimers, a known source of UVR-induced DNA damage.[18] Knowing that inflammation and oxidative stress play a considerable role in the aging process, green tea may, therefore, reveal anti-aging properties through its ability to limit inflammation and scavenge free radicals.

Pomegranate

The pomegranate (*Punica granatum* L.) is native from Iran to the Himalayas in northern India and has been grown and eaten throughout the Mediterranean region since ancient times. Pomegranate extract is primarily composed of alkaloids and polyphenols, the active constituent being ellagic acid. Ellagic acid is a naturally occurring phenolic compound found in many fruits and nuts. Pomegranate extract, in particular, has demonstrated a variety of beneficial functions including antioxidative and anti-viral activity. Pomegranate juice is believed to be confer more potent antioxidative benefits than comparable quantities of green tea and red wine. In addition, pomegranate peel fractions may foster dermal regeneration and pomegranate seed oil fractions may facilitate epidermal regeneration.[19]

Pomegranate also acts as a photochemoprotective agent, enhancing the sun protection factor (SPF) rating of topical sunscreens through its antioxidant properties. In several independent studies, SPF measurements increased up to 25% after the ingestion of one pomegranate tablet containing 5% ellagic acid. The biological mechanism has been further elucidated in vitro. Pomegranate fruit extract treatment of normal human epidermal keratinocytes inhibits UVA-mediated activation of signal transducers and activators of transcription 3 (STAT3), AKT and extracellular signal-regulated kinase (ERK1/2), thereby ameliorating UVA-mediated damage by modulating these cellular pathways.[20]

Depigmenting Ingredients

Licorice

Licochalcone is a major component derived from the root of Xinjiang (or Chinese) licorice, or *Glycyrrhiza inflata* (*G. inflata*), and is considered a natural, soothing extract. The primary active ingredient isolated and extracted from Chinese licorice root is, specifically, licochalcone A, an oxygenated or reverse-constructed chalcone or "retrochalcone." It has exhibited antiparasitic and antibacterial activity,[21] as well as antitumorigenic activity,[21] and has also been incorporated into a formulation intended to treat rosacea.

In addition, extract of licorice, or *Glycyrrhiza glabra* (*G. glabra*), has been used to treat inflammatory skin disease, such as eczema. *G. glabra* has demonstrated antimutagenic, anticarcinogenic and tumor-suppressive capacity against skin cancer in animal models, and the National Cancer Institute (NCI) has formally recognized the chemopreventive value of its primary constituent glycyrrhizin.[22] Liquiritin, derived from *G. glabra*, has shown efficacy in the treatment of melasma. In Europe, licorice extract is widely used as an anti-inflammatory agent.

Paper Mulberry

Paper mulberry (*Broussonetia papyrifera* L.) is a deciduous tree with milky sap that grows to a maximum height of about 45 feet, the bark of which is composed of very strong fibers that are also used for making high-quality paper and cloth. Biochemically and medicinally, extracts of the paper mulberry root are potent inhibitors of tyrosinase. The active constituents present in the extract are prenylated, polyhydroxylated mono-and bis-phenylderivatives. A 0.4% concentration of paper mulberry

TABLE 1.

Overview of Various Natural Ingredients in Cosmetic Dermatology

Hydrating Agents	Anti-inflammatory Agents	Antioxidants	Depigmenting Agents
Olive Oil	Chamomile	Acai Berry	Licorice
Colloidal Oatmeal	Colloidal Oatmeal	Coffee Berry	Paper Mulberry
	Avenanthramide Extract	Circumin/Tumeric	Arbutin
	Feverfew	Green Tea	Soy
		Pomegranate	Aloesin
		Feverfew	Linoleic Acid
			N-acetylglucosamone
			Niacinamide
			Vitamin C

extract inhibits tyrosinase by 50% compared to 5.5% for hydroquinone and 10.0% for kojic acid. Even at a concentration of 1%, paper mulberry extract is not a significant irritant.[23]

Arbutin

Arbutin, a naturally occurring D-glucopyranoside derivative of hydroquinone, is found in the dried leaves of certain plant species, such as bearberry (*Arctostaphylos uva-ursi*). The proposed mechanism of action is through inhibition of melanosomal tyrosinase and DHICA (5,6-dihydroxyindole-2-carboxylic acid) polymerase activities—its impact is believed to be through non-cytotoxic effects means rather than via suppression of synthesis and expression of tryosinase that are seen with paper mulberry.[24]

It is thought that the activity of arbutin is driven by the structural homologies that it shares with the substrate tyrosine, and therefore leads to the competitive inhibition of the catalytic function of tyrosinase. Investigations have revealed that alpha arbutin (4-hydroxyphenyl-α-glucopyranoside) demonstrates an even stronger inhibitory effect on human tyrosinase activity than arbutin itself.[25] Alpha arbutin has widely replaced arbutin as the chosen skin-lightening agent in topical skin preparations because it is commonly believed to be more effective and stable in producing the desired effects on human skin.

Soy

Soy (*Glycine max* L.) has been used in traditional Chinese medicine for thousands of years for its health and nutritional benefits, including treatment and care of the skin. Total Soy (a proprietary composition) contains a broad spectrum of non-denatured active components that are believed to convey certain skincare benefits. Soy contains more than 15% unsaturated fatty acids, more than two thirds of which are essential fatty acids that help provide anti-inflammatory benefits. Phytosterols help restore barrier function and replenish moisture. Vitamin E is a natural component of soy with antioxidant properties, which helps to protect the skin from environmental stresses such as free radicals. Natural soy surfactants provide a gentle cleansing action. Therefore, topical use of soy has offered a broad spectrum of therapeutic potential, including treating hyperpigmentation, enhancing skin elasticity, delaying hair regrowth, controlling oil production and moisturizing the skin. Soy is even thought to have the potential to decrease photoaging and prevent skin cancers through the estrogen-type and antioxidant effects of its metabolites.

Small proteins such as soybean trypsin inhibitor (STI) and Bowman-Birk inhibitor (BBI) act to inhibit skin pigmentation, while large proteins have been found to smooth and soften the skin. STI, BBI, and soy milk have been shown to not only exhibit depigmenting activity but also prevent UV-induced pigmentation in vitro and in vivo; specifically, STI and BBI influence melanosome transfer and, thus, pigmentation.[26]

The primary metabolites of soy are isoflavones, genistein and diadzein, and have been identified in various studies in animal and human cell cultures as phytoestrogens, which are plant compounds with a weak estrogenic effect.

Several studies have shown that postmenopausal women have a measurably thinner dermis and less collagen as compared to premenopausal women. Topical estrogen has been demonstrated to retard the skin thinning and collagen loss seen in postmenopausal patients not on hormone replacement therapy, likely because estrogen receptor levels are highest in the granular layer of the skin. Therefore, the phytoestrogens genistein and diadzein have the potential to confer beneficial cutaneous effects, though this has not yet been conclusively established.

Neverless, genistein has been shown to significantly inhibit chemical carcinogen-induced reactive oxygen species, oxidative DNA damage and proto-oncogene expression. Genistein also inhibits the initiation and promotion of skin carcinogenesis in mouse skin, and UVB-induced erythema in human skin.[27] Patients at high risk for, or with a history of, estrogen-sensitive tumors—such as breast or uterine cancer—should avoid excessive consumption of soy.

In a 12-week, double-blind, randomized clinical study that was conducted to evaluate the properties of skin firmness using Total Soy compared with a composition of retinol/ascorbic acid, the former stimulated in vitro collagen synthesis and in vivo elastin repair, thereby clinically improving skin firmness and reducing facial skin laxity.[28] In an 8-week study conducted to evaluate the overall effectiveness of applying a preparation of the proprietary composition and a skin conditioner/moisturizer twice daily, shaving twice-weekly, in reducing the appearance of unwanted leg hair, the proprietary formulation was found to improve the appearance of unwanted leg hair by week 4.[29]

CONCLUSION

There are multiple natural ingredients with antioxidant, anti-inflammatory, and depigmenting properties that are commercially available and easily attainable. Many of these agents have biologically active components which require further in vitro and in vivo investigation in order to properly educate ourselves, and our patients, regarding these over-the-counter products.

DISCLOSURES

Dr. Baumann has served as an advisory board member for Stiefel, Philosophy, Vichy, Proctor and Gamble, Borba, Topix and Medicis. She has served on the speaker's bureau for La Roche Posay. She has also served as an investigator for Dermik, Galderma, Medicis, Allergan, Johnson and Johnson, Unilever, Dermworx and Avon.

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ADDRESS FOR CORRESPONDENCE

Leslie Baumann, MD
Director — University of Miami, Cosmetic Medicine and Research Institute
Professor of Dermatology
4701 Meridian Avenue, Miami Heart Institute 7450
Miami Beach, FL 33139
Telephone: ..... (305) 532-5552
E-mail: ..... LBaumann@med.miami.edu

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

Heather Woolery-Lloyd MD[a] and Adam Friedman MD[b]

a. Director of Ethnic Skin Care, Miller/University of Miami School of Medicine, University of Miami Cosmetic Medicine and Research Institute
b. Division of Dermatology, Albert Einstein College of Medicine

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.

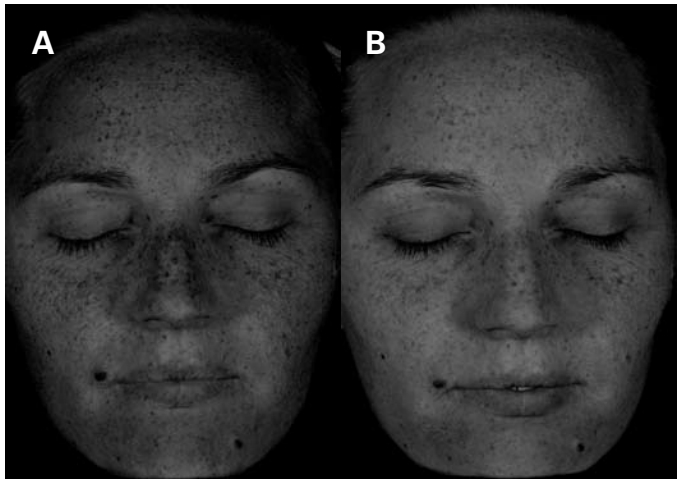

FIGURE 1a-1b. 1a) Baseline before treatment. **1b)** After 12 weeks of Total Soy with sunscreen

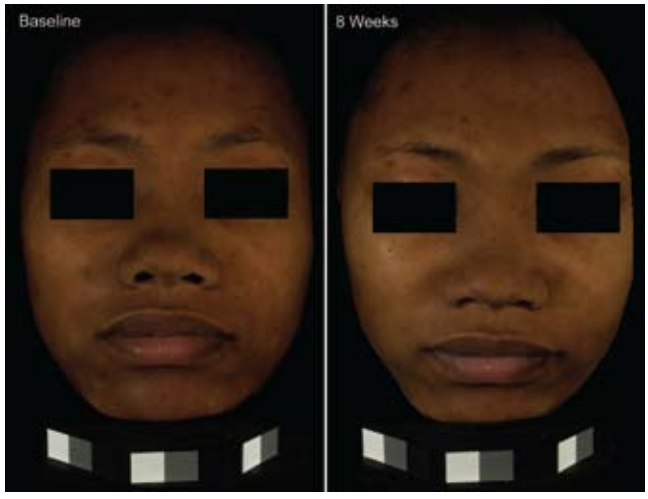

FIGURE 2. Cross polarized images. Subject shows reduction in pigmentation intensity and improvement of skin tone after 8 weeks of Total Soy with sunscreen

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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ADDRESS FOR CORRESPONDENCE

Heather Woolery-Lloyd, MD
Cosmetic Medicine and Research Institute
4701 North Meridian Avenue
Suite 7450
Miami Beach, FL 33140
E-mail:.....wooleryllloyd@yahoo.com

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1. Which of the following must be avoided in patients with known histories of ragweed allergy?
   a. Soy
   b. Feverfew
   c. Camomille
   d. Curcumin
   e. None of the above

2. Extracts from which of the following has the highest Oxygen Radical Absorbance Capacity (ORAC)?
   a. Green tea
   b. Coffee berry
   c. Acai berry
   d. Pomegranate
   e. None of the above

3. Which of the following are phytoestrogens found in soy?
   a. Soybean trypsin inhibitor (STI)
   b. Bowman-Birk inhibitor (BBI)
   c. Vitamin E
   d. Genistein
   e. All of the above

4. Which of the following naturally occurring ingredients is cited to be effective by the FDA in the OTC Skin Protectant Monograph?
   a. Arbutin
   b. Tumeric
   c. Oatmeal
   d. Paper mulberry
   e. Coffee berry

5. Which of the following active ingredients has demonstrated sunblock SPF enhancement potential?
   a. Prenylated, polyhydroxylated mono-and bis-phenylderivatives
   b. Bowman-Birk inhibitor
   c. Licochalcone A
   d. Ellagic acid
   e. All of the above

6. The PAR-2 pathway influences pigmentation via:
   a. Inhibition of tyrosinase
   b. Inhibition of protyrosinase
   c. Regulation of melanosome transfer
   d. Antioxidant activity
   e. All of the above

7. Which of the following acts via direct tyrosinase inhibition?
   a. N-acetylglucosamine
   b. Aloesin
   c. Niacinamide
   d. Soy
   e. All of the above

8. The limitations of topical VC-PMG delivery have been overcome via:
   a. Liposomal encapsulation
   b. Oil based delivery vehicle
   c. Iontophoresis
   d. Intravenous infusion
   e. None of the above

9. Which of the following active ingredients in soy directly inhibits PAR2 activation?
   a. Soymilk-derived proteins
   b. Phytoestrogens
   c. Glabridin
   d. SLIGRL
   e. None of the above

10. Which of the following is best known for its systemic photochemoprotective properties?
    a. N-Acetylgucosamine
    b. Arbutin
    c. Polypodium leucotomos
    d. Soy
    e. Aloesin

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