

“Natural” Ingredients in Cosmetic Dermatology

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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 kernel 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 Administration (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

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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 (açai) 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 antioxi-

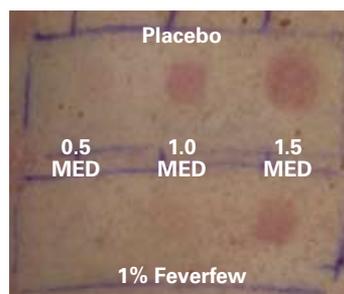


FIGURE 1. Topically applied feverfew reduces UV-induced erythema

dant capacity as green tea by ORAC measurement.^{11,12} Its major polyphenolic components include: chlorogenic acid, quinic acid, ferulic acid and condensed proanthocyanidins.¹³

Curcumin/Turmeric

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.

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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 (EGCG) 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 anti-parasitic and antibacterial activity,²¹ as well as antitumorogenic 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-phenyl derivatives. 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-acetylglucosamine |
| | | | 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 tyrosinase 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.

Nevertheless, 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.

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, Medici, Allergan, and Johnson and Johnson.

Dr. Friedman has no relevant disclosures.

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