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Identifying Natural Ingredients & Their Use in Skin Care

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ORIGINAL ARTICLES

IDENTIFYING NATURAL INGREDIENTS & THEIR USE IN SKIN CARE

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Statement of Need

The dermatologic application of natural ingredients in skin care has evolved significantly in the past two decades. Research into the mechanisms and biochemistry of natural ingredients has led to the development of new technologies and formulations that provide a therapeutic benefit in the treatment of dermatologic conditions and the aging process.

Providing optimal patient outcomes continues to be a challenge in the treatment and management of dermatologic conditions. Most physicians and patients are interested in doing everything possible to optimize the treatment of their skin disease. This is especially important in treating patients with chronic disorders such as eczema, acne, psoriasis, rosacea, photodamage and the negative effects of aging. Physicians and patients often explore the therapeutic benefits of natural ingredients as alternative or complementary treatments to conventional methods. It is important that dermatologists remain up-to-date on the research and new advances in skin care products with natural ingredients.

Educational Objectives

At the conclusion of this CME activity, attendees will be able to:

- Identify the active natural ingredients and their clinical uses in disorders of the skin.
- List key properties of natural ingredients and their relative usage in eczema, photo-aging and dermatologic conditions.
- Select potential treatment regimens for products with natural ingredients alone or in conjunction with conventional therapies.
- Recall the safety, tolerability and efficacy of natural ingredients.

Target Audience

This activity is developed for dermatologists and residents in dermatology who have an interest in the use of natural ingredients and their applications in skin care.

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 the National Association for Continuing Education and the *Journal of Drugs in Dermatology*. The National Association for Continuing Education is accredited by the ACCME to provide Continuing Medical Education (CME) for physicians.

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Dr. Baumann serves as an investigator for Johnson & Johnson Consumer Companies, L'Oreal, Avon and Innovative Skin Care; she has also served as a speaker for Johnson and Johnson Consumer Companies.

Dr. Dohil has served as a speaker for Johnson & Johnson Consumer Companies and Hill Pharmaceuticals. Her husband has served as a consultant for Raptor Pharma.

Dr. Sundaram is a consultant to Johnson & Johnson Consumer Companies, Inc., and a consultant and investigator for SkinMedica, Biopelle and Syneron/Candela.

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Atopic Dermatitis and Other Inflammatory Skin Disease – Natural Ingredients for Skin Care and Treatment

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INTRODUCTION

Atopic dermatitis (AD) presents a daily challenge for almost one in five children and their families in the US. Our understanding of the pathophysiology of AD has continuously improved over the past decade and treatment options have similarly evolved. The disease represents a complex interplay of genetic, immunologic, metabolic, infectious and environmental factors. Three of the main issues that have been identified as causative include a genetically determined skin barrier defect due to mutations in the structural epidermal protein fillagrin, a TH1/Th2 imbalance of the immune system and a lack of defensins as major players of our innate immunity. Corresponding to these pathophysiologic mechanisms, treatment is aimed at restoration of the skin barrier, anti-inflammatory response to rebalance the immune system and prevention and control of cutaneous infection.

While topical corticosteroids are the mainstay of anti-inflammatory treatment and their judicious use has been shown to be both efficacious and safe, their continuous sometimes daily use over months raises concerns particularly in the pediatric age group. Often caregivers tend to undertreat due to widespread fear of side effects of topical steroids, not infrequently to the degree of steroid-phobia. Topical calcineurin inhibitors offer a second line treatment approach, but are not currently approved by the U.S. Food and Drug Administration (FDA) for children under two years of age and thus their use raises concerns in parents to whom the black box warning is communicated.

The search for alternative options and a renewed focus on the importance of restoring the epidermal skin barrier, has expanded the choice of over-the-counter (OTC) products and prescription FDA 501(K)-cleared barrier creams available for the adjunct treatment of atopic dermatitis. This has also led to renewed interest in trusted "home remedies" containing naturals such as oatmeal, chamomile, feverfew, licorice, aloe vera and dexapanthenol, long considered safe and effective for various skin conditions.[1] The properties of some of these products have been shown to reach well beyond their moisturizing effects.

These natural agents are increasingly used in modern dermatology for their anti-inflammatory, anti-pruritic, skin protectant and skin moisturizing properties. An increasing number of studies attest to their efficacy and safety in the clinical setting and, most excitingly, scientists have been able to unravel their underlying pharmacologic mechanisms. This provides clinicians with the tools to apply these agents in various clinical settings in an evidence based treatment approach. These natural ingredients are labeled as such since they consist of extracts directly derived from plants or animal products, however, unlike some products marketed as "organic," their constituents have been dermatologically tested for pharmaceutical-grade purity, efficacy and safety demanded from modern medicine.

Colloidal Oatmeal

Derived from the common or wild oat (*Avena sativa*), oatmeal has a long history of traditional folk use dating back to 2000 B.C. in Egypt and the Arabian peninsula. Oats have been used internally and externally for various conditions, most prominently skin ailments. Oatmeal baths were popular as recently as the 19th century for pruritic and irritant dermatoses. Colloidal oatmeal stands out among the natural products since it has even been officially recognized by the FDA for its anti-pruritic and skin soothing properties in the context of eczema and contact allergy. It stems from dehulled oat kernels that are ground into a very fine powder which is readily dispersible in water. Most of the constituents of the powder are smaller than 75 microns in particle size, allowing for superior dispersion and permitting its formulation as topical skin care and bath products. Colloidal oatmeal consists of various oat fractions including 2-11 percent of lipids, up to 64 percent of sugars and amino acids, vitamins, saponins, flavonoids, prostaglandin inhibitors , ash and just a very small fraction of 0.06 percent of avenanthramides.[2-4]

Avenathramides, a newly discovered oat fraction, are the principle polyphenolic antioxidants in oats and have been shown to exert their anti-inflammatory properties[5-9] via activation of NF-kB and inhibition of pro-inflammatory cytokines in keratinocytes. In one particular murine study, researchers were able to demonstrate the ability of avenathramides to block the irritation associated with contact hypersensitivity in a dose-dependent response with activity of the 3% avenanthramide formulation comparable to hydro-

cortisone 1%.[5] Clinical studies indicate that avenanthramides may be of particular value in restoring the cutaneous barrier and reducing symptoms of atopic dermatitis.[9] It is therefore not surprising that clinical efficacy of colloidal oatmeal has been demonstrated in such various skin conditions as atopic dermatitis, contact dermatitis, fungal infections, seborrheic dermatitis, burns and post-chemotherapy dermatologic toxicity. In an early clinical study, colloidal oatmeal was used as a bath and a cleanser for three months by 139 patients aged 21-91 with various pruritic dermatoses and was able to achieve complete or marked relief in over 71 percent of these patients.[4] It has also been used successfully in the treatment of burn patients promoting skin healing.[6]

More recently, colloidal oatmeal has been shown to provide symptomatic relief of the dermatologic side effects of chemotherapy, specifically in the treatment of the acneiform eruption induced by epidermal growth factor receptor and multiple tyrosine-kinase inhibitors.[7] Similarly it has been effective in controlling the pruritus caused by erlotinib.[8]

Infants and children aged two months to six years suffering from atopic dermatitis, contact dermatitis or seborrheic dermatitis were treated with a colloidal oatmeal cream and cleanser for four weeks. Dermatologist evaluation at two and four weeks showed significant improvement in dryness, roughness and itch using a visual analog scale and significant improvement ($p<0.05$) in mean scores for IGA and EASI composite scores resulting in a significant improvement of the Quality of Life Index (QOL).[10]

These studies support previous clinical observations that the combination of colloidal oatmeal and emollient oils is synergistic.[4] In one investigation, researchers found that baths with colloidal oatmeal in an oil form soothed and cleansed the skin without irritation when used in children (n=152) presenting with a range of inflammatory dermatoses. Many attribute these positive effects on skin healing in the ability of colloidal oatmeal to reduce transepidermal water loss (TEWL) in the skin indicating an improvement in the skin barrier. In a clinical study of 27 female subjects presenting with very dry skin, TEWL values were significantly reduced comparable to the efficacy of an RX barrier emulsion. In another clinical study of this colloidal oatmeal cream and cleanser as a skin-care regimen on atopic skin, there was a statistically significant ($p<0.01$) improvement in the IGA scores, EASI composite scores and in itch severity at weeks 2,4 and 8 in patients ranging from 12 to 60 years of age, demonstrating the importance of proper skin care in the management of atopic dermatitis. These results further translated into a significant improvement of the QOL scores of enrolled patients.[11]

Feverfew

Feverfew (*Tanacetum parthenium*) has been, as its common name implies, traditionally used to treat fever, headache and arthritis. More recently experiments using human epidermal keratinocytes have shown that its antioxidant, anti-inflammatory and anti-irritant properties are based on its inhibitory effects on various pro-inflammatory enzymes and mediators including 5-lipooxygenase and phosphodiesterase as well as TNF-alpha, IL-2, IL-4 and PGE2. However, extracts from the plant retaining parthenolide are unsuitable for topical use because they often cause significant skin sensitization and irritation.

This apparent limitation to its use does not apply to the purified feverfew extract, which was specifically developed to allow the beneficial use of feverfew in topical skin care products. This extract has been refined to selectively collect the beneficial constituents from feverfew, while removing the sensitizing element. The purified feverfew extract has been proven not to induce either phototoxic or photo-allergic responses when applied to the skin in topical formulations.[2,12,13] The following examples of its clinical use are all based on the use of the purified extract. This formulation has particularly shown efficacy in the prevention of skin redness in volunteers in a dose dependent manner. Redness was induced by the topical application of methyl nicotinate which causes rapid vasodilatation of peripheral blood capillaries mediated by prostaglandins.

Topical administration of purified feverfew extract at different concentrations was effective at preventing redness with increased efficacy when higher concentrations of purified feverfew extract were added.[14] Encouraged by these results, purified feverfew extract has been evaluated for the treatment of women with sensitive skin resulting in significant improvement in facial redness, roughness and irritation. In another study, a moisturizer containing the extract and SPF 30 sunscreen were evaluated for the treatment of women aged 25 to 62 years with sensitive skin over a period of three weeks with similar reductions of redness, dryness and skin irritability as well as increased textural skin improvement.[15] One further practical application has been the use of purified feverfew extract in the prevention and treatment of shaving irritation.[16]

Most interesting however are observations in preclinical studies using normal human epidermal keratinocytes (NHEK) that if purified feverfew extract was added immediately before UV exposure to the cells, inhibition of the release of reactive oxygen species (ROS) in a dose dependent fashion was observed.[17] A similar potent antioxidant effect was noted in an experiment measured from skin cells acquired by tape stripping. Different moisturizing products each containing different ingredients claiming antioxidative properties were applied to the volar forearm of panelists, one of them containing purified feverfew extract.

After four hours, skin cells were tape stripped and assessed for reactive oxygen species ex vivo. Only the product containing purified feverfew extract significantly inhibited ROS produc-

tion.[18] Applying these results to skin in the context of UV exposure, suggests potential clinical use as a sun protective agent.

Chamomile

Chamomile (*Matricaria recutita* or *Chamameleum nobile*) has a long-standing history in folk medicine both internally and externally, in particular for gastrointestinal symptoms but also as a skin-soothing agent and aromatherapy ingredient. The flower contains as active ingredients flavonoids, volatile oils, courmarines, mucilages and saccharides that show inhibition of cyclooxygenase, lipooxygenase and histamine. It is well tolerated when used topically and is frequently used for minor irritations of the skin comparable in its efficacy to 0.25% hydrocortisone cream for atopic dermatitis. In a study in Helsinki, 48 women who had undergone surgery for breast cancer applied chamomile cream above the wound area compared to almond oil below the wound half an hour prior to radiotherapy and again at bedtime. Chamomile appeared to delay the onset of radiation dermatitis and reduced the severity grade compared with almond oil although neither was able to prevent radiation dermatitis altogether or prevent symptoms of itch and pain.[19-21]

Aloe Vera

Aloe vera (*Aloe barbadensis*) has long been known for its antipruritic, analgesic, bactericidal and antifungal effects and for promoting healing. Active components include salicylic acid, magnesium lactate and polysaccharides gel that decrease thromboxane A2 and B2 and prostaglandin 2a and function as lipid-radical scavengers. Studies have in particular underscored its skin healing properties in psoriasis.[22]

Licorice

Licorice (*Glycyrrhiza glabra* or *Glycyrrhiza inflate*) exerts its anti-inflammatory and skin lightening properties via glabridin, licochalcone A and liquiritin and has been shown to be suitable even for sensitive skin. Glabridin is the main active ingredient derived from *G. glabra* and is a constituent in many different botanicals. It is known to have anti-irritant effects by inhibiting superoxide anion production and as a cyclooxygenase (COX) inhibitor. The licorice extract licochalcone A is derived from a different kind of licorice plant grown in northwest China, *G. inflate.* It appears to exert its likewise anti-irritant effect via the same biochemical pathways. Liquiritin is a flavonoid in licorice that along with other components imparts the natural yellow color.[23,24] Studies using a skin care regimen containing a licochalcone A based cleanser, SPF 15 lotion, spot concealer and night cream over eight weeks showed good redness-neutralizing properties that were confirmed using cross polarized photographs.[25] Liquiritin applied in the clinical setting for idiopathic epidermal dyspigmentation has been shown to exert a skin brightening effect in a vehicle-controlled four-week study.[26]

Dexpanthenol

Dexpanthenol is another natural long treasured for its skin healing and soothing properties and historically used on superficial wounds, burns and dermatitis. Pantothenic acid, a member of the vitamin B5 complex, is essential to normal epithelial function and a component of co-enzyme A. Studies have shown significant reduction in itching and scaling in AD patients using a colloidal oatmeal cleanser with ceramides and dexpanthenol.[27]

Many of the natural anti-inflammatory agents are considered safe for sensitive skin, however caution should be used when applying oil based products such as tea tree oil, camphor oil and lavender oil. Pruritus, the key symptom of AD and many other inflammatory skin conditions, has been shown to respond to mucilage-containing naturals—oatmeal, flax, fenugreek, slippery elm, marshmallow—and tannin-containing naturals—witch hazel, lavender, English walnut leaf, St. John's wort. Other antipruritic agents, such as pansy flower, exert their effect via their salicylic acid content, arnica due to its sesquiterpene lactones and German chamomile (*M. recutita*) via sesquiterpene alcohols, chamazulene and flavonoids.[2]

CONCLUSION

The traditional use of natural ingredients has been largely based on empiric evidence and folk medicine recipes, but increasing data to support their use in various clinical settings are emerging. A wide range of natural ingredients have been shown useful as adjunct treatment in atopic dermatitis including in pediatric patients where the concern for potential side effects of topical steroids and/ or calcineurin inhibitors is considerable. These "new naturals" open up exciting avenues by expanding our choices for the management of atopic dermatitis as we continue to keep a keen eye on efficacy and safety data that continue to build.

DISCLOSURES

Dr. Magdalene Dohil has been a speaker for Johnson & Johnson Consumer Companies, Inc. on natural ingredients in dermatology and has received honoraria in this context. She has also served as a speaker on atopic dermatitis for Hill Dermaceuticals. As medical director of the Eczema Center at UCSD/Rady Children's Hospital San Diego, Dr. Dohil has participated in various clinical studies on atopic dermatitis, but has not received any direct compensation. The division of pediatric dermatology at UCSD/Rady Children's Hospital has received an educational grant from Johnson & Johnson Consumer Companies, Inc.

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Aesthetic Benefits of Natural Ingredients in Skin Care

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INTRODUCTION

Interest in what are perceived to be the healthiest skin care product ingredients has risen steadily over the last two decades, spurring the emergence of terms such as "organic," "natural," "naturally-derived," and "botanical." There is considerable confusion regarding the actual meaning of these labels, however. This article discusses recent developments in personal care product labeling and focuses on the skin care benefits of several botanical ingredients.

Defining Terms

Certifying products as "organic" is a current trend. However, among the various bodies creating standards and certifications, some represent actual profit-generating businesses. One should be wary of the organic label and understand the differences in the various certifications. The term "organic" was first coined in 1940 by J.I. Rodale, founder of the Rodale book and magazine publishing company,[1] and originally applied primarily to agricultural foods and practices. In 1992, the U.S. Department of Agriculture (USDA) officially approved the "USDA Organic" label and its accompanying standards for agricultural products. Although many skin care products made with "organic foods" claimed to be "organic," there was no official "organic" label for skin care products in the U.S. until 2005.

In August 2005, the USDA enacted new organic standards for skin and body care products. Accordingly, a product labeled as "organic" contains at least 95 percent organic ingredients. One that is "made with organic ingredients" contains at least 75 percent and up to 94 percent organic ingredients. These standards are derived from the organic food standards. This regulation prohibits the use of synthetic preservatives, and most chemical processing of ingredients. Organic personal care products such as skin cleansers are therefore derived from organically grown plant products, rather than conventionally grown plants, synthetic chemicals, or petroleum byproducts. In order to meet this standard, they also exclude or minimize ingredients that could be considered potentially harmful to people, animals, waterways, or the environment.

There are many different organic certifications worldwide and there is an ongoing discussion about which is the best one to use. Because these companies may be for profit, each organization would greatly benefit if their standard were universally adopted. In Europe, there were many different certifications that wisely joined forces to form one organization known as COSMOS. The European Cosmetics Standards Working Group (COSMOS) established the first European harmonized standard for skin care products in 2009. The for-profit consortium that commissioned the work was created by the first six European Union organic certifiers. They require 95 percent of agricultural ingredients to be organic; a maximum of five percent can be synthetic content. Also, 20 percent of the total product by weight must be organic, including water. COSMOS has effectively marketed itself and made the public aware of its existence. Its non-profit competitors question its objectivity, however.

In 2008, NaTrue, a non-profit begun by German organic beauty manufacturers, established a three-star system to characterize or label skin care products. One star refers to "natural cosmetics." Two stars indicate "natural cosmetics with organic content." Three stars refer to "organic cosmetics," for which 95 percent of all agricultural ingredients must be certified as organic. There are many other organic certifications but the USDA, COSMOS and NaTrue are the most recognized.

Natural, Naturally Derived, Botanical

The terms "natural," "naturally derived," and "botanical" are descriptive terms that have no legal definition. Products that are labeled as "natural" may or may not be organic. These products contain ingredients of plant origin but can also contain chemicals intended to act as preservatives or to improve its texture. In addition, "naturally derived" ingredients often are plant-derived ingredients that have been improved upon in the laboratory. For example, active soy is derived from soybeans but processed in a way that preserves the delicate, small proteins while minimizing the estrogenic components. Sales of products that claim to be organic, natural, naturally derived or botanical have soared in recent years. In order for the consumer to choose the correct products for their skin from this plethora of products, they must first define their skin type, learn what ingredients are right for their skin type, and then evaluate the brands that contain that ingredient. There are several effective botanical products on the market but, unfortunately, consumers may miss out when enticed by copycat generic products with similar ingredients and packaging. The order of ingredients, pH, and temperature at time of addition of ingredients are all patented trade secrets that influence the efficacy of the product.

Ingredients From Nature

Depigmenting Agents

Skin lighteners or depigmenting agents comprise tyrosinase inhibitors, which suppress the enzyme tyrosinase, and protease-activated receptor (PAR)-2 blockers, which block the PAR-2 receptor.

Tyrosinase

Widely distributed in nature, tyrosinase, also known as polyphenol oxidase, exists in slightly varying forms in several organisms. Tyrosinase is noteworthy in the discussion of depigmenting agents because it is the rate-limiting enzyme that controls melanin production and is a unique product of melanocytes. Tyrosinase oxidizes phenols and diphenols using a catalytic mechanism that depends on the presence of copper atoms at the active site. Two copper atoms within the active site of the tyrosinase enzyme interact with dioxygen to form a highly reactive chemical intermediate that oxidizes the substrate. Most tyrosinase inhibitors chelate copper, which inactivates tyrosinase. Kojic acid, a byproduct of the fermenting of malting rice, which is used in Japanese sake production, is an effective chelator of transition metal ions such as iron and copper.

Tyrosinase Inhibitors

Aloesin, arbutin, kojic acid, hydroquinone, licorice, paper mulberry and Pycnogenol are among the popular natural tyrosinase inhibitors. This discussion will be limited to aloesin, arbutin, and paper mulberry.

Aloesin

Isolated from the Aloe vera plant, aloesin has been proven to competitively inhibit tyrosinase from human, murine, and mushroom sources. In fact, this C-glycosylated chromone has been shown to dose-dependently inhibit tyrosinase, by hindering the hydroxylation of tyrosine to 3,4-dihydroxyphenylalanine (DOPA) and the oxidation of DOPA to dopaquinone, as well as melanin production in cultured normal melanocytes.[2] Slower than hydroquinone to penetrate the skin owing to its hydrophilic nature,[3] aloesin is thought by some to have greater potential for this reason as a skin-lightening agent for cosmetic purposes.[4] Aloesin has been found, thus far, to be safest and most effective when used in hypopigmenting regimens for its synergistic activity in combination therapies with two or more agents.[4]

Arbutin

A naturally-occurring derivative of hydroquinone, arbutin is extracted from the dried leaves of certain plant species, such as wheat and bearberry. The structural homologies that it shares with the substrate tyrosine lead to the competitive inhibition of the catalytic function of tyrosinase. Arbutin has been demonstrated in human skin and guinea pig skin tissue cultures to neutralize the hyperigmentary effect of alpha-melanocyte stimulating hormone and is believed to be effective as a skin-lightening agent.[5]

Paper Mulberry or Mulberry Extract

Paper mulberry, *Broussonetia papyrifera*, is an East Asian deciduous tree with milky sap that grows to a maximum height of about 45 feet.[6] Its bark is composed of very strong fibers and can be used for making high-quality paper. It exhibits activity as a tyrosinase inhibitor, but, to date, its use in treating pigmentary disorders has not been assessed in peer-reviewed clinical studies.

PAR-2 Blockers

Soy Constituents

The soybean plant, a member of the pea family, has been used for food and in Traditional Chinese Medicine (TCM) for several thousand years and was among the first crops grown in ancient China. Two proteins derived from soymilk, soybean trypsin inhibitor (STI) and Bowmann-Birk inhibitor (BBI), exhibit the capacity to induce skin depigmentation by inhibiting PAR-2 activation, a G-protein-coupled receptor responsible for the regulation of the ingestion of melanosomes by keratinocytes.[7] Essentially, these small proteins block the transfer of melanosomes to keratinocytes. These results have been displayed in vivo and in vitro, but have only been observed with fresh soymilk, not pasteurized. This suggests a heat-labile soymilk constituent, STI, is the primary depigmenting ingredient.

Antioxidants

Free radicals are oxygen molecules with an uneven number of electrons. This imbalance drives the search to steal electrons from surrounding tissues, ultimately resulting in lipid peroxidation, DNA damage, and the initiation of inflammation. Antioxidants counteract this effect. As a wide and varied group of compounds, antioxidants are known to exert anti-aging, anti-inflammatory, and tyrosinase-inhibiting activity. Derived from a wide variety of fruits and vegetables, antioxidants have for several years been incorporated into topical skin care products, oral supplements, and beverages. A review of some newly popularized antioxidant ingredients follows.

Açaí Berry

Found in South America, especially the Amazon River and its tributaries and estuaries,[8] the açaí palm (*Euterpe oleracea* Mart.) yields a fruit with the symmetry of a grape and the size of a giant blueberry. It tastes similar to wild raspberry with a hint of grape. These berries are high in essential fatty acids [60% oleic (omega 9) and 12% linoleic (omega 6) acids]. Açaí berry also contains many valuable phytosterols; it is a dense source of a class of flavonoids called anthocyanins. In addition, the oxygen radical absorbance capacity (ORAC) of açaí berry is higher than any other edible berry, suggesting greater antioxidant capacity. Topical products noting inclusion of açaí berry only contain modest amounts because high concentrations would stain the skin and hair. The healthiest and most practical way to benefit from açaí berry may be to eat it.

Coffeeberry

The coffee plant *Coffea arabica*, source of the globally popular beverage, originates in Ethiopia but is now cultivated worldwide. Coffeeberry is the unripe stage of the coffee bean that is eventually roasted for consumption. The extracts from the roasted beans have been shown to possess antioxidant activity.[9] Indeed, it contains several constituents known for such activity; its major polyphenolic components include chlorogenic acid, quinic acid, ferulic acid, and condensed proanthocyanidins.[10,11] A recent study showed greater antioxidant activity associated with a proprietary formulation derived from *C. arabica*, coffeeberry, than green tea, pomegranate extract, and vitamins C and E, as indicated by ORAC score.[12]

Turmeric/Curcumin

Turmeric (*Curcuma longa*), a member of the Zingiberaceae or ginger family, is best known as a spice typically used in Indian cuisine, particularly in curry. It also has long been used in traditional medicine, particularly Ayurvedic and Chinese, to treat various conditions. Curcumin (diferuloylmethane) is the yellow pigment and key biologically active component of turmeric derived from the root of the tropical plant. Although it is difficult to formulate because of its smell and color, curcumin is known to display anticancer, antioxidant, and anti-inflammatory activity.[13,14] It has not yet been established if topically applied or orally administered curcumin can inhibit skin carcinogenesis in humans.[15]

Green Tea

Originating in China, green tea, a globally popular beverage, is made from the steaming and drying of the fresh leaves of the tea plant, *Camellia sinensis*. Green tea has been used for centuries to boost the immune system, stimulate weight loss, and improve health. It is prepared to preserve its polyphenolic components, known to deliver potent antioxidant and anticarcinogenic effects. Indeed, its popularity in the West can be ascribed to these properties, as green tea has become one of the most studied antioxidants, with numerous in vitro and in vivo studies examining its effects.[16]

The polyphenolic contents in the leaves of C. sinensis are flavanols, commonly known as catechins, consisting of ECG [(-)EpiCatechin-3-O-Gallate], GCG [(-)GalloCatechin-3-O-Gallate], EGC [(-)EpiGalloCatechin], and EGCG [(-)EpiG-alloCatechin-3-O-Gallate], the latter of which is the most abundant (30% to 40% of the dry weight of green tea leaves) and biologically active component and to which most of green tea's antioxidant effects are attributed.[17] Green tea is a powerful antioxidant when used orally and topically and which needs to be carefully formulated to maintain its stability and to minimize discoloration of the product.

Pomegranate

Pomegranate (*Punica granatum*), an edible fruit and fruit juice originating from Persia, has been grown and eaten since ancient times and is now widely cultivated, particularly in the drier areas of California and Arizona. Pomegranates are believed in Ayurvedic medicine to restore balance to the skin. It is known to possess anti-viral qualities and extracts from the fruit,[18] seeds, and peel all display strong antioxidant properties, particularly the phenolic constituents, which include anthocyanins (e.g., delphinidin, cyanidin and pelargonidin) and hydrolyzable tannins (e.g., punicalin, pedunculagin, punicalagin, gallagic and ellagic acid esters of glucose).[19,20] Anticarcinogenic activity has also been exhibited by pomegranates in vitro and in vivo, particularly against skin cancer.[21,22]

Anti-inflammatories

Inflammation is a dynamic, complex, multi-step process that serves a protective function by removing deleterious stimuli and initiating the healing process for damaged tissue. Prolonged inflammation, however, can achieve the opposite result, contributing to multiple disease processes and accelerated aging. Two agents of botanical origin that exhibit anti-inflammatory activity are briefly reviewed.

Feverfew

A flowering plant from the daisy (Asteraceae or Compositae) family, feverfew has a long history of traditional use, and, as its name implies, was used as a fever reducer.[23] Western medicine has compiled evidence over the last several decades suggesting that feverfew indeed exhibits significant anti-inflammatory activity.[24] The strong antioxidant melatonin is one component of feverfew.[25] Parthenolide is the primary active ingredient of feverfew, though, and is obtained as an extract of aerial parts of the plant.[26] It inhibits nuclear factor-kappaB (NF-kappaB), a transcription factor implicated in UVR-induced photodamage,[27] and displays antiproliferative properties.[28] Unfortunately, parthenolide has become known as a powerful skin sensitizer.[29] Recent success has been seen with purified extract of feverfew, however, in delivering anti-inflammatory activity without causing skin sensitivity.[29] In fact, this new formulation has been shown to inhibit proinflammatory cytokine release from activated macrophages.[30]

Licorice

Two species of licorice root, *Glycyrrhiza inflata* and *Glycyrrhiza glabra*, have been used for thousands of years in Western and Eastern medical traditions.[31] Both are increasingly being used in therapeutic and cosmeceutical formulations, particularly as anti-inflammatory agents. Licochalcone-A, which reduces proinflammatory cytokines, is the primary active ingredient isolated and extracted from Chinese licorice root (*G. inflata*).[32,33] G. glabra appears to exert anti-inflammatory activity via inhibition of superoxide anion production and cyclooxygenase activity. It has been used to treat dermatitis, eczema, pruritus, cysts, and skin irritation.[34] In addition, the U.S. National Cancer Institute (NCI) has formally recognized the chemopreventive value of its primary active constituent glyccyrrhizin.[35] Liquiri-

tin, also derived from *G. glabra*, has exhibited efficacy in the treatment of melasma.[36] Licorice extract is widely used as an anti-inflammatory agent in Europe.[37]

Skin Hydration

Olive Oil

Long a staple of the Mediterranean diet, considered one of the healthiest in the world, olive oil (*Olea europaea*) is the primary source of fat in that diet and one of the most important of the natural essential oils.[38] For as long as olive oil has been used in the human diet, it has also served other functions, including for skin health. The ancient Greeks used olive oil as a base for many perfumed unguents, which were massaged into the skin and then scraped off instead of taking a shower or a bath,[39] and the ancient Egyptians and Romans used it for wound healing. Olive oil is known to contain a lengthy list of beneficial active ingredients, including polyphenols, squalene, fatty acids (particularly the monounsaturated fat oleic acid), triglycerides, tocopherols, carotenoids, sterols, and chlorophylls.[40] Currently, several soaps, lip balms, shampoos, and moisturizers contain olive oil.

CONCLUSION

Interest in natural ingredients continues to steadily increase. A bevy of products touting such components seems to enter the market on a continual basis. Nevertheless, some confusion remains regarding the labeling of products, particularly the meaning of the term "organic," since there is no recognized standard definition. Research is ongoing to determine the most viable natural ingredients to incorporate into skin care formulations and, as ever, new ingredients and products are on the horizon.

DISCLOSURES

Dr. Leslie Baumann is a speaker and/or advisor for Johnson & Johnson Consumer Companies, Inc., Unilever, Avon, Mary Kay and L'Oréal.

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Natural Therapies for Hyperpigmentation

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ABSTRACT

Skin hyperpigmentation is a common condition that results in a large number of patient visits to dermatology offices annually, and an even larger number of purchases of over-the-counter and prescription skin lightening treatments. Hyperpigmentation is not merely a cosmetic annoyance, but a source of significant distress and social stigma that can profoundly impact the self-esteem of those who suffer from it. The problem is exacerbated by the lack of satisfactory long-term therapies or prophylactic measures. Hyperpigmentation may occur as a sequela of skin inflammation or following other triggers, such as ultraviolet light exposure or hormonal changes. Typical therapy includes skin lightening with topical hydroquinone in conjunction with photoprotection via sun avoidance and the application of broad-spectrum sunscreen. Other prescription topicals such as tretinoin, azaleic acid, mequinol, and corticosteroids have documented efficacy, as do chemical peels, microdermabrasion, cryotherapy, and laser or light energy treatments in appropriately selected patients. However, these topical treatments and procedures often yield limited results and are associated with high recurrence rates. Adverse effects such as skin irritation may limit their therapeutic potential and the length of time for which they can be used, especially in patients with darker skin (Fitzpatrick skin phototypes III-VI) who have a predisposition to develop further hyperpigmentation following inflammation.

Recent research has elucidated the mechanisms of action of several natural ingredients that can serve as useful adjuncts or even monotherapies for hyperpigmentation. Aside from being efficacious, these ingredients may be considered safe for long-term use, including maintenance treatment, by virtue of being relatively free of adverse effects. The use of natural ingredients resonates with the lifestyle and wellness philosophy of those patients – typically members of the Baby Boomer and Generation X demographics – who most frequently seek dermatologic interventions. This paper will present an overview of some available natural therapies for hyperpigmentation and an evidence-based discussion of their efficacy for the treatment of this condition.

INTRODUCTION

Hyperpigmentation, which is common both as a primary dermatologic complaint and as a sequela of various dermatoses, accounts for numerous dermatology visits each year. A 2007 survey reported that pigmentary disorders were the second most common group of dermatoses among African American patients presenting to dermatologists.[1] For many patients, hyperpigmentation is not simply a cosmetic concern, but can also cause psychological and emotional distress, and impact quality of life by decreasing social functioning, lowering productivity at work and reducing self-esteem.[2] Face and neck hyperpigmentation is most commonly seen in women of reproductive age with darker skin tones as a result of ultraviolet (UV) light exposure. It may also be caused by drugs such as oral contraceptives, minocycline, amiodarone, antimalarials and anti-seizure medications; and also by pregnancy, thyroid dysfunction or other hormonally-related conditions.[3] Facial hyperpigmentation may also be a result of inflammation from common dermatoses such as acne or eczema, and less frequently due to heavy metal exposure.[4] These triggers may more frequently cause hyperpigmentation in patients of color such as African Americans, Hispanics, Asians and Pacific Islanders, and those of Middle Eastern descent.[1] The melanocytes of darker skinned individuals (Fitzpatrick skin types IV-VI) have been reported to exhibit unstable and exaggerated responses to cutaneous injury.[2,5]

Although the pathogenesis of increased pigmentation is not completely understood, the condition is known to be multifactorial and to depend on alterations in the density of active melanocytes and on specific abnormalities of the complex melanogenesis pathway that may be secondary to an inflammatory process.[6] Excess pigment may be deposited in the epidermis, the dermis or both, as a result of a significant increase in melanin production or an abnormal distribution of melanin pigment after initiation of an inflammatory cascade that results in the generation of cytokines, other inflammatory mediators, and reactive oxygen species.[7-10] Thus, an evidence-based approach to hyperpigmentation entails identification of the underlying cause wherever possible, and prompt data-driven selection and initiation of treatment to help prevent progression and hasten resolution.

Topical hydroquinone, which inhibits the conversion of tyrosine to melanin, has been historically considered a gold standard of therapy for hyperpigmentation and a mainstay of skin lightening products. Adjunctive photoprotection with sun avoidance and broad-spectrum sunscreens is considered important, and various other topical agents such as tretinoin, azelaic acid, corticosteroids, glycolic acid, and vitamin C may also be used with the aim of synergistic improvement.[11-13]

The development of novel natural ingredients for hyperpigmentation is not only of therapeutic benefit but can also help to advance our understanding of melanocyte biology and melanogenesis and the genetic, endogeneous and environmental factors that impact them.[14] Natural ingredients are available in both over-the-counter and physician-dispensed products. It is important for dermatologists to be aware of both genres of product, in order to make the most appropriate treatment recommendations to patients.

In this article, we will summarize the current understanding of melanocyte biology and provide an overview of the mechanisms of action and clinical studies performed to evaluate natural ingredients for hyperpigmentation, including soy extract, kojic acid, and copper and zinc ions.

Regulation of Melanin Synthesis and Melanosome Transfer

Evaluation of therapeutic approaches to hyperpigmentation requires an understanding of the intricate pathways and proteins that regulate melanin synthesis, uptake and distribution of melanosomes into recipient keratinocytes, and degradation and turnover of pigmented keratinocytes.[15] The melanization process is complex and is influenced by exogenous factors such as ultraviolet radiation, and by endogenous factors such as reactive oxygen species (also known as free radicals), leukotrienes, prostaglandins, cytokines and growth factors. The quest for safe and effective skin lightening agents has been somewhat difficult.[6] Ideally, depigmenting agents must have an affinity for key components of the melanin biosynthesis pathway with few adverse effects.[2]

The challenge of finding consistently efficacious treatments is magnified by innate differences between lightly and darkly pigmented individuals in the concentration of melanin in melanosomes, the size and dispersion of melanosomes, and the speed of melanosomes degradation. The enzyme, tyrosinase, is a key target when treating hyperpigmentation. However, novel lightening agents have been developed that affect other steps of the melanization and degradation pathway. These agents may also have anti-inflammatory and antioxidant properties that are of utility, as studies have documented that inflammatory mediators such as leukotrienes, prostaglandins, cytokines, growth factors, and reactive oxygen species have melanocyte-stimulating properties.[9,16]

Natural Ingredients for Hyperpigmentation

Soy Extract

Soy extract is derived from fresh soy beans and contains phytosterols and small protein serine protease inhibitors such as soybean trypsin inhibitors (STIs) and Bowman-Birk inhibitors (BBIs) that have been shown both by in vitro research and in randomized, double-blind vehicle controlled studies to interfere with the transfer of melanosomes to keratinocytes.[17] Fresh soy products contain soy proteins and amino acids while fermented products contain isoflavones; only fresh soy extracts have demonstrated clinical benefits in skin care.[18]

Soy interferes with melanin transfer by reversibly inhibiting the protease-activated receptor-2 (PAR-2) pathway, a G protein-coupled receptor pathway that regulates the uptake of melanosomes by keratinocytes, thus producing skin lightening. PARs are members of the G protein-coupled receptor family with seven helical hydrophobic transmembrane domains that activate signal transduction via either cyclic adenosine monophosphate (cAMP) or phosphatidylinositol pathways.[19,20,21] Four subtypes have been defined (PAR-1, -2,-3,-4), each activated in a protease-dependent matter and each having a tissue specific distribution.[22] The PAR-2 receptor is expressed on the cell surface of keratinocytes but not melanocytes; it is regulated by the activating peptide Ser-Leu-Ile-Gly-Arg-Leu (SLIGRL) which has been hypothesized to control melanosome ingestion or phagocytosis by keratinocytes, thus exerting a regulatory role in skin pigmentation.[23,24] In vitro and in vivo murine studies have demonstrated that SLIGRL and Leu-Ile-Gly-Arg-Leu (LIGR) stimulated activation of PAR-2 signaling pathways results in keratinocyte phagocytosis without enhancing inflammatory processes such as the induction of cyclooxygenase-2 (COX-2) expression and the secretion of prostaglandin E2, interleukin (IL)-6 and -8. It appears that the modulation of PAR-2 activity can impact the process of melanosome transfer and therefore affect skin pigmentation.[24-27]

Additional research is needed, but preclinical studies have demonstrated that modulation of PAR-2 activation by serine protease inhibitors present in soy extract can affect the transfer of melanosomes to keratinocytes and ameliorate hyperpigmentation.[26,27] Serine protease inhibitors inhibited PAR-2 activation, resulting in reduced melanosome transfer and distribution that led to a dose-dependent skin lightening effect in vivo.[27,28]

Data suggest that keratinocyte PAR-2 is differentially expressed in skin of color and that hyperpigmented skin has higher levels of PAR-2 expression than lighter skin.[23] Thus, future studies may focus on PAR-2 expression in skin of color as compared to lighter skin types, with the objective of developing therapies that influence these pathways.

Soy is considered clinically safe, as the inhibition of melanosome transfer is reversible, but its lightening effect is not as pronounced as that of hydroquinone, which is directly cytotoxic to melanocytes and also a tyrosinase inhibitor. One 12-week, double-blind, placebo-controlled study evaluated 68 female patients aged 30-61 years with Fitzpatrick skin phototypes I-III and tactile roughness, mottled hyperpigmentation, lentigines, blotchiness, and dullness.[17]

The study compared an active moisturizer containing stabilized soy extracts against its vehicle, both containing sunscreen (SPF 30). The active soy moisturizer contained non-denatured STIs and BBIs, vitamins, and fatty acids. Blinded clinical evaluation (for skin tone), colorimetry (for skin brightness and color), digital photography, and study subject self-assessment were used to measure efficacy. Improvement of skin tone was defined as a reduction in mottled hyperpigmentation, lentigines, and blotchiness with an increase in skin brightness. Improvement in skin texture was defined as a reduction in the surface roughness and/or improvement in fine lines and wrinkling. A significant improvement in photodamage parameters was seen with both the active soy and vehicle groups, but the active soy group was superior to the vehicle group in regards to improvement in facial skin tone, clarity, mottled hyperpigmentation, blotchiness, and fine lines as well as overall texture and appearance

Additional studies with soy extracts have demonstrated improvement of dyschromias including post-inflammatory hyperpigmentation with the use of a daily soy moisturizer and a whole soy extract formulated with salicylic acid and retinol.[29,30]

Kojic Acid

Kojic acid is a hydrophilic metabolic product of several fungal species, such as Aspergillus, Penicillum, and Acetobacter.[12] It functions as a depigmenting agent by inhibiting tyrosinase via the chelation of copper at the active site of this enzyme.[31] Kojic acid is available in 1-4% concentrations and a number of studies of kojic acid combined with glycolic acid or hydroquinone have documented efficacy in the treatment of melasma. Further evaluation of the efficacy of kojic acid for post-inflammatory hyperpigmentation would be informative.[32,33]

In one prospective randomized split-face study, 40 Chinese women with epidermal hyperpigmentation were treated for 12 weeks with applications of 2% kojic acid in a gel containing 10% glycolic acid and 2% hydroquinone on one half of the face and the same gel application without kojic acid on the other half of the face.[32]

Determination of efficacy was based on clinical evaluation, photographs, and self-assessment questionnaires. At the end of the study, all subjects showed improvement in hyperpigmentation on both sides of the face, but results were better when kojic acid was part of the treatment regimen: 24 of 40 (60%) subjects receiving the gel with kojic acid had a greater than 50 percent improvement in hyperpigmentation, while 19 of 40 subjects (47.5%) receiving the gel without kojic acid had the same degree of improvement. Side effects, including redness, stinging, and exfoliation, occurred with and without the addition of kojic acid to the gel and resolved in all subjects by the third week. Three subjects (7.0%) asked to be withdrawn from the study because of redness and peeling and were not included in the data analysis; in these patients the redness and peeling resolved after discontinued therapy.

Contact dermatitis has been documented as an adverse effect of kojic acid. Kojic acid was recently removed from markets in the Far East following concerns regarding mutagenicity, and then later reinstated as these concerns were not supported by any controlled studies.[6,34] In one study on melasma, two similar combination formulations of glycolic acid with hydroquinone and glycolic acid with kojic acid demonstrated statistically similar clinical improvements, but the kojic acid preparation was more irritating.[33] The addition of a topical corticosteroid may help to reduce irritation and create clinical synergy but long-term use, particularly on the face, should be avoided due to steroid-associated adverse effects such as skin atrophy, infection, and acne/rosacea. Patients given a combination of 4% kojic acid, 0.05% tretinoin, and 0.05% betamethasone nightly for three-to-six months have demonstrated clinical improvement of melasma (12% excellent, 42% satisfactory, 27% some, 13% none) with few instances of irritation.[35]

Licorice Extract

Licorice extract, which is derived from licorice root, contains glabridin (*Glycyrrhiza glabra* species), lichochalone A (*Glycyrhiza inflata* species) and the flavonoid, liquiritin. Licorice extract inhibits melanosome development and functions as a tyrosinase inhibitor. In addition, it has anti-inflammatory effects; glabridin inhibits superoxide anion production and is a cyclo-oxygenase (COX) inhibitor, while licochalcone A is a COX and lipoxygenase inhibitor. Licorice extract has utility as a skin lightening and brightening agent — and also for redness reduction, which may be of value in reducing the incidence of post-inflammatory hyperpigmentation in patients with darker skin.

In a study of 20 women aged 18 to 40 years with bilateral, symmetrical idiopathic epidermal hyperpigmentation, liquiritin cream was applied on one side of the face and a vehicle cream on the other side twice daily for four weeks. Sixteen of the study subjects (80%) exhibited an excellent response, with no discernible differences between the normal skin and previously pigmented areas. Two subjects showed a fair response, and two showed a good response. Pigmentary intensity was markedly reduced in the liquiritin-treated subjects: by three levels in 70 percent, by two levels in 15 percent and by one level in 15 percent of these subjects, and 90 percent of these treated subjects showed at least

a 75 percent reduction in lesion size. In contrast, reduction in pigmentary intensity was seen in only 10 percent of the subjects treated with placebo vehicle.[36]

Copper and Zinc Ions

Copper and zinc are trace elements that function as cofactors in pathways important for development, physiological homeostasis, and epithelial repair following injury.[37] Gradients of metal ions in epidermal tissue appear to serve critical functions in cell differentiation and in cutaneous repair after injury. Toxic injuries (e.g., ultraviolet-induced cutaneous damage) may lead to imbalances or functional impairment of trace metals and impede their interactions with cell membranes or cellular enzymes important for healthy skin function. Superoxide dismutase (which catalyzes antioxidation) and the enzymes lysyl oxidase and prolyl hydroxylase (which facilitate crosslinking of collage and elastin), are examples of copper-dependent enzymes that are essential for normal skin function.[38] The amino acids, glycine, histidine and lysine, bind copper and have been studied during research into copper peptide-based technologies that could have utility in anti-aging and in wound care via possible increased production of dermal matrix components such as collagen and matrix metalloproteinases.[39-42]

Zinc is also associated with the antioxidant proteins, superoxide dismutase and metallothionein, and thus has the potential to impact antioxidant activity.[43] Current investigations into the anti-inflammatory action of zinc are myriad, including studies of the inhibition of leukocyte chemotaxis, lymphocyte transformation, mast cell degranulation, lysosomal enzyme release, bacteriostatic effect against Propionibacterium acnes, inhibition of vasoactive amines, preservation of intracellular coenzyme hemostasis, and decreased sebum production.[44] It is hypothesized that the cutaneous application of trace elements may have antioxidant, skin rejuvenation, anti-irritant, and immunomodulatory effects.

The biologic activity of elemental copper and zinc delivered to the skin in a bi-mineral complex gel has been assessed in human skin explants that were treated topically once daily except on weekends with water alone or with 1% bi-mineral complex reconstituted with water immediately before application. The skin explants were harvested after seven days. It was found that the explants that were treated topically with the bimineral complex had increased elastin gene expression and elastin fibers, increased gene expression of type I and IV collagen and increased total collagen content compared to the water-treated explants.[45]

A 12-week, placebo controlled, randomized, double-blind clinical study of the bi-mineral complex has demonstrated potential benefits for signs of photoaging including dyspigmentation. Ninety-four healthy females aged 40-65 years with Fitzpatrick Skin Types of II-IV and mild-to-moderate photoaging were divided into three groups. The first group was treated with placebo gel plus activating moisturizer A (n=31), and the second and third groups with bi-mineral complex gel plus activating moisturizers (n=30 and n=33 respectively). Comparison of results with the bi-mineral complex versus placebo showed that the bi-mineral complex produced clinically significant improvements as early as week 2 and continuing through week 12 in key signs of photoaging including dyspigmentation, irritation, the appearance of firmness, fullness and rhytides, and overall appearance of the skin.[46]

The bi-mineral complex is postulated to create physiological levels of electricity that may restore integrity and function of the dermal extracellular matrix and may also have anti-irritant properties.[47] Formulations have been developed that consist of a facial serum containing bi-mineral complex that is applied to the face and then activated by a water-based moisturizer. The aim is to provide a continuous flow of electricity — which is described as biomimetic because it is similar to the skin's intrinsic bioelectricity during healing and regeneration — and essential ion release at the skin surface. It is hypothesized that the activated bi-mineral complex could help to compensate for the loss of intrinsic bioelectricity that occurs as the skin ages.

Another randomized, investigator-blinded study evaluated a copper zinc malonate lotion applied twice daily for 24 weeks to the skin of the neck and anterior chest area (décolletage) of 42 females, in combination with 4% hydroquinone cream and 0.025% or 0.05% tretinoin cream.[48] Treatment was well-tolerated, with 94% of subjects reporting that they were satisfied or very satisfied with the overall improvement. Investigator assessment showed a progressive increase in the number of subjects treated with the décolletage system plus 0.025% tretinoin who had a 2-point improvement of their overall integrated assessment score—from 15 percent at week 8 to 25 percent at week 16 to 35 percent at week 24. The group treated with 0.05% tretinoin cream showed better responses, increasing from 25 percent at week 8 to 33 percent at week 16 to 39 percent at week 24. Mean scores for investigator-assessed signs of photodamage were reduced from baseline in both groups ($P \leq 0.05$). There were improvements in tactile roughness (from week 2 onward); mottled hyperpigmentation, lentigines and fine wrinkling (from week 4 onward); laxity (from week 8 onward); and crepiness and coarse wrinkling (from week 12 onward).

Future Developments

Current studies are investigating the potential of antioxidants and anti-inflammatory actives to decrease erythema in response to UV injury and other pro-inflammatory triggers and, in doing so, to diminish the risk of post-inflammatory hyperpigmentation in patients with darker skin. One such natural active is the botanical antioxidant, feverfew, which has exhibited efficacy in purified feverfew extract formulations for reducing facial redness and irritation. The PGE2 inhibitor, ethoxybenzaldehyde, is approved by the FDA as a food additive and commercially available in a

formulation for reduction of skin erythema that also contains niacinamide, jojoba (*Simmondsia chinensis*) seed oil, squalane and glycerine. This product provided greater protection against UV-induced hyperpigmentation in a double-blind study of 17 subjects with Fitzpatrick skin phototypes III and IV than three antioxidant formulations. Whereas prevention of UV-induced erythema indicates short-term antioxidant protection, prevention of UV-induced hyperpigmentation for 21 days after UV exposure may be considered a measure of longer term antioxidant protection and blocking of the progression of UV-induced skin damage. Larger studies would be of value to establish this as a clinical approach to preventing post-inflammatory hyperpigmentation.

Another focus of current research is on actives that act at early stages in the pathway of melanogenesis, such as by inhibiting tyrosinase transfer within melanocytes from microsomes (endosomes) to melanosomes. New compounds that hold promise as skin lightening agents, including those that are naturally-derived or nature-inspired, can be screened efficiently in vitro using a 3-dimensional co-culture of human keratinocytes and melanocytes. The availability of co-cultures with Black, Asian or Caucasian melanocytes enhances the versatility and applications of this screening system.

CONCLUSION

Natural ingredients for hyperpigmentation are currently available as adjunctive therapies or novel monotherapies and are the subject of active research and development. Whereas traditional use of natural ingredients was largely empiric, modern use is increasingly subject to scientific scrutiny.

Natural ingredients fill a niche for patients who seek quality-controlled, safe, and efficacious products that are alternatives to prescription medications, including hydroquinone. An evidence-based approach provides insight into the mechanisms of hyperpigmentation, and enhances understanding of the depigmenting, anti-inflammatory, antioxidant and anti-irritant actions of natural ingredients. While prescription and procedural therapies may be considered the standard of care in many patients, it is important for clinicians to be aware of alternative and emerging therapies and when it may be clinically appropriate to recommend them. Hyperpigmentation is a primary cosmetic concern for many patients who consult dermatologists, and the advent of natural ingredients with the potential to improve hyperpigmentation represents a significant clinical advance.

DISCLOSURES

Dr. Sundaram is a consultant to Johnson & Johnson Consumer Companies, Inc., and a consultant and investigator for SkinMedica, Biopelle and Syneron/Candela.

Dr. Jason Emer has no relevant conflicts of interest to disclose.

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1. Which of the active ingredients in Colloidal Oatmeal has been shown to have anti-inflammatory properties?
   a. Saponins
   b. Flavonoids
   c. Lipids
   d. Avenanthramides
   e. Ash

2. Why does colloidal oatmeal stand out among the naturals?
   a. It has better anti-irritant properties than other naturals
   b. It is particularly indicated for sensitive skin
   c. It is FDA approved
   d. It has immune-modulating properties
   e. It is cosmetically superior to other naturals

3. Which of these natural ingredients has anti-inflammatory properties, but should be used with caution on sensitive skin?
   a. Oatmeal
   b. Licorice
   c. Lavender oil
   d. *Aloe vera*
   e. Chamomile

4. Which of the following pro-inflammatory enzymes/modulators is inhibited by feverfew extract?
   a. 5 – lipooxygenase
   b. phosphodiesterase 3
   c. phosphodiesterase 4
   d. PGE2
   e. All of the above

5. There is a recognized certification standard to label skin care products as “organic” that is used worldwide.
   a. True
   b. False – each country has its own
   c. Most countries follow the USDA labeling, but not all do
   d. There is disagreement worldwide about which standard to use
   e. All organic standard labeling is set by non-profit organizations

6. Which of the following is not a tyrosinase inhibitor?
   a. Paper mulberry
   b. Coffeeberry
   c. Kojic acid
   d. Arbutin
   e. Licorice

7. The rate-limiting enzyme controlling melanin synthesis is:
   a. Cyclooxygenase
   b. Protease
   c. Tyrosinase
   d. Oxidase
   e. Superoxide Dismutase

8. How do antioxidants help treat unwanted pigmentation?
   a. Copper chelation
   b. Anti-inflammatory activity
   c. Inhibition of tyrosinase
   d. All of the above
   e. None of the above

9. Which of these medications does not inhibit the conversion of tyrosine to melanin?
   a. Licorice extract
   b. Kojic acid
   c. Hydroquinone
   d. Fresh soy extract

10. Natural skin lightening agents take advantage of which steps in the melanogenesis pathways?
    a. Melanosome transfer inhibition
    b. Tyrosinase inhibition
    c. Regulation of exogenous factors
    d. Regulation of endogenous factors
    e. All of the above

11. Soy proteins exert their effects on skin pigmentation by:
    a. Serine protease inhibitor activity on tyrosinase
    b. Regulating the production of melanosomes
    c. Activating G protein-coupled receptor pathways on eratinocytes
    d. Activating PAR-2 receptor expression on melanocytes
    e. An irreversible inhibition of melanosome transfer

12. The efficacy and/or tolerability of products containing kojic acid may be related to its ability to:
    a. Regulate the chelation of zinc at enzyme binding sites
    b. Decrease inflammatory mediators in affected skin
    c. Be formulated at varying drug concentrations
    d. Be combined with other agents such as glycolic acid or hydroquinone
    e. Produce documented mutagenicity in controlled studies

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