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Innovations in Natural Ingredients and Their Use in Skincare

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Innovations in Natural Ingredients and Their Use in Skincare

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Statement of Need

A dermatologist is singularly qualified to prevent, diagnose and treat a wide variety of benign and malignant skin conditions.

The use of natural ingredients in skin care directly relates to dermatologists' scope of practice. The emotional toll and dissatisfaction of conventional treatments for chronic disease explains why physicians and patients look outside conventional methods and explore the therapeutic benefits of natural ingredients. Results from a national survey on the use of nonconventional therapies in skin disorders found that 28.3 percent of patients sought information on natural products because conventional treatments were not helpful, 35.8 percent thought it would be interesting to try and 49.8 percent thought combining natural products with conventional treatments would optimize the treatment of their condition.

Educational Objectives

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

- Identify the active ingredients in commonly used natural products and their clinical uses in disorders of the skin.
- List key pharmacologic properties of natural ingredients and their relative usage in acne, rosacea, eczema, psoriasis, skin of color, skin cancer and anti-aging treatments.
- Name several factors that affect patient compliance in chronic conditions and the potential benefit of combining natural ingredients with conventional treatment.
- Recall the safety, tolerability and efficacy of natural ingredients and the importance of patient-physician communication.

Target Audience

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

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Dr. Joseph F. Fowler is a consultant for: Ferndale, Galderma, Graceway, Hyland, Johnson & Johnson, L'Oreal, Quinnova, Ranbaxy, Stiefel, Triax and Valeant. He is on the speaker's bureau for: Galderma, Medicis, Ranbaxy, Shire, Stiefel and Valeant. He is a research investigator for: Abbott, Allerderm, Allergan, Amgen, Astellas, Centocor, Coria, Dermik, Dow, Galderma, Genentech, Johnson & Johnson, Medicis, Novartis, Quinnova, Shire, Stiefel, Taisho, Taro and 3M.

Dr. Heather Woolery-Lloyd is an investigator, speaker, and is on the advisory board for Johnson & Johnson. She is an investigator and consultant for Allergan; is on the advisory board for Galerma; and is a speaker for Stiefel/GlaxoSmithKline.

Dr. Heidi Waldorf is on the speaker's bureau and advisory board for Allergan, Medicis and Unilever. She is a consultant for Avon, Bioform/Merz, Proctor & Gamble and Johnson & Johnson.

Dr. Ritu Saini has no relevant conflicts of interest to disclose.

The planning committee of this activity, James Gormley, Jamie Trapp, Elizabeth Borges and Lauren Schubert, have no relevant conflicts of interest to disclose.

Innovations in Natural Ingredients and Their Use in Skin Care

Joseph F. Fowler Jr. MD,[a] Heather Woolery-Lloyd MD,[b] Heidi Waldorf MD,[c] Ritu Saini MD[d]

[a]University of Louisville Division of Dermatology, Louisville, KY
[b]Miller/University of Miami School of Medicine, Depatment of Dermatology and Cutaneous Surgery, Miami, FL
[c]Laser & Cosmetic Dermatology, Mount Sinai Medical Center, New York, NY; Mount Sinai Medical Center, New York, NY; Private practice, Waldorf Dermatology & Laser Associates, PC, Nanuet, NY
[d]New York Langone Medical Center, Department of Dermatology, New York, NY

ABSTRACT

Natural ingredients have been used traditionally for millennia and their application in topical creams, lotions and preparations within the traditional medicines and healing traditions of many cultures has been observed. Over the last 20 years, clinical and laboratory studies have identified the benefits of an array of natural ingredients for skin care. Consequently, a number of these ingredients and compounds are today being developed, used or considered not only for anti-aging effects, but also for use in dermatologic disorders. Certain ingredients, such as colloidal oatmeal and aloe vera, have been identified as beneficial in the treatment of psoriasis and atopic dermatitis, respectively, due to their anti-inflammatory properties. For combating acne and rosacea, green tea, niacinamide and feverfew are considered efficacious. As to hyperpigmentation and antioxidative capabilities, licorice, green tea, arbutin, soy, acai berry, turmeric and pomegranate are among those plants and compounds found to be most beneficial. Additional research is needed to determine to confirm and elucidate the benefits of these ingredients in the prevention and management of skin disease.

INTRODUCTION

Although they have actually been used for centuries, natural ingredients in skin care are becoming more prevalent in contemporary formulations. In fact, natural ingredients are incorporated into almost half of all new skin care products. What is meant by the term "natural?" Natural has been defined to be something that is neither artificial nor pathologic and an ingredient, one that is produced by nature or found in nature, and that is extracted directly from plant and animal products.[1,2] Other sources of natural ingredients include herbs, fruits, florals, minerals and water, as well as the sea and earth.

The efficacy of natural ingredients in skin products depends on many factors. Among these are whether there is biologic activity in vivo and not just in vitro and the type of vehicle used to deliver the product to the skin. The product must be biologically active and stable once applied to the skin to exert the desired effect. It also must be cosmetically acceptable with respect to color, odor and texture.

Natural ingredients vary in therapeutic indices. The following will review natural ingredients found to be beneficial in the treatment of skin conditions such as atopic dermatitis, psoriasis, acne, rosacea and hyperpigmentation, as well as those purported to play a role in anti-aging and overall skin rejuvenation.

Atopic/Contact Dermatitis

Colloidal Oatmeal

Avena sativa or cultivated oat is an annual grass with straight, hollow stems which has been utilized for over 2,000 years in traditional medicines, especially as a soak or poultice.[3] Ancient Romans considered oats a coarse food and used it as animal fodder whereas the Ancient Greeks had a dessert made of oats.[4]

Colloidal oatmeal is derived from dehulled oat kernels, the active components of which include: polysaccharides (60–64%), proteins (12.5–18%), lipids (3–9%), saponins, enzymes, prostaglandin-synthesis inhibitors, flavonoids and vitamins. Among the most well known components are vitamins A, B and E and avenanthramides—phenolic compounds with potent antioxidative effects. Other characteristics associated with these compounds are: anti-inflammatory/anti-irritative; immunomodulatory; and inhibitory of prostaglandin synthesis.

Therefore, it should be not be unexpected that colloidal oatmeal is widely used as a skin barrier protectant and in the treatment of various inflammatory/immune-mediated skin disorders such as contact dermatitis (e.g., poison ivy, etc.), atopic dermatitis, diaper rash and the overall restoration of moisture in dry skin.[5,6] In fact, for decades colloidal oat grain suspensions have been used as treatment complements for atopic dermatitis.[7]

Oatmeal saponins help to solubilize dirt, oil and sebaceous secretions. Another benefit of colloidal oatmeal is the general lack of common allergens such as preservative, which can exacerbate many of these conditions. In a study of 10 patients who were treated with colloidal oatmeal lotion for a rash induced by EGFR/TK inhibitors, six experienced total resolution of their symptoms while three experienced a partial response.[8]

As briefly noted, the most active class of polyphenolic antioxidants in oat products is avenanthramides, which have been

found to possess anti-atherogenic and anti-inflammatory effects when administered orally. A proprietary standardized formulation containing 100 ppm avenanthramide has been introduced for topical products, know as Avena Sativa Kernel Extract.[9,10]

At a cellular level, avenanthramide hinders inflammation by inhibiting NF-KappaB activation, the release of proinflammatory cytokines, skin immune responses and neurogenic inflammatory response. Avenanthramides also reduce the release IL-8 from keratinocytes. IL-8 is a pro-inflammatory cytokine that is elevated in inflamed skin. In addition, it is a potent chemotactic factor that can induce migration of neutrophils to inflamed skin.[11] The overall anti-inflammatory effects of avenanthramides can approach that of hydrocortisone 1 percent in increasing concentrations.

Psoriasis

Aloe Vera

Aloe vera (Figure 1) can be found throughout the tropics and warmer regions worldwide, the genus of which contains at least 324 species of herbs, shrubs and trees.[12] Aloe has played a significant medicinal role for thousands of years. Egyptians, Assyrians and Mediterranean peoples used the dried latex, from cells inside the leaves, and the gel. Called "the plant of immortality" in Egypt, aloe was given as an offering at the funerals of pharaohs and was used in the baths of Egyptian queens; the plant was also used for embalming. In the first century A.D., the Greek physician, Dioscorides, used aloe for sores and wounds. Externally, aloe gel has been used in many applications, including skin irritation. In cosmetics, the gel is added to moisturizers, cleansers, shampoos, suntan lotions and sunburn treatments.

Aloe vera gel contains salicylic acid, magnesium lactate and gel polysaccharides. By lowering levels of thromboxane A2, thromboxane B2 and prostaglandin 2□, aloe vera exhibits potent anti-inflammatory effects. Clinically it is also used as an antipruritic to accelerate skin healing, as an analgesic and as a bactericidal/antifungal agent.[13]

With respect to psoriasis, in a study of 30 patients, 83.3 percent demonstrated significant improvement in the Psoriasis Area and Severity Index (PASI) score after treatment with aloe vera compared to placebo.[14] Alternatively, in a study of 40 patients in which aloe vera gel was compared to placebo, 72 percent of aloe patients improved in a PASI score of 10–15 percent compared to 82 percent of placebo patients.[15] This suggests the lack of reproducibility and inconsistency sometimes seen in studies of natural ingredients in skin care products.

Indigo Naturalis

Indigo naturalis is derived from the *Strobilanthes formosanus* plant and is used in a 1.4 percent concentration in ointment. It is so named due to its dark blue color. In a Chinese psoriasis study, 42 patients underwent treatment of indigo naturalis to one lesion compared to a control lesion for 12 weeks. Those lesions treated with indigo naturalis exhibited reduced scaling, redness and induration double that of the control lesions. Overall, there was a 74 percent clearance rate of lesions treated with the natural ingredient.[16]

Acne

Tea Tree Oil

Tea tree oil, also known as melaleuca oil, is obtained by steam distillation of the leaves of *Melaleuca alternifolia*. Tea tree oil, a clear to pale-golden hydrophobic essential oil, is purported to have antiseptic properties and has been used traditionally to prevent and treat infections. In a randomized double-blind trial of 60 patients with mild-to-moderate acne, 30 patients were treated with tea tree oil and 30 patients were treated with placebo. Tea tree oil gel was found to be 3.55 times more effective than placebo for total acne lesion count and 5.75 times more effective than placebo for acne severity index.[17,18]

Green Tea

Green tea is made from the steaming and drying of the fresh leaves of the tea plant *Cammelia sinensis* through a process that preserves its polyphenolic compounds.

The most studied of these are (-)-epigallocatechin-3-gallate (ECGC) and (-)-epicathechin-3-gallate (ECG) which are known as potent photoprotectants and antioxidants. In an open-label trial in mild-to-moderate acne of 20 patients in which green tea was applied for six weeks versus placebo, the mean total lesion count decreased from 24–10 after six weeks (58.33%, $P<0.0001$) and the mean severity index (SI) decreased from 2.05–1.25 after six weeks (39.02%, $P<0.0001$).[19]

FIGURE 1. One source of aloe vera grows in the wild in the Drakensberg Mountains of South Africa. Photo by Thomas Elias. USDA.

Zinc

Zinc is an essential trace element for the human organism. It functions as a co-factor for the metalloenzymes involved in many cellular processes and has anti-inflammatory properties. Zinc gluconate is much better tolerated than zinc sulfate. Many studies on the efficacy of oral zinc have been performed. Doses have varied from 30–150 mg of elemental zinc and studies against the tetracycline antibiotics have shown that minocycline is superior. Overall, good tolerance of doses at the usual doses of 200 mg of zinc gluconate or 30 mg of elemental zinc daily. Some side effects were noted including nausea and vomiting but are typically temporary and dose-dependent.[20]

A multicenter, randomized, double-blind, controlled trial of 332 patients comparing the efficacy of 30 mg of elemental zinc or 100 mg minocycline for three months against acne vulgaris demonstrated a clinical success rate of 31.2 percent for zinc and 63.4 percent for minocycline. Clinical success rate was defined as more than a 66.7 percent decrease in inflammatory lesions. Oral zinc may be an option where tetracyclines are contraindicated.[21] Risks associated with high doses of zinc intake include hypocupremia in which chronic high oral doses of greater than 100 mg of zinc daily can lead to low copper levels. This has been reported in cases of sickle cell disease. Hypocupremia is associated with microcytosis and relative neutropenia. These complications can be easily corrected with copper supplementation.[22]

The effects of topical zinc have also been examined in a clinical trial of 12 weeks involving 73 patients who received 4% erythromycin plus 1.2% zinc acetate compared to vehicle. The study was continued for 40 weeks after the 12-week double-blind phase by switching vehicle-treated patients to active treatment. In the first 12 weeks, statistically significant differences were noted in the efficacy of the erythromycin-zinc compared with vehicle for acne severity grades. After crossover, the vehicle-treated group receiving active therapy duplicated the improvement of the group initially treated with erythromycin-zinc.[23]

In a single-blind randomly comparative trial of tea versus zinc (n=47) for acne vulgaris, patients were treated with either 2% tea lotion or 5% zinc sulfate solution twice daily for two months. Those who had received the 2% tea lotion had a statistically significant reduction in inflammatory lesions. Patients receiving the 5% zinc sulfate solution had beneficial results that were not statistically significant.[24]

Niacinamide

Niacinamide is a water-soluble B vitamin also known as nicotinamide. Although it is derived from niacin, it does not cause the same side effects as niacin, such as flushing and low cholesterol. Topically, nicotinamide gel provides the anti-inflammatory activity without the risk of bacterial resistance. Four percent nicotinamide gel was compared to 1% clindamycin gel for the treatment of moderate inflammatory acne in a trial of 76 patients who received twice-daily treatment for eight weeks. At eight weeks, both treatments had comparable involvement in the Physician's Global Evaluation of Inflammatory acne: 82 percent of the patients treated with nicotinamide gel and 68 percent treated with clindamycin gel were improved (P=0.19). Both treatments produced similar reductions in acne lesion counts and acne severity rating.[25]

Rosacea

Niacinamide

Niacinamide also has been shown to be effective in the treatment of rosacea. In a study of 198 patients with either acne vulgaris or rosacea receiving nicotinamide 750 mg, zinc 25 mg, copper 1.5 mg and folic acid 500 µg for four weeks, 79 percent reported their improvement as moderately or much better (P<0.001) and, of those, approximately 55 percent (109 patients) reported moderate (26–50% reduction in lesions) or substantial (>50% reduction in lesions) improvement (P<0.001). Of all of the patients treated, 24 percent of them were on concomitant oral antibiotic therapym, while 74 percent were on monotherapy. Interestingly, the clinical response was not significantly different between these two groups.[26]

Feverfew

Feverfew (*Tanaceetum parthenium*) is an aromatic, perennial flowering plant, the leaves of which have been used in folk medicine for millennia. Its main compounds are: volatile oils (e.g., L-camphor, linalool, terpinenes); flavonoids and sesquiterperne lactones (e.g., parthenolides). The parthenolides are skin irritants that are removed through a patented process. Once this process is completed, the extract possesses antioxidative, anti-irritative and anti-inflammatory properties.[27]

Feverfew extract also exhibits activity against 5-lipo-oxygenase and inhibits proinflammatory cytokine release from macrophages, including TNF-alpha, IL-2, IL-4 and IFN-gamma. Feverfew also reduces neutrophil chemotaxis and NF-kappaB-dependent gene transcription and inhibits the release of IL-8 and adhesion molecules on keratinocytes.[28]

Licorice Extract

The main components of licorice (Glycyrrhiza glabra) extract are triterpene saponins (e.g., glycyrrizin), flavonoids (e.g., liquiritigenin) and isoflavonoids (e.g., glabridin).[29]

Licorice extract has anti-inflammatory properties and is also well documented to inhibit melanogenesis.[30–32] In a study of 62 subjects with mild-to-moderate facial redness placed on a four product skin care regimen for eight weeks, there was significant improvement in average erythema scores observed at four and eight weeks. The clinical assessments were erythema, subjective irritation, cross-polarized photography and self-assessment

questionnaires. Overall, it was shown that licorice improved the appearance of persistent facial redness.[33]

Green Tea

In addition to its anti-inflammatory properties, green tea is a potent antioxidant. It also provides natural protection from ultraviolet light, which is a rosacea trigger and inhibits the erythema response.[34,35]

Coffeberry

Coffee's bioactive profile contains many of the most important constituents known to exist within functional foods: flavonoids (catechins, anthcyanins), caffeic acid and ferrulic acid. Additional bioactive components found in coffee include: nicotinic acid, trigonelline, quinolinic acid, tannic acid, pyrogallic acid and caffeine.[36]

Scientific literature suggests that antibacterial and antiviral properties may be present in coffee, as well. Coffee is also rich in antioxidants.

Coffeeberry is the unripe stage of the coffee bean. Its polyphenols and related compounds help to prevent damage caused by free radical exposure and oxidative stress.[37–39] It has also been shown to protect against ultraviolet A and B radiation and is therefore beneficial for treating photoaging, dyspigmentation and erythema.[40]

Hyperpigmentation

Soy

Soybeans have been used as a source of protein and as a medicinal food in Asia for centuries. Soybeans were used in several food products that are traditionally Japanese, such as soy milk, tempeh, tofu, miso, natto and soy sauce. Tempeh, miso and natto are all made from the fermentation of the soybean. Soy protein products have been important to nutrition in the U.S. since the 1960s when they were incorporated into cereals as a protein supplement.[41]

Soy has been used in Traditional Chinese Medicine (TCM) for its benefits in nutrition, health and skin. The fatty acid component, which is about 15 percent, provides some anti-inflammatory properties, while the phytosterols and vitamin E provide moisture and barrier protection, as well as antioxidative benefit, respectively.

Small soy proteins, such as soybean trypsin inhibitor (STI) and Bowman-Birk inhibitor (BBI), function to inhibit pigmentation in the skin. Soy interferes with melanin transfer by inhibiting the protein-activated receptor 2 (PAR-2) pathway via trypsin inhibitors. PAR-2 is a G-protein-coupled receptor that regulates the ingestion of melanosomes by keratinocytes, and inhibition of this pathway results in reduced phagocytosis of melanosomes, reduced melanosome transfer and consequently reduced pigment production. The mechanism of action is thought to be the cleavage of peptide chains at the carboxyl side of the amino acids lysine and arginine by trypsin and UVB, allowing for binding of its ligand SLIGRL, the PAR-2 specific activating peptide.[42,43] Other sources of trypsin inhibitor include lima beans, yams, black-eyed peas and chick peas.[44]

In a three-month, open-label study comparing stabilized soy, 20% azelaic acid, 5% ascorbyl glucosamine, 1% kojic acid and alpha-hydroxyacid esters in the treatment of solar lentigos in Asian women, stabilized soy extract showed a significant lightning effect.[45] In a 12-week randomized, double-blind, vehicle controlled study comparing moisturizer with soy and vehicle in Fitzpatrick skin types I–III ages 31–60 years old with mottled hyperpigmentation, lentigines, blotchiness, tactile roughness and dullness, there was significant improvement in pigmentation, blotchiness, dullness, fine lines, overall texture, skin tone and appearance. Assessments included clinical observation, self-assessment, colorimetry and digital photography.[46]

Licorice Extract

Glabridin inhibits superoxide anions and cycloxygenase, which contributes to an anti-inflammatory effect. It was found that 0.5% glabridin inhibits UVB-induced pigmentation and erythema in guinea pig skin.[47] Lichochalcone A, derived from *Glycyrrhiza inflate*, is also known for its anti-inflammatory properties.

Liquirtin was compared to vehicle in a blinded controlled split-face study of 20 women aged 18–40 years with melasma in which they received treatment twice daily for four weeks. Seventy percent, or 16 patients experienced an "excellent" response (75–100% reduction) in pigmentation, and 60 percent experienced a 75–100 percent reduction in lesion size. Only 10 percent of those participants (two patients) treated with placebo vehicle showed any reduction in pigmentary intensity.[48]

N-acetylglucosamine

N-acetylglucosamine (NAG) is a monosaccharide derivative of glucose and monometric unit of chitin. Chitin (poly-N-acetyl-glucosamine) is one of the most common polymers found in nature. Structurally, chitin is related to cellulose, which consists of long chains of glucose molecules linked to each other; in chitin, however, the building block of the chains is a slightly modified form of glucose. Chitin is present in the shells of all crustaceans and insects, and in certain other organisms including many fungi, algae and yeast. Commercially, chitin is isolated from the shells of crustaceans after the edible parts have been removed.

NAG inhibits the conversion of protyrosinase to tyrosinase and as a result helps to inhibit pigmentation.[49] In an eight-week, double-blind, placebo-controlled, randomized, split-face clinical trial, 2% NAG reduced the appearance of facial hyperpigmentaion. The effects were even greater when it was combined with 4% niacinamide.[50]

Niacinamide

Niacinamide has also been shown to inhibit the transfer of melanosomes to keratinocytes, in addition to its effects on acne and rosacea. In a clinical study, 3.5% niacinamide/retinyl palmitate demonstrated significantly decreased hyperpigmetation and increased skin lightness compared with vehicle alone after four weeks of use in Asian women.[51]

Vitamin C

Magnesium-L-ascorbyl-2-phosphate (VC-PMG) is a stable derivative of ascorbic acid that, when administered topically on patients with melasma or solar lentigos, demonstrated a significant lightening effect in 19 of 34 patients.[52]

Issues with absorption and product stability have limited the use of vitamin C (Figure 2). Efforts have been made to circumvent this problem. Iontopheresis has been shown to increase the penetration of vitamin C leading to significantly decreased pigmentation compared to placebo in a randomized, double-blind, placebo-controlled study.[53]

Arbutin

Arbutin is a naturally occurring beta-D-glucopyranoside derivative of hydroquinone, which is found in pear (*Pyrus communis*), cranberry (*Vaccinium macrocarpon*), blueberry (*Vaccinium* spp.) and uva-ursi (*Arctostaphylos uva-ursi*).[54] Arbutin works by inhibiting melanosomal tyrosinase and DHICA (5,6-dihydroxyindole-2-carboxylic acid), two components required for melanogenesis. Most skin-lightening products contain alpha-arbutin, rather than arbutin. Arbutin exhibits tyrosinase inhibition in vitro and acts as a glycosylated hydroquinone.[55] It is currently available in 1–3% formulations and few controlled trials have been performed to determine its efficacy.

Aloesin

Aloesin, from aloe (*Aloe vera*), inhibits tyroinase and DOPA (3,4-dihydroxyphenylalanine). DOPA is a priming agent in the enzymatic conversion of tyrosine into melanin. Aloesin and arbutin can synergistically inhibit melanin production in vitro. Aloesin is derived from the aloe vera plant and has a similar tyrosinase inhibition effect as arbutin. In a clinical study evaluating the efficacy in conjunction with arbutin in preventing UV-induced tanning on the inner forearm, aloesin suppressed pigmentation by 34 percent, as compared to arbutin by 43 percent and the combination of the two by 63 percent.[56]

FIGURE 2. Vitamin C-rich oranges and juice. Photo by Scott Bauer. USDA.

Fatty Acids

Alpha linoleic acid is a polyunsaturated omega-3 fat, is found in soybeans, flaxseed, hemp seed, pumpkin seed, ocean-dwelling microalgae and cold-water fish. Linoleic acid, a polyunsaturated omega-6 fat, is found in nuts, seeds and vegetable oils. Other fats include: the omega-6 fat, gamma linoleic acid—which is found in black currant seeds and evening primrose; the omega-6 arachidonic acid, found in meat; and oleic acid, an omega-9 monounsaturated fat found in such sources as olive, almond, peanut, pecan, cashew and macadamia nut oils.

Topically applied linoleic acid was found to be efficacious in inhibiting UV-induced hyperpigmentation in guinea pig skin following the application of linoleic acid, alpha linolenic and oleic acid.[57] In a study of both guinea pig and human skin, four distinct areas on the human upper inner arm were exposed to UVB radiation five to seven times per week for two consecutive weeks, and test samples were applied twice daily for two months. In both the guinea pig and human group, liposomal linoleic acid application lightened the hyperpigmentation the most.[58]

Oral Agents in the Treatment of Hyperpigmentation

Proanthocyanidins

Proanthocyadins were first identified by a French scientist, Jacques Masquelier, who developed a process to extract these compounds from pine tree bark in 1951 and grape seed in 1970. He used the term "pycnogenol" to refer to this whole family of oligomeric proanthocyanidins or OPCs.

Pycnogenol, containing monomeric phenolic compounds (catechin, epicatechin and taxifolin) and condensed flavonoids has demonstrated antioxidant and anti-inflammatory properties.[59,60] In an open label 30-day trial of women with melasma, oral pycnogenol (25 mg thrice-daily) resulted in an improvement of hyperpigmentation.[61]

Grape Seed Extract

Vitis vinifera is a deciduous woody climber with coiled climbing tendrils and large leaves. There are 6,000 or more varieties of grape of which no more than 50 are commercially important. Most wine grapes and hybrids belong to *V. vinifera*. There are other Vitis species that are native to Asia, America and South Africa. The leaves, stems and fruits (including the seeds) are used.[62]

Grape seeds garnish cheeses or are pressed for oil. Grapeseed oil is used for cooking and is safe and potentially useful

as a dietary source of essential fatty acids and tocopherols. Grape skin extracts are colorants in food supplements and the drink industry.

Grape seed extract contains multiple active components including flavonoids, polyphenols, anthocyanins, proanthocyanidins, procyanidines and resveratrol. Consequently, grape seed extract has been reported to possess antioxidative, anti-inflammatory and anti-microbial activities.[63] In a study of UV-induced pigmentation in guinea pig skin, oral administration of grape seed extract has been shown to reduce this pigmentation.[64]

Polypodium Leucotomos

Polypodium leucotomos is a type of fern native to the tropical and subtropical regions of the Americas where in Honduras it has a long history of use as a traditional remedy. Commercial extracts of *P. leucotomos* have been available since the 1970s. When ingested, it functions as an antioxidant and provides systemic photoprotection by significantly decreasing UV-induced erythema and generation of cyclobutane pyrimidine dimers.[65]

Paper Mulberry

Paper mulberry (*Broussonetia papyrifera L.*) is a deciduous with milky sap the bark of which is composed of very strong fibers that are also used for making high-quality paper and cloth. The extracts of paper mulberry root are potent inhibitors of tyrosinase. A 0.4 percent concentration of paper mulberry extract inhibits tyrosinase by 50 percent compared to 5.5 percent for hydroquinone and 10 percent for kojic acid without causing significant irritation.[66]

Anti-aging (Antioxidants)

Antioxidants have been shown to help reduce the signs of intrinsic (natural) aging, while restoring skin and protecting from extrinsic (environmental) aging.[67] They reduce the appearance of fine lines and wrinkles and even skin tone, giving a smoother texture to the skin. This is accomplished by quenching free radicals before extensive damage occurs from everyday environmental factors (e.g., sun, wind, heat, pollution).[68] Many of the above-mentioned natural ingredients—such as feverfew, vitamin C, tea extracts, pycnogenol, grape seed extracts and licorice—also possess antioxidative properties. The following will elaborate where necessary on these ingredients as well as touch upon the antioxidative capabilities of those ingredients not already mentioned.

Retinoids (Vitamin A)

Retinoids have been shown histopathologically to decrease stratum corneum cohesion, normalize the epidermal-dermal junction, increase collagen, elastin and fibronectin and increase glycoaminoglycans. In addition, it decreases melanin, collagenases and metalloproteinases, improves angiogenesis and is comedolytic. Retinyl esters are hydrolyzed to form retinol and this is then oxidized to form retinaldehyde which is finally oxidized into retinoic acid, the most efficacious form of retinoids.[69]

Retinol is the metabolic precursor to retinoic acid and can reverse photodamage while causing less irritation. Topical retinol 0.1% applied to photodamaged skin for seven days results in increased fibroblast growth and collagen synthesis, decreased matrix metalloproteinases and was found to improve skin texture and clarity, sallowness, mottled hyperpigmentation, pore size and overall photodamage versus baseline and vehicle.[70,71]

Alpha Hydroxy Acids

Alpha hydroxy acids (AHAs) consist of glycolic (sugar), lactic (milk), tartaric (grape), citric (citrus), malic (apple) and phytic (rice) acids. They generally function as exfoliants by reducing corneocyte cohesion and moisturizers by increasing dermal glycosaminoglycans (GAGs) and also increase collagen synthesis and elastin. AHAs reduce hyperpigmentation and improve signs of photoaging.

Vitamin C

Vitamin C is a potent antioxidant that stimulates collagen synthesis via direct activation of collagen gene regulation through its role in prolyl hydroxylase and lysyl hydroxylase formation. Vitamin C is in its natural form, as L-ascorbic acid, and a pitfall of its use in topical skin care products is its relative instability in the presence of air and other oxidizing agents. Oxidized vitamin C is not only incapable of boosting collagen synthesis or scavenging free radicals but may actually promote free radical formation, causing damage to vital molecules such as proteins and DNA. Fortunately, processes to circumvent this problem have been developed, ensuring stabilized L-ascorbic acid. A stabilized vitamin C also helps regenerate alpha-tocopherol.[72–74]

Vitamin E

Alpha tocopherol (vitamin E) is a major lipid-soluble antioxidant in the human epidermis. It acts as a lipid radical scavenger and is especially useful for terminating lipid radical chain reactions, thus protecting cellular membranes from lipid peroxidation by free radicals. Depletion is an early and sensitive marker of environmental oxidative damage.[75,76]

Pycnogenol

In addition to antioxidative and photoprotective effects, Pycnogenol has also been found to be chemoprotective. In a study of UV-irradiated hairless mice, 0.2% topical pycnogenol delayed tumor formation from 100–85% versus control. Because of dose-dependent reductions in inflammatory sunburn reaction and immunosuppression, pycnogenol may be a useful complement to sunscreens.[77]

Niacinamide

Niacinamide is a precursor to niacin and is an essential component in coenzyme 1 (oxidized form of nicotinamide adenine

dinucleotide [NAD] and coenzyme 2 (reduced form of NADP). In addition to its anti-acne, rosacea and pigmentation properties in which niacinamide improves barrier function, reduces facial erythema and pigmentation, it also reduces skin sallowness and improves skin texture and pore size by reducing sebum production. With respect to anti-aging, a reduction in facial rhytides has been noted with an increase in dermal collagen production and decreased excess dermal glycosaminoglycans production.

Natural Shiitake Complex

Shiitake mushrooms have exhibited antioxidant properties through enhanced superoxide dismutase activity that converts harmful free radicals into less damaging species and diminished elastase enzyme activity, inhibiting the enzyme that breaks down elasin. Through AP-1 activation, the production of enzymes that break down collagen is inhibited and the growth of epidermal skin cells is stimulated.

Açai Berry

The açai berry grows on the Amazon Heart of Palm tree in Brazil and is similar in taste to a wild raspberry or grape. It has been used in wines, liqueurs, flavorings, colorants and ingested as a juice. Acai berries are high in essential fatty acids—60 percent oleic acid (omega-9) and 12 percent linoeic acid (omega-6)—and contain phytosterols.[78]

The açai berry contains a class of flavonoinds known as anthocyanins and the oxygen radical absorbance capacity (ORAC) antioxidant value is thought to be higher than that of other edible berries. Besides its health properties, it may be useful as a radiocontrast agent for nuclear magnetic resonance imaging (MRI) of the gastrointestinal tract.[79] At this time, the use of açai berry as a topical skin care ingredient is limited due to the risk of staining in high concentrations.

Coffeeberry

The coffee plant, *Coffea arabica*, originates from Ethiopia and is thought to have been introduced into the West Indies and the Americas in the 1700s. The unripe stage of the coffee bean, coffee berry extract has demonstrated significant antioxidative activity.[77–79]

Curcumic/Turmeric

Turmeric (*Curcuma longa*) is widely known as a ubiquitous spice used in Asian/Indian cuisine and is also found in topical and cosmetic skin care products in South Asia. It has long been touted as an anti-inflammatory agent in TCM and Ayurvedic medicine to treat sprains and swelling following trauma.[80] Curcumin, the major biologically active component of turmeric, has shown potency against acute inflammation, and has exhibited wound-healing, anti-carcinogenic, anti-inflammatory and antioxidative properties.[80,81]

Topical application of curcumin has been shown to inhibit initiation and promotion of tumorigenesis in various animal models.[82] Furthermore, 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. Because of its great potential as a therapeutic agent for wound repair, topical curcumin is considered one of the only safe therapies for radiation exposure.

Pomegranate

Pomegranate (*Punica granatum L.*) fruit is native from Iran to the Himalayas in northern India and has been consumed since ancient times. The extract is primarily composed of alkaloids and polyphenols and the active constituent is ellagic acid, a naturally occurring phenolic compound found in many fruits and nuts. In addition to possessing antioxidative activity in which the juice is thought to have more antioxidative benefits than comparable quantities of green tea and wine, pomegranate extract has also demonstrated anti-viral activity. The peel fractions may foster dermal regeneration and pomegranate seed oil fractions may facilitate epidermal regeneration.[83]

Pomegranate has also exhibited photoprotective properties and can enhance the sun protection factor (SPF) rating of topical sunscreens. In several studies, the SPF was found to increase by 25 percent after the ingestion of one pomegranate tablet containing 5% ellagic acid. The mechanism of action was studied in vitro and thought to be via the inhibition of UVA-mediated activation of signal transducers and activators of transcription 3 (STAT3), AKT and extracellular signal-regulated kinase (ERK1/2) by the pomegranate fruit extract.[84]

Soy

The primary metabolites of soy are isoflavones, genistein and diadzein and are referred to as phytoestrogens for their weak estrogenic effect. Several studies indicate that postmenopausal women have a thinner dermis and less collagen compared to premenopausal women. It is widely known that topical estrogen can retard skin thinning and collagen loss due to the presence of high amounts of estrogen receptors in the granular layer of the epidermis. This could potentially suggest a role for these metabolites of soy. Nevertheless, patients with history of or high risk for estrogen-sensitive tumors should avoid ingestion of excessive amounts of soy.

Genistein also possesses capabilities related to inhibition of reactive oxygen species, DNA damage and proto-oncogene expression. It has been shown to inhibit the initiation and promotion of skin carcinogenesis in mouse skin and UVB-induced erythema in human skin.[85] In a placebo-controlled in vivo study, topical application of a soy isoflavone emulsion significantly enhanced the number of dermal papillae after two weeks, which is important considering that flattening of the dermal-epidermal

junction is the most reproducible change in aging skin, indicating that topical soy can "rejuvenate the structure of mature skin."[86] In a 2008 study, skin sites treated with topical soybean phytosterols "showed an appreciable recovery of skin barrier function" compared to those treated with the control vehicle.[87] Other studies have suggested that topical soy isoflavones serve a potent role against photoaging and photodamage.[88]

CONCLUSION

The incorporation of natural ingredients in the treatment of common skin conditions is becoming increasingly prevalent. Frequently, prescribed medications for the management of acne, rosacea, psoriasis and hyperpigmentation may be fraught with irritating components leading patients and physicians alike to search for natural ingredients as a more acceptable alternative. The persistent quest for anti-aging has also resulted in a boon for natural ingredients in cosmeceuticals.

While preliminary findings are promising, several of these natural ingredients are limited by the lack of information regarding their activity in vivo. It is without doubt that further investigation is needed to fully ascertain and measure, as appropriate, the maximum benefits of these natural ingredients in skin therapeutics and rejuvenation.

DISCLOSURES

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Dr. Fowler is a consultant for: Ferndale, Galderma, Graceway, Hyland, Johnson & Johnson, L'Oreal, Quinnova, Ranbaxy, Stiefel, Triax and Valeant. He is on the speaker's bureau for: Galderma, Medicis, Ranbaxy, Shire, Stiefel and Valeant. He is a research investigator for: Abbott, Allerderm, Allergan, Amgen, Astellas, Centocor, Coria, Dermik,Dow, Galderma, Genentech, Johnson & Johnson, Medicis, Novartis, Quinnova, Shire, Stiefel, Taisho, Taro and 3M.

Dr. Woolery-Lloyd is an investigator, speaker, and is on the advisory board for Johnson & Johnson. She is an investigator and consultant for Allergan; is on the advisory board for Galerma; an is a speaker for Stiefel/GlaxoSmithKline.

Dr. Waldorf is on the speaker's bureau and advisory board for Allergan, Medicis and Unilever. She is a consultant for Avon, Bioform/Merz, Proctor & Gamble and Johnson & Johnson.

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ADDRESS FOR CORRESPONDENCE

Joseph F. Fowler Jr., MD, FAAD
University of Louisville Division of Dermatology
501 S. 2nd St.
Louisville, KY 40202
E-mail:..... fowlerjoe@msn.com

CME Post-Test: Please select your best answer for each of the following questions and insert into the Answer Grid found on the Evaluation/Certificate Request Form on the next page and **return along with your completed Evaluation/Certificate Request Form** to *JDD* by fax to (212) 213-5435, mail to 377 Park Avenue South, 6th Floor, New York, NY 10016, or to complete this activity online, please visit www.JDDonline.com in the Medical Education Library. Successful completion of the Post-Test is required to earn *AMA PRA Category 1 Credit*™.

1. The efficacy of natural ingredients in skin care products depends on the following factor(s):

   a. Whether there is in vivo activity, not just in vitro.
   b. The type of vehicle used to deliver the product to the skin.
   c. Whether the ingredient or product is biologically active and stable once applied to the skin or ingested.
   d. Whether the product is cosmetically acceptable with respect to color, odor and texture.
   e. All of the above.
   f. None of the above.

2. In colloidal oatmeal, the compound or class of compounds that has generated the most research interest recently is:

   a. Alliin.
   b. Selenium.
   c. Vitamin K.
   d. Avenanthramides.
   e. All of the above.

3. In psoriasis, a study of 30 patients found that what percentage of patients demonstrated significant improvement in the Psoriasis Area and Severity Index (PASI) after treatment with aloe vera compared to placebo?

   a. 23.3 percent.
   b. 83.3 percent.
   c. 13.3 percent.
   d. 47.7 percent.
   e. None of the above.

4. In acne, what natural ingredient was found to be 3.55 times more effective than placebo for total acne lesion count and 5.75 times more effective than placebo for acne severity index in a 2007 study?

   a. Tea tree oil.
   b. Olive oil.
   c. Camphor oil.
   d. Menthol.
   e. None of the above.

5. The polyphenols and related compounds in coffeeberry are beneficial for treating photoaging, dyspigmentation and erythema mainly because they protect against:

   a. Free radicals removing negatively charged electrons from biological molecules.
   b. Wind damage.
   c. Hyperplasia.
   d. Ultraviolet A and B radiation.
   e. None of the above.

6. In a 2009 one-month, open-label study in women with what condition did oral pycnogenol (25 mg thrice-daily) result in improvement in hyperpigmentation?

   a. Urticaria.
   b. Darier's disease.
   c. Melasma.
   d. Tinea capitis.
   e. None of the above.

7. In several studies, oral ingestion of what extract increased the sun protection factor (SPF) by 25 percent?

   a. Pomegranate.
   b. Carrot.
   c. Spinach.
   d. Mandarin orange peel.
   e. None of the above.
   f. All of the above.

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Innovations in Natural Ingredients and Their Use in Skincare

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this Evaluation/Certificate Form and return to *JDD* by fax to (212) 213-5435, mail to 377 Park Avenue South, 6th Floor, NY, NY 10016, or complete online at JDDonline.com in the Medical Education Library. ***You must complete and submit this form or complete the CME activity online to receive credit for completing this activity.***

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1 2 3 4 5

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1 2 3 4 5

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1 2 3 4 5

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_____

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_____

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Name one thing you intend to change in your practice as a result of completing this activity:

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Signature		Date	

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

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