COSMETIC BENEFITS OF NATURAL INGREDIENTS

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Media/Method of Participation: Journal article, web-based post-test, and evaluation
Hardware/Software Requirements: Any web browser

Statement of Need

The use of products using natural ingredients for skin care have evolved significantly in recent years. Advances in the understanding of the mechanisms and biochemistry of natural ingredients has led to the development of new technologies and product formulations that provide benefits to the management of various cutaneous disorders as well as the natural aging process. Therefore it has become increasingly important for dermatology health care practitioners of all experience levels to have access to the latest evidence-based research on advances in the understanding of product containing natural ingredients and clinical experience in their application to the practice of dermatology.

Educational Objectives

This activity is designed to increase the knowledge of dermatology clinicians and residents on the latest research and new advances in skincare products with natural ingredients. The goal of the activity is to allow participants to explore emerging research on the intrinsic and extrinsic benefits of natural ingredients and their application in patient-care. Participants will gain information on how to practically apply this research and knowledge to real, day-to-day, patient encounters.

Upon completion of this enduring material, participants should be able to:

- Identify the active natural ingredients and their clinical uses in disorders of the skin
- Classify active natural ingredients and their cosmetic benefits in skincare products
- List key properties of natural ingredients and their relative usage in inflammatory dermatoses
- Review scientific efficacy, development, and clinical studies regarding the science of natural ingredients in skin care
- Recall the safety, stability, tolerability, and efficacy of natural ingredients

Target Audience

This activity is designed to increase the knowledge of dermatology clinicians and residents on the latest research and new advances in skincare products with natural ingredients.

Accreditation Statement

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ORIGINAL ARTICLES
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Cosmetic Benefits of Natural Ingredients

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ABSTRACT

Photoaging is a leading concern for patients and many of these patients will express a desire to utilize natural ingredients as treatment. Mushrooms, feverfew, green tea, licorice, olive oil, soy, and coffee berry have been shown to have antioxidant properties and may play a role in the treatment and prevention of photoaging. In this manuscript, the most recent select basic science and clinical studies examining the mechanisms and efficacy of these ingredients will be discussed.

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INTRODUCTION

Photoaging is a leading concern for patients seeking dermatologic care. The long-term effects of ultraviolet (UV) radiation include rhytides, dyschromia, lentigines, actinic damage, and malignant neoplasms. As public knowledge has increased regarding the link between sun exposure and photoaging, patients have become interested in both preventing and treating the adverse effects of UV radiation.

Today's dermatology patient has often sought online medical advice prior to their consultation, and may have a strong desire to utilize only organic and natural ingredients. What is meant by the terms "organic" and "natural"? Organic is a term designated by the United States Department of Agriculture (USDA), but it is not regulated by the US Food and Drug Administration (FDA). To complicate matters, the FDA has no definition for the term natural. Despite a lack of standardized guidelines across organizations to set parameters for organic labeling, organic products have multiplied and some organic products may be equally, if not more, modified than conventional products. In addition, natural products are not necessarily organic. For the purposes of this article, natural products will refer to ingredients derived from nature, mainly plants, which are later improved upon in the laboratory. This improvement is what allows the natural ingredient to perform its intended effect on the skin: by increasing its ability to penetrate into the epidermis, by allowing it to remain on the skin without denaturing, and by ensuring that it plays an active role in vivo.

Natural products have gained popularity in recent years due to the presence of antioxidants, and increased use of this term in the popular media. Free radicals are highly reactive oxygen species that can cause significant damage to lipids, proteins, carbohydrates and DNA. They accumulate during daily activities such as respiration and exercise, but can be exacerbated by inflammation, drugs, and the environment, enhancing the degree of oxidative damage.[1] The environmental factors that can drastically increase free radical production include UV radiation, smoking, and stress. Free radical production can overwhelm endogenous antioxidant activity, leading to oxidative stress and contributing to the aging process. Replenishment of endogenous antioxidant stores with natural products containing a wealth of antioxidants is protective against oxidative damage.

Natural products that may play a role in preventing and treating photoaging include mushrooms, feverfew, green tea, licorice, olive oil, soy, and coffee berry. In this review, we will discuss clinical studies to support this claim, with basic science studies included when there is a paucity of clinical data. It is important to remember that while basic science data may hint at the efficacy of a product or its mechanism of action, this will not necessarily translate to in vivo effect or mechanism. Although it is encouraging that the clinical studies discussed show a benefit when used in human subjects, the studies are limited and the data is not powered to allow for definitive recommendations. As an additional caveat, some mentioned studies discuss the use of extracts, or ingredients obtained from a particular substance. Extracts do not always contain all of the active ingredients of the original product and can vary from one another based on the method of removal. This variation makes it difficult to generalize data from individual studies, especially when the method of extraction, ingredients within the extract, and additive substances are not defined.

Mushrooms

Mushrooms have been utilized for medicinal purposes for many years. They contain potent antioxidants, including phenolic acids, flavonoids, tocopherols, ascorbic acid, and carotenoids.[1] Mushroom polysaccharides prevent oncogenesis, exhibit antitumor activity, and prevent tumor metastasis via activation of the host immune response.[2] Mushroom species vary in composition, and some mushrooms may exhibit minimal antioxidant properties. In addition, the efficacy of mushrooms can be affected by variations in preparation.

In addition to shiitake (*Lentinus edodes*) and reishi (*Ganoderma lucidum*) mushrooms, which have anti-irritant and antioxidant properties,[3] *Cordyceps taii* and *Sparassi crispa* show promise for the treatment of photoaging. *Cordyceps* species have been utilized for years in traditional Chinese medicine. In vitro studies have shown that aqueous extracts (freeze-dried samples) of *Cordyceps sinensis* and *militaris* exhibit antioxidant properties.[4] Xiao et al conducted an in vivo study on D-galactose aged mice, to evaluate the ability of *Cordycepts taii* extracts to reduce oxidative stress and enhance endogenous antioxidant production. Polysaccharides from *C. taii* promoted endogenous antioxidant activity while also scavenging free radicals and inhibiting lipid peroxidation.[5]

Veratric acid is phenolic acid found in *Sparassis crispa*. After exposing HaCat keratinocytes to UVB, some cells were treated with veratric acid and the remaining cells received no post-UV treatment. Veratric acid-treated cells exhibited a reduced amount of DNA damage, a decreased number of cyclobutane pyrimidine dimers, and prevention of UVB-mediated apoptosis.[6] Shin et al also conducted a UVB erythema test on 18 human subjects who applied veratric acid or the vehicle to their forearms for 30 minutes prior to exposure to 1.5 MED. Erythema was measured at 0, 1, 2, 3, and 6 days after exposure. Participants who applied veratric acid displayed significantly reduced ($P < 0.01$) UV-induced erythema as compared to the vehicle-treated control group. No allergic or irritant reactions were noted after application of veratric acid to the skin.[6]

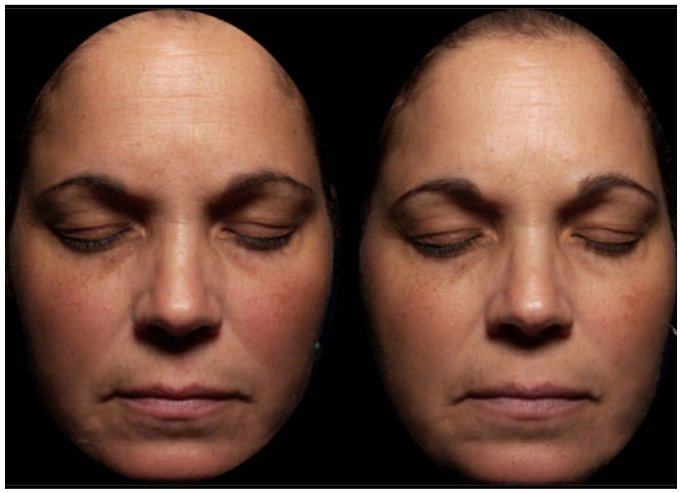
Feverfew

Feverfew (*Tanacetum parthenium*) is a member of the *Asteraceae* family, which also includes daisies and chrysanthemums. Originally used as a fever reducer, it is known to have anti-inflammatory, anti-irritant, and antioxidant properties.[3] It contains volatile oils, flavonoids, and sesquiterpene lactones,[7] including parthenolide, a potent contact sensitizer. To avoid the complications associated with parthenolide, parthenolide-depleted feverfew extracts have been developed.

Parthenolide-depleted feverfew is believed to enhance DNA repair activity via activation of a PI3K-dependent Nrf2/ARE pathway. Phosphatidylinositol-3-kinase (PI3K) is a signaling kinase that induces Nrf2 to bind to the antioxidant response element (ARE) promoter. Among many functions, the ARE promoter ultimately regulates the transcription of antioxidant proteins. Parthenolide-depleted feverfew extract was shown to significantly reduce both UVA and UVB-induced DNA damage of human keratinocyte cells after UV exposure, thus reducing the degree of oxidative damage.[8]

In a randomized double-blinded study of 12 participants, topical formulations of 1% parthenolide-depleted feverfew and placebo were applied to the skin of the back twice daily for two days, irradiated with UVB at 0.5, 1.0, and 1.5 MED, and then re-applied for two days. Erythema was evaluated at 24 and 48 hours post-irradiation. The feverfew-treated skin showed a statistically significant ($P < 0.05$) decrease in erythema at 24 and 48 hours post-irradiation as assessed by clinical grading and confirmed by chromameter readings.[9] Figure 1 demonstrates a subject who used a topical feverfew product on her face for 3 weeks. The significant reduction in erythema is clearly evident.[10]

FIGURE 1. Purified feverfew extract: benefit for sensitive skin. This patient demonstrated significant reduction in the appearance of redness in the cheek area.



Green Tea

Green tea is derived from the *Camellia sinensis* plant. It has garnered much attention due to its antioxidant, photochemopreventive, and anti-aging effects, which are attributed to polyphenols such as epicatechin, epicatechin-3-gallate, epigallocatechin, and epigallocatechin-3-gallate. Although topical green tea has been utilized as monotherapy, we review two studies that enhance its effects with adjunct ingredients.

One such study examined tannase-converted green tea extract. Tannase is an inducible enzyme that can enhance the effect of polyphenolic compounds. 42 Korean females were asked to apply either a tannase-converted green tea extract or a normal green tea extract to their crows' feet twice daily for 8. Although both extracts displayed free radical scavenging activity, the tannase-converted green tea extract exhibited significantly higher activity ($P < 0.01$). While both extracts displayed anti-wrinkle effects, as measured by a Skin-Visiometer SV 600 (Courage and Khazaka electronic GmbH), the tannase-converted green tea extract showed a more visible decrease in small wrinkles and deep furrows.[11] The methods by which these extracts were produced were not detailed.

Lotus plant extract has been shown to improve the efficacy of green tea in the treatment of rhytides. In a placebo-controlled,

split-face study involving 33 Asian males, participants were divided into three groups. Each group applied one of the following formulations onto half of their face: green tea only, lotus only, or a combination of green tea and lotus. The other half of the face was treated with a placebo. Although both green tea and lotus independently improved the appearance of rhytides, combination treatment with green tea and lotus most significantly improved the appearance of rhytides ($P = 0.003$ at 60 days).[12]

The combination appeared to have a synergistic effect, allowing for lower concentrations of each ingredient to be utilized in the combination formulation. Again, the methods by which the lotus and green tea extracts were obtained were not further characterized by the authors.

Licorice

Licorice extract is derived from *Glycyrrhiza glabra* and active compounds of licorice extract include licochalcone A, glabridin, liquiritin, and glabrene. Glabridin has an anti-inflammatory effect while liquirtin has been used for the treatment of hyperpigmentation.[7] Licochalcone A is a phenolic compound with antibacterial, anti-inflammatory, and antitumor effects.

Twelve volunteers had test sites on their back treated with a 1.4 minimal erythemal dose of UV light. Directly following treatment and 5 hours after treatment, a control (vehicle) formulation or a test formulation containing 0.05% licochalcone A extract was applied. This extract was composed of 20% licocalchone A, contained no terpenes or flavonoids, and was produced via aqueous extraction. As compared to the vehicle-treated sites, participants treated with licochalcone A showed significantly reduced erythema ($P < 0.05$). This same study evaluated the use of licochalcone A on the irritated shave sites of 45 subjects and found that prostaglandin E2, leukotriene B4, IL-6, and TNF-alpha were all reduced by the extract.[13] These findings support an anti-inflammatory as well as a photoprotective role for licorice extract.

Olive Oil

Olive oil (*Olea europaea*) is considered one of the healthiest forms of dietary fat, has anti-inflammatory effects, and may be useful in a variety of dermatologic conditions.

Ichihashi et al divided 75 hairless female mice into 5 groups, the control group of which was treated with UVB radiation only. Two groups were treated with either extra virgin olive oil or regular olive oil after UVB radiation and two groups were treated with either extra virgin olive oil or regular olive oil before UVB radiation. Only extra virgin olive oil applied to the skin of mice immediately after UVB exposure was shown to delay the onset and reduce the incidence of skin cancer development. The mechanism of action was believed to be via reduction of 8-hydroxy-deoxyguanosine (8-OHdG) formation, based on the reduced number of 8-OHdG positive cells in mice treated with extra virgin olive oil. Cyclobutane pyrimidine dimers and (6-4) photoproducts were not reduced by any of the treatment arms. The authors postulated that extra virgin olive oil applied to human skin after sun exposure could play a role in the prevention of skin cancer, although further research would be necessary in order to support this hypothesis.[14]

Much like feverfew, olive oil is believed to protect against oxidative stress via upregulation of antioxidant response elements. Olive oil derived fatty acid ethoxylates were found to increase transcription of an ARE reporter cell line to levels four to five times higher than the control as measured by luminescence.[15] In addition, human skin keratinocytes and fibroblasts treated with fatty acid ethoxylates displayed increased heme oxygenase 1 (Ho-1), an enzyme thought to monitor and repair damage by reactive oxygen species.[15] Therefore, not only does olive oil appear to increase endogenous antioxidant levels, it also allows the cells to better manage oxidative stress.

Chamomile

Chamomile is a medicinal herb with anti-inflammatory and emollient properties and bisabolol is a sesquiterpene alcohol extract from chamomile. Chamomile has been utilized to treat pruritus, modulate photodamage, and improve the texture and elasticity of the skin.[16] Bisabolol application at concentrations ranging from 0.01-0.0001% displayed significant inhibition of hydrogen peroxide-induced reactive oxygen species in fibroblasts.[17] These findings support the antioxidant properties of chamomile and suggest that it may be a useful ingredient to treat photoaging. As clinicians, it is important to recognize that chamomile cross-reacts with ragweed, and should therefore be used with caution in patients with ragweed allergy.[16]

Colloidal Oatmeal

Fine grinding of oat (*Avena sativa*) and subsequent boiling produces colloidal oatmeal. It is best known for its use in atopic dermatitis and its ability to hydrate the skin. Oats also display antioxidant properties, and are believed to protect and repair the skin and hair from UV radiation, free radicals, and smoke.[18]

Colloidal oatmeal is composed of polysaccharides, proteins, lipids, saponins, flavonoids, vitamins, and avenanthramides.[7] The main antioxidants in oats are polyphenolic alkaloids called avenanthramides. Avenanthramides consumed orally are bioavailable and have been shown to enhance antioxidant defenses.[19] Although the topical antioxidant benefits of colloidal oatmeal have not been studied extensively, this may be a promising agent to treat photoaging.

Criquet et al found that personal care products containing oatmeal were very tolerable, with a low potential to cause irritation and sensitization. Only 1% of subjects (23 out of 2291) experienced a transient, low-level erythema. Participants also

displayed a significant moisturizing effect, as determined via use of a Corneometer® CM 825 (Courage + Khazaka Electronic GmbH, Germany), which was present up to two weeks after discontinuing treatment.[20] Effective moisturizing potential is important to the photoaged population, as many of these patients will present with xerosis and an impaired skin barrier. A safe, tolerable, natural moisturizing agent with low irritant potential makes for an excellent product to rapidly improve skin appearance.

Acai Berry

Acai is a berry that grows on the acai palm tree (*Euterpe oleracea*). An evidence-based systematic review of acai by the Natural Standard Research Collaboration, which summarizes efficacy data via a validated, reproducible grading algorithm, concluded that acai is a potent antioxidant.[21] When acai polyphenolics were applied to HL-60 leukemia cancer cells, cell proliferation decreased.[22] The antioxidant capability of acai berry is believed to be greater than that of other berries. However, topical use of this supplement is challenging given the risk of skin staining at high concentrations.[7] Perhaps for this reason, there is a paucity of clinical research on the use of acai berry for the treatment and prevention of photoaging. A clinical trial evaluating the use of a dietary supplement containing pomegranate, apple, and acai is seeking to evaluate erythema inhibition, antioxidant concentration, skin hydration, skin firmness, and skin texture in study subjects as compared to placebo. The study has closed but the results are not yet available.[23]

Soy

Soy extracts are found in many cosmetic products. Lipids, lecithins, and phytosterols enhance the normal skin barrier, while isoflavones impart an antioxidant effect. A study of hairless mice examined the effects of a soy isoflavone extract from soybean cake composed of daidzein, genistein, glycitein, acetyldaidzin, acetylgenistin, and acetylglycitin. Extract-treated mice and untreated mice were exposed to UVB radiation. Treated mice showed a decrease in UVB-induced death of keratinocytes and reduced erythema. The skin of extract-treated mice also displayed less transepidermal water loss and less apparent wrinkles. Many of these results were deemed secondary to reduced oxidative stress.[24]

Serine protease inhibitors such as soybean trypsin inhibitor (STI) and Bowman-Birk protease inhibitor (BBI) play a role in pigment development. Wallo et al tested a formulation containing nondenatured STI and BBI (as heat can inactivate these protease inhibitors) on 68 females with Fitzpatrick skin types I to III. All patients had moderately rough, blotchy, dull skin, mottled hyperpigmentation and lentigines at baseline. The women were randomly selected to apply either the active moisturizer or the vehicle daily for 12 weeks. Both formulations contained SPF 30. Although both groups showed improvement from baseline, the active moisturizer group exhibited enhanced performance ($P < 0.05$) in improvement of overall texture, blotchiness, dullness, fine lines, overall tone, and overall appearance.[25]

The use of soy is controversial among consumers, who worry about an increased risk of endometrial and breast cancer development. A recent Cochrane Review of the use of oral phytoestrogens for menopausal vasomotor symptoms found that phytoestrogens were not associated with an increased risk of endometrial or breast cancer when used for up two years. Unlike hormone replacement therapy, phytoestrogens did not have an estrogen agonistic effect on the endometrium. Long-term safety studies have not been conducted.[26]

Coffee Berry

Coffee berry is the fruit of the coffee plant (*Coffee Arabica*). It contains polyphenols, including chlorogenic acid, anthocyanins, quinic acid, and ferulic acid.[16] Polyphenols are believed to impart antioxidant as well as anti-inflammatory properties.

One patented formulation of coffee berry appears to have antioxidant capacity that rivals green tea extract. In a clinic trial of this specific formulation, patients treated actinic damage with a 0.1% cleanser, a 1% day cream (containing also 7.5% octinate and 4% oxybenzone), and a 1% night cream. Two-thirds of the patients applied the products to their entire face, showing statistically significant improvement in fine lines, wrinkles, pigmentation, and overall appearance compared to baseline. One-third of the patients applied the product to only half of their face, showing statistically significant improvement in fine lines, wrinkles, pigmentation, and overall appearance compared to the vehicle-treated half of the face.[27]

CONCLUSIONS

Patients are highly motivated to treat and prevent photoaging, and may inquire as to the availability of natural ingredients to treat rhytides, dyschromia, and actinic damage. As dermatologists, we can provide guidance as to which ingredients may be of benefit based on available scientific evidence. Mushrooms, feverfew, green tea, licorice, olive oil, soy, and coffee berry all display antioxidant properties. They are among the most scientifically sound natural ingredients available to consumers. Importantly, we can also help direct patient to those proprietary formulations that have undergone clinical testing and demonstrate safety and efficacy. Just because a product label lists an ingredient does not mean that ingredient is stable or active once it reaches the skin. It is important to remind patients that the efficacy of a product relies on the stability of the ingredients, their ability to penetrate the skin, and their capability to act in vivo. This is a very exciting area, and as consumer interest in natural ingredients continues to grow, the science behind these ingredients grows stronger each year.

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1. Olive oil is derived from *Olea europaea* and has been shown to have anti-inflammatory as well as photoprotective effects. What is its presumed mechanism of action in reducing the onset of skin cancer development?

a. Reduction of cyclobutane pyrimidine dimers

b. Reduction of 8-hydroxy-deoxyguanosine formation

c. Increased transcription of ARE reporter cell line

d. Reduction of 6-4 photoproducts

e. Activation of PI3K-dependent Nrf2/ARE pathway

2. Acai berry is a potent antioxidant. It's use in topical preparations is limited due to:

a. Allergic contact dermatitis

b. Carcinogenic potential

c. Irritant contact dermatitis

d. Skin staining

e. Greater antioxidant activity of other berries

3. Colloidal oatmeal is best known for its role in barrier maintenance. The main antioxidant in colloidal oatmeal is:

a. Avenanthramide

b. Veratric acid

c. Epicatechin

d. Glabrene

e. Isoflavone

4. Naturally-derived ingredients can have cutaneous side effects if certain components are not removed in a laboratory setting. Which component of feverfew is a potent contact sensitizer?

a. Flavonoid

b. Bisabolol

c. Anthocyanin

d. Daidzein

e. Parthenolide

5. Mushrooms have been shown to prevent oncogenesis, exhibit anti-tumor activity, and prevent tumor metastasis. Mushrooms include all the entities listed below except for:

a. Lentinus edodes

b. Ganoderma lucidum

c. Glycyrrhiza glabra

d. Cordyceps taii

e. Sparassi crispa

Evaluation Form

Cosmetic Benefits of Natural Ingredients

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Post-test Answer Key

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Please answer the following questions by circling the appropriate rating:

1 = Strongly Disagree	*2 = Disagree*	*3 = Neutral*	*4 = Agree*	*5 = Strongly Agree*

Was timely and will influence how I practice
1 2 3 4 5

Enhanced my current knowledge base
1 2 3 4 5

Addressed my most pressing questions
1 2 3 4 5

Provided new ideas or information I expect to use
1 2 3 4 5

Addressed competencies identified by my specialty
1 2 3 4 5

Avoided commercial bias or influence
1 2 3 4 5

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Name one new strategy you learned as a result of completing this activity:

_____

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

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Please list any topics you would like to see addressed in future educational activities:

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