A SUPPLEMENT TO

JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS

Advances in Natural Ingredients and Their Use in Skin Care

CME Supplement

Take the Online CME Test Now for Instant Results!

ISSN: 1545 9616

September 2013 • Volume 12 • Issue 9 (Supplement)

JO0913

Disclosure of Commercial Support

This supplement to the *Journal of Drugs in Dermatology* has been made possible by an unrestricted educational grant from Johnson & Johnson Consumer Companies, Inc.

This supplement to the *Journal of Drugs in Dermatology* is supported by Johnson & Johnson Consumer Companies, Inc,

CONSUMER PRODUCTS COMPANY

Division of Johnson & Johnson Consumer Companies, Inc.

CME

EDITORIAL

ORIGINAL ARTICLES

ADVANCES IN NATURAL INGREDIENTS AND THEIR USE IN SKIN CARE

Original Release Date: September 1, 2013
Most Recent Review Date: August 1, 2013
Termination Date: August 31, 2014
Estimated Time to Complete This CME Activity: 1 hour
Medium or Combination of Media Used: Written supplement
Method of Physical Participation: Journal article, web-based post-test, and evaluation
Hardware/Software Requirements: High speed internet connection

Statement of Need

In 2012, Physicians Continuing Education Corporation conducted a needs assessment survey of over 140 dermatologists to determine their questions, concerns, and use of natural products in dermatology. Of the respondents, 90% stated that while they do not have experience with natural products, they would like to learn more.

Results from a national survey conducted by the National Center for Complementary and Alternative Medicine and the National Health Interview Survey on the use of nonconventional therapies in skin disorders indicated that approximately 38% of adults (n=83 million) are currently using some form of complementary or alternative medicine. Additionally, of those surveyed (n=23,393), 35.8% thought it would be interesting to try and 49.8% thought combining natural products with conventional treatments would optimize the treatment of their condition. In 2007 alone, adults in the United States spent approximately 33.9 billion dollars on complementary and alternative medicine, of which 14.8 billion dollars was spent on non-vitamin, non-mineral, natural products. Furthermore, a study focusing on those older than 50 years of age concluded that 43% of respondents (n=1,013) had used complementary and alternative medicine within the past 12 months.

Educational Objectives

This activity is a multi-specialty, evidence-based initiative designed to increase the knowledge and competence of dermatological practitioners by providing them with the simultaneous integration of knowledge, skills, and judgment from thought-leader testimonials, science-based research, and evidence-based data to address the difference between present patient outcomes and those considered achievable in the field of dermatology.

Upon completion of this activity, 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
- Select potential treatment regimens with natural ingredients for patients with darker skin types
- Recall the safety, tolerability, and efficacy of natural ingredients

Target Audience

This activity is intended for dermatologists, residents in dermatology, and physician assistants who need continued education in the key properties and practical application of natural ingredients.

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 University of Louisville and Physicians Continuing Education Corporation. The University of Louisville is accredited by the ACCME to provide continuing education for physicians.

UNIVERSITY OF LOUISVILLE
CONTINUING MEDICAL EDUCATION & PROFESSIONAL DEVELOPMENT

Credit Designation

The University of Louisville Continuing Medical Education designates this enduring material for a maximum of one (1.0) *AMA PRA Category 1 Credit*™. Physicians should only claim credit commensurate with the extent of their participation in this activity.

How to Obtain CME Credit

You can earn one (1.0) *AMA PRA Category 1 Credit*™ by reading the 3 articles contained in this supplement and completing a web-based post-test and evaluation.

Test is valid through August 31, 2014 (no credit will be given after this date).

To receive credit for this activity, please go to www.JDDonline.com and click on CME Activities under "Library." You will find instructions for taking the post-test and completing the program evaluation. You must earn a passing score of at least 70% and complete and submit the activity evaluation form in order to receive a certificate for an *AMA PRA Category 1 Credit*™. There is no fee for this CME activity. Once you have completed the form online, you will be able to print your certificate directly. You can also receive credit for this activity by completing the post-test and evaluation at the end of this supplement and

faxing or mailing it to JDD, 377 Park Avenue South, 6th Floor, NY, NY 10016; fax: (718) 407-0898.

Faculty Credentials

Whitney P. Bowe MD (SUNY Downstate College of Medicine, Brooklyn, NY), Andrew F. Alexis MD MPH (Skin of Color Center, St. Luke's Roosevelt Hospital, New York, NY), Magdalene A. Dohil MD (Departments of Pediatrics and Medicine [Dermatology], University of California, San Diego School of Medicine, San Diego, CA), Paul Blackcloud BA.

Disclosures

Policy on Faculty and Provider Disclosure: It is the policy of the University of Louisville to ensure fair balance, independence, objectivity, and scientific rigor in all activities. All faculty participating in CME activities sponsored by the University of Louisville are required to present evidence-based data, identify and reference off-label product use, and disclose all relevant financial relationships with those supporting the activity or others whose products or services are discussed.

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

The faculty/authors have the following disclosed conflicts of interest: Whitney P. Bowe MD has served as a consultant for Johnson & Johnson Consumer Companies, Inc, on an advisory panel for Galderma Labs, and as a consultant for Procter and Gamble. Andrew F. Alexis MD MPH has served as a consultant for Estée Lauder, Johnson & Johnson Consumer Companies, Inc, L'Oréal, and SkinMedica. Magdalene A. Dohil MD has served as a speaker and on an advisory committee for Johnson & Johnson Consumer Companies, Inc. Paul Blackcloud BA has no conflicts of interest to disclose.

The peer reviewers have no relevant conflicts of interest to disclose.

The planning committee of this activity, Nick Gillespie (Assistant Publisher JDD), Lucy James (Editorial Project Manager JDD), Melissa Kerr (Marking Associate JDD), Luciana Halliday (Director of Sales JDD), and James Creg (University of Louisville) have no relevant conflicts of interest to disclose.

Disclosure of Unlabeled Use: This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the U.S. FDA. The University of Louisville, *Journal of Drugs in Dermatology*, and the activity supporters do not recommend the use of any agent outside of the labeled indications. The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of the University of Louisville, the *Journal of Drugs in Dermatology*, and the activity supporters. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

Disclosure of Commercial Support: This supplement to the *Journal of Drugs in Dermatology* has been made possible by an unrestricted educational grant from Johnson & Johnson Consumer Companies, Inc.

Special Services

If you need special accommodations due to a disability, or require an alternative form of course materials, e-mail Nick Gillespie at Nick.Gillespie@jddonline.com. The *Journal of Drugs in Dermatology* is committed to providing whatever special assistance its users require to complete this educational activity.

Contact Information

If you need technical support or have questions about the course, please e-mail Nick.Gillespie@jddonline.com.

For questions about the Internet CME activity content, please contact University of Louisville Continuing Medical Education at cmepd@louisville.edu.

University of Louisville CME & PD Privacy Policy

All information provided by course participants is confidential and will not be shared with any other parties for any reason without permission.

Copyright

All of the content in this educational activity is copyrighted by the *Journal of Drugs in Dermatology*. The University of Louisville has obtained permission from the *Journal of Drugs in Dermatology* to use the content in this educational activity.

Introduction

Whitney P. Bowe MD

Interest in the use of "natural" ingredients to combat skin diseases and signs of aging remains strong. These ingredients are sought either as first-line options prior to scheduling an appointment with a physician or as adjunctive treatments alongside traditional medical interventions. They have also served as alternative options for patients and providers in cases where standard therapies have proven ineffective, intolerable, or less desirable. Natural ingredients are commonly perceived as being gentler and safer than prescription therapies, and patients often turn to their dermatologists for an expert opinion on which ingredients might best meet their particular skin care needs.

As consumer and patient demand for such products continues to increase, our scientific understanding of how these ingredients work has also deepened. Just in the last few decades, several naturally-derived ingredients have been subjected to rigorous scientific study. Carefully designed clinical and bench studies have begun to provide sound scientific evidence supporting the role of certain natural ingredients in skin care, turning what used to be home remedies into scientifically-sound medicaments. Dermatologists are also learning more about the important roles of inflammation and oxidative stress on skin behavior, and naturally-derived ingredients tend to possess potent anti-inflammatory and antioxidant properties. Consequently, even though natural/botanical compounds have been used for centuries for purported medicinal and healing properties, the science is just now becoming sophisticated enough to explain the mechanisms behind these healing effects.

> "The goal of this supplement is to arm practitioners with the knowledge they need to discriminate potentially effective over-the-counter products from those that lack any scientific basis for their claims."

In this supplement, a select group of natural ingredients will be reviewed in the context of both cosmetic and medical concerns. Data supporting the use of certain natural ingredients such as colloidal oatmeal and avenanthramides in the treatment of atopic dermatitis and a defective skin barrier is discussed by Dr. Dohil. Dr. Alexis focuses on skin of color, and the use of natural ingredients such as soy and niacinamide in the management of hyperpigmentation. Finally, I address the cosmetic benefits of natural ingredients such as mushrooms, feverfew, and tea on the skin, and discuss the benefits that wheat can have on damaged hair. The goal of this supplement is to arm practitioners with the knowledge they need to discriminate potentially effective over-the-counter products from those that lack any scientific basis for their claims. When patients turn to their dermatologists asking for guidance, we will be equipped to provide evidence-based counsel.

Whitney P. Bowe MD
Clinical Assistant Professor of Dermatology
SUNY Downstate College of Medicine
Brooklyn, NY

 ORIGINAL ARTICLE Journal of Drugs in Dermatology

Natural Ingredients for Darker Skin Types: Growing Options for Hyperpigmentation

Andrew F. Alexis MD MPH[a] and Paul Blackcloud BA

[a]Skin of Color Center, St. Luke's Roosevelt Hospital, New York, NY; Columbia University College of Physicians & Surgeons, New York, NY

ABSTRACT

Dyschromia is one of the most common dermatological concerns in patients with darker skin.[1] Disorders of hyperpigmentation, including postinflammatory hyperpigmentation, melasma, solar lentigines, and miscellaneous causes of facial hyperpigmentation, are the most frequently treated dyschromias and can have a considerable psychosocial impact. Given the high prevalence of hyperpigmentation and the considerable demand for an even complexion, newer treatment options for hyperpigmentation are of growing interest among consumers, manufacturers, and dermatologists. Blinded, controlled studies demonstrating skin lightening effects in soy, niacinamide, n-acetylglucosamine, licorice extract, arbutin, vitamin c, kojic acid, emblica extract, lignin peroxidase, and glutathione have led to the development of a growing list of non-prescription skin care products that can be incorporated (mostly as adjuncts) in the management of hyperpigmentation.

J Drugs Dermatol. 2013;12(suppl 9):s123-s127.

INTRODUCTION

Increasing demand among consumers for naturally derived or botanical ingredients in skin care products has led to the development of numerous over-the-counter or physician-dispensed cosmeceutical products that are marketed as having natural active ingredients. Among patients and consumers with darker skin types, interest in newer products that promote an even skin tone and/or improve hyperpigmentation is especially strong. Over the past 15 years, a growing list of products containing naturally derived or botanical active ingredients with effects on hyperpigmentation have been evaluated in blinded, controlled clinical studies (Table 1). Knowledge of these products is useful to the practicing dermatologist so that questions from patients about non-prescription options can be answered effectively and the potential to use such products as adjunctive, maintenance, or alternative therapy in the management of dyschromias can be considered. In this article, naturally derived active ingredients with effects on hyperpigmentation are reviewed, with a focus on those that have been evaluated in published clinical trials.

Soy

Soy contains a variety of active components, including phytosterols, which help restore barrier function and replenish moisture; vitamin E, an antioxidant; large soy proteins, which provide skin smoothing and softening effects; and natural soy surfactants, which provide a gentle cleansing action. Soybeans contain small protein serine protease inhibitors, Bowman-Birk inhibitor, and soybean trypsin inhibitor, all of which have been shown to inhibit the proteinase-activated receptor-2 (PAR-2) pathway.[2] PAR-2 is a G-protein couple receptor that regulates phagocytosis of melanosomes by keratinocytes. Inhibition of this pathway reduces this phagocytosis, leading to reduced melanin transfer and reduced cutaneous pigmentation.[3] Small soybean-derived proteins have been shown to reduce ultraviolet B (UVB)-induced pigmentation.[2]

In a study of 16 Latina women with mottled pigmentation, a stabilized total soy extract was applied once daily to the areas of dyspigmentation for 3 months, with untreated areas of dyspigmented lesions serving as controls. Improvements were observed in 14 of the 16 subjects, with a mean reduction in hyperpigmentation of 12%.[4] A larger double-blind, placebo-controlled, 12-week clinical study was conducted comparing a soy-containing moisturizer with broad spectrum sunscreen (SPF 30) with its vehicle (also containing sunscreen). Enrolled in the study were 68 participants between 30 and 50 years old, with moderate levels of skin roughness, blotchiness, and mottled hyperpigmentation, who applied product daily. Significant improvements in the mean scores for fine lines, mottled hyperpigmentation, blotchiness, and skin clarity were observed as early as week 2 when compared with baseline values. At week 12, patients using the soy-containing moisturizer with

TABLE 1.

Summary of Natural Active Ingredients, Mechanism(s) of Action, and Clinical Studies

Ingredient	Mechanism	Conditions	Patient Population
Soy	Inhibition of PAR-2 pathway	Mottled pigmentation	Latina women (n=16)[4]
		Skin roughness, blotchiness, and mottled hyperpigmentation	Women with Fitzpatrick skin types I-III (n=68)[5]
Niacinamide	Inhibition of melanosome transfer to keratinocytes	Facial hyperpigmentation	Asian women (n=18)[6] Indian women (n=200)[7]
		Melasma	(n=27)[8]
N-acetylglucosamine (with niacinamide)	Inhibition of conversion of pro-tyrosinase to tyrosinase	Irregular hyperpigmentation/ solar lentigines	Caucasian women (n=202)[9]
Licorice extract	Inhibition of tyrosinase	Melasma	Egyptian women (n=20)[11]
Arbutin	Inhibition of melanosomal tyrosinase and DHICA polymerase	Solar lentigines	Caucasian women (n=34)[13] Non-Caucasian women (n=16)[13]
Vitamin C	Inhibition of tyrosinase activity	Melasma, solar lentigines	Asian patients (n=34)[16]
Kojic acid (with glycolic acid)	Inhibition of tyrosinase activity	Melasma	Chinese women (n=40)[19]
		Melasma	(n=39)[20]
Emblica extract (with kojic acid and glycolic acid)	Inhibition of melanogenesis	Facial dyschromia	Multiethnic patients (n=80)[21]
Lignin peroxidase	Degrades/depolymerizes melanin	Skin lightening	Asian women (n=51)[22]
Glutathione	Inhibition of tyrosinase activity	Skin lightening	Thai patients (n=60)[24]

DHICA, 5,6-dihydroxyindole-2-carboxylic acid; PAR-2, proteinase-activated receptor-2

sunscreen (SPF 30) exhibited significant mean improvements in all of these facial parameters compared with patients using the placebo moisturizer.[5]

Niacinamide

Niacinamide is the biologically active amide of vitamin B3 and is found in many root vegetables and yeasts. In vitro studies have shown that niacinamide inhibits the transfer of melanosomes to keratinocytes.[6] In a randomized split-face study of 18 Asian women with hyperpigmentation, a 5% niacinamide moisturizer applied for 4 weeks significantly decreased hyperpigmentation compared with the vehicle.[6] In a 10-week control study of more than 200 Indian women with facial hyperpigmentation, results showed that a topical lotion made with niacinamide, panthenol, and tocopheral-acetate yielded improvement in hyperpigmentation and evenness in skin tone compared with control.[7] In a randomized, split-face study comparing niacinamide 4% cream with 4% hydroquinone (HQ) cream in the treatment of melasma (n=27), colorimetric improvement was similar in the 2 treatment arms at week 8.[8]

Chitin (N-Acetylglucosamine)

N-acetylglucosamine (NAG) is a derivative of glucose and the monomeric unit of chitin, the primary component of the outer shell of insects and crustaceans. As a skin-lightening agent, it works by inhibiting the conversion of pro-tyrosinase to tyrosinase, modulating expression of various pigmentation-related genes.[2] In a 10-week, double-blind, vehicle-controlled study of 202 women, a moisturizer with 2% NAG and niacinamide demonstrated significant improvement in reducing areas of facial spots and the appearance of hyperpigmentation compared with the vehicle control.[9]

Licorice Extract

Licorice extract comes from the root of *Glycyrrhiza glabra*. Glabridin, a component of licorice, is a tyrosinase inhibitor that was shown to reduce UVB pigmentation and erythema in guinea pigs when applied for 3 weeks after UVB irradiation.[10] Liquitin, another component of licorice, also yielded a reduction in pigmentation in a double-blind, controlled, split-face study of 20 women with melasma. In the study, the patients applied a 20% liquiritin cream twice daily (1 gram/day) for 4 weeks. Sixteen of the 20 patients treated with liquiritin showed an "excellent response" compared with none in the vehicle control.[11]

Arbutin

Arbutin is a naturally occurring derivative of HQ found in bearberry that converts to HQ in vivo. It is structurally homologous to tyrosinase and therefore competitively inhibits melanosomal tyrosinase and 5,6-dihydroxyindole-2-carboxylic acid (DHICA) polymerase activities.[12] In a clinical trial of 50 females (34 Caucasian lighter skinned individuals and 16 non-Caucasian darker skinned individuals) with solar lentigines, topical treatment of deoxyarbutin (dA) for 12 weeks resulted in a slight to significant

reduction in overall skin lightness and improvement of solar lentigines. In another component of this study, guinea pigs were treated with dA, HQ, kojic acid, or arbutin for 9 weeks. Those treated with dA showed a decrease in pigmentation with no signs of skin irritation, while those treated with HQ showed signs of irritation that resulted in irregular darkening, beginning at week 3 of treatment.[13]

Vitamin C

Vitamin C is a water-soluble vitamin and antioxidant found in many fruits and vegetables. Ascorbic acid, a form of vitamin C, works by inhibiting tyrosinase activity through interacting with copper; but the method of delivery needs to be considered because it is rapidly oxidized and unstable. An active lipid form of pro-vitamin C called tetrahexyldecyl ascorbate has been found to be more stable than ascorbic acid and other vitamin C preparations, and has been shown to deliver vitamin C to the dermis and fibroblasts.[14]

In a randomized, double-blind study of 22 individuals in Japan, results showed that areas applied with a lipophilic pro-vitamin (VC-IP) cream after UV exposure showed significantly less UVB-induced skin pigmentation compared with control.[15] In another study using magnesium-L-ascorbyl-2-phosphate, a stable derivative of ascorbic acid, 19 of 34 Asian patients demonstrated significant lightening of melasma or solar lentigines, as measured by colorimetry.[16]

"Among patients and consumers with darker skin types, interest in newer products that promote an even skin tone and/or improve hyperpigmentation is especially strong."

Kojic Acid

Kojic acid is a chelation agent produced by several species of fungi, especially *Aspergillus oryzae*, and is a by-product of the malted rice fermentation used to manufacture sake. It is also a well-known skin lightening ingredient that inhibits tyrosinase activity by binding to copper.[17,18] In order to increase the skin lightening activity of kojic acid, it may be combined with glycolic acid as a penetration enhancer. In a 12-week, split-face, randomized study of 40 Chinese women with melasma comparing 10% glycolic acid/2% HQ with 2% kojic acid added to the same formulation, greater improvement was seen in those who received the added kojic acid.[19] In another split-face study of 39 individuals using a 2% kojic acid/5% glycolic acid and a 2% HQ/5% glycolic acid, equal efficacy in melasma and other hyperigmentation was seen in both formulations.[20]

Emblica Extract

Emblica extract comes from *Emblica officinalis*—Indian gooseberry or amla. Emblica is known to have antioxidant and skin lightening properties. Tannins from emblica inhibit melanogenesis, as demonstrated in human melanocyte cultures.[21] In one double-blind study that compared a topical formulation containing emblica extract, kojic acid, and glycolic acid with prescription generic 4% HQ cream in multiethnic participants with mild to moderate facial dyschromia (n=80), improvement in pigment lightening at weeks 8 or 12 was comparable between the 2 treatment arms.[21]

Lignin Peroxidase

Lignin peroxidase (LIP) is a naturally occurring enzyme derived from the tree fungus *Phanerochaete chrysosporium*. In decaying trees it degrades lignin, causing rapid decolorization. Lignin is structurally similar to melanin, and LIP has been show to degrade or depolymerize melanin.[22] In a split-face study, 51 participants applied a cream containing LIP to one side of the face, and either a 2% HQ cream or placebo to the other side, twice daily. On day 31, significant change from baseline was seen in the LIP side of the face, while the HQ and placebo side demonstrated no significant difference.[22]

Glutathione

Glutathione is a tripeptide and a ubiquitous antioxidant in cells. It is made endogenously, but its amino acid precursors, which have been shown to increase glutathione levels when consumed, are found in many vegetables such as asparagus and broccoli. As it relates to skin, glutathione limits melanogenesis through inhibition of tyrosinase.[23] In a study done in Thailand, 60 participants were given either 500 mg oral glutathione or a placebo once daily for 4 weeks. At the end of the trial, the glutathione group showed a statistically significant reduction of melanin indices at all 6 measured sites compared with the placebo group. Both the oral glutathione and placebo were well tolerated.[24] There have been no long-term studies to establish safety.

Mulitmodal Formulations

A formulation containing multiple active ingredients combines tetrahexyldecl ascorbate, a stable, lipid-soluble vitamin C product, to reduce melanocyte activation; glabridin (licorice extract) to reduce melanin synthesis by limiting tyrosinase availability; niacinamide to reduce melanin transfer to keratinocytes; and retinol to remove epidermal melanin; as well as other ingredients. In an initial study of 18 individuals with Fitzpatrick III skin type, participants were treated at separate sites with the combination product, with 4% HQ cream, and with control areas left untreated. Participants were exposed to UV radiation and results showed significant brightness in both the areas treated with the combination product and the 4% HQ, as compared with the control areas. Statistically similar results were seen in the combination product as compared with 4% HQ.[25]

TABLE 2.

Summary of Commercially Available Skin Care Products Containing Natural Active Ingredients[a]

Ingredients	Product	Est. Price/ Size[b]	Published Studies
Soy	Aveeno® Active Naturals Positively Radiant Daily Moisturizer	$15 (2.5 oz)	5
Soy	Neutrogena Visibly Even® Daily Moisturizer	$13 (1.7 oz)	
Soy, vitamin C	Ambi® Even & Clear™ Daily Moisturizer SPF 30	$12 (3 oz)	
Soy, vitamin C, licorice extract	MD Formulations® Vit-A-Plus Illuminating Serum	$54 (1 oz)	
Niacinamide	L'Oreal Youth Code™ Dark Spot Serum Corrector	$21 (1 oz)	
Niacinamide	Philosophy Miracle Worker® Dark Spot Corrector	$41 (1 oz)	
Niacinamide, N-acetylglucosamine	Olay™ Total Effects Tone Correcting Moisturizer	$18 (1.7 oz)	
Arbutin, vitamin C, kojic acid	Timeless Skin Care Skin Lightening Cream	$22 (1.7 oz)	
Vitamin C	Garnier Skin Renew Clinical Dark Spot Corrector	$14 (1.7 oz)	
Vitamin C	Shiseido White Lucent Intensive Spot Targeting Serum	$55 (1 oz)	
Vitamin C	Elizabeth Arden Prevage® Anti-Aging Targeted Skin Tone Corrector	$125 (1 oz)	
Vitamin C, emblica and licorice extract, arbutin	Dermelect Cosmeceuticals Beautone® Enlightening Facial Serum	$45 (.5 oz)	
Vitamin C, licorice extract, niacinamide	SkinMedica® Lytera Skin Brightening Complex	$120 (2 oz)	25,26
Kojic acid, arbutin	Skinceuticals Phyto + Botanical Gel for Hyperpigmentation	$54 (1 oz)	
Kojic acid, LHA	La Roche-Posay Mela-D Dark Spots SPF 15	$41 (1 oz)	
Kojic acid, LHA, glycolic acid	La Roche-Posay Mela-D Pigment Control	$52 (1.01 oz)	
Emblica, kojic acid	SkinCeuticals Pigment Regulator Daily High Potency Brightening Treatment	$67 (1 oz)	21
Lignin peroxidase	Elure™ Advanced Lightening Lotion	$135 (1 oz)	
Licorice extract	The Body Shop® Moisture White™ Shiso Moisture Cream	$25 (1.7 oz)	
Licorice extract	DDF® Brightening Cleanser	$32 (8.45 oz)	
Licorice extract	Chanel Le Blanc Whitening Spot Corrector TXC™	$120 (.34 oz)	
Licorice extract	Lancôme Bright Expert Dark Spot Corrector	$60 (1 oz)	

[a]Partial list of commonly used skin care products with skin lightening/brightening natural ingredients mentioned in this article.
[b]Estimated prices taken from Amazon.com except where otherwise noted.

A larger study done using a similar formulation with the addition of SMA-432, a prostaglandin E2 inhibitor, showed similar results in a randomized, double-blind, split-face study of 68 Caucasian females with moderate to severe facial hyperpigmentation. Participants were given 2 of 4 different products to apply (3 different formulations of the combination product, as well as 4% HQ). All participants showed improvements from baseline at weeks 4, 8, and 12, with patients rating the combination products more favorably than 4% HQ. No major tolerability issues were noted.[26]

CONCLUSION

Numerous botanical and other natural ingredients have skin lightening effects, and a growing list of these agents have been studied in small, controlled clinical trials. Many skin care products containing these ingredients are commercially available in retail stores or via the internet, or dispensed at physician offices (Table 2). Although prescription HQ products remain the gold standard, non-prescription formulations containing the aforementioned naturally derived skin lightening agents can serve as adjuncts or alternatives in the management of hyperpigmentation.

DISCLOSURES

Andrew F. Alexis MD MPH has served as a consultant for Estée Lauder, Johnson & Johnson Consumer Companies, Inc, L'Oréal, and SkinMedica. Paul Blackcloud BA has no conflicts of interest to disclose.

REFERENCES

1. Balkrishnan R, Feldman SR, McMichael AJ, DeHart KE, Cayce K, Fleischer AB Jr. Racial differences in the treatment of pigmentation disorders in outpatient settings: analysis of US national practice data. *J Dermatolog Treat.* 2004;15(4):227-230.
2. Leyden JJ, Shergill B, Micali G, Downie J, Wallo W. Natural options for the management of hyperpigmentation. *J Eur Acad Dermatol Venereol.* 2011;25(10):1140-1145.
3. Seiberg M, Paine C, Sharlow E, et al. The protease-activated receptor 2 regulates pigmentation via keratinocyte-melanocyte interactions. *Exp Cell Res.* 2000;254(1):25-32.
4. Gonzalez R, Cauwenbergh G. Effects of soy on hyperpigmentation in Caucasian and Hispanic populations. Poster presented at: 59th Annual Meeting of the American Academy of Dermatology. March 2-7, 2001; Washington, DC.
5. Wallo W, Nebus J, Leyden JJ. Efficacy of a soy moisturizer in photoaging: a double-blind, vehicle-controlled, 12-week study. *J Drugs Dermatol.* 2007;6(9):917-922.
6. Hakozaki T, Minwalla L, Zhuang J, et al. The effect of niacinamide on reducing cutaneous pigmentation and suppression of melanosome transfer. *Br J Dermatol.* 2002;147(1):20-31.
7. Jerajani HR, Mizoguchi H, Li J, Whittenbarger DJ, Marmor MJ. The effects of a daily facial lotion containing vitamins B3 and E and provitamin B5 on the facial skin of Indian women: a randomized, double-blind trial. *Indian J Dermatol Venereol Leprol.* 2010;76(1):20-26.
8. Navarrete-Solís J, Castanedo-Cázares JP, Torres-Álvarez B, et al. A Double-Blind, Randomized Clinical Trial of Niacinamide 4% versus Hydroquinone 4% in the Treatment of Melasma. *Dermatol Res Pract.* 2011;2011:379173.
9. Kimball AB, Kaczvinsky JR, Li J, et al. Reduction in the appearance of facial hyperpigmentation after use of moisturizers with a combination of topical niacinamide and N-acetyl glucosamine: results of a randomized, double-blind, vehicle-controlled trial. *Brit J Dermatol.* 2010;162(2):435-441.
10. Woolery-Lloyd H, Friedman A. Optimizing patient care with "natural" products: treatment of hyperpigmentation. *J Drugs Dermatol.* 2009;8(suppl 6):s10-s13.
11. Amer M, Metwalli M. Topical liquiritin improves melasma. *Int J Dermatol.* 2000;39(4):299-301.
12. Chakraborty AK, Funasaka Y, Komoto M, Ichihashi M. Effect of arbutin on melanogenic proteins in human melanocytes. *Pigment Cell Res.* 1998;11(4):206-212.
13. Boissy RE, Visscher M, DeLong MA. DeoxyArbutin: a novel reversible tyrosinase inhibitor with effective in vivo skin lightening potency. *Exp Dermatol.* 2005;14(8):601-8.
14. Shah GK. Efficacy of diode laser for treating acne keloidalis nuchae. *Indian J Dermatol Venereol Leprol.* 2005;71(1):31-34.
15. Ochiai Y, Kaburagi S, Obayashi K, et al. A new lipophilic pro-vitamin C, tetra-isopalmitoyl ascorbic acid (VC-IP), prevents UV-induced skin pigmentation through its anti-oxidative properties. *J Dermatol Sci.* 2006;44(1):37-44.
16. Kameyama K, Sakai C, Kondoh S, et al. Inhibitory effect of magnesium L-ascorbyl-2-phosphate (VC-PMG) on melanogenesis in vitro and in vivo. *J Am Acad Dermatol.* 1996;34(1):29-33.
17. Cabanes J, Chazarra S, Garcia-Carmona F. Kojic acid, a cosmetic skin whitening agent, is a slow-binding inhibitor of catecholase activity of tyrosinase. *J Pharm Pharmacol.* 1994;46(12):982-985.
18. Hakozaki T SC, Bissett DL. Hyperpigmentation in aging skin. In: Farage MA, Miller KW, Maibach HI, eds. *Textbook of Aging Skin.* Berlin, Germany: Springer-Verlag, 2010:495-501.
19. Lim JT. Treatment of melasma using kojic acid in a gel containing hydroquinone and glycolic acid. *Dermatol Surg.* 1999;25(4):282-284.
20. Garcia A, Fulton JE Jr. The combination of glycolic acid and hydroquinone or kojic acid for the treatment of melasma and related conditions. *Dermatol Surg.* 1996;22(5):443-447.
21. Draelos ZD, Yatskayer M, Bhushan P, Pillai S, Oresajo C. Evaluation of a kojic acid, emblica extract, and glycolic acid formulation compared with hydroquinone 4% for skin lightening. *Cutis.* 2010;86(3):153-158.
22. Mauricio T, Karmon Y, Khaiat A. A randomized and placebo-controlled study to compare the skin-lightening efficacy and safety of lignin peroxidase cream vs 2% hydroquinone cream. *J Cosmet Dermatol.* 2011;10(4):253-259.
23. Imokawa G. Analysis of initial melanogenesis including tyrosinase transfer and melanosome differentiation through interrupted melanization by glutathione. *J Invest Dermatol.* 1989;93(1):100-107.
24. Arjinpathana N, Asawanonda P. Glutathione as an oral whitening agent: a randomized, double-blind, placebo-controlled study. *J Dermatolog Treat.* 2012;23(2):97-102.
25. Makino ET, Mehta RC, Banga A, Jain P, Sigler ML, Sonti S. Evaluation of a hydroquinone-free skin brightening product using in vitro inhibition of melanogenesis and clinical reduction of ultraviolet-induced hyperpigmentation. *J Drugs Dermatol.* 2013;12(suppl 3):s16-s20.
26. Makino ET, Mehta RC, Garruto J, Gotz V, Sigler ML, Herndon JH. Clinical efficacy and safety of a multimodality skin brightener composition compared with 4% hydroquinone. *J Drugs Dermatol.* 2013;12(suppl 3):s21-s26.

AUTHOR CORRESPONDENCE

Andrew F. Alexis MD MPH
E-mail:.....andrew.alexis@columbia.edu

 ORIGINAL ARTICLE

Natural Ingredients in Atopic Dermatitis and Other Inflammatory Skin Disease

Magdalene A. Dohil MD

Departments of Pediatrics and Medicine (Dermatology), University of California, San Diego School of Medicine, San Diego, CA

ABSTRACT

Active naturals in dermatology have been experiencing a renaissance. Many of the naturals that have been known for centuries to be effective for various skin conditions have now been scientifically validated with the unraveling of the pathophysiology behind their medicinal mechanism. This article seeks to present data on the clinical use of key dermatological active naturals such as oatmeal, feverfew, chamomile, aloe vera, licorice, and dexpanthenol, as well as on recent multicenter and international clinical studies that support their efficacy and safety profile for a variety of inflammatory skin conditions.

J Drugs Dermatol. 2013;12(suppl 9):s128-s132.

INTRODUCTION

Atopic dermatitis (AD) is the most common inflammatory skin disease in childhood and affects about 20% of children in the industrialized world. Our current understanding of the pathophysiology has shown that the disease represents a complex interplay of genetic, immunologic, metabolic, infectious, and environmental factors. Over the past decade, research has particularly focused on the defective skin barrier due to a genetic mutation in fillagrin, an integral structural protein of the epidermis. Affected individuals are more prone to increased transepidermal water loss (TEWL) via the epidermis, increased penetration of sensitizing agents resulting in inappropriate stimulation of the immune system, and increased loss of natural moisturizing factor. In addition, the resulting T-helper 1 (Th1)/T-helper 2 (Th2) imbalance of the immune system promotes a hyperreactivity of the skin that is clinically manifest in various forms of dermatitis, and the lack of defensins as major players of their innate immunity leaves patients more susceptible to skin infections. It is increasingly evident that our treatment efforts need to focus on the correction and reversal of these pathophysiologic mechanisms. New studies to support this claim are underway and this article will present some of the latest data.

Numerous moisturizers and so-called barrier creams aim at the restoration of the compromised skin barrier function. This has been identified as key to minimizing progression of the "atopic march" and evolution into further atopic disorders such as asthma, allergic rhinitis, and eosinophilic esophagitis. The search for safe and efficacious agents has led to renewed interest in natural ingredients that have been known and trusted as "home remedies" for centuries. From among these ingredients, oatmeal, feverfew, chamomile, aloe vera, licorice, and dexpanthenol deserve particular citation because they have recently been researched more thoroughly and are considered safe and effective for various skin conditions. However, in contrast to previous experience based solely on observation and heresay, our current knowledge of these agents and their pharmacologic mechanism is based on sound scientific research and clinical studies. Based on controlled clinical data and reproducible pharmacologic compounding, these agents have been catapulted from their traditional use into modern medicine.

While topical corticosteroids remain 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. Caregivers often shy away from the appropriate duration and intensity of required treatment due to widespread fear of side effects of topical steroids and widespread steroid phobia. Topical calcineurin inhibitors offer a second line treatment approach, but are not US Food and Drug Administration (FDA)-approved for children under 2 years of age. Their use raises concerns in parents, given the "black box" warning that remains active even after the recent FDA review of use data over the past 10 years.

The search for alternative options has rekindled the interest in natural ingredients as adjunct treatment for AD. Recent data have further corroborated that the properties of these "new naturals" reach well beyond their moisturizing effects. They are increasingly valued in modern dermatology for their additional anti-inflammatory, anti-pruritic, and skin-protectant properties.

These natural ingredients are labeled as such because they consist of extracts derived directly from plants or animal products; however, unlike some products marketed as "organic", their constituents have been dermatologically tested for the pharmacology grade purity, efficacy, and safety demanded from modern medicine.[1,2]

"Based on controlled clinical data and reproducible pharmacologic compounding, these agents have been catapulted from their traditional use into modern medicine."

Colloidal Oatmeal

Derived from the common or wild oat (*Avena sativa*), colloidal oatmeal has a long history of traditional folk use dating back to 2000 BC in Egypt and the Arabian peninsula. Oats have been used internally and externally for various conditions, most prominently skin ailments. Oatmeal baths were popular even in 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 that is readily dispersible in water. Most of the constituents of the powder are less 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% to 11% of lipids, up to 64% of sugars and amino acids, 12.5% to 18% of vitamins including A, E, B, and saponins, flavonoids, prostaglandin inhibitors, and just a very small fraction of 0.06% avenanthramides.

Ongoing research has provided new data on the function of each of these subfractions. Colloidal oatmeal proteins have been shown to be capable of buffering both acids and bases. Oatmeal has many components that repair or preserve barrier function. Its proteins and polysaccharides bind to the skin and provide a protective barrier to external insults. The anti-pruritic activity of colloidal oatmeal is generally attributed to its ability to maintain barrier integrity and protect against external insults, its ability to moisturize the skin and alleviate itching due to lack of hydration and abnormal subcutaneous buildup arising from abnormal desquamation, and its anti-inflammatory components, such as linoleic acid, which have been shown to reduce skin inflammation. It is able to bind to the skin and help form a barrier that reduces TEWL and also helps prevent the entry of environmental irritants. An additional barrier-protective and anti-pruritic effect derives from oatmeal's hydrocolloid effect, which creates a film that stays on the skin.[2-12]

A newly discovered oat fraction, avenanthramides are the principle polyphenolic antioxidants in oats and have been shown to exert their anti-inflammatory properties via NF-κb activation and inhibition of pro-inflammatory cytokines in keratinocytes. In one study on mice, researchers were able to demonstrate the ability of avenanthramides to block the irritation associated with contact hypersensitivity in a dose dependent response, with activity of the 3% avenanthramide formulation comparable to 1% hydrocortisone. In a skin erythema model, separated oat fractions were tested to further explore the functional properties of various oat components. Compared with other oat subfractions, the avenanthramide fraction most effectively reduced ultraviolet (UV)-induced erythema 24 hours after skin application. In preclinical models, avenanthramides were found to decrease the stimulated release of interleukin 8 (IL-8) from human epidermal keratinocytes. Significant reductions of IL-8 release were obtained with 1, 10, and 100 µg/mL avenanthramides ($P<.05$). Clinical studies indicate that avenanthramides may be of particular value in restoring the cutaneous barrier and reducing symptoms of AD. It is therefore not surprising that clinical efficacy of colloidal oatmeal has been demonstrated in such varied skin conditions as AD, contact dermatitis, fungal infections, seborrheic dermatitis, burns, and postchemotherapy dermatologic toxicity.[7-12]

New focus has been shifted onto the various lipid components within the oat subfractions. When fractionated, whole oat oil is composed of a mixture of lipids, falling into 4 main lipid classes: triglycerides, diacylglycerol, phospholipids, and free fatty acids, with smaller amounts of sterols, phosphatidylethanolamine, and other compounds. The buffering capacity of colloidal oatmeal restores the pH of damaged skin to within the normal range, a capacity that has been well documented in the medical literature since the early 1950s.

In another early clinical study, colloidal oatmeal was used as a bath and a cleanser for 3 months by 139 patients aged 21 to 91 years with various pruritic dermatoses, and was able to achieve complete or marked relief in more than 71% of these patients.[5] It has also been used successfully in the treatment of burn patients, promoting skin healing.[7] 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.[8] Similarly it has been effective in controlling the pruritus caused by erlotinib.[9]

Infants and children aged 2 months to 6 years suffering from AD, contact dermatitis, or seborrheic dermatitis were treated with a colloidal oatmeal cream and cleanser for 4 weeks. Dermatologist evaluation at weeks 2 and 4 showed significant

improvement in dryness, roughness, and itchiness using a visual analog scale, and significant improvement (P<.05) in mean scores for the Investigator's Global Assessment (IGA) and Eczema Area and Severity Index (EASI) composite scores, all resulting in a significant improvement of the Quality of Life (QOL) Index. These studies support previous clinical observations that the combination of colloidal oatmeal and emollient oils is synergistic.[4,5] In one investigation, researchers found that baths with colloidal oatmeal in an oil form soothed and cleansed the skin without irritation when used in 152 children presenting with a range of inflammatory dermatoses.

Many attribute these positive effects on skin healing to the ability of colloidal oatmeal to reduceTEWL in the skin, indicating an improvement in the skin barrier. In a clinical study of 27 female subjects using a colloidal oatmeal cream, TEWL values were significantly reduced, comparable to the efficacy of a prescription (R_x) barrier emulsion. Applying these observed properties to the skin care regimen of atopic skin showed a statistically significant (P<.01) improvement in the IGA scores and 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 AD. These results further translated into a significant improvement of the QOL scores of enrolled patients.[12]

Most recent data are documented in an international, multicenter, open-label, 12-week study conducted in Portugal, Italy, and Greece in November 2010.[33] The objective of the study was to assess the efficacy of a soothing colloidal oatmeal emollient cream to improve the signs of atopic skin. A total of 99 patients with mild-to-moderate eczema, aged 6 months to adult, were enrolled in the study. More than 60% of enrollees were aged 5 years and under. The study protocol started with a 1-month washout period, and patients with a score greater than T0 entered the study. The patients applied the study medication to the affected eczema areas. They were instructed to continue their normal skin regimen. Evaluations were conducted at weeks 4, 8, and 12. Any patient who had a score of 0 at the 1- or 2-month evaluation did not enter the analysis. A total of 71 patients were used in the efficacy analyses. At week 12, 100% of patients had improvement in skin hydration, 96% had improvement in pruritus, 82% had improvement in scaling, and 88% had improvement in erythema. Scoring atopic dermatitis (SCORAD) scores also improved. Overall, more than 90% of patients had improvement in SCORAD at week 12. The mean percentage improvement was 37% for children aged 5 years and under, 58% for children and adolescents aged 6 to 20 years, and 48% overall.

As the result of the study it was shown that regular use of colloidal oatmeal cream has a corticosteroid-sparing effect as the inflammatory skin condition continued to improve. During the washout period, patients averaged 5.5 grams of corticoids. After 4 weeks of using colloidal oatmeal cream, the measured corticosteroid use declined by 39.4% (9.24 grams/patient). Sixty-three percent of patients felt that they used fewer corticoids/immunomodulators than prior to the start of the study.[28-32]

These are significant results when looking at the management of any chronic skin condition that has to rely heavily on repeated use of topical steroids for acute flare control and maintenance, and shows that colloidal oatmeal deserves ongoing clinical research and application in various inflammatory skin diseases.

Feverfew

Feverfew (*Tanacetum parthenium*) has, as the name implies, traditionally been 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 tumor necrosis factor α (TNFα), IL-2, IL-4, and prostaglandin E2 (PGE2).

However, extracts from the plant that retain 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 parthenolide-free 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 parthenolide-free feverfew extract has been proven to induce neither phototoxic nor photoallergic responses when applied to the skin in topical formulations.[2,13,14] The following examples of its clinical use are all based on the use of the parthenolide-free feverfew extract.

This formulation has particularly shown efficacy in preventing 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 administrations of feverfew at different concentrations were all effective at preventing redness with increased efficacy when higher concentrations of feverfew were added.[13] In response to these encouraging results, feverfew has been evaluated for the treatment of women with sensitive skin, resulting in significant improvement in facial redness, roughness, and irritation.[14]

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 3 weeks with a similar reduction of redness, dryness, and skin irritability, as well as

increased textural skin improvement. One further practical application has been the use of feverfew in the prevention and treatment of shaving irritation.[16] Most interesting, however, are the preclinical studies using normal human epidermal keratinocytes, which showed that when 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.[17,18]

A similar potent antioxidant effect was noted in an experiment measured from skin cells acquired by tape stripping. Various moisturizing products each containing different ingredients that claim antioxidantive properties were applied to the volar forearm of panelists, one of them containing feverfew extract. After 4 hours, skin cells were tape stripped and assessed for ROS ex vivo. Only the product containing feverfew significantly inhibited ROS production. Applying these results to skin in the context of UV exposure suggests potential clinical use as a sun-protective agent.

Chamomile

Chamomile has a long-standing history in folk medicine both internally and externally, mainly for gastrointestinal symptoms but also as a skin soothing agent and aromatherapy ingredient. The flower's active ingredients are flavonoids, volatile oils, courmarines, mucilages, and saccharides, which show inhibition of cyclooxygenase, lipooxygenase, and histamine. Chamomile 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 AD. In a study in Helsinki, 48 women who had undergone surgery for breast cancer applied chamomile cream above the wound area and almond oil below the wound area 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, even though neither was able to prevent radiation dermatitis altogether or prevent symptoms of itchiness and pain.[19-21]

Aloe Vera

Aloe vera has long been known for its anti-pruritic, analgesic, bactericidal, antifungal, and health-promoting effects. Active components include salicylic acid, magnesium lactate, and polysaccharides gel, which 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 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 *Glycyrrhiza glabra* and is a constituent in many different botanicals. It is known to have anti-irritant effects through inhibiting superoxide anion production and as a cyclooxygenase inhibitor. The licorice extract licochalcone A is derived from a different kind of licorice plant grown in northwest China, *Glycyrrhiza inflate*. It appears to exert it's own 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 of a skin care regimen containing a licochalcone A based cleanser, SPF 15 lotion, spot concealer, and night cream applied over 8 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 4-week study.

Dexpanthenol

Dexpanthenol is another natural that has long been 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 burning in AD patients using a colloidal oatmeal bath with ceramides and dexpanthenol.[27]

CONCLUSIONS

The traditional use of natural ingredients, which was largely based on empiric evidence and folk medicine recipes, has been completely updated and scientifically validated by recent bench side and clinical research. An increasing body of scientific data now supports their use in various clinical settings, and new indications are continuously emerging. Most of the "new naturals" are specifically 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. These naturals have been shown to be useful as adjunct treatment in a variety of inflammatory skin conditions, including AD, contact dermatitis, drug-induced cutaneous rashes, and burn injuries. They have in particular emerged as alternative options in the treatment of pediatric patients, where the concern about potential side effects of topical steroids and/or calcineurin inhibitors remains a major consideration. These "new naturals" are expanding our treatment choices for the management of inflammatory skin disorders on an ongoing basis, with new emerging usage and research data supporting their strong reputation as safe and effective options.

DISCLOSURES

Magdalene A. Dohil MD has served as a speaker and on an advisory committee for Johnson & Johnson Consumer Companies, Inc.

REFERENCES

1. Fowler JF Jr, Woolery-Lloyd H, Waldorf H, Saini R. Innovations in natural ingredients and their use in skin care. *J Drugs Dermatol.* 2010;9(suppl 6):s72-s83.
2. Brown DJ, Dattner AM. Phytotherapeutic approaches to common dermatologic conditions. *Arch Dermatol.* 1998;134(11):1401-1404.
3. Baumann L. Oatmeal. Skin & Allergy News. 2004;35:44-45.
4. Kurtz ES, Wallo W. Colloidal oatmeal: history, chemistry and clinical properties. *J Drugs Dermatol.* 2007;6(2):167-170.
5. Eichenfield LF, Fowler JF Jr, Rigel DS, Taylor SC. Natural advances in eczema care. *Cutis.* 2007;80(suppl 6):s2-s16.
6. Sur R, Nigam A, Grote D, Liebel F, Southall MD. Avenanthramides, polyphenols from oats, exhibit anti-inflammatory and anti-itch activity. *Arch Dermatol Res.* 2008;300(10):569-574.
7. Matheson JD,Clayton J, Muller MJ. The reduction of itch during burn wound healing. *J Burn Care Rehabil.* 2001;22(1):76-81.
8. Alexandrescu DT, Vaillant JG, Dasanu CA. Effect of treatment with a colloidal oatmeal lotion on the acneiform eruption induced by epidermal growth factor receptor and multiple tyrosine-kinase inhibitors. *Clin Exp Dermatol.* 2007;32(1):71-74.
9. Talsania N, Loffeld A, Orpin SD. Colloidal oatmeal lotion is an effective treatment for pruritus caused by erlotinib. *Clin Exp Dermatol.* 2008;33(1):108.
10. Lee PW, Krakowski A, Chayavichitsilp P, Nebus J, Wallo W, Eichenfield LF. Evaluating the tolerance of a colloidal oatmeal cream and cleanser in infants and children with atopic dermatitis. Poster presented at: 34th Annual Meeting of the Society of Pediatric Dermatology, July 2008.
11. Food and Drug Administration, HHS. Skin Protectant Drug Products for Over-the-Counter Human Use; Final Monograph. Federal Register 68 (4 June 2003):33362-33381.
12. Nebus J, Wallo W, Nystrand G, Fowler J. A daily oat based skin care regimen for atopic skin. Poster presented at: 67th Annual Meeting of the American Academy of Dermatology, March 6-10, 2009; San Francisco, CA.
13. Martin K, Southall M, Lyte P, et al. Parthenolide-free extract of feverfew: an extract with effective anti-irritant activity in vitro. Poster presented at: 63rd Annual Meeting of the American Academy of Dermatology; February 18-22, 2005; New Orleans, LA.
14. Sur R, Martin K, Liebel F, Lyte P, Shapiro S, Southall M. Anti-inflammatory activity of parthenolide-depleted Feverfew (Tanacetum parthenium). *Inflammopharmacology.* 2009;17(1):42-49.
15. Miller D, Wallo W, Leyden JL. Facial Tolerance and Efficacy of a Daily Moisturizer Containing a Purified Feverfew Extract and SPF 30 in a Sensitive Skin Population. Poster presented at: 67th Annual Meeting of the American Academy of Dermatology; March 6-10, 2009; San Francisco, CA.
16. Halas L, Liebel F, Martin K. Clinical evaluation of a formulation containing parthenolide-free extract of feverfew for shaving-induced irritation. Poster presented at: 63rd Annual Meeting of the American Academy of Dermatology; February 18-22, 2005; New Orleans, LA.
17. Linton GM, Anthonavage M, Southall M. Broad antioxidant activity of feverfew provides all day skin protection from oxidative stress. Poster presented at: 66th Annual Meeting of the American Academy of Dermatology; February 1-5, 2008; San Antonio, TX.
18. Martin K, Sur R, Liebel F. Parthenolide-depleted Feverfew (Tanacetum parthenium) protects skin from UV irradiation and external aggression. *Arch Dermatol Res.* 2008;300(2):69-80.
19. Bedi MK, Shenefelt PD. Herbal therapy in dermatology. *Arch Dermatol.* 2002;138(2):232-242.
20. Patzelt-Wenczler R, Ponce-Pöschl E. Proof of efficacy of Kamillosan® cream in atopic eczema. *Eur J Med Res.* 2000;5(4):171-175.
21. Maiche AG, Gröhn P, Mäki-Hokkonen H. Effects of chamomile cream and almond ointment on acute radiation skin reaction. *Acta Oncol.* 1991;3(3):395-396.
22. Choonhakarn C, Busaracome P, Sripanidkulchai B, Sarakarn P. A prospective, randomized clinical trial comparing topical aloe vera with 0.1% triamcinolone acetonide in mild to moderate plaque psoriasis. *J Eur Acad Dermatol Venereol.* 2010;24(2):168-172.
23. Yokota T, Nishio H, Kubota Y, Mizoguchi M. The inhibitory effect of glabridin from licorice extracts on melanogenesis and inflammation. *Pigment Cell Res.* 1998;11(6):355-361.
24. Kolbe L, Immeyer J, Batzer J, et al. Anti-inflammatory efficacy of Licochalcone A: correlation of clinical potency and in vitro effects. *Arch Dermatol Res.* 2006;298(1):23-30.
25. Weber TM, Ceilley RI, Buerger A, et al. Skin tolerance, efficacy, and quality of life of patients with red facial skin using a skin care regimen containing Licochalcone A. *J Cosmet Dermatol.* 2006;5(3):227-232.
26. Amer M, Metwalli M. Topical liquiritin treatment improves melasma. *Int J Dermatol.* 2000;39(4):299-301.
27. Kobayashi D, Kusama M, Onda M, Nakahata N. The effect of pantothenic acid deficiency on keratinocyte proliferation and the synthesis of keratinocyte growth factor and collagen in fibroblasts. *J Pharmacol Sci.* 2011;115(2):230-234.
28. Cerio R, Dohil M, Jeanine D, Magina S, Mahé E, Stratigos AJ. Mechanism of action and clinical benefits of colloidal oatmeal for dermatologic practice. *J Drugs Dermatol.* 2010;9(9):1116-1120.
29. Zhou M, Robards K, Glennie-Holmes M, Helliwell S. Oat lipids. *J Am Oil Chem Soc.* 1999;76:159-169.
30. Vollhardt J, Fielder DA, Redmont MJ. Identification and cosmetic application of powerful anti-irritant constituents of oat grain. Poster presented at: XXI IFSCC International Congress; 2000; Berlin, Germany. Proceedings; 395-402.
31. Southall M, Pappas A, Nystrand G, Nebus J. Oat oil improves the skin barrier. *Dermatologist.* 2012(suppl):1-4. http://www.the-dermatologist.com/sites/default/files/Aveeno_SeptInsert_2012_0.pdf. Accessed July 17 2013.
32. Grais ML. Role of colloidal oatmeal in dermatologic treatment of the aged. *AMA Arch Derm Syphilol.* 1953;68(4):402-407.
33. Data on file, Johnson & Johnson 2012.

AUTHOR CORRESPONDENCE

Magdalene A. Dohil MD

E-mail:.....mdohil@rchsd.org

 ORIGINAL ARTICLE

Cosmetic Benefits of Natural Ingredients: Mushrooms, Feverfew, Tea, and Wheat Complex

Whitney P. Bowe MD
SUNY Downstate College of Medicine, Brooklyn, NY

ABSTRACT

Natural ingredients are frequently used in an effort to address cosmetic concerns such as fine lines, wrinkles, uneven tone, and texture. Many of these ingredients found in nature possess potent antioxidant as well as anti-inflammatory properties. Some, such as mushroom extracts, are even capable of accelerating the skin turnover rate and repairing dermal molecular components that provide structure and elasticity to the skin. Others, such as green tea, provide photoprotection against ultraviolet-induced DNA damage. In this manuscript, the cosmetic benefits of mushrooms, feverfew, and tea are discussed in the context of their ability to improve the appearance of the skin. The healing effects that wheat complex can have on damaged hair are also addressed.

J Drugs Dermatol. 2013;12(suppl 9):s133-s136.

INTRODUCTION

The cosmetic patients who enter our practices today do not appear to be the typical cosmetic patients we were seeing just a decade or two ago. The modern cosmetic patient is younger, perhaps even in her twenties or thirties, and she puts as much focus on prevention as on correction. She is also far more concerned about the source of her products, frequently requesting natural or organic alternatives to prescription medications. She might even perceive products that are not natural as unsafe, and peruses the ingredient list for chemicals and preservatives that she has read are "toxic" on the Internet.

Sales of products claiming to be "organic," "natural," or "naturally derived" have soared in recent years. But what do these terms really mean? Certifying products as organic has become a trend of late, but there are a number of worldwide organizations that have differing definitions of "organic." A common misconception among patients and consumers alike is that organic is better, but, in reality, organic is not necessarily better. Naturally derived ingredients are not invariably organic, rather they contain plant-derived elements that are actually improved upon in the laboratory setting.

One of the reasons why natural ingredients have gained such popularity is their abundance of antioxidants. Oxidative stress is a major driving force behind aging. Free radicals are highly reactive species, capable of damaging biomolecules such as lipids, proteins, and DNA, and they are continuously formed during our normal metabolic processes. Their production is increased with exposure to environmental factors such as sunlight and cigarette smoke. As a result, humans have evolved an antioxidant defense system to minimize the potential for free radical damage. However, we need to keep replenishing our antioxidant stores, and natural ingredients are an excellent source of these desirable antioxidants. Several natural ingredients that exhibit antioxidant and photoprotective effects on the skin include, among others: shiitake mushrooms, vitamin E (alpha-tocopherol), feverfew parthenolide-free extract (PFE), tea extracts (green and black), coffeeberry, grape seed extract, and licorice. In this article we will focus on shiitake mushrooms, feverfew, and tea, and then shift gears and discuss the benefits of wheat for damaged hair.

Shiitake Mushroom Complex

Mushroom extracts, including shiitake mushroom extract, possess not only antioxidant properties but also anti-irritant properties. Therefore, the right combination of mushroom extracts could be the ideal ingredient in anti-aging skin formulations. Shiitake mushrooms and mannetake (reishi) mushrooms contain polysaccharides, triterpenes, proteins, lipids, phenols, and cerebrosides.[1] These serve as anti-irritants and antioxidants, and stimulate the skin's natural renewal process. Mushroom extract skin care applications include protection against photoaging and improved skin elasticity.[2] Natural shiitake complex inhibits elastase activity. As we age, enzymes such as elastase diminish our elastin, compromising the integrity of the dermal layer. Natural shiitake complex has been shown to inhibit elastase in a dramatic fashion. The degree of elastase enzyme inhibition increases as the concentration of the shiitake complex is increased (Figure 1).[3] Shiitake derivatives also display potent antioxidant activity, which is critical for anti-aging because oxidative stress and reactive oxygen species are major

players in the aging process.[4] Miller et al have demonstrated that twice daily use of cleansing pads containing a mushroom extract lead to significant improvements in a number of parameters including roughness, sallowness, tone, fine lines, pore size, and mottled pigmentation. Significant improvements were detected by both dermatologists and the subjects themselves, with a number of improvements seen within the first 4 weeks.[5]

Feverfew

Feverfew is a flowering plant from the daisy family, and it has a long history of use in traditional European medicine and folk medicine. Feverfew was originally named for its fever-reducing properties, but was also commonly used for headaches and arthritis. The feverfew plant, *Tanacetum parthenium*, has anti-inflammatory, anti-irritant, and antioxidant properties. Its skin care applications include treatment of sensitive skin and shaving-induced irritation or redness, and photoprotection.[6] In its completely natural or organic state, feverfew contains an ingredient known to be a contact sensitizer, called parthenolide. Purified feverfew extract (PFE) is a purified extract that has been developed by extracting the beneficial components of feverfew while removing the harmful parthenolide component. This is an example of how naturally derived products can be more beneficial and less irritating than organic products, despite what many consumers believe.

In a randomized, placebo-controlled, double-blind, trial, subjects applied either PFE or placebo to their back skin for 2 days prior to ultraviolent (UV) exposure and then for 2 days following the UV exposure. Feverfew treatment significantly reduced erythema vs placebo after UV exposure.[7] Figure 2 demonstrates a subject who used a topical feverfew product on her face for 3 weeks. The significant reduction in erythema is clearly evident.[8]

Teas

All teas (green, oolong, and black) are derived from the plant *Camellia sinensis*, but they differ in the degree of fermentation of the leaves. The manufacture of green tea does not involve fermentation and, as such, the polyphenols of the plant are preserved. Teas contain flavanols, which include epicatechin, epacatechin-3-gallate, epigallocatechin, and epigallocatechin-3-gallate.[9]They function as antioxidants (lipid radical scavengers) and provide anti-inflammatory and photoprotective benefits.[10] Topical treatment with green tea polyphenols prior to UVB exposure inhibited the formation of cyclobutane pyrimidine dimers in the DNA of human skin.[11]

In a clinical trial of 40 women who were randomized to receive 8 weeks of treatment with a combination oral-topical green tea regimen or a placebo pill and placebo cream, skin biopsies demonstrated significant improvement in the elastic tissue content of those on the green tea regimen ($P<.05$).[12]

FIGURE 1. Natural shiitake complex inhibits elastase activity.

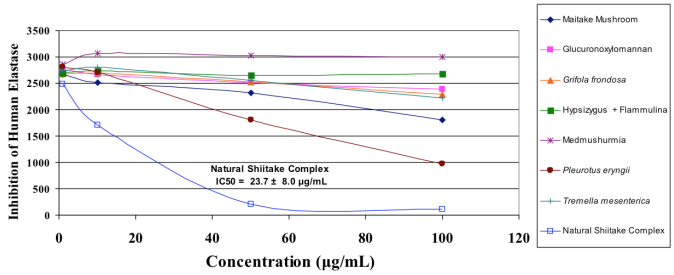
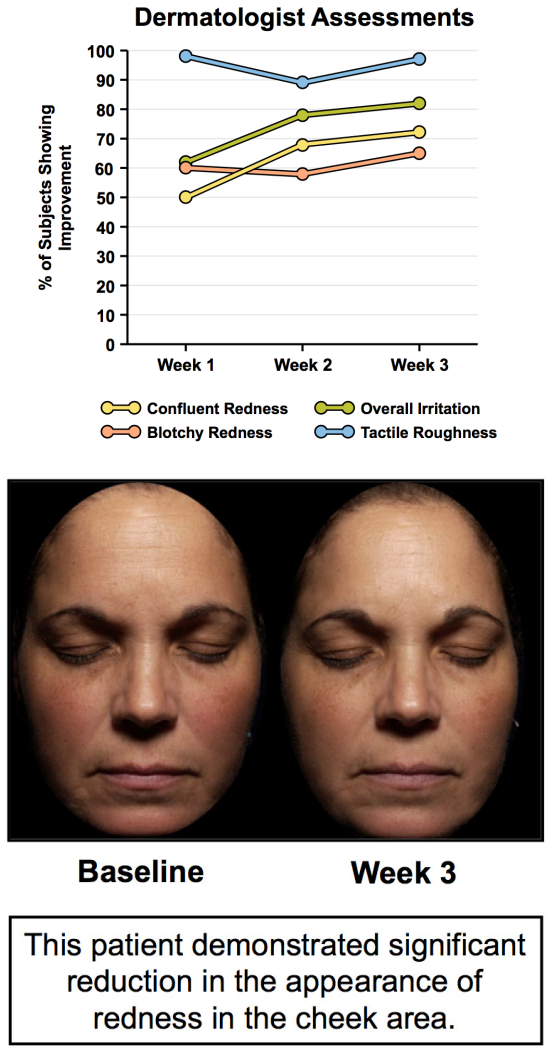


FIGURE 2. Purified feverfew extract: benefits for sensitive skin.



Wheat Complex for Damaged Hair

There are 2 naturally active components of wheat that make it unique: wheat protein and wheat germ oil. Wheat protein has the ability to bond to the damaged areas on the hair shaft, whereas the wheat germ oil can provide benefits with regards

FIGURE 3. How does coloring affect hair?

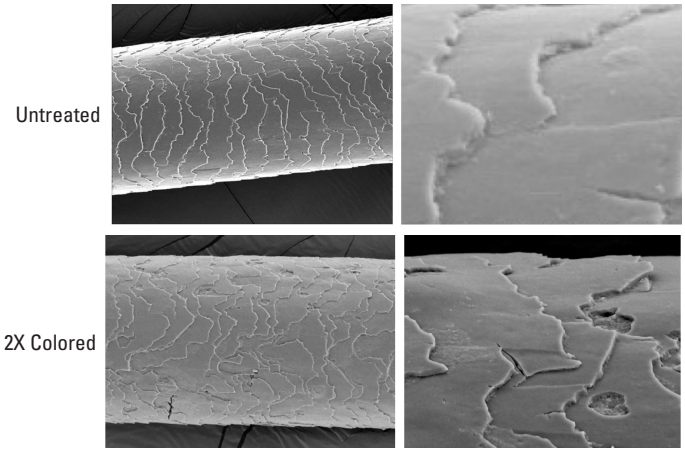
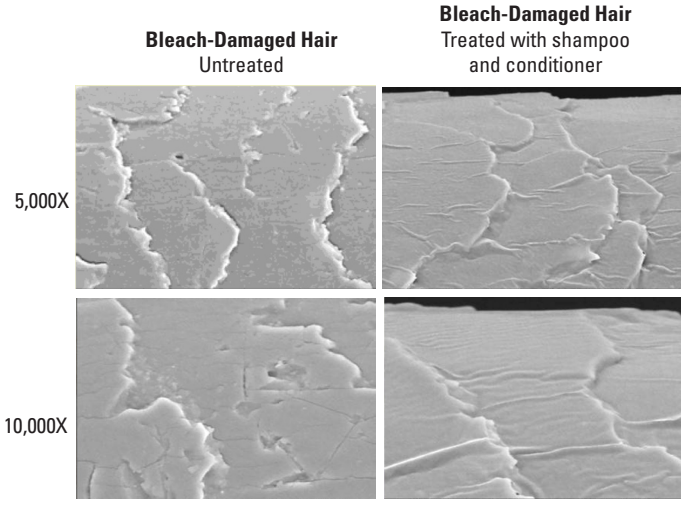


FIGURE 4. Effects of shampoo and conditioner with wheat complex.



to shine and lubrication of the hair shaft. When hair is damaged through coloring, blow-drying, or perming, bonds in the hair break and create a negative charge. The wheat protein in the Nourishing Wheat Complex (Aveeno® positively nourishing™ Hair Care Collection; Johnson & Johnson Inc, Skillman, NJ) has a naturally positive charge that is attracted to the charge on damaged hair. Wheat protein deposition is targeted to the most damaged areas of the hair (the tip region, rather than the root region), helping to prevent future build-up. Wheat protein is unique because it is non-hydrolyzed protein (not soluble in water and so not broken down with use in the shower).

In the interaction between the wheat complex and the surface of a hair fiber, damaged areas on the hair shaft have a negative charge due to the presence of sulfhydryl groups. The wheat complex has a positive charge, and so it binds to the negatively charged site. This wheat complex technology provides a beneficial protective function on the hair shaft.

Repeated coloring of hair can cause damage to the hair cuticle. The images in Figure 3 show the surface of a hair fiber captured using Scanning Electron Microscopy. These images show the cuticle on the surface of the hair fiber. The untreated hair seen in the top 2 photos is called “virgin hair” because it has never been colored. The cuticle structure is uniform, thick, and undamaged. The images on the bottom represent hair fibers that were color treated twice. They show damage to the cuticle including "wearing-away," pitting, and non-uniformity of the cuticle structures.

> "As more and more of our patients seek natural remedies to address their cosmetic concerns, our advice will be sought regarding which ingredients to choose and which products are not only effective but safe."

The images in Figure 4 demonstrate how the wheat complex can nourish and repair damaged hair. The hair was treated with wheat-complex–containing shampoo and conditioner 3 times. The images on the right show the improvement to the cuticle structure. It looks smooth and uniform. Smoothing of the surface of the hair evens out the reflectivity of light, allowing the hair to look shiny, which patients perceive as healthier hair. This technology provides the damaged hair shaft with a lubricated layer to help protect against damage, which can be caused by chemical treatments or even by grooming the hair with combs or brushes.

CONCLUSIONS

Interest in natural ingredients continues to rise, and numerous products claiming to be natural in origin continue to enter the marketplace, finding shelf space in local pharmacies, department stores, and beauty boutiques. However, only a select few of these products contain ingredients that have scientific studies backing the claims made on their labels. Furthermore, confusion remains about the definition of terms such as “organic.” As more and more of our patients seek natural remedies to address their cosmetic concerns, our advice will be sought regarding which ingredients to choose and which products are not only effective but safe. While further research is needed to better understand the full scope of the properties these natural ingredients possess, clinicians should have a working knowledge of which ingredients appear to provide a true benefit. We want to be in a position to best assist our patients, arm them with knowledge, and help them to become savvy consumers.

DISCLOSURES

Whitney P. Bowe MD has served as a consultant for Johnson & Johnson Consumer Companies, Inc, on an advisory panel for Galderma Labs, and as a consultant for Procter and Gamble.

REFERENCES

1. Sliva D. Cellular and physiological effects of Ganoderma lucidum (Reishi). *Mini Rev Med Chem*. 2004;4(8):873-879.
2. Mau JL, Lin HC, Chen CC. Antioxidant properties of several medicinal mushrooms. *J Agric Food Chem*. 2002;50(21):6072-6077.
3. Wallo W, Nebus J, Nystrand G, Southall M. New approaches demonstrate the skin care benefits provided by natural ingredients in topical formulations. Poster presented at: 21st World Congress of Dermatology; Sept 30-Oct 5, 2007; Buenos Aires, Argentina.
4. Southall M. Anti-oxidant activity of natural shiitake complex. Unpublished raw data. 2006. http://www.activenaturalsinstitute.com/library_shiitake. Accessed July 15 2013.
5. Miller D, Wallo W, Leyden JJ. Clinical evaluation of exfoliating cleansing pads containing a complex of mushroom extracts for improving photoaged skin. Poster presented at: 67th Annual Meeting of the American Academy of Dermatology; March 6-10, 2009; San Francisco, CA.
6. Brown DJ, Dattner AM. Phytotherapeutic approaches to common dermatologic conditions. *Arch Dermatol*. 1998;134(11):1401-1404.
7. Martin K, Sur R, Liebel F, et al. Parthenolide-depleted Feverfew (Tanacetum parthenium) protects skin from UV irradiation and external aggression. *Arch Dermatol Res*. 2008;300(2):69-80.
8. Nebus J, et al. Poster presented at: 63rd Annual Meeting of the American Academy of Dermatology; February 18-22, 2005; New Orleans, LA.
9. Camouse MM, Domingo DS, Swain FR, et al. Topical application of green and white tea extracts provides protection from solar-simulated ultraviolet light in human skin. *Exp Dermatol*. 2009;18(6):522-526.
10. Camouse MM, Hanneman KK, Conrad EP, Baron ED. Protective effects of tea polyphenols and caffeine. *Expert Rev Anticancer Ther*. 2005;5(6):1061-1068.
11. Katiyar SK, Perez A, Mukhtar H. Green tea polyphenol treatment to human skin prevents formation of ultraviolet light B-induced pyrimidine dimers in DNA. *Clin Cancer Res*. 2000;6(10):3864-3869.
12. Chiu AE, Chan JL, Kern DG, Kohler S, Rehmus WE, Kimball AB. Double-blinded, placebo-controlled trial of green tea extracts in the clinical and histologic appearance of photoaging skin. *Dermatol Surg*. 2005;31(7 Pt 2):855-860.

AUTHOR CORRESPONDENCE

Whitney P. Bowe MD
E-mail:.....wpbowe@gmail.com

CME Post-Test: For fastest results, please complete this activity online by scanning the QR code below or visiting www.JDDonline.com in the Medical Education Library, where you will be able to receive your CME certificate immediately upon achieving the passing score. Successful completion of the Post-Test is required to earn *AMA PRA Category 1 Credits*™. You must earn a passing score of at least 70% and complete the activity evaluation form in order to complete the course, and receive a certificate for *AMA PRA Category 1 Credits*™. You can take the test online as many times as you require to achieve the passing score. Alternatively, you may select your best answer for each of the following questions and insert them into the Answer Grid found on the Evaluation/Certificate Request Form on page s138, and return your completed Evaluation/Certificate Request Form to JDD by fax to (718) 407-0898, or by mail to 377 Park Avenue South, 6th Floor, New York, NY 10016.

1. Soybean trypsin inhibitor has been shown to reduce pigmentation by which of the following mechanisms?

   a. Decreased melanin production via inhibition of tyrosinase
   b. Removal of epidermal melanin
   c. Decreased melanosome transfer via inhibition of the PAR-2 pathway
   d. Photoprotection

2. Which of the following agents has been studied in the treatment of melasma? [This question pertains to published studies only].

   a. Lignin peroxidase
   b. Kojic acid (with glycolic acid)
   c. Glutathione
   d. Green tea

3. Which of the following non-prescription topical formulations have been compared with hydroquinone 4% cream in published studies?

   a. Licorice extract
   b. Vitamin C
   c. N-acetylglucosamine
   d. Kojic acid (with emblica extract and glycolic acid)

4. Which of the following natural ingredients has been shown to be effective in controlling pruritus as a side effect from treatment with epidermal growth factor receptor and multiple tyrosine-kinase inhibitors?

   a. Chamomile
   b. Aloe vera
   c. Feverfew
   d. Avenanthramides
   e. Licorice

5. Chamomile has been shown to reduce skin irritation via inhibition of which inflammatory pathways?

   a. C1-C3 esterase
   b. Prostaglandin 2a
   c. Thromboxane A2 and B2
   d. Cyclooxygenase and histamine
   e. Krebs cycle

6. Which component is not an active part of aloe vera?

   a. Salicylic acid
   b. Magnesium lactate
   c. Lipids
   d. Polysaccharides
   e. Glycyrrhiza glabra

7. Shiitake mushrooms, feverfew, and green tea are examples of natural ingredients with:

   a. High rates of allergic contact dermatitis
   b. High rates of irritant contact dermatitis
   c. Antioxidant properties
   d. Proven benefits in psoriasis patients

8. The ingredient in feverfew that can act as a contact sensitizer, leading to an inflamed skin reaction, is:

   a. Chamomile
   b. Parthenolide
   c. Epigallocatechin-3-gallate
   d. Shiitake

9. Wheat complex has been shown to:

   a. Lighten hyperpigmentation
   b. Repair damaged hair
   c. Improve the appearance of wrinkles
   d. Build collagen

Evaluation Form

Advances In Natural Ingredients And Their Use In Skin Care

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. **For fastest results, please complete this form 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. There is no fee for this CME activity.*** You must earn a passing score of at least 70% and complete the activity evaluation form in order to complete the course and receive a certificate for *AMA PRA Category 1 Credits™*. Alternatively, you may return this form to JDD by fax to (718) 407-0898, or by mail to 377 Park Avenue South, 6th Floor, NY, NY 10016.

Request for Credit

Name _____ Degree _____

Organization _____ Specialty _____

Address _____

City _____ State _____ ZIP _____

Telephone _____ Fax _____

Email _____

Signature _____ Date _____

I am registered on JDDonline.com
☐ Yes ☐ No

If yes:
User Name _____ Password _____

Post-test Answer Key

1	2	3	4	5	6	7	8	9

☐ I certify my actual time spent to complete this educational activity to be: _____

☐ I participated in the entire activity and claim 1 *AMA PRA Category 1 Credit™*.

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

Impact of the Activity

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:

_____

Additional comments about this activity:

_____

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

_____

JOURNAL OF DRUGS IN DERMATOLOGY
JDD
DRUGS • DEVICES • METHODS

JO0913