A Supplement to
Skin & Allergy News®

Cosmeceutical Critique
COMPENDIUM

TOPIC HIGHLIGHTS:

Rosemary
Polypodium Leucotomos
Propolis
Oatmeal
Olive Oil
Dexpanthenol
Grape Seed Extract
Lavender
Chamomile
Soy and Its Isoflavones
Vitamin A, Retinol, and Retinoids
Vitamin E
Green Tea
Tea Tree Oil

GUEST EDITOR:

Leslie Baumann, MD
Professor of Dermatology
Chief, Division of Cosmetic Dermatology
University of Miami
Miami, Fla.

Skin & Allergy News®

President, Elsevier/IMNG
Alan J. Imhoff

Contributing Writer
Charles Bankhead

National Account Manager
Sally A. Cioci

Art Director
Louise A. Koenig

Production Manager
Judi Sheffer

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Guest Editor:

Leslie Baumann, MD
Professor of Dermatology
Chief, Division of Cosmetic Dermatology
University of Miami
Miami, Fla.

Topic Highlights:

Introduction

Applying Nature to Dermatology Practice

Long before manufacturing processes evolved to produce synthetic and chemical compounds, naturally occurring ingredients formed the basis for cosmetics. In recent years, the pendulum has changed directions in response to a growing demand for cosmetic products that contain natural ingredients.

In many instances, manufacturers have responded by employing modern technology to enhance the beneficial effects of natural substances or to minimize or eliminate potentially detrimental effects. Today, myriad examples of "improved" natural ingredients can be found in the field of cosmetics, including:

Leslie Baumann, MD

Soy. In its natural state, soybeans have specific, active, non-denatured components that have documented benefits for the skin. Advances in cosmetic manufacturing using specialized propriety processing ensures that the integrity of the soy is maintained after processing so that the benefits of the natural ingredients are delivered to the skin. Soy has many beneficial skin components including antioxidants, lipids which moisturize to smooth skin texture and proteins which help in skin depigmentation.

Feverfew. Valued in folklore medicine as an herbal treatment for fever and headache, topical cosmetics containing feverfew can help in reducing (or alleviating) facial redness and skin irritation. However, feverfew contains a parthenolide component which is a potential sensitizer, but removal of the parthenolide allows for the antioxidant and anti-irritant benefits of the herb to be available safely to the skin.

Oatmeal. Oatmeal baths have long been recommended for patients with a variety of sensitive skin conditions, providing a soothing, comforting effect while enhancing the protective barrier and promoting improved skin health. Development of colloidal oatmeal, a coarse version of the popular grain, has led to multiple applications in cosmetics and cosmetic dermatology. Colloidal oatmeal has a texture and protein and lipid content that makes it well suited for use in moisturizers, topical anti-inflammatory compounds, cleansing soaps, and other products that help clean, soothe, and preserve the skin.

Retinol. A modified derivative of vitamin A, retinol has won favor as a key ingredient in topical preparations for wrinkles, age lines, and other age-related skin conditions. Advances in technology have resulted in well-stabilized formulations and improved delivery of retinol to the skin.

The cosmetics industry's ability to improve products with modified natural ingredients hints at the research that underlies modern product development. Critics of the current enthusiasm for natural or organic skin care products often scoff at what they perceive as a lack of research basis for these products. In reality, most of these products have evolved from an extensive research background, both in the laboratory and in the clinic.

Unfortunately, the supporting research data for cosmetic products often is difficult to locate. Some of the work has remained unpublished. Some has involved proprietary information that manufacturers are reluctant to share publicly. However, in many cases, the research has been done and can be found by anyone who has sufficient motivation to look for it. For example, an investigation of a soy-derived serine protease inhibitor demonstrated that modulation of the protease-activated receptor 2 pathway (PAR-2) might offer an effective new approach to depigmentation.[1] A similar study showed that soymilk may also inhibit PAR-2 and induce depigmentation.[2]

More recently, a topical total soy preparation was evaluated as a potential treatment for photodamaged skin.[3] The 12-week study showed that daily treatment with the soy preparation led to significant ($P<0.05$) improvement in multiple parameters, including facial skin brightness, smoothness, overall skin tone and texture, mottled hyperpigmentation, and wrinkling. Dermatology investigators noted improvement within 2 weeks of initiating treatment.

In my column "Cosmeceutical Critique," which has been published monthly in SKIN AND ALLERGY NEWS for more than 5 years, I discuss the research on the various "natural" cosmetic ingredients. My goal is to make this research more accessible to anyone interested in skin care. In this manner, it will become obvious to the reader which ingredients have research to support their marketing claims and which ones do not. Obviously, the manufacturing technology and the products have continued to improve over the past 5 years, and all of the latest developments might not be captured in the following summaries. For an overview of some of the recent developments, go to http://www.aveeno.com.

A major obstacle to cosmetics clinical research relates to the inherent difficulties of clinical studies. A well-designed clinical study has carefully matched experimental and control groups, which can be difficult to achieve in that patients in the two groups would have to exhibit nearly identical skin characteristics, including similar types and degrees of aging, envi-

Continued on page 23

Rosemary

In Western culture, rosemary is regarded primarily, if not exclusively, as a spice. It is typically used to flavor food and some beverages but is increasingly included as an ingredient in cosmetic products.

Rosemary (*Rosmarinus officinalis L.*) is cultivated throughout the world and is considered a common household herb. This aromatic evergreen shrub is native to western Asia and southern Europe, particularly the Mediterranean area (Indian J. Exp. Biol. 1999;37:124-30).

In traditional or folk medicine dating as far back as 1,000 years, rosemary was used to treat headaches, colds, respiratory disorders, dysmenorrhea, and as an antispasmodic-renal colic. Other traditional uses were as an eyewash, rubefacient, tonic, and hair growth stimulant (Phytother. Res. 2004;18:343-57; Phytother. Res. 2003;17:987-1000; Indian J. Exp. Biol. 1999;37:124-30).

Research conducted during the past 2 decades has shown that the herb exhibits significant potential for treating or preventing several medical conditions, including atherosclerosis, asthma, cancer, cataracts, ischemic heart disease, inflammatory diseases, hepatotoxicity, spasmogenic disorders, peptic ulcer, and poor sperm motility (Indian J. Exp. Biol. 1999;37:124-30).

The high phenolic content and correspondingly high antioxidant activity characteristic of rosemary ethanolic extracts and essential oil are believed to be responsible for antimutagenic and hepatoprotective activities associated with this increasingly researched botanical (Int. J. Food Sci. Nutr. 1999;50:413-27).

Antineoplastic Action

Several other studies have shown that rosemary's extracts or their active constituents have anticarcinogenic properties, including the ability to diminish skin tumorigenicity (Biofactors 2000;13:161-6; Indian J. Exp. Biol. 1999;37:124-30; Cancer Res. 1994;54:701-8; Oncology 1991;48:72-6; Cancer Lett. 1986;33:279-85).

More than a decade ago, a wide-ranging evaluation of rosemary leaves showed that the plant inhibits tumor formation. Specifically, a methanol extract of leaves applied to mouse skin inhibited the covalent binding of benzo[*a*]pyrene (BaP) to epidermal DNA, as well as tumor initiation by BaP and 7,12-dimethylbenz[*a*]anthracene (DMBA) (Cancer Res. 1994;54:701-8).

Furthermore, the investigators conducted a parallel study in which a group of mice was topically treated with BaP to initiate and 12-*O*-tetradecanoylphorbol-13-acetate (TPA) to promote tumors while another group underwent the same treatment after first receiving topically applied rosemary extract.

Application of 1.2 mg or 3.6 mg of rosemary extract lowered the number of tumors per mouse by 54% and 64%, respectively. Rosemary was also found to inhibit inflammation, hyperplasia, and tumor promotion all induced by TPA, as well as arachidonic acid–induced inflammation.

In addition, the herb inhibited ornithine decarboxylase activity, which is interesting because this is the mechanism of action of the drug eflornithine (Vaniqa), which is approved by the Food and Drug Administration for slowing hair growth (Cancer Res. 1994;54:701-8).

When skin tumors were initiated by DMBA and promoted with TPA, treatment with rosemary concurrent with TPA significantly inhibited the number of TPA-induced tumors in a dose-dependent manner.

The investigators also found that the topical application of two constituents isolated from rosemary—carnosol and ursolic acid—inhibited TPA-induced ear inflammation and tumor promotion, thus reducing the number of tumors per mouse in the initiation/promotion model (Cancer Res. 1994;54:701-8).

In a study of the effects of rosemary extract on BaP-induced carcinogenesis in human bronchial epithelial cells (BEAS-2B), the whole extract or equivalent concentrations of carnosol or carnosic acid (the strongest antioxidant components of rosemary) effectively inhibited DNA adduct development.

The researchers also noted that carnosol triggered expression of the phase II enzyme glutathione *S*-transferase, which detoxifies a carcinogenic derivative of BaP. Rosemary and its constituents emerged from this study as viable components of a chemopreventive anticarcinogenic approach, according to the investigators (Carcinogenesis 1995;16:2057-62).

Carnosic acid displays antimutagenic activity in bacteria and anticarcinogenic activity in various cell and animal models, and has been shown to inhibit the proliferation of HL60 and U937 human myeloid leukemia cells without induction of apoptotic or necrotic cell death (Nutr. Cancer 2001;41:135-44).

Antioxidant Action

A decade ago, the actions of rosemary in biologic systems and foods were characterized as antioxidant in nature. Researchers performing bioassays isolated the phenolic diterpenoids carnosic acid, carnosol, rosmanol, and epirosmanol as antioxidant constituents from rosemary leaves.

Each compound inhibited superoxide anion production in the xanthine/xanthine oxidase system as well as nicotinamide adenine dinucleotide- or nicotinamide adenine dinucleotide phosphate-induced mitochondrial and microsomal lipid peroxidation.

The investigators also discovered that carnosic acid protect-

ed red blood cells against oxidative hemolysis (Planta Med. 1995;61:333-6).

The key constituents of rosemary are thought to be the phenolic acid caffeic acid and its derivatives such as rosmarinic acid, as well as carnosol and carnosic acid, all of which exhibit antioxidant activity.

Rosmarinic acid, which is well absorbed via the gastrointestinal tract and the skin, increases prostaglandin E_2 production and decreases leukotriene B4 production in human polymorphonuclear leukocytes (Phytother. Res. 2003;17:987-1000; Indian J. Exp. Biol. 1999;37:124-30).

Carnosol exhibits potent antioxidant activity (Carcinogenesis 2002;23:983-91). In addition, carnosol, rosmanol, and epirosmanol have been shown to inhibit low-density lipoprotein oxidation (Acta Pharmacol. Sin. 2001;22:1094-8). Most significantly, carnosol has exhibited anticancer activity, inducing apoptosis in several pro-B and pre-B acute lymphoblastic leukemia cell lines (Cancer Lett. 2001;170:33-9).

In a study examining the roles of oxidative stress and sulfhydryl (SH) groups in heat shock protein 70 (HSP70) induction in human skin fibroblasts and the effect of antioxidants, rosemary extract significantly protected against stress-induced alterations of cellular SH and carbonyl content, allowing for stability in the functional levels of cytoprotective HSP70.

Rosemary extract significantly protected against stress-induced alterations of cellular SH and carbonyl content, allowing for stability in the functional levels of cytoprotective HSP70.

The authors concluded that the antioxidant activity of hydrophilic rosemary extract has the potential to confer cosmetic benefits while efficiently reducing skin damage caused by free radicals (Int. J. Tissue React. 2001;23:51-8).

A great deal of other recent research has demonstrated that rosemary is a potent source of antioxidant activity (Phytother. Res. 2004;18:343-57; Biosci. Biotechnol. Biochem. 2004; 68:781-6; Br. J. Dermatol. 2003;149:681-91; J. Med. Food 2003;6:267-70; Free Radic. Biol. Med. 2002;32:1293-303; Cancer Lett. 2002;177:145-53; Nutr. Cancer 2001;41:135-44; Int. J. Tissue React. 2000;22:5-13; J. Agric. Food Chem. 2000;48:5548-56; Food Chem. Toxicol. 1996;34:449-56; Xenobiotica 1992;22:257-68). The herb also exhibits anti-inflammatory activity (Br. J. Dermatol. 2003;149:681-91; Indian J. Exp. Biol. 1999;37:124-30).

Dermatologic Benefits

Rosemary has demonstrated significant dermatologic results in recent studies.

In a study evaluating the photoprotective potential of several dietary antioxidants in human dermal fibroblasts exposed to UVA, carnosic acid was found to suppress UVA-induced elevation in matrix metalloproteinase 1 (MMP-1) mRNA, thereby showing photoprotective potential (Free Radic. Biol. Med. 2002;32:1293-303).

Rosemary extract displayed antioxidant properties in a study of human surface lipids, when skin treated with the extract was found to be less susceptible to oxidative stress caused by *t*-butyl hydroperoxide (Br. J. Dermatol. 2003; 149:681-91; J. Agric. Food Chem. 2000; 48:5548-56). In a recent in vitro and in vivo study, a natural alcoholic extract derived from rosemary protected against free radical-induced skin damage, inhibiting oxidative changes to skin surface lipids (Int. J. Tissue React. 2000;22:5-13).

Rosemary is considered an effective conditioner for greasy hair, a general tonic providing body and sheen to hair, and an effective dandruff treatment when used in combination with sage (Phytother. Res. 2003;17:987-1000).

Other Benefits

Rosemary has been shown to confer antiseptic, antispasmodic, astringent, antidepressant, carminative, cholagogue, and diaphoretic effects (Phytother. Res. 2004;18:343-57), as well as antimicrobial activity (Microbios 1995;82:171-2).

In addition, rosemary extract has been found to enhance the production of nerve growth factor in T98 human glioblastoma cells (Biol. Pharm. Bull. 2003;26:1620-2).

In a study of the effect of aromatherapy on cognition and mood in healthy adults, the essential oil of rosemary was associated with significant improvement in subjective reports of mood and in performance assessments of overall quality of memory and secondary memory factors, although it seemed to reduce the speed of memory compared with controls (Int. J. Neurosci. 2003;113:15-38).

Like most of the herbal sources covered in this column, rosemary is now a common ingredient in cosmetic and cosmeceutical products. There appears to be reason for optimism regarding the role of rosemary in the medical— and particularly the dermatologic—armamentarium, with recent findings warranting additional research. Much more knowledge is necessary, however, to ascertain the relative significance of this popular herb in the therapeutic realm. ■

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Polypodium Leucotomos

Polypodium leucotomos extract, derived from a tropical fern, has been used to treat inflammatory conditions and has also been demonstrated to exhibit immunomodulating activity in vitro and in vivo. This plant extract has shown antioxidant and photoprotective effects against acute UV exposure (Photodermatol. Photoimmunol. Photomed. 1997; 13:50-60; Photodermatol. Photoimmunol. Photomed. 1999; 15:120-6).

P. leucotomos is found in abundance in the Honduran rain forest as well as throughout the tropics of Central and South America and the Caribbean. Various parts of the fern are used in traditional medicine in these regions for many indications, including tumors, psoriasis, atopic dermatitis, vitiligo, rheumatoid arthritis, and arthritis.

Early evidence supporting the traditional uses of *P. leucotomos* extract (PLE) was seen more than 20 years ago in 304 psoriasis patients (Med. Cutan. Ibero. Lat. Am. 1983;11:65-72).

In the 1990s, Dr. Thomas Fitzpatrick and his team at Harvard Medical School heard that this substance, when given orally, had utility in the treatment of vitiligo. They tested it and found, to their surprise, that it did not help vitiligo, but when they gave it to patients with vitiligo who were receiving psoralen-UVA (PUVA) treatment, the recipients developed less erythema from the PUVA.

Dr. Fitzpatrick had spent years looking at β-carotene as a photoprotective agent and found it inadequate, so he was excited to discover that PLE had this capacity. This excitement eventually led to the published studies, making this botanical extract one of the best studied of the antioxidants.

I first heard about *P. leucotomos* in 2001 at a cocktail party hosted by the American Academy of Dermatology, where Dr. Fitzpatrick told me about his PLE findings. Since then, many studies evaluating this extract have been published.

Photoprotection

Investigators evaluated PLE's free-radical-scavenging activity as part of a study of reactive oxygen species and lipid peroxidation. The authors reported that the fern extract exhibited antioxidant, anti-inflammatory, and photoprotective activity against photooxidative stress in vitro and in vivo.

Testing human and guinea pig skin, they showed that the topical application of PLE significantly inhibited the erythemal response induced by UVB, as well as the phototoxic reaction to PUVA after topical or oral administration of a photosensitizer (Photodermatol. Photoimmunol. Photomed. 1996; 12:45-56).

The researchers concluded from their results that the apparent photoprotection exhibited by PLE against reactive oxygen species may have potential clinical applications against sunburn and phototoxic reactions. Current research seems to support that conclusion.

In a recent study, researchers evaluated the capacity of oral PLE to reduce the clinical and histologic damage to human skin induced by PUVA treatment. Ten healthy patients with skin types II-III were exposed to PUVA alone and to PUVA with 7.5 mg/kg of oral PLE.

Clinical results showed consistently lower phototoxicity in PLE-treated skin after 48-72 hours, and less pigmentation after 4 months. Histologic results revealed notable differences in PLE-treated skin, with significantly fewer sunburn cells, preservation of Langerhans cells, and reduction in vasodilation and tryptase-positive mast cell infiltration (J. Am. Acad. Dermatol. 2004;50:41-9).

The authors concluded that the PLE conferred significant protection to the skin against the known harmful effects of PUVA. This study was clearly small, but its encouraging results led the team to further investigate the fern constituent.

In research reported later that year by the same group, nine healthy people with skin types II-III were exposed to different doses of artificial UV either without or following oral administration of 7.5 mg/kg of PLE.

At 24 hours after exposure, the investigators evaluated erythematous reactions and obtained paired biopsy specimens from PLE-treated skin and untreated skin. Significantly less erythema was seen in the skin treated with PLE. The biopsy specimens showed fewer sunburn cells, cyclobutane pyrimidine dimers, and proliferating epidermal cells, along with less mast cell infiltration. Signs of Langerhans cell preservation were also noted.

This small study supported the team's earlier findings, as they concluded that oral PLE imparts significant systemic protection to the skin against UV radiation (J. Am. Acad. Dermatol. 2004;51:910-8).

Other evidence buttresses the reports of PLE's photoprotective effect on human cells. A recent in vitro study showed that the hydrophilic PLE efficiently and in a dose-dependent manner preserved human fibroblasts and restored their proliferative capacity when the cells were exposed to UVA.

PLE conferred the same photoprotection on the human keratinocyte cell line HaCaT. PLE-treated human fibroblasts were also protected from UV-induced morphologic changes.

The authors concluded that PLE could play an important role in preventing sunburn and skin disorders mediated by UV exposure (J. Photochem. Photobiol. B 2003;70:31-7).

Researchers, citing PLE's antioxidant characteristics and its

reported photoprotective effects in vitiligo treatment, set out to assess the photoprotective effects of the topically or orally administered extract. The investigators exposed 21 healthy volunteers—previously untreated or treated with oral psoralens—to solar radiation, and evaluated immediate pigment darkening (IPD), minimal erythema dose (MED), minimal melanogenic dose (MMD), and minimal phototoxic dose (MPD) before and after topical or oral PLE administration.

They discovered that the extract was effective in both forms, with PLE increasing the UV doses required for IPD, MED, and MPD. An immunohistochemical assessment showed that Langerhans cells received photoprotection from both the topical and oral formulations (Photodermatol. Photoimmunol. Photomed. 1997;13:50-60).

The investigators concluded that PLE should be considered as a possible approach for systemic photoprotection, and may serve as an adjuvant to photochemotherapy and phototherapy, perhaps enhancing the safety and efficacy of PUVA or UVB.

In a recent study, there was consistently lower phototoxicity in PLE-treated skin after 48-72 hours, and less pigmentation after 4 months.

Effects on Cell Expression

Researchers used fibroblasts and keratinocytes to test the effects of PLE—in the presence of UVA or UVB—on membrane damage, lipid peroxidation, and the expression of elastin and matrix metalloproteinase 1 (MMP-1).

The cell samples were separately irradiated with a single exposure of UVA or UVB radiation and then incubated with or without PLE (0.01%, 0.1%, and 1%). Although UV did not significantly influence membrane integrity, lipid peroxidation, or MMP-1 expression, PLE did significantly enhance membrane integrity, inhibit lipid peroxidation, and inhibit MMP-1 expression in both fibroblasts and keratinocytes. Elastin expression was increased by UV radiation and PLE (J. Dermatol. Sci. 2003;32:1-9).

The authors suggested that PLE concentrations less than 0.1% may help combat photoaging by ameliorating membrane integrity and hampering MMP-1 expression without promoting elastin expression, whereas concentrations greater than 0.1% may reverse natural elastic fiber degradation.

Researchers recently showed that PLE partially inhibits the production of cytokines that exhibit a Th1 pattern (IL-2, IFN-γ, and TNF-α) in human phytohemagglutinin-stimulated peripheral blood mononuclear cells.

At all doses tested, PLE completely eliminated production of the inflammatory cytokine IL-6. A second experiment by the same laboratory demonstrated that topically applied PLE significantly lessened mast cell infiltration and the angiogenesis promoted by chronic UVB irradiation in hairless albino SKH-1 mice (Anticancer Res. 2000;20:1567-75).

The authors concluded that PLE's moderate inhibition of the immunologic Th1 response accounts for the immunosuppressive, anti-inflammatory, and antioxidant properties previously ascribed to the fern extract. Furthermore, they inferred that the demonstrable inhibitory effect on TNF-α and IL-6 production may account for PLE's inhibition of angiogenesis and protection of human Langerhans cells from depletion initiated by solar irradiation.

They speculated that PLE may be a potential treatment for autoaggressive and inflammatory conditions characterized by aggravated Th1 responses.

Antitumor Activity

Researchers looked at whether topical PLE could prevent or ameliorate cutaneous UVB-induced damage and photoaging in hairless mice. The results showed that mice treated with PLE had significantly reduced skinfold thickness and dermal elastosis, compared with untreated controls.

A reduction was also seen in the number of mice that had skin tumors 8 weeks after cessation of UV exposure (Photodermatol. Photoimmunol. Photomed. 1999;15:120-6).

The investigators concluded that PLE treatment improved or mitigated the histologic damage linked to skin photoaging and reduced UVB-induced skin tumor prevalence in mice.

Products

P. leucotomos extract is available in an oral supplement marketed as Heliocare. It is sold by pharmacists behind the counter but without a prescription. The directions say to take one per day, but I tell my patients to take one per day except on days when they anticipate significant sun exposure, in which case they should take two per day.

Conclusion

Many studies suggest the efficacy of both oral and topical antioxidants in protecting the skin against photodamage (J. Invest. Dermatol. 2005;125:xii-xiii). One study showed that a combination of topical and oral antioxidants has a synergistic effect (Biofactors 2003;18:289-97).

I believe that antiaging regimens should include an oral antioxidant in addition to a topical antioxidant. Long-term studies are required to test this theory. ■

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Propolis

Propolis, also known as bee glue, is an extract of beehives that has been used for hundreds of years in naturopathic medicine. Currently, some radiation therapists use propolis to treat actinic stomatitis and mucositis (Wurzbg. Medizinhist. Mitt. 2004;23:133-45), but this bee product is used more often for wound care and minor cutaneous indications as well as for a dietary supplement. In folk remedies, it has served as a potent anti-inflammatory agent (Cancer Res. 1993;53:1255-61) and its use dates back to ancient Greece and Rome (Wurzbg. Medizinhist. Mitt. 2004;23:133-45). In fact, the word propolis is derived from the Greek words "pro" (before) and "polis" (city), and reflects the ancient observation that bees built walls of the substance near the entrance of their hives. It was considered the third natural product of bees, in addition to honey and wax. Propolis is a resinous material that originates in the buds and barks of certain trees, mostly poplars (Wurzbg. Medizinhist. Mitt. 2004;23:133-45), and is gathered by honeybees and used inside the hive (Anticancer Res. 1996;16:2669-72). Propolis stabilizes beehives and honeycombs and protects bees against cold weather and potential intruders (Wurzbg. Medizinhist. Mitt. 2004;23:133-45).

In traditional medicine, propolis was most successful in treating a wide range of wounds because of its antiedematous and anti-infectious properties, presumably. Propolis was also used in the ancient world for muscle, tendon, and joint pain. More germane to this column, bee glue was used to treat cutaneous conditions such as lichens and condylomata (Wurzbg. Medizinhist. Mitt. 2004;23:133-45).

In a recent study, investigators evaluated the reputed antimicrobial, anti-inflammatory, and scar-healing capacity of a high-grade Brazilian propolis cream. Patients presenting with bilateral superficial second-degree burns over less than 20% of their body surface—with wounds of similar depth and quality—were admitted into the study within 48 hours of their injuries and then treated with propolis cream on one wound and silver sulfadiazene (SSD) applied to a similar wound on the other side. Wounds were debrided and dressings changed on the following morning. Patients returned to the clinic at 3-day intervals to have their wounds checked and dressings changed, with reapplication of the ointment taking place only at these visits. In addition, investigators cultured the wounds for microbial growth and took photographs to record inflammation and scar formation. No significant differences were noted in microbial colonization, but wounds treated with the propolis cream showed less inflammation and quicker scar formation, compared with the SSD-treated burns. While noting the beneficial effects of propolis on burns, the researchers speculated that more frequent changing of wound dressings would have evinced antimicrobial results also (J. Altern. Complement. Med. 2002;8:77-83).

Propolis was recently evaluated for efficacy in the treatment of recurrent genital herpes simplex virus type 2. Ninety adults, all with local symptoms, participated in a randomized, single-blind, masked-investigator, controlled study at seven medical centers in which Canadian propolis ointment containing natural flavonoids was compared with ointments of acyclovir and placebo, with 30 people randomized to each group. Study ointments were applied four times daily. Participants were examined on the 3rd, 7th, and 10th days of treatment for clinical symptoms, including the number and size of herpetic lesions, with lesions classified into four stages: vesicular, ulcerated, crusted, and healed. On day 3, 15 members of the propolis group had crusted lesions as opposed to 8 in the acyclovir group and 0 on placebo. Local symptoms were noted in three propolis group members, eight acyclovir individuals, and nine on placebo. On day 7, healing was observed in 10 propolis patients, 4 acyclovir patients, and 3 in the placebo group. Investigators reported that 24 propolis patients and 14 acyclovir patients healed by day 10. Overall, the propolis ointment was considered more effective in healing lesions and reducing local symptoms (Phytomedicine 2000;7:1-6). In an earlier study of 65 patients, a topical ointment containing propolis (Nivcrisol-D) showed a significant therapeutic effect against recurrent herpes and zona zoster, with patients who used the study drug healing from outbreaks in an average of 4 days, while patients using placebo took an average of 8 days to heal from outbreaks (Virologie 1988;39:21-4).

Various components of propolis have also been isolated and found to possess anticarcinogenic properties. Flavonoid aglycones are some of the significant constituents of propolis that are believed to contribute antitumorigenic properties (Anticancer Res. 1996;16:2669-72). A study with a fractionated methanol extract of a Brazilian propolis resulted in the isolation of a tumoricidal substance characterized as a new clerodane diterpenoid, which reduced the growth and number of skin tumors induced by 7,12-dimethylbenz(*a*)anthracene (DMBA) application on mouse back skin by inhibition of DNA synthesis (Anticancer Res. 1996;16:2669-72).

In a study to determine whether caffeic acid phenethyl ester (CAPE), a propolis constituent, inhibits the tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA)–induced processes associated with carcinogenesis, low doses of CAPE were top-

Continued on page 10

Oatmeal

Like many botanical products, the common or wild oat (*Avena sativa*) has a long history of traditional folk use, particularly in poultices or soaks.

The use of oats in skin care dates back to 2000 B.C. in Egypt and the Arabian peninsula. Oats have been used internally and externally for conditions such as insomnia, anxiety, and skin conditions, and in forms ranging from tea to baths.

Oatmeal baths were frequently used in the 19th and early 20th centuries for various cutaneous conditions, particularly pruritic inflammatory outbreaks.

Although there is a dearth of information in the literature on the therapeutic benefits of oats and oat products (Cosmet. Toiletries 1995; 110:63-70), recent research seems to bear out the anti-inflammatory properties that are ascribed to oats in folk medicine and clinical practice.

Avena sativa is also believed to promote the release of luteinizing hormone, which is integral in the production and release of sex hormones such as testosterone. This might explain the traditional use of oats as an aphrodisiac and, in turn, shed light on the origin of the expression "sowing wild oats." In addition, oatmeal is one of the few natural products or ingredients acknowledged by the Food and Drug Administration to be an effective skin protectant.

The Science Behind Colloidal Oatmeal

As a component in the modern dermatologic armamentarium, colloidal oatmeal has replaced rolled oats and oatmeals.

For decades, colloidal grain suspensions have been used as adjuncts in the treatment of atopic dermatitis (Am. J. Contact Dermat. 1997;8:207-9). Generally, better benefits are seen with the use of oat fractions rather than whole oatmeal (Phytother. Res. 2003;17:987-1000).

The composition of colloidal oatmeal is diverse, and includes polysaccharides (60%-64%), proteins (10%-18%), lipids (3%-9%), saponins, enzymes (such as the potent antioxidant superoxide dismutase), prostaglandin-synthesis inhibitors, flavonoids, and vitamins.

Colloidal oatmeal has been found to be safe, cosmetically stable, and nonirritating. Evidence suggests that this modern version of the traditional elixir is effective in protecting and repairing skin and hair that has been damaged by environmental insults such as ultraviolet radiation, smoke, bacteria, and free radicals. Colloidal oatmeal also eases cutaneous inflammation and discomfort (Phytother. Res. 2003;17:987-1000).

Evidence also shows that colloidal oatmeal repairs damage from other chemicals, such as alpha hydroxy acids, surfactants, and bleaches (Cosmet. Toiletries 1998;113:45-52).

The biologic activity of oat compounds appears to be quite dynamic.

Whole oat flour is believed to be cleansing and protective in nature, with antioxidant properties and the ability to inhibit prostaglandin synthesis. Another oat compound, oat β-glucan, is believed to be immunomodulatory. Oat proteins exhibit various capacities and effects, including emulsifying activity, fat-binding activity, water-hydration capacity, low foaming potential, and antioxidant activity (courtesy of superoxide dismutase). Oat lipids may influence viscosity and pasting properties and may decrease transepidermal water loss.

In a double-blind, randomized patch study of two concentrations of colloidal oat and rice grains (0.007% and 0.7%), the products were applied topically to the backs of 65 Italian children (43 atopic, 22 normal) who were aged 6 months to 2 years old. Both topical colloidal grains demonstrated efficacy as adjuncts in the treatment of mild atopic dermatitis, with no evidence of inducing sensitization (Am. J. Contact Dermat. 1997;8:207-9).

The Studies

Recent evidence points toward an expanding range of indications for colloidal oatmeal. A clinical study compared the effectiveness of two shower and bath oils—one containing liquid paraffin, and the other containing liquid paraffin with 5% colloidal oatmeal—to alleviate pruritus that was experienced by 35 acute burn patients. Analysis of patient assessments of pain (recorded twice daily) and the daily number of their antihistamine requests demonstrated that the colloidal oatmeal group reported significantly less pruritus and requested significantly less antihistamine (J. Burn Care Rehabil. 2001;22:76-81).

In an influential study on 12 healthy individuals, researchers evaluated the anti-inflammatory activity of two topically applied oatmeal extracts, *Avena sativa* and the trademarked Avena Rhealba. Using the sodium lauryl sulfate irritation model, the researchers found that both extracts exhibited preventive effects on skin irritation (Skin Pharmacol. Appl. Skin Physiol. 2002;15:120-4).

Another study focused on the anti-inflammatory effect of oatmeal extract oligomer on skin fragments (from plastic surgery) that were stimulated by the inflammation-inducing neuromediator vasoactive intestinal peptide (VIP).

In that study, researchers found that application of VIP resulted in significant increases in vasodilation, but subsequent application of oatmeal extract oligomer significantly reduced that vasodilation, along with edema (Int. J. Tissue React. 2003;25:41-6).

Results from the few available studies suggest that oatmeal compounds provide relief for several conditions. Clinical indications for colloidal oatmeal include poison ivy, poison oak, sumac, insect bites, chicken pox, eczema, rashes, hives, diaper rash, prickly heat, sunburn, pruritic conditions, psoriasis, senile and pediatric dermatoses, xerosis, and epidermolysis bullosa. Oatmeal extracts also confer modulating effects in the sodium lauryl sulfate skin irritancy model.

Oatmeal on the Shelf

New oatmeal-containing skin care products have recently become available at pharmacies and drug outlets in the wake of recent scientific evidence.

Most products come in the form of colloidal baths. Aveeno, a division of Johnson & Johnson, derived its name from the Latin name for the oat plant (*avena*), and many of their products contain colloidal oatmeal. [Dr. Baumann has served on the Aveeno advisory board.]

Aveeno Daily Moisturizing Bath ($6.29 for an eight-packet box) is a colloidal oatmeal formulation indicated for most of the conditions discussed above.

Other brands also contain colloidal oatmeal, including Queen Helene's Batherapy 100% Natural Colloidal Oatmeal Bath ($6.99 for 7 ounces), manufactured by Para Laboratories Inc.

As part of a daily skin care regimen, colloidal oatmeal is suitable for cleansing (especially dry, sensitive, or atopic skin), moisturizing, and providing protection to the skin.

Tradition and Anecdotal Evidence

Given all the evidence, it looks as if oatmeal isn't just for breakfast anymore! In fact, oatmeal has a surprisingly long tradition in skin care.

Although there are few trials demonstrating the efficacy of oatmeal products in the clinical setting, anecdotal evidence is compelling regarding the therapeutic uses of oatmeal and its derivatives in dermatologic practice. ■

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Propolis

Continued from page 8

ically applied to SENCAR mice. CAPE was found to strongly inhibit several TPA-mediated oxidative processes considered sine qua non for tumor promotion, including polymorphonuclear leukocyte infiltration into mouse skin and ears; hydrogen peroxide (H_2O_2) production; and formation of oxidized bases in epidermal DNA. In addition, researchers noted inhibition of edema and ornithine decarboxylase induction in CD-1 and SENCAR mice after CAPE application, as well as the inhibition of TPA-induced H_2O_2 production in bovine lenses. Researchers concluded that CAPE appears to have potent chemopreventive capacity, particularly in treating disorders associated with strong inflammatory and/or oxidative stress processes, such as cancer and cataracts (Cancer Res. 1993;53:1255-61).

In a different study on skin tumors, CD-1 mice were initiated with DMBA and then treated twice weekly with topically applied TPA, resulting in 18.8 skin papillomas per mouse. Subsequent topical application of CAPE to the backs of the mice together with TPA twice a week for 20 weeks inhibited the number of skin papillomas and reduced tumor size in a dose-dependent manner. The same combination also decreased the level of 5-hydroxymethyl-2´ deoxyuridine (HMdU) in epidermal DNA produced through the previous initiation with DMBA. In addition, in vitro CAPE introduction to cultured HeLa cells inhibited DNA, RNA, and protein synthesis. All of these inhibitory effects conferred by CAPE were deemed by investigators to be potent (Carcinogenesis 1996;17:761-5).

In a more recent study on polyphenolic compounds and antitumorigenic properties, a water-soluble derivative of propolis, caffeic acid (CA), CAPE, and quercetin administered to mice resulted in a reduction in the number of lung tumor nodules. Researchers related the antitumor properties of the tested substances to their immunomodulatory capacity, cytotoxicity to tumor cells, and ability to induce apoptosis and necrosis, suggesting that propolis, CA, CAPE, and quercetin show promising potential for combating tumor growth (J. Ethnopharmacol. 2004;94:307-15).

There are several commercially available products—such as creams, shampoos, lipsticks, toothpastes, and mouthwashes—that contain propolis as an active ingredient. It is also used as a dietary supplement.

Conclusion

Although the body of research on propolis is comparatively meager at the present time, the reports on this resinous substance appear very promising. I am particularly encouraged by the reports on its potential uses as an anticarcinogenic agent and an antiherpetic agent. Of course, much more research, in the form of randomized, controlled trials, is needed prior to incorporating propolis into the armamentarium as a first-line therapy. Given its historical or traditional uses, propolis is probably more effective in that context as compared with its use as an ingredient in new topical cosmeceuticals. In the latter case, research and efficacy remain to be established. ■

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Olive Oil

A staple of the Mediterranean diet, olive oil has long been considered one of the most important of the natural essential oils.

For as long as it has been a component of the human diet, olive oil (*Olea europaea*) has also been used for its beneficial effects on the skin. Ancient Greeks bathed with olive oil (Phytother. Res. 17[9]:987-1000, 2003), and the essential oil was also used in a variety of ways by the ancient Egyptians and Romans, including uses as a food, cosmetic, anointing oil, massage oil for athletes, and salve for soothing wounds.

In contemporary times, the topical application of olive oil has reportedly been successful in treating xerosis, rosacea, psoriasis, atopic dermatitis, contact dermatitis (especially in the diaper area), eczema (including severe cases on the hands and feet), seborrhea, and various inflammations, burns, and other skin damage (Phytother. Res. 17[9]:987-1000, 2003).

Abounding With Antioxidants

Olive oil contains a variety of potent compounds, many with antioxidant properties. Those compounds include polyphenols, squalene, fatty acids (particularly oleic acid), triglycerides, tocopherols, carotenoids, sterols, and chlorophylls (Phytother. Res. 17[9]:987-1000, 2003). The phenols in virgin olive oil are known to scavenge reactive oxygen and nitrogen species active in human disease. Whether the influence of these compounds extends beyond the extracellular environment is unknown, however (Life Sci. 69[10]:1213-22, 2001).

The chief components of the unsaponifiable fraction of virgin olive oil include erythrodiol, β-sitosterol, and squalene. The major components of the polar fraction include the polyphenols oleuropein, tyrosol, hydroxytyrosol, and caffeic acid (Z. Naturforsch. [C] 55[9-10]:814-19, 2000).

The antioxidant characteristics of these phenolic compounds are well established (Life Sci. 69[10]:1213-22, 2001).

A study of the topical application of olive oil revealed anti-inflammatory effects (Z. Naturforsch. [C] 55[9-10]:814-19, 2000). Other studies have also demonstrated that polyphenolic compounds in olive oil yield protective effects against inflammation (Phytother. Res. 17[9]:987-1000, 2003; Inflamm. Res. 50[2]:102-106, 2001).

Olive oil is a very weak irritant, and adverse side effects from topical use are rare (Contact Dermatitis 36[1]:5-10, 1997).

The primary phenolic compounds found in olive oil—all of which exhibit significant antioxidant activity—are simple phenols (hydroxytyrosol and tyrosol), secoiridoids (oleuropein, the aglycone of ligstroside, and their respective decarboxylated dialdehyde derivatives), and the lignans acetoxypinoresinol and pinoresinol (Lancet Oncol. 1:107-12, 2000).

High consumption of extra-virgin olive oil, which is laden with antioxidants from these polyphenols as well as other compounds, may offer protection against oxidative stress and its effects, such as aging and skin and other cancers (Lancet Oncol. 1:107-12, 2000).

A subsequent study also found that the high consumption of olive oil, along with vegetables and legumes, conferred protection against actinic damage (J. Am. Coll. Nutr. 20[1]:71-80, 2001).

Counter to Skin Cancer?

Researchers recently examined the capacity of extra-virgin olive oil to combat reactive oxygen species and skin tumors induced by UV light exposure. Topical application of the oil to mice before or after repeated exposure to UVB resulted in delayed onset of skin tumors, compared with control mice. As UVB exposures increased, differences between control mice and mice pretreated with olive oil diminished.

Mice that were treated with olive oil after UVB exposure, however, showed significantly fewer tumors than mice in the control group.

Researchers concluded that topical application of olive oil following UVB exposure is effective in mitigating murine skin tumors caused by UVB exposure (Carcinogenesis 21[11]:2085-90, 2000).

Similar results were obtained in another study. Researchers set out to determine if topical application of olive oil delays the onset and reduces the number of UV-induced skin cancers. The authors speculated that extra-virgin olive oil, but not regular olive oil (which neither delayed nor reduced skin cancer development), may work by reducing free-radical–induced 8-hydroxydeoxyguanosine formation, known to be responsible for gene mutation (J. Dermatol. Sci. 23[Suppl. 1]:S45-50, 2000).

Marketing Beyond the Mediterranean

Olive oil is now found in most types of over-the-counter skin care products, including soaps, lip balms, shampoos, and moisturizers. There are even a few lines that feature olive oil as the primary active ingredient.

The Macrovita Face Products with Olive Oil line includes Olive Oil and Calendula Cleansing Milk, Olive Oil and Calendula Tonic Lotion, Olive Oil and Propolis Deep Cleansing Liquid Soap, Olive Oil and White Tea Beauty Peel-Off Mask, and various other products such as hydrating cream, eye-con-

Continued on page 13

Dexpanthenol

Dexpanthenol, also known as provitamin B_5, is the stable alcohol form of pantothenic acid—a key player in maintenance of epithelial function and skin regrowth. Not found naturally, synthetic dexpanthenol is converted to pantothenic acid in the skin, stimulating skin regeneration in a manner comparable to vitamin A. This process of cell division and formation of new skin tissue restores skin elasticity and promotes wound healing.

Water-soluble dexpanthenol is therefore used topically to advance wound healing. It is also used in a wide range of cosmetic products, usually to moisturize the skin, and is formulated in some intramuscular and intravenous products.

The topical application of dexpanthenol also acts to prevent transepidermal water loss while moisturizing the skin. Dermatologists report that it is well tolerated and poses minimal risk of irritation or sensitivity.

Studies have shown that dexpanthenol is a versatile compound that is effective in treating various dermatoses.

Alone, it is used most often as a moisturizing agent. Dexpanthenol also has been used in combination therapy for the treatment of rhinitis (Laryngorhinootologie 79[3]:151-54, 2000). In addition, a prospective, randomized, double-blind study showed that the prophylactic, continued use of an emollient containing dexpanthenol ameliorated the effects of radiation dermatitis (Br. J. Dermatol. 146[6]:983-91, 2002). In addition, dexpanthenol has been shown to promote fibroblast proliferation both in vitro and in vivo (Am. J. Clin. Dermatol. 3[6]:427-33, 2002).

In a randomized, prospective, double-blind, placebo-controlled study, researchers assessed the effectiveness of dexpanthenol in protecting against skin irritation in 25 healthy volunteers aged 18-45 years (Contact Dermatitis 49[2]:80-84, 2003). In another study, when a product containing either 5% dexpanthenol or placebo was applied twice daily for 26 days to the inner aspect of both forearms, the dexpanthenol-containing product was shown effective in treating skin irritation. In a different study, treatment with dexpanthenol over 3-4 weeks resulted in significant amelioration in skin irritation symptoms such as xerosis, pruritus, erythema, roughness, scaling, and fissures (Am. J. Clin. Dermatol. 3[6]:427-33, 2002).

Several other benefits to the skin have been associated with dexpanthenol. In a randomized, double-blind, placebo-controlled study, treatment with topical dexpanthenol over 7 days resulted in enhanced stratum corneum hydration and decreased transepidermal water loss (Arzneimittelforschung 50[7]:659-63, 2000).

According to a recent study, formulations containing dexpanthenol were shown to stimulate epithelialization and granulation and had an antipruritic, anti-inflammatory effect on experimental UV-induced erythema (Am. J. Clin. Dermatol. 3[6]:427-33, 2002).

Dexpanthenol confers soothing effects to formulations for the treatment of sunburn and other types of burns. Topically applied dexpanthenol is considered safe, with minimal association with local skin reactions or sensitization. However, products with a high concentration of dexpanthenol may be contraindicated in people with hemophilia.

Dexpanthenol is included as an ingredient in a variety of topically applied skin creams and shampoos. In fact, this form of vitamin B_5 has long been considered an effective ingredient in cosmetic products.

The foundation for the use of dexpanthenol in shampoo—and anecdotal reports that its use restores color to gray hair—stems from a study several years ago evaluating dexpanthenol deficiency in rats. Deficiency was correlated with hair turning gray or falling out.

Pantothenic acid deficiency in humans is exceedingly rare, though, and is not likely associated with hair changes, according to nutritional studies by Nora Plesofsky-Vig. Clearly, the etiologies of hair graying and baldness are not related to this vitamin. Also, no oral or topical formulations containing pantothenic acid or dexpanthenol as the main active ingredient have been shown to prevent gray hair or balding in humans. Nevertheless, it is believed that dexpanthenol penetrates well into the hair shaft, promotes luster and elasticity, and renders the hair easier to comb.

Dexpanthenol is an important component in several types of skin and hair care products. Panoplex Hydrogel Wound Dressing (Sage Laboratories) is a water-based gel formulated with aloe vera and dexpanthenol. It's recommended for the management of pressure and dermal ulcers, first- and third-degree burns, radiation therapy burns, cuts, abrasions, postoperative incisions, partial- and full-thickness wounds, and skin conditions related to peristomal care.

The Roche Bepanthen product line is a fairly extensive group of formulations containing dexpanthenol for its healing properties. The line includes Bepanthen Ointment for baby skin and breast care, Bepanthen Cream for minor injuries and stressed skin, Bepanthen Plus for disinfecting and healing minor wounds, Bepanthen Nasal Ointment for treating crusted nasal mucosa, Bepanthol Body Lotion for reddened skin, Bepanthol Intensive Body Lotion for especially dry and sensitive skin, Bepanthol Handbalm, and Bepanthol Lipcream.

Dormer 211 Moisturizers, which feature exclusive high–molecular-weight hyaluronic acid complexes in its formulations, also contain dexpanthenol as a main ingredient in its Face & Hand Cream (70 mL; light texture), Cream (110 mL and 500 mL; maximum moisturizer), Cream SPF 15 (60 mL; daily moisturizing and broad-spectrum sun protection), and Cream SPF 30 (60 mL; with broad-spectrum UVA and UVB protection).

Eucerin's pH5 Soft Creme contains highly concentrated dexpanthenol that is said to be rapidly absorbed by the skin, improving its regeneration capacity and overall stratum corneum barrier function. The formulation is also touted as an effective moisturizer.

This form of vitamin B_5 is considered an effective ingredient in cosmetic products.

Dexpanthenol acts as a humectant in a new night firming product, Olay's Total Effects Night Firming Cream, also containing niacinamide, tocopherol acetate, and hydrolyzed wheat protein, that was introduced late in 2002. The formulation is said to lessen transepidermal water loss according to studies performed by the manufacturer, Procter & Gamble.

Dexpanthenol is even included, as a moisturizer, in Cellulite Attack thigh cream by Nutrition Farm.

Few controlled clinical trials have been conducted evaluating the efficacy of topical formulations containing dexpanthenol intended for skin care. Despite a dearth of randomized, double-blind, case-controlled studies establishing the efficacy of such products, current data warrant further study and support the conclusion that dexpanthenol as an active ingredient at least confers some benefit as a moisturizer.

There is an increasing body of anecdotal, empiric evidence also suggesting significant potential additional contributions by provitamin B_5 as an ingredient in topical formulations. More studies are needed to explore other potential benefits of this active ingredient. ■

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Olive Oil

Continued from page 11

tour cream, skin-reinforcing oil complex, and shampoo for dry scalps. The 7 Wonders Miracle Oil and Lotion line also contains olive oil as the primary active ingredient in various oil formulations (body, bath, baby, tanning, massage, cuticle, and hot oils).

The abundance of glycerides and fatty acids in olive oil render it gentle enough to use even on sensitive skin, according to the manufacturers of the Jardin de l'Olivier products. This diverse line includes Bath & Shower Crème, Bath Oil, Body Lotion, Hand Cream, Crème Shampoo, Tonic Lotion, Cleansing Cream, and Dry Skin Cream, with olive oil as the chief component.

The presence in olive oil of several compounds with known antioxidant activity provides a rationale for further research.

MedAssist Therapeutic Skin Cremes is a line of products made from all-natural ingredients. Their varied line of olive oil formulations includes Olive Branch Moisturizing Crème, Olive Branch Hydrating Lotion, Olive Branch Soothing Oil, Olive Branch Revitalizing Cleanser, Olive Branch Hair and Scalp Treatment, Olive Essence Hand and Body Lotion, Olive Essence Silky Moisturizing Body Spray, and Olive Essence Gentle Cleansing Herbal Shampoo.

Country Rose Soap Co. uses blends of olive, coconut, palm, castor, and jojoba oils, with all of the products containing a high percentage of olive oil (such as 100% Olive Oil Castile Soap). Besides these specific lines, there are numerous companies featuring olive oil as an active ingredient in select products.

The wider benefits of olive oil, like many other botanical ingredients, were known in the ancient world and are just in the process of being rediscovered.

As is the case with the plethora of herbal ingredients, olive oil has been incorporated into a wide array of topical products.

The presence in olive oil of several compounds with known antioxidant activity, along with the results of a few studies suggesting anti-inflammatory and anticarcinogenic effects, provide a rationale for further research.

As is often the case with herbal products, however, there is a dearth of randomized, double-blind, controlled trials on the topical application of olive oil.

Olive oil is highly regarded as a healthy food and cooking oil. If it turns out to be even half as well regarded as an antioxidant ingredient in topical formulations, it might leap to the head of the growing list of potent herbal antioxidants being used and studied in medicine. ■

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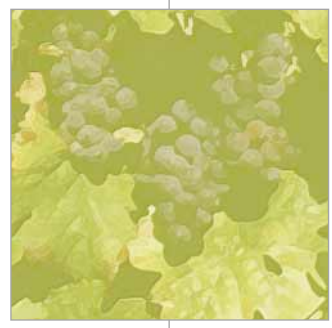
Grape Seed Extract

Grape seed extract is a powerful antioxidant that is emerging as a key element in the armamentarium against several diseases and the cutaneous manifestations of aging.

Also known as *Vitis vinifera*, pine bark, *Pinus maritima*, and Pycnogenol, grape seed extract has an antioxidant capacity derived from oligomeric proanthocyanidins, usually referred to as simply proanthocyanidins.

Proanthocyanidins have captured the popular imagination, convincing many that grape seed extract can improve skin elasticity and tone, prevent or ameliorate scars and stretch marks, and prevent or reduce wrinkling by protecting against UV radiation. Proanthocyanidins, which belong to the flavonoid family, are found in several plant sources, including pine bark, grape seed, grape skin, bilberry, cranberry, black currant, green tea, and black tea.



These polyphenolic bioflavonoids reportedly boast a wide range of biologic, pharmacologic, chemoprotective, and antioxidant activities (Res. Commun. Mol. Pathol. Pharmacol. 95[2]:179-89, 1997). Proanthocyanidins, or condensed tannins, are said to have the capacity to stabilize collagen and elastin and thus enhance the elasticity, flexibility, and appearance of skin.

Anecdotal Effectiveness

Much of the anecdotal evidence regarding the use of grape seed extract comes from Europe, where proanthocyanidins have been used therapeutically for decades to improve circulatory disorders such as atherosclerosis, vascular insufficiency, and varicose veins. Europeans have also used preparations containing proanthocyanidins to treat edema, particularly when associated with surgery.

Proanthocyanidins are considered by many to have the ability to enhance vision and protect the skin against UVB damage. Proanthocyanidins and other tannins have also been shown to foster wound healing.

In one study, a combination of grape seed extract and resveratrol was shown to promote vascular endothelial growth factor (VEGF) expression, which is an important step in wound angiogenesis (Ann. N.Y. Acad. Sci. 957:239-49, 2002). Earlier research suggested that grape seed extract, by inducing VEGF expression in keratinocytes, shows the potential to confer beneficial results in dermal wound healing and related skin problems (Free Radic. Biol. Med. 31[1]:38-42, 2001). Topical application has also been shown to improve the sun protection factor in human volunteers (Toxicology 148[2-3]:187-97, 2000).

Respiratory conditions such as asthma, emphysema, and sinusitis have been treated with grape seed extract, with varying degrees of success. Allergic reactions are believed to be treatable with proanthocyanidins, which may inhibit histamine production and reduce susceptibility to pollens and food allergens.

Promising research suggests that the anti-inflammatory effects of grape seed extract may make it suitable for wound healing and the treatment of arthritis. Supplementation with grape seed extract has also been shown to improve chronic pancreatitis in humans (Toxicology 148[2-3]:187-97, 2000).

The most popular use of grape seed extract is as a supplement for the treatment of cutaneous aging. Data do suggest that grape seed extract is a significantly more potent scavenger of free radicals than are vitamins C and E (Res. Commun. Mol. Pathol. Pharmacol. 95[2]:179-89, 1997). The bioflavonoids in grape seed extract appear to foster a symbiotic relationship for the other nutrients, promoting the body's ability to absorb the vitamins.

In fact, in vitro and in vivo research have shown grape seed extract to be highly bioavailable, conferring much more protection against free radical–induced lipid peroxidation and DNA damage than vitamin C, vitamin E, or β-carotene (Toxicology 148[2-3]:187-97, 2000).

Despite the reported beneficial effects of grape seed proanthocyanidins, little is understood about their mechanism of action.

Research has shown, however, that exposure to grape seed proanthocyanidins was associated with a significant reduction in apoptosis in response to cytotoxic chemotherapeutic agents. Investigators believe the chemopreventive effects of the extract are mediated by upregulating *Bcl-2* and downregulating *c-myc* and *p53* genes (Curr. Pharm. Biotechnol. 2[2]:187-200, 2001).

There are also data to suggest that the proanthocyanidin-rich polyphenol fraction of grape seed extract effectively achieves balance between the cell-mediated types of action in protecting LDL cholesterol against oxidation (Free Radic. Res. 37[5]:573-84, 2003).

The most promising research on grape seed proanthocyanidins might be in the realm of anticarcinogenesis. Researchers have shown that grape seed extract displays cytotoxicity toward human breast, lung, and gastric adenocarcinoma cells while promoting growth of normal gastric mucosal cells (Toxicology 148[2-3]:187-97, 2000).

Extracting Sales

Manufacturers that include grape seed extract in their topical cosmetic formulations tout the antiaging effects that the ingredient is believed to confer.

Continued on page 17

Lavender

Widely cultivated for its essential oil, lavender is a fragrant, hardy, perennial shrub belonging to the *Lamiaceae*, or mint, family.

Seeds of the lavender shrub were transported from their native Mediterranean region to England and France through human migration hundreds of years ago. However, several species of lavender have actually been used for therapeutic, cosmetic, and commercial purposes for thousands of years.

Though all 28 lavender species are believed to confer some degree of therapeutic benefit, *Lavandula officinalis* is the species used in medicinal formulations. The active chemical components that give lavender its reputed medicinal properties include tannins, coumarins, flavonoids, and triterpenoids. Linalool also is an important phytochemical constituent of lavender (Phytother. Res. 13[6]:540-42, 1999).

Derived from the Latin word "lavare," meaning "to wash,"the lavender plant was named for its practical applications in the ancient world. Lavender blossoms were used by ancient Greeks and Romans to scent bath water, bathe wounds, and prevent infections at communal baths.

Traditionally, lavender was hung in the home to repel mosquitoes, flies, and other insects, and placed in linen closets to repel moths. Its disinfectant and fumigant properties also were useful for sanitizing floors. Other actions and properties associated with lavender oil include anticonvulsive, antidepressant, antibacterial, and carminative effects (Phytother. Res. 16[4]:301-08, 2002).

In addition, the essential oil distillate of lavender has been used to treat wounds, bites, burns (including sunburns), lacerations, and even acne, psoriasis, fungal conditions, and herpes.

The Research Findings

Studies have shown that lavender has beneficial effects on human skin. Investigators studying perineal pain among women who had recently given birth found an association between use of lavender oil in baths and reduced discomfort (Mod. Midwife 5[3]:31-33, 1995).

Although the treatment record for alopecia areata is checkered at best, there is a report in the literature of lavender oil (among several other essential oils) being used with moderate success for this condition.

In a randomized, double-blind, controlled trial, 86 patients received daily scalp massage treatments with either essential oil in a mixture of carrier oils or carrier oil only for 7 months. Six of 41 patients in the control group showed improvement, whereas 19 of 43 patients in the treatment group exhibited significant improvement (Arch. Dermatol. 134[11]:1349-52, 1998).

There are no reports of significant adverse effects from the use of lavender for therapeutic or cosmetic purposes. Mild contact dermatitis has been identified, though, from the use of dried lavender flowers to scent items such as pillows and to disinfect ambient air (Contact Dermatitis 43[3]:157-60, 2000).

Conversely, researchers have shown, in vivo and in vitro, that lavender oil has the capacity to mediate sudden allergic reactions by inhibiting mast cell degranulation (J. Pharm. Pharmacol. 51[2]:221-26, 1999).

Products for the Skin

Lavender is an ingredient in a wide variety of skin care products including soaps, moisturizers, lotions, bath gels, lip balms, hand creams, shampoos, and hair conditioners.

The Softsoap line of products features a body wash touting the therapeutic effects of lavender and chamomile. Softsoap Relaxing Body Wash with Moisture Beads, Lavender and Chamomile is available in most grocery stores and large retail chains that sell personal care items. Life Tree Lavender Soft Skin Body Wash ($33 per gallon) is a wild lavender soap that is also available.

Profaces Body Contour Gel ($39) contains lavender as well as seaweed, grape seed, green tea, licorice extract, and essential oils of mandarin, rosemary, and lemon, and is recommended for skin firming and toning, according to the company.

DermAlive Skin Recovery Formula with Lavender (2 oz, $15) contains lavender oil, among numerous other ingredients, in an aloe vera base. Miss Rona's Lavender Anti-Aging Crème with SPF 18 ($60 per ounce) also contains lavender. Lavender is also an ingredient in many bath salts and candles.

Clinically Significant Benefits?

Topical products that contain lavender appear to be safe, with mild allergic reactions as the most likely adverse responses. Research has established a scientific and clinical foundation for the traditional uses of lavender.

It remains to be seen if double-blind, randomized, placebo-controlled trials will establish the use of lavender for dermatologic purposes.

While it's unlikely that commercially available topical formulations including lavender are harmful, it appears just as unlikely that such products confer clinically significant benefits.

Linking a well-regarded plant—known for its soothing, even potentially therapeutic qualities—to their products remains an effective marketing strategy that manufacturers employ with lavender and several other herbal ingredients. ■

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Chamomile

Chamomile is one of the seven most commonly used medicinal herbs. Native to Western Europe, Western Asia, and India, and now abundant throughout North America, this sweet-scented plant has been recognized for its therapeutic properties since the age of Hippocrates in 500 B.C. The ancient Greeks and Egyptians used crushed chamomile flowers to treat erythema and dry skin brought on by harsh, dry weather (J. Sch. Nurs. 16[3]:53-58, 2000).

The generic designation "chamomile" is derived from the Greek words "khamai" (on the ground) and "melon" (apple). Two species of this bittersweet herb, Roman chamomile (*Chamaemelum nobile*) and German chamomile (*Matricaria recutita* or *Chamomilla recutita*), have been labeled as the true chamomile because of their therapeutic applications and similar appearance. Roman chamomile is considered therapeutic for burns, boils, and small cuts and reputed to foster the natural healing of acne, dermatitis, and athlete's foot. However, the official medicinal chamomile is German chamomile, with even broader applications.

The flowers of German chamomile, which contain the key active ingredient chamazulene α-bisabolol in the highest concentration among all the chamomiles, have been used throughout history as an herbal treatment for various skin ailments. Chamazulene α-bisabolol promotes wound healing and exhibits anti-inflammatory activity, according to the "Physician's Desk Reference for Herbal Medicines" (Montvale, N.J.: Medical Economics Co., 1998). As a result, companies include chamomile in several cosmetic products that are intended to soothe the skin.

Despite a long history of traditional use, chamomile has only been subjected to the rigors of the scientific method during the past 40 years.

Chemistry

Chamazulene (-), -α-bisabolol, bisabololoxides, flavonoids (which have documented antioxidant properties), coumarins, mucilages, mono- and oligosaccharides, and farnesenes are the primary active components of *Matricaria recutita* that are deemed medically important (Eur. J. Drug Metab. Pharmacokinet. 24[4]:303-08, 1999). Fatty acids, cyanogenicglycosides, choline, tannin, and salicylate derivatives also are among the notable phytochemical constituents.

Chamazulene is a transformation product of matricine. Both of these constituents of chamomile extracts have shown anti-inflammatory activity in vivo (Planta Med. 60[5]:410-18, 1994). It is believed that chamazulene contributes to this process by inhibiting leukotriene synthesis (Planta Med 60[5]:410-18, 1994).

Levomenol is another key anti-inflammatory component found in great abundance in German chamomile. It is believed to confer significant effects on skin, such as ameliorating texture and elasticity and diminishing pruritus and signs of photodamage. Further, the combined effects of levomenol, a natural moisturizer, and chamazulene are said to soothe skin exhibiting eczema, allergic effects, and sunburn.

A study was conducted with Wistar albino rats in which inflammation was induced via the injection of carrageenan and prostaglandin E1 to evaluate the anti-inflammatory activity of freeze-dried plant extracts of four different herbs. All four, including chamomile (*Matricaria chamomilla*), were found to suppress both the inflammatory effect and the leukocyte infiltration (Vet. Med. Nauki 18[6]:87-94, 1981). In addition to reports of anti-inflammatory effects, chamomile is said to have some antioxidant properties, which have been identified through chemical assays (J. Agric. Food Chem. 50[17]:4947-52, 2002).

Indications

Chamomile is notably versatile in the medicinal realm, with the dried flowers of *Matricaria recutita* conferring sedative and spasmolytic properties (Biochem. Pharmacol. 59[11]:1387-94, 2000). Chamomile also acts as an anodyne, anti-allergenic, antibacterial, anti-inflammatory, carminative, and tonic. The traditional indications for chamomile and its various teas and topical formulations range from stomach cramping and pains, menstrual cramping, and diarrhea to inflammatory skin and eye problems, mood disorders, and even the flu. Chamomile is one of the most commonly used herbs for treating morning sickness, but there is contradictory evidence amid an overall dearth of data on whether use of chamomile is safe during pregnancy (Midwifery 16[3]:224-28, 2000). As an essential oil administered via skin absorption and inhalation used in aromatherapy, chamomile has been shown to be effective in alleviating the pain related to childbirth (Complement Ther. Nurs. Midwifery 6[1]:33-34, 2000).

As an infusion, chamomile has also been traditionally used to ease colic and teething in babies, and to calm restless children. In addition, this bittersweet herb has been shown to be effective in relieving acid indigestion, intestinal gas, constipation, and peptic ulcers. The use of chamomile tea as an eyewash for conjunctivitis and other external ocular symptoms is a traditional remedy (Ann. Allergy 65[2]:127-32, 1990). Chamomile also is effective when used in a vaginal douche, in a mouthwash for oral ulcers, and in a rinse to enhance hair color.

Side Effects

The use of chamomile in any form is considered generally safe, with few side effects reported. Chamomile is one among the several herbs that can interact with warfarin, elevating the risk of bleeding or other adverse effects for a patient on warfarin therapy (Am. J. Health Syst. Pharm. 57[13]:122-27, 2000). There have been some reports of contact dermatitis following the topical application of chamomile products, and allergic conjunctivitis also has been linked to eye washing with chamomile tea (Ann. Allergy 65[2]:127-32, 1990).

Products

Chamomile is included in a wide array of cosmetic products for various purposes. In skin formulations, chamomile often is added as an emollient and to provide anti-inflammatory and soothing activity for sensitive skin. Chamomile also is used in several hair products intended to enhance the color of blonde hair.

The Murad line of skin products includes chamomile in several formulations. Moisture Rich Skin Cleanser ($22/6 oz) and Sensitive Skin Smoothing ($48/1.7 oz) include chamomile extract to soothe the skin. The Hydrating Toner ($16/6 oz) claims to confer the anti-inflammatory and soothing properties of chamomile.

Chamomile also is included in products in the Wildflower Natural Care line of vegan skin products for babies and young children. Chamomile Baby Lotion ($8.99/8 oz) is a moisturizer intended to provide the soothing and anti-inflammatory characteristics of chamomile. Chamomile Cleansing Lotion ($8.99/8 oz) is a soap-free, extra-gentle cleanser enriched with chamomile extract to help prevent irritation.

The European company Camocare manufactures a line of skin products largely centered on chamomile. The company claims its patented product Camillosan is the most potent chamomile extract available. Camocare's Ultimate Body Therapy for Extra Dry Skin ($17.95/8 fl. oz) contains Camillosan and standardized antioxidant components. Camocare Gold Facial Therapy ($21.95/2.4 oz) is said to combine the benefits of chamomile and an alpha lipotene antioxidant.

Conclusion

While the popular consciousness most often associates the health benefits of chamomile with chamomile tea, there is a long history of effective, therapeutic application of chamomile to the skin. The body of scientific research on chamomile is relatively slim, but it appears to support traditional beliefs. Nevertheless, double-blind, placebo-controlled trials are necessary to establish the range of therapeutic potential of this hardy herb, and to evaluate the relative efficacy of products featuring it as an active component. ■

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Grape Seed Extract

Continued from page 14

California North's Appellation grape seed moisturizer ($28.75 for 4 ounces) is a nongreasy, oil-free, pH-balanced moisturizer containing several naturally derived extracts. According to the company, this formula also reduces the appearance of fine lines. Appellation microfine grape seed scrub ($24.50 for 4 ounces) is a pH-balanced exfoliating facial scrub containing high levels of vitamins C and E from grape seed extract intended for healthy cell turnover and regeneration, as well as moisturization.

Another herbal cocktail product aimed at removing dead skin cells and smoothing complexion is Aubrey Organics' blue green algae with grape seed extract soothing mask ($8.75 for 4 ounces). This is an antioxidant clay mask with active enzymes intended to draw out excess oil and debris and tone the skin, according to the manufacturer.

A product line that features grapefruit, Archipelago Botanicals' Yuzu (Japanese grapefruit) Collection, offers several products in which grape seed extract is a primary active ingredient.

Products from the line containing grape seed extract include: antioxidant body soak ($18 for 11 ounces), refreshing body mist ($14 for 12 ounces), antioxidant body lotion ($25 for 17 ounces), antioxidant body scrub ($18 for 16 ounces), antioxidant moisturizing creme ($15 for 3.2 ounces), soap in tin ($13 for 8.8 ounces), body wash ($18 for 32 ounces), conditioner ($11 for 16 ounces), and relaxing bath salts ($16 for 16 ounces).

There are no significant reports of adverse effects from the use of products containing grape seed extracts. In fact, flavonoids generally and proanthocyanidins specifically are not associated with any side effect patterns.

Potent Protection?

Preliminary research, anecdotal evidence, and even early experience with grape seed extract products suggest beneficial effects on vascular disease and wound healing. They may even turn out to have a preventive effect against some cancers. At this stage, results are convincing that grape seed extract confers potent protection against oxidative stress and free radical–mediated tissue damage. Several European authors contend that proanthocyanidins inhibit enzymes integral to the breakdown of the skin, such as collagenase, elastase, and hyaluronidase.

Much more research in the form of double-blind, placebo-controlled clinical trials is necessary before grape seed extract warrants recommendation as a primary ingredient in topical cosmeceuticals. ■

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Soy and Its Isoflavones

The topical use of soy has been touted to reduce the appearance of hyperpigmentation, enhance skin elasticity, delay hair regrowth, control oil production, and moisturize the skin. Some also believe that soy has the potential to decrease aging of the skin and prevent skin cancers through the estrogen-type and antioxidant effects of its metabolites.

The components of soy have been suggested to have a variety of effects that may make them useful in skin care products. Small proteins such as soybean trypsin inhibitor (STI) and Bowman-Birk inhibitor (BBI) have been suggested to inhibit skin pigmentation, while large proteins have been found to smooth and soften the skin.

Unsaturated fatty acids found in soy are believed to provide antioxidant benefits, and soy lipids, lecithins, and phytosterols are believed to restore barrier function and replenish moisture. Natural soy surfactants such as saponins and lecithins are thought to provide cleansing activity, according to a poster presented at the annual meeting of the American Academy of Dermatology, held in Washington, D.C., in March.

In another recent study, STI, BBI, and soy milk were found not only to have depigmenting activity but also to prevent UV-induced pigmentation both in vitro and in vivo.

The investigators found that these proteins inhibit the cleavage of protease-activated receptor 2 (PAR-2). PAR-2 is a seven-transmembrane, G protein–coupled receptor that is activated by a serine protease cleavage. It is expressed in keratinocytes but not in melanocytes. By inhibiting this cleavage, STI and BBI are believed to affect melanosome transfer and thus pigmentation (J. Invest. Dermatol. 116[4]:587-95, 2001).

These data suggest that soy might be a useful adjuvant for treating hyperpigmentation disorders; melasma, however, is an exception. Because soy exerts some estrogen-type effects and melasma is somewhat estrogen mediated, the use of soy might be deleterious in this situation.

Various studies in animal and human cell cultures have shown genistein and diadzein—the primary metabolites of soy isoflavones—to be phytoestrogens, which are plant compounds that have a weak estrogenic effect (Int. J. Oncol. 16[2]:333-38, 2000).

When estrogen levels in the body are high, they may work by competing for and binding to the body's estrogen receptor sites, causing excess circulating estrogen to be sent to the liver for elimination. When the body is low in estrogen, as is the case during menopause, phyto-estrogens such as genistein and diadzein may substitute for the lack of human estrogen, mitigating the effects of its absence.

Estrogen receptor levels are highest in the granular layer of the skin. Multiple studies have shown that postmenopausal women have a measurably thinner dermis and less collagen than premenopausal women. Topical estrogen has been shown to decrease the skin thinning and collagen loss seen in postmenopausal patients not on hormone replacement therapy.

Because of this, it is believed—but has not yet been shown—that supplementation with phytoestrogens could have the same beneficial effects on the skin as topical estrogen.

Several studies have suggested that genistein in particular is a potential anticancer agent. Dr. Huachen Wei and colleagues at Mount Sinai Medical Center in New York demonstrated that genistein significantly inhibited chemical carcinogen-induced reactive oxygen species, oxidative DNA damage, and protooncogene expression, as well as the initiation and promotion of skin carcinogenesis in mouse skin (J. Am. Acad. Dermatol. 39[2, pt. 1]:271-72, 1998). The investigators also found that genistein potently inhibited UVB-induced erythema in human skin. Because most research on topical genistein has been limited to mouse skin—except for one human-skin study—its effect on human skin must be considered unknown.

These scientific findings have prompted cosmetic companies to include soy and soy derivatives in sometimes extremely expensive products, including some from Johnson & Johnson (such as Aveeno skin brightening daily moisturizer), Soy Soft Inc. (Soy Soft daily moisturizing lotion), and Woodridge Labs Inc.'s Soylutions line.

Another poster presented at the annual AAD meeting claimed that test subjects did not exhibit any irritation, allergy, and photoreactivity to a number of soy formulations studied.

Although studies are promising, more research needs to be done to determine the safety and actual benefits of topical soy use. Until then, soy products should be considered a safe and possibly effective treatment for post-menopausal female patients and patients with hyperpigmentation disorders other than melasma.

Although it has not been reported to have an effect on tumor growth, soy use should be avoided in patients at high risk for or with a history of estrogen-sensitive tumors, such as breast or uterine cancer. ■

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Vitamin A, Retinol, and Retinoids

Vitamin A and its derivatives are very popular ingredients in cosmeceutical products. All of the natural and synthetic derivatives of vitamin A are included in a group known as the retinoids.

The retinoids have many important biologic effects: They regulate growth and differentiation of epithelial cells, inhibit tumor promotion during experimental carcinogenesis, diminish malignant cell growth, decrease inflammation, and enhance the immune system (J. Am. Acad. Dermatol. 39[4, pt. 1]:611-25, 1998).

Retinoic acid, or tretinoin, is now known to reverse photoaging by reducing wrinkles and smoothing skin texture as well as decreasing actinic keratoses and lentigines (Dermatol. Clin. 18[4]:699-709, 2000).

Retinoids have also been shown to improve the appearance of striae and improve skin discoloration (J. Am. Acad. Dermatol. 39 [2, pt. 3]:S1-122, 1998).

Long-term studies have shown that the visible skin changes found with tretinoin use result primarily from an increase in dermal collagen, a decrease in abnormal elastin, increased dermal and epidermal mucin, an improved dermal-epidermal junction, and decreased melanin (Dermatol. Clin. 18[1]:99-112, 2000).

Tretinoin also decreases the transcription factor AP-1, leading to reduced levels of collagenase and other metalloproteinases (N. Engl. J. Med. 337[20]:1419-28, 1997).

Tretinoin, however, is available by prescription only. It has two approved uses: treating acne and improving photodamaged skin.

Because tretinoin is expensive and usually not covered by prescription drug insurance, many patients are interested in using over-the-counter products that contain retinoids. Most such products contain either retinyl palmitate or retinol.

Retinyl palmitate has not been found to be biologically active in the skin (J. Am. Acad. Dermatol. 39[2, pt. 3]:S2-7,1998). To be converted to retinol, retinyl palmitate requires cutaneous cleavage of its ester bond and then conversion to retinoic acid in order to exert an activity when applied topically. Many products that claim to contain retinol actually contain retinyl palmitate.

Retinol, on the other hand, is highly useful in skin care. Retinol is a pro-drug that can be converted to retinoic acid by the skin. The change to all-*trans* retinoic acid within the keratinocytes is essential for retinol to be active (J. Biol. Chem. 269[52]:32821-27, 1994).

Early reviews of retinol found it to be ineffective; however, further research determined that this was due to the molecule's photoinstability. Upon exposure to light, retinol degrades into a biologically inactive molecule. This breakdown can be prevented by adding an antioxidant or by incorporating retinol into an oxidation-resistant vehicle.

Recent investigations of retinol in an appropriate vehicle and in the correct concentration have shown it to be as effective as tretinoin for the same indications.

In one study, unoccluded retinol at 0.25% was found to induce the same cellular and molecular changes observed with the application of 0.025% tretinoin—without the irritation usually seen with tretinoin. In addition, the investigators found that retinol penetrated the skin better than tretinoin (J. Invest. Dermatol. 109[3]:301-05, 1997).

Side effects have been found to be fewer than those seen with tretinoin; therefore, retinol may be an excellent alternative for patients with sensitive skin. In addition, vitamin A is also known to be a humectant moisturizer and therefore is a useful additive in products meant to moisturize the skin (Dermatol. Clin. 18[4]:597-607, 2000).

While prescription-strength retinoids are known to be successful in reversing and preventing the signs of aging, it is important to remember that properly formulated retinol products can be efficacious as well. These products must be packaged in special low-light conditions to ensure stability. They should be packaged in lightproof aluminum tubes. Most over-the-counter products contain 0.04%-0.08% retinol.

It is impossible to ascertain by reading the label which products are manufactured and packaged properly, so it is best to stick with reputable brands that you can trust.

In order to better guide our patients, we went to a local pharmacy and purchased every product containing or claiming to contain retinol. For each, we examined the packaging and the product inside as well as any labeling or marketing from the company.

Two examples of brands that are manufactured and packaged properly are RoC Retinol Actif Pur and Neutrogena Healthy Skin. I feel comfortable recommending these to my patients.

Advise your patients to use retinol products at night, when degradation by light is minimal. Some products are marketed with added sunscreens for daytime use. It is very important for patients on retinoids of any kind to apply sunscreen daily, as retinoid use is associated with increased photosensitivity. ■

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Vitamin E

Vitamin E is frequently found in cosmeceutical products. It functions as a preservative, has excellent moisturizing capabilities, and has been promoted most recently for its photoprotective effects. However, its use has been also associated with a high incidence of contact dermatitis.

Vitamin E includes the tocopherols and the tocotrienols. It is found naturally in many vegetables, corn, oils, seeds, soy, wholewheat flour, nuts, and margarine. It is also found in some meat and dairy products.

The biologically active forms are α-tocopherol and γ-tocopherol; free α-tocopherol is the most biologically active form. These forms act as lipid-soluble antioxidants.

Vitamin E is found naturally in the membranes of cells and organelles. It protects cell membranes from peroxidation and scavenges free radicals; therefore, it is believed to help prevent cardiovascular disease and the "aging" of the arteries.

While studies outside the field of dermatology have convincingly suggested the benefits of oral vitamin E supplementation, the dermatologic benefits are still unknown.

A study by Dr. Karla Werninghaus and her colleagues at Boston University showed that oral supplementation with 400 IU vitamin E was not photoprotective in humans and did not increase vitamin E levels in skin biopsy specimens after 1 month and 6 months of supplementation (Arch. Dermatol. 130[10]:1257-61, 1994).

Conversely, a study by C. Weber and colleagues at the University of California, Berkeley, showed that vitamin E levels were depleted in animal skin exposed to UV radiation, and this depletion was prevented by the topical application of vitamin E (Free Radic. Biol. Med. 22[5]:761-69, 1997).

Further, a study by Beth Anne Jurkiewicz and her colleagues at the University of Iowa, Iowa City, showed that topical tocopherol provided significant protection against UV-radiation–induced damage to animal skin (J. Invest. Dermatol. 104[4]:484-88, 1995).

While it has been suggested that topical application of α-tocopherol confers an SPF of 3 after multiple applications, this effect is believed to be due to its ability to marginally absorb light (Cosmet. Dermatol. 12[9]:17-20, 1999).

Inhibition of UV-induced skin erythema and edema with the use of topical vitamin E has not been shown in human skin. If vitamin E provides any photoprotective effect at all, it may require interaction with other antioxidants to do so, particularly since other antioxidants (such as vitamin C, selenium, and thiols) are essential for the recycling of tocopherol.

It has also been suggested that vitamin E may exert anti-inflammatory effects on the skin through the inhibition of chemical mediator production and release. Vitamin E stabilizes lysosomes, reduces prostaglandin E_2 synthesis, and increases interleukin-2 production. This results in anti-inflammatory and immunostimulatory effects (J. Am. Acad. Dermatol. 39[4, pt. 1]:611-25, 1998).

Topically applied vitamin E has been associated with several different adverse reactions at the application site, including contact urticaria, eczematous dermatitis, and erythema multiforme–like reactions (Cutis 47[3]:193-96, 1991).

While the majority of these adverse reaction reports are anecdotal, a study conducted by M. Jenkins and colleagues at the Shriners Burn Institute in Cincinnati on the use of topical vitamin E for postoperative scarring showed that local reactions occurred in 20% of cases (J. Burn Care Rehabil. 7[4]:309-10, 1986).

A study that I conducted on the use of vitamin E for scars showed a 33% rate of localized reaction in study patients (Dermatol. Surg. 25[4]:311-15, 1999).

The addition of vitamin E to cosmetic and hygiene products has spurred reports of adverse reactions.

A Swiss study in 1992 examined 1,000 cases of an unusual papular and follicular contact dermatitis caused by vitamin E linoleate that was used as an additive to cosmetic products. The investigator concluded that oxidized vitamin E derivatives could act synergistically in vivo as haptens or as irritants (Dermatology 189[3]:225-33,1994).

Mennen E aerosol deodorant was removed from the market also following many reports of allergic contact dermatitis (Rietschel, R., and Fowler, J. "Fisher's Contact Dermatitis," 4th ed. [Baltimore: Lippincott Williams & Wilkins, 1995]).

Even though vitamin E appears to be a very effective antioxidant when taken systemically, its role as a topical antioxidant remains unclear. A study conducted by H. Kappus and A.T. Diplock of Free University Berlin suggests that daily doses up to 400 mg are completely safe and that doses between 400 mg and 2,000 mg are not likely to cause adverse side effects (Free Radic. Biol. Med. 13[1]:55-74, 1992).

However, doses greater than 3,000 mg daily when taken over a long period may cause side effects. Patients on anticoagulant therapy and patients undergoing surgical procedures should avoid doses of vitamin E greater than 4,000 IU (J. Am. Acad. Dermatol. 39[4, pt. 1]:611-25, 1998).

In addition, vitamin E should be stopped 10 days prior to collagen injections, and other treatments that can cause bruising, in order to decrease the chance of bruising.

Continued on page 23

Green Tea

Green tea is a popular beverage that is consumed worldwide. It is also a popular ingredient found in beauty products, including moisturizers, cleansers, shower gels, toothpastes, depilatories, shampoos, and perfumes.

Its inclusion in such products is due to the purported antioxidant effects of polyphenols that occur naturally in the green tea leaf.

Antioxidants have the ability to decrease free radicals, in turn preventing lipid peroxidation, DNA damage, and inflammation. Via this mechanism, these ingredients are believed to have anti-inflammatory, antiaging, and anticarcinogenic effects.

Green tea is made from the steaming and drying of the fresh leaves of the tea plant *Camellia sinensis*, a process that preserves its polyphenolic components.

The majority of these compounds are flavanols, commonly known as catechins, which are considered to be the active ingredients in the leaves. These catechins include epicatechin, epicatechin-3-gallate, epigallocatechin, and epigallocatechin-3-gallate (EGCG). These polyphenols have been shown to modulate biochemical pathways that are important in cell proliferation, inflammatory responses, and responses of tumor promoters (Arch. Dermatol. 136[8]:989-94, 2000).

The anticarcinogenic effects of green tea on human skin have not been demonstrated but have been suggested by multiple study findings. Individuals who consume green tea frequently have a lower rate of gastric cancer (Jpn. J. Cancer Res. 79[10]:1067-74, 1988). In mouse skin, green tea phenols were found to inhibit both stage I and II of skin tumor promotion (Carcinogenesis 14[12]:2641-43, 1993).

Studies in mice found that green tea phenols inhibit the biochemical markers of tumor initiation, scavenge the activated metabolites of carcinogens, and inhibit biochemical markers of tumor promotion (J. Invest. Dermatol. 102[1]:3-7, 1994).

Hasan Mukhtar, Ph.D., found that in human skin, topical treatment with EGCG before UV exposure led to decreased formation of cyclobutane pyrimidine dimers induced in DNA, an initiator of UV-induced mutagenesis and carcinogenesis (Proceedings of the Society of Cosmetic Chemists annual scientific meeting, New York, 1999).

Green tea has been shown to have anti-inflammatory and antioxidant effects in both human and animal skin.

As inflammation and oxidative stress are believed to play a role in the aging process, green tea may also have antiaging effects by decreasing inflammation and scavenging free radicals.

Ronald L. Prior, Ph.D., and Dr. Guohua Cao of the Jean Mayer Human Nutrition Research Center on Aging at Tufts University, Boston, found that green tea was able to increase antioxidant status in vivo through oral consumption of 8-10 glasses of tea per day (Proc. Soc. Exp. Biol. Med. 220[4]:255-61, 1999).

In human skin, Dr. Mukhtar and associates found that topically applied EGCG before exposure to UVB radiation blocked UVB-induced infiltration and reduced myeloperoxidase activity.

They also found that UVB-induced erythema was decreased in skin previously treated with topical EGCG. In mice, topical administration of EGCG to exposed areas was shown to decrease UV-induced hyperplastic response and free radical production, as well as decreasing the infiltration of inflammatory leukocytes and the inhibition of contact hypersensitivity response (Proceedings of the Society of Cosmetic Chemists annual scientific meeting, 1999).

Another interesting aspect of green tea consumption is that oral ingestion of green tea may exert an effect in the skin. Drinking green tea has been shown to increase green tea phenol levels in skin as demonstrated by tape-stripping analysis (Interview with Dr. Mukhtar at the Society of Cosmetic Chemists annual scientific meeting, 1999).

Chronic oral feeding of green tea phenols to mice followed by UVB irradiation was found to result in protection against UV-induced cutaneous erythema and prevention of the depletion of antioxidant defense enzymes.

Green tea was also found to decrease prostaglandin production by inhibiting cyclooxygenase activity (Proceedings of the Society of Cosmetic Chemists annual scientific meeting, 1999).

Products containing green tea extracts can be easily obtained by the consumer. They can be found at department store cosmetic counters, in drugstores, and in supermarkets.

While evidence is mounting as to the effectiveness of green tea phenols as antioxidants, most products containing these ingredients have not been tested in controlled clinical trials. The concentration of phenols in these products is not standardized, nor is it known for the majority of these products.

It is also not clear if the inclusion of products containing green tea extracts in cosmeceuticals is advantageous to patients. In addition, these products can be extremely expensive due to the difficulties in extracting EGCG.

Despite these drawbacks, green tea is a relatively harmless ingredient with much promise as an antioxidant.

Although more studies need to be performed, patients should be encouraged to consume green tea and should not be discouraged from using topical formulations, as many patients find the scent alone appealing.

Green tea also appears to be safe, and contact allergy has not

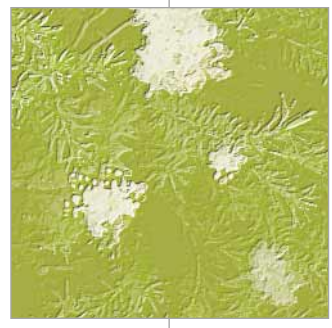
Continued on page 23

Tea Tree Oil

The use of essential oils in dermatology is rapidly accelerating throughout the world, and tea tree oil is one such essential oil that is finding its way into many new cosmeceutical products.

Although three species of coniferous *Myrtaceae* in Australia, New Zealand, and Southeast Asia are called tea trees, only the essential oil derived from the needles of the Australian *Melaleuca alternifolia* is used in medical and cosmetic products.

Aromatherapists use the essential oils of all three species, but only *M. alternifolia's* oil has been extensively tested for toxicity and evaluated for antimicrobial activity (Phytother. Res. 14[8]:623-29, 2000).



Tea tree oil, a clear liquid that ranges from colorless to faint yellow and has a distinct aroma, contains more than 100 natural compounds. Indigenous Australians have used it for centuries as an herbal medicine, topical antiseptic, and broad-spectrum antimicrobial agent.

In recent years, a more expansive demographic has come to use tea tree oil for a wide range of indications—from acne, psoriasis, fungal infections, and vaginal infections to tinea, lice, rashes, cold sores, cuts, scratches, burns including sunburn, and dental applications.

Tea tree oil is also being studied for its potential effectiveness against herpes simplex virus (J. Antimicrob. Chemother. 48[3]:450-51, 2001).

Tea tree oil is considered safe for use by most patients, and its broad-spectrum antimicrobial activity has been acknowledged with increasing frequency in the literature (J. Appl. Microbiol. 88[1]:170-75, 2000; Antimicrob. Agents Chemother. 46[6]:1914-20, 2002).

Given its reputation and anecdotal reports of effectiveness, tea tree oil has been incorporated into antifungal formulations in soaps and shampoos, dental products (such as mouthwash and toothpaste), veterinary products (to ward off fleas and ticks), and various household and industrial disinfectants.

Other potential applications include use as a laundry detergent ingredient (to eliminate mites) and as an antioxidant—though one study suggests that tea tree oil lacks antioxidant activity (Phytother. Res. 14[8]:623-29, 2000).

In an often-cited tea tree oil study by I.B. Bassett and colleagues, both 5% tea tree oil and 5% benzoyl peroxide exhibited significant effects in improving patients' acne by reducing the number of inflamed lesions, both open and closed comedones.

Although tea tree oil's onset of action was slower, patients who were treated with tea tree oil had fewer side effects (Med. J. Aust. 153[8]:455-58, 1990).

A recent study demonstrating the effectiveness of lipophilic tea tree oil in blocking the conversion of *Candida albicans* from the yeast to the pathogenic mycelial form suggests that tea tree oil may be a suitable agent for treating fungal mucosal and cutaneous infections (J. Chemother. 13[4]:377-83, 2001).

It also may have potential as an effective means of attacking several of the microbes typically associated with otitis externa and otitis media, though some ototoxicity is feared (Audiol. Neurootol. 5[2]:64-68, 2000).

Despite favorable reports on tea tree oil's many beneficial effects, there is little research showing the positive effects of tea tree oil on dermatologic conditions.

In one study, neither aloe vera gel nor tea tree oil was effective in treating atopic dermatitis and chronic venous insufficiency (Am. J. Clin. Dermatol. 3[5]:341-48, 2002).

In a review of four randomized clinical trials, researchers acknowledged that tea tree oil might be effective in treating acne and fungal infections, but they said that there is no compelling evidence showing that tea tree oil is truly effective in treating any dermatologic condition (Forsch. Komplementarmed. Klass. Naturheilkd 7[1]:17-20, 2000).

In fact, tea tree oil may be implicated in triggering mild allergic reactions, such as allergic contact dermatitis.

Cineole and terpinen appear to be the key medicinal components in tea tree oil, though terpinen has been implicated in allergic contact reactions. Several cases of sensitization to tea tree oil have been reported in the last decade. Photoaged *M. alternifolia*, in particular, has emerged as a strong sensitizer (Ann. Dermatol. Venereol. 128[2]:123-26, 2001).

Photooxidation within a few days to several months of exposure leads to the production of peroxides, epoxides, and endoperoxides, such as ascaridol and 1,2,4-trihydroxymenthane—the likely culprits in allergic contact dermatitis (Am. J. Contact Dermat. 10[2]:68-77, 1999). The increased use of tea tree oil over the last 15 years is expected to contribute to a higher incidence of contact dermatitis and eczema, according to some authors (Am. J. Contact Dermat. 11[4]:238-42, 2000; J. Am. Acad. Dermatol. 30[3]:423-27, 1994).

Some components of tea tree oil, however, may actually reduce hypersensitivity reactions, according to recent studies on mice conducted by C. Brand and colleagues. In one study, two components of topical tea tree oil—terpin-4-ol and alpha-terpineol—were found to regulate the edema associated with the efferent phase of a contact hypersensitivity reaction (Inflamm. Res. 51[5]:236-44, 2002). Terpin-4-ol was also shown, in a different study by the same author, to be effective in controlling the histamine-induced edema often linked to type 1 allergic reactions (Inflamm. Res. 51[6]:283-89, 2002).

As always, it is important for dermatologists to be aware of

the products that patients might be using on their own.

Many people view tea tree oil as a panacea for a long list of cutaneous conditions, as well as a potent weapon against many bacteria and fungi (Australas. J. Dermatol. 39[4]:244-47, 1998).

There is little research showing the positive effects of tea tree oil on dermatologic conditions.

Melaleuca oil—which is widely available, particularly in health-food establishments—appears to be generally safe for healthy skin. The most adverse reactions so far have been mild cases of allergic contact dermatitis and eczema.

More research into the different components of tea tree oil should yield a greater understanding among product developers about how to reduce the likelihood of adverse reactions.

In the meantime, expect tea tree oil to be included in an expanding list of cosmeceuticals. Gillette, for example, now touts tea tree oil as the key ingredient in its new shaving gels and foams. The company included tea tree oil for its astringent effect, claiming that the oil should render the skin "clean and fresh."

With the paucity of reliable research in the Western medical canon, traditional practices and anecdotal reports fill the knowledge gaps.

Considerably more research—particularly randomized, double-blind, controlled trials—is necessary to establish the efficacy of products with tea tree oil in the treatment of dermatologic conditions for which patients are now self-treating. ■

Reprinted from Skin & Allergy News, November 2002.

Vitamin E

Continued from page 20

When used topically, α-tocopherol acetate is an excellent moisturizer and is included in many products for this reason (Dermatol. Clin. 18[4]:597-607, 2000). It has also been shown to prevent light damage to products while they are on the shelves in stores and is added for preservative benefits. ■

Reprinted from Skin & Allergy News, July 2001. Melissa Lazarus, a research fellow at the University of Miami, contributed to the column.

Green Tea

Continued from page 21

been reported. A study conducted in which volunteers consumed 15 tablets of green tea per day for 6 months (2.25 mg of green tea extract, 337.5 mg of EGCG, and 135 mg of caffeine) showed no severe adverse effects (Proc. Soc. Exp. Biol. Med. 220[4]:225-28, 1999). ■

Reprinted from Skin & Allergy News, February 2001. Melissa Chesler, a research fellow at the University of Miami, contributed to the column.

Applying Nature

Continued from page 3

ronmental exposures, and skin care practices. Even when the patient groups are matched appropriately, a trial to evaluate prevention of aging would take at least 20 years to complete.

Physicians do not expect cosmetic clinical research to meet the exact same requirements that regulatory agencies have established for prescription drugs. Patient usage and physiologic response are distinctly different with cosmetic products compared to prescription drugs. However, cosmetic clinical studies that demonstrate dermatologic benefits of an active product versus a vehicle can still prove valuable to clinicians by establishing a basis for recommending specific cosmetic products to patients. In the process, the patients' historical beliefs about natural ingredients can be supported with published scientific results.

The content of this supplement to Skin and Allergy News reflects some of the success stories in the development of cosmetic products based on natural ingredients or natural ingredients that have been improved by science. Cosmetic dermatologists will find the information readily applicable to clinical practice. The information can help improve practitioners' knowledge of cosmetic products that patients hear about on a regular basis and then apply that information to make informed decisions about prescribing and patient counseling.

Although I hope practitioners find useful information in each of the articles, much of the basis for this supplement lies in the discussion of the 16 skin types that I have identified in my clinical and research experience in cosmetic dermatology.[4] To make a truly informed decision about selecting and using skin care products—or to counsel patients about those products—requires identification and understanding of an individual's specific skin type. A questionnaire found in the book *The Skin Type Solution* can be used to accurately determine the skin type and what ingredients are appropriate for that type. The key to effective skin care is to know the patient's skin type and to choose the products and ingredients that are most appropriate for that specific skin type. ■

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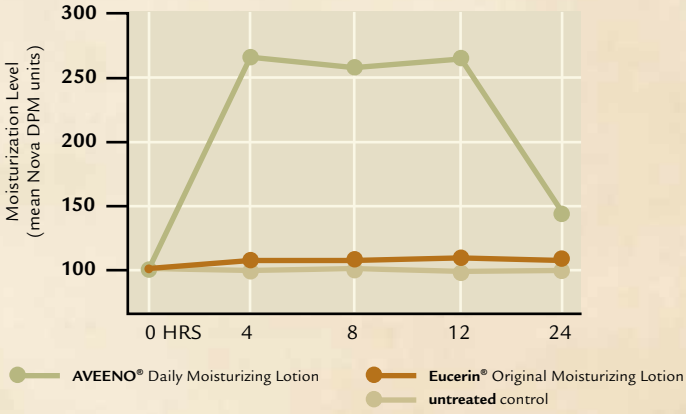

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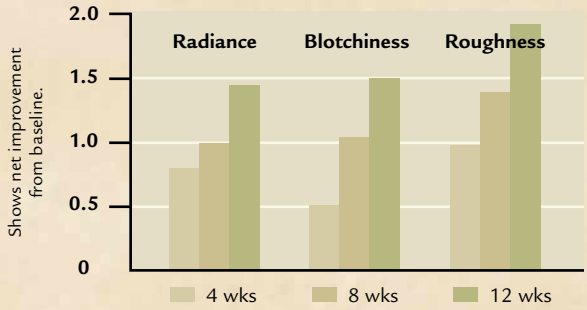

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