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# Cosmeceuticals Containing Herbs: Fact, Fiction, and Future

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**BACKGROUND.** Modern medicine is rooted in ethnobotanical traditions using indigenous flora to treat symptoms of human diseases or to improve specific aspects of the body condition. Herbal medicine is now used by over half of the American population. Yet the American medical community generally lacks knowledge of the function, metabolism, interaction, adverse reactions, and preparation of herbal products.

**OBJECTIVE.** Because over 60 botanicals are marketed in cosmetic formulations, dermatologists need to obtain working knowledge of the major botanicals. The preparation, traditional uses, mechanisms of action, human clinical data, adverse reactions, and interactions all impact herbal efficacy and are discussed below.

*CARL THORNFELDT, MD, FAAD, HAS INDICATED NO SIGNIFICANT INTEREST WITH COMMERCIAL SUPPORTERS.*

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THE FOUNDATION of modern pharmacologic medicine is rooted in ethnobotanical traditions using indigenous flora. Over 200 indigenous medicinals were listed in the first *U.S. Pharmacopeia* in 1820, including podophyllin resin, white willow bark, wintergreen, and juniper tar, which are still used today.<sup>1</sup>

Botanicals used for medicinal, flavoring, or fragrances are known as herbs.<sup>1,2</sup> The guiding principle of herbal medicine is that the naturally occurring mixture of active compounds in plants is more effective and safer than individual molecules and manufactured combinations of synthetic molecules. The natural composition is the comminuted, powdered, or galenic extracts of the whole or specific anatomic parts of the plant. Botanical medicinals are focused more on the treatment of signs and symptoms of disease, while improving the total “body condition,” than the etiology.

Botanical sales in 2002 in the United States exceeded \$4.3 billion and grew by one-third over only 6 years. Echinacea was the largest selling botanical in 2002, with sales of nearly \$190 million. Botanical product growth has flourished to now consume 25% of all health- and lifestyle-related dollars.<sup>3</sup> Now over 60 different botanicals are formulated into cosmeceuticals. Thus, dermatologists

**METHOD.** English-language medical journal and symposium searches.

**RESULTS.** The most important botanicals pertaining to dermatologic uses, such as cosmeceuticals, include teas, soy, pomegranate, date, grape seed, Pycnogenol, horse chestnut, German chamomile, curcumin, comfrey, allantoin, and aloe. All are documented to treat dermatologic conditions. Only green and black tea, soy, pomegranate, and date have published clinical trials for the treatment of parameters of extrinsic aging.

**CONCLUSIONS.** Preparation of botanical-based cosmeceuticals is complex. Very few of these products are supported by evidence-based science.

must have a working knowledge of botanicals to provide optimal medical care.

Several botanical treatments for cutaneous diseases have stood the test of time for their effectiveness, as documented by modern scientific evidence. Podophyllotoxin is a prescription purified podophyllin resin, a galenic extract of mayapple (*Podophyllum peltatum*). Capsaicin is a non-prescription therapy for pruritis and pain extracted from cayenne peppers (*Capsicum* species). Henna (*Lawsonia inermis*) is a hair dye used by people sensitized to other commercial coloring agents.<sup>4</sup>

## Scientific Issues

Herbal medicine plays a vital role in current American health care by (1) providing alternatives to prescription medications, (2) enhancing the therapeutic effects of other prescriptives, (3) protecting against adverse reactions to allopathic therapy, and (4) providing treatment for diseases for which there is no current prescription therapy or only poorly effective or high-risk therapy. Herbal and other alternative medical strategies are used by over half of the population, especially by those suffering from chronic diseases, such as psoriasis; those with less hope for a cure, such as human immunodeficiency virus (HIV); and those with terminal diseases.<sup>5,6</sup> Extensive public use of complementary and alternative medicine resulted in the National Institutes of Health establishing the Office of Alternative Medicine in 1995.<sup>1</sup>

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Unfortunately, two major myths taint herbal medicine. Most patients believe the myth that there are no side effects because herbal medicine uses “natural substances.” In fact, experienced Chinese practitioners are concerned about the well-known side effects of hepatotoxicity and contact dermatitis with oral and topical Chinese herbal medicinals and preparations, respectively.<sup>7</sup>

Many allopathic physicians believe the myth that double-blinded, placebo-controlled studies do not exist for traditional medicines. Yet there are many such studies conducted throughout Asia and India, including studies investigating the mechanisms of action of the medicinal botanicals.<sup>7</sup>

Chinese medicine herbs must be used cautiously because in Taiwan, 40% were adulterated with corticosteroids, nonsteroidal anti-inflammatory drugs, and/or central nervous system medicines. Over 50% of the Chinese herbal medicines have two or more of these synthetics.<sup>8</sup>

The understanding of the function, metabolism, and interaction of these medicinal botanicals is often lacking. The specific scientific issues include documenting (1) complete characterization of the multiple active compounds in each plant source; (2) the activity and synergistic or additive interaction of each of these compounds and their metabolites; (3) interaction of these active components with food, nutrients, nutritional supplements, and other medicines; and (4) how the potential toxicity of specific compounds is reduced.<sup>2</sup> For example, ricin, a bioterrorist weapon, and azelaic acid, a nontoxic prescription dermatologic medicine, are both extracted from the castor bean.

## Preparation of Herbs

Botanicals must undergo a significant amount of chemical processing prior to incorporation into a cosmeceutical, and this processing greatly affects the biologic activity of the botanical. The most important factor for the biologic activity of an herb to be incorporated into a cosmeceutical product is the source of the plant material because each plant part may contain hundreds of different individual chemicals and molecules. Growing conditions, including soil composition, amount of available water, climate variations, plant stress, and harvesting conditions, such as time from harvest to transport, care of plant materials during shipping, storage conditions prior to manufacture, and preparation of the herb and final product, as well as mixing with other herbs, are other factors that may substantially alter solubility, stability, biologic availability, pharmacokinetics, pharmacologic activity, and toxicity.

Galenic extracts are made from leaves, roots, fruits, berries, stems, twigs, barks, and flowers by crushing, grinding, comminuting, boiling, distilling, pressing, drying, or exposing them to solvents. Usually, the plant material is heated or processed to obtain essential oils or other

distillates that can be easily added to a cosmetic formulation. However, this processing may destroy or adversely modify some of the physiologically active molecules. The results are oil, wax, juice, tincture, decoction, tea, infusion, and/or powders, which are then formulated into topical applications, including solutions, gels, lotions, creams, ointments, and pastes. Some of these preparations are further applied as fomentation, a compress, or a poultice.<sup>2</sup> See the glossary in Table 1.<sup>9</sup>

The concentration of the herb, its extract, and the active molecules affects therapeutic activity. Usually in cosmeceuticals, the medicinal botanicals are added in very small, subtherapeutic amounts for the marketing story. Few herbs, unlike most synthetic pharmaceuticals, are required only in a very low concentration to provide the desired effect because their high potency is so high. Herbal efficacy is first challenged by the stratum corneum permeability barrier. Delivery across the mucocutaneous surface is difficult owing to the botanical's multiple active compounds with different solubility, polarity, and therapeutic concentration, as well as the reactivity of different mucocutaneous targets.

These complex biologic science and formulation issues indicate that the only validation of herbal activity in a cosmeceutical formulation is a human clinical trial conducted by a reputable third-party researcher. Without such studies, health care providers and the public are being asked to trust in products based on “voodoo” science.

**Table 1.** Glossary

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<i>Antiphlogistic</i> :	preventing and/or relieving inflammation
<i>Astringent</i> :	arrests secretions, contracts tissue, and controls bleeding
<i>Comminuted</i> :	whole plant or portion broken into multiple pieces
<i>Decoction</i> :	liquid extract produced by simmering the plant part in water for over 20 min
<i>Elixir</i> :	sweetened alcohol extract
<i>Essential oil</i> :	concentrated oil from the whole plant, usually volatile and fragrant
<i>Fomentation</i> :	liquid extract-soaked cloth
<i>Galenic</i> :	crude plant remedies
<i>Herb</i> :	botanical used for medicine, flavoring, or fragrance
<i>Infusion</i> :	liquid extracts combined in hot water
<i>Mucilage</i> :	botanicals that swell with exposure to water for soothing application
<i>Poultice</i> :	liquid extract combined with powdered herb applied directly to lesions while mass is moist
<i>Rubefacient</i> :	substance that causes cutaneous erythema by counterirritant effects
<i>Tea</i> :	dried whole or parts of plant simmered in hot water, usually 5–10 min
<i>Tincture</i> :	alcoholic solution of whole or portion of plant or extract

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## Regulation

Medicinal botanicals used in cosmeceuticals are considered food additives or dietary supplements by the US Food and Drug Administration (FDA), which declared them as safe. The herbs are allowed to be marketed to consumers directly without obtaining drug status or being restricted by FDA's over-the-counter monograph requirements. Thus, no standards of herbal potency, concentration in the marketed product, safety, or efficacy studies exist.

The regulatory authority for herbs in Germany is the "Commission E." It is the best consensus of experts for weighing the quality of clinical evidence and systemic and topical safety to identify reasonably effective uses of over 300 botanicals.

For those herbs or indications not considered by Commission E, one of the most complete herbal compendiums is the *PDR for Herbal Medicines*.<sup>4</sup> This publication completed an exhaustive literature review conducted by the respected PhytoPharm US Institute of Phytopharmaceuticals for approximately 400 more herbs with regard to their use and adverse reactions.

## Safety

A news magazine in 2001 revealed that over 2,900 adverse events requiring medical care were attributed to herbs during the previous year. In addition, 104 deaths were attributed primarily to ephedra, St. John's wort, ginkgo, and ginseng.<sup>10</sup> In 2003, the FDA removed ephedra and ma huang (*Ephedra sinica*) from the market owing to 155 deaths directly attributed to it.<sup>11</sup>

The most common adverse cutaneous reactions to herbal products include allergic and/or irritant contact dermatitis. Cross-sensitivity to the most sensitizing botanicals is not uncommon. For example, 12 of 106 dermatitis patients had a positive patch test to tea tree oil (TTO), and all of these patients had positive reactions to 1 or more of 12 other natural compounds, including lavender (*Lavandula angustifolia*).<sup>12</sup> Severe cutaneous reactions include angioedema/urticaria, exfoliative erythroderma, linear immunoglobulin A bullous dermatosis, lupus erythematosus, malignancies, pemphigus, Stevens-Johnson syndrome, Sweet's syndrome, ulcerative stomatitis, and vasculitis.<sup>4</sup> Ten herbs used to treat dermatologic conditions have induced fatal reactions, including aristolochia (*Aristolochia* species), arnica (*Arnica montana*), cayenne (*Cap-sicum annuum*), comfrey (*Symphytum officinale*), henna (*Lawsonia inermis*), kava kava (*Piper methysticum*), mistletoe (*Phoradendron* species), rue (*Ruta* species), senna (*Cassia* species), and yohimbine (*Pausinystalia yohimbe*). Other severe reactions include anaphylaxis, coma, rhabdomyolysis, and shock. Herbs known to pose dermatologic surgery dangers include St. John's wort, ginkgo, ginseng, garlic, echinacea, kava, and valerian.<sup>13</sup> See the adverse reactions listed in Table 2.

Even simple plants contain multiple reactive and interactive compounds, but natural medicine advocates and the media frequently do not warn the public of the importance of interactions between different herbs and between herbal and prescription medicines. Moreover, 70% of patients fail to disclose their use of herbal products pre-operatively.<sup>13</sup> Interactions with medical consequences probably are underreported. There are many herb-food, herb-drug, and herb-herb interactions, as shown in Table 3.<sup>4</sup>

**Table 2.** Adverse Cutaneous Reactions

Anaphylaxis	German chamomile ( <i>Matricaria recutita</i> ) and horse chestnut ( <i>Aesculus hippocastanum</i> )
Blistering (immunoglobulin A linear dermatosis)	Tea tree ( <i>Melaleuca alternifolia</i> )
Carcinogenic	Aloe vera ( <i>Aloe barbadensis</i> ) and comfrey ( <i>Symphytum officinale</i> )
Cutaneous, nonspecific	Tea tree
Death	Comfrey
Dermatitis	German chamomile, horse chestnut, and tea tree
Dermatitis, allergic contact	German chamomile and tea tree
Edematous	Aloe vera
Erythematous	Horse chestnut
Erythema multiforme	Tea tree
Fasciculation	Horse chestnut
Hypesthesia	Tea tree
Mucositis/stomatitis	Horse chestnut
Pruritis	Horse chestnut

**Table 3.** Herb-Drug Interactions

Aloe	Antiarrhythmics (aloe-induced hypokalemia may affect cardiac rhythm), digitalis glycosides (increases effect), corticosteroids, thiazide diuretics, and licorice (increased potassium loss)
German chamomile	Alcohol or benzodiazepines (may increase sedative effect), warfarin (may be additive)
Green tea	Alkaline drugs (decreased absorption)
Horse chestnut	Anticoagulant drugs (may be additive with anticoagulant drugs)

The medicinal botanicals of proven and potential dermatologic significance are listed in Table 4.<sup>4</sup> Multiple herbs are effective for several different indications. Herbal medicines may be divided into several groups. Clinically validated ones have published human-controlled clinical trials. These herbs are among the most commonly used by the public and alternative medicine practitioners and would be expected to be the most commonly used in cosmeceuticals. Photoaging clinical trials have been published only on green and black tea, soy, pomegranate, and date. Those botanicals with published human studies for dermatologic conditions using topical formulations include allantoin and comfrey, aloe, anise, bitter orange, black nightshade, black seed, camptotheca, curcumin, German chamomile, grape seed, horse chestnut, lemon balm, neem, olive oil, onion, Oregon grape, Pycnogenol (PYC), St.

**Table 4.** Herbal Indications

Acne	German chamomile ( <i>Matricaria recutita</i> ) and tea tree ( <i>Melaleuca alternifolia</i> )
Bites	Tea tree
Bruises	Comfrey ( <i>Symphytum officinale</i> ), horse chestnut ( <i>Aesculus hippocastanum</i> ), and turmeric ( <i>Curcuma longa</i> )
Burns	Tea tree
Carcinoma, squamous cell prevention of	Green tea
Furunculosis/abscess	German chamomile
Hemorrhoids	Horse chestnut
Infections, fungal	Aloe ( <i>Aloe barbadensis</i> , <i>A. capensis</i> , <i>A. vera</i> )
Infections, bacterial and mixed organisms/cellulitis/erysipelas	Tea tree
Inflammation	German chamomile, horse chesnut, and turmeric
Leprosy	Turmeric
Mucocutaneous pain	Comfrey
Mucocutaneous pruritus	Turmeric
Stomatitis	German chamomile, tea tree, and turmeric
Ulcers, skin/decubitus, leg, vascular	Tea tree
Venous insufficiency/varicosities/venous stasis	Horse chestnut
Wound care	Date palm ( <i>Phoenix dactylifera</i> ), German chamomile, and turmeric

John's wort, tea tree, and oolong tea. Borage, evening primrose, gotu kola, grape seed, black tea, PYC, and Chinese herbal mixtures have been documented to treat dermatologic conditions when administered orally. The botanicals discussed include teas, soy, pomegranate, date, grape seed, PYC, horse chestnut, tea tree, German chamomile, curcumin, comfrey, allantoin, and aloe vera.

## Specific Herbs

### Allantoin and Comfrey (*Symphytum officinale*)

Comfrey is approved by the German Commission E to treat blunt injuries owing to the activity of triterpene saponins, tannins, and silicic acid, as well as allantoin.<sup>4</sup>

Allantoin has been extracted from the comfrey root and leaves but is now commercially manufactured. Allantoin is an antiphlogistic, antioxidant, and soothing keratolytic that has an antitrichomonal effect and induces cell proliferation. It is listed in the FDA over-the-counter monograph as a safe and effective skin protectant at 0.1 to 2.0%.<sup>14</sup> Allantoin and/or comfrey-based products are used to treat wounds, ulcers, burns, dermatitis, psoriasis, impetigo, and acne. When formulated with surfactant and benzalkonium chloride, it is an effective hand sanitizer and onychomycosis therapy.<sup>15</sup>

Comfrey contains hepatotoxic pyrrolizidine alkaloids, which have resulted in deaths with oral consumption. It is carcinogenic and contraindicated in pregnancy and lactation.<sup>4</sup>

Allantoin formulated with onion (*Allium cepa*) extract in a proprietary topical formulation improved the signs and symptoms of scars and keloids.<sup>16</sup> No photoaging clinical trials using topical allantoin and/or comfrey have been published.

### Aloe (*Aloe barbadensis*, *A. capensis*, *A. vera*)

Aloe is used in Asian medicine for therapy of fungal and other infections, infestations, tumors, and other skin diseases. The aloe substance released from comminuted leaves contains mucopolysaccharides; glucomannan, including beta mannan; allantoin; anthracenes, such as aloin and emodin; alkylchromone, including aletinic acid and choline salicylate; flavonoids; amino acids; hydroxyquinine glycosides; carboxypeptidases; and minerals.<sup>4,17</sup> The hydroxyanthraquinone emodin inhibits neuroectodermal tumors, such as Merkel cell carcinoma.<sup>18</sup> Acetylated mannans and lectins appear to have immunomodulatory effects. Aloe is antibacterial to *Staphylococcus aureus*, *Helicobacter pylori*, and dermatophyte fungus.<sup>19</sup> It is viricidal to herpes simplex and varicella zoster and is clinically effective in treating genital herpes. This herb inhibits thromboxane vasoconstriction. Aloe inhibits photoimmunosuppression

of ultraviolet B (UVB) and inhibits cyclooxygenase for anti-inflammatory effects. It also increases collagen biosynthesis and degradation in granulation tissue. The antineoplasia effect is improved with melatonin and ascorbic acid.<sup>20</sup> Aloe vera applied topically is accepted therapy for radiation and stasis dermatitis and ulcers, frostbite, burns, fungal and bacterial infections, cold sores, pruritis, pain, psoriasis, and contact irritant dermatitis. The latter two were documented in blinded studies.<sup>21-23</sup>

No photoaging clinical studies using topical aloe vera have been published, despite its use as one of the two most common extracts in skin care formulations. The health risks of aloe are cutaneous eruptions and mutagenicity.<sup>4,18</sup> It is contraindicated in pregnancy and lactation.<sup>4,23</sup>

### *Curcumin Derived from Turmeric (Curcuma domestica)*

This herb is used in Asian medicine for cutaneous inflammation, pruritis, wounds, and ulcers. Its active compounds include volatile oils, such as tumerone; curcuminoids; and heptanoids. Tumerone, the volatile oil, provides the unique aroma. This extract provides the yellow color and much of the flavor for curry in foods.<sup>4</sup> These molecules provide antioxidant, antitumor, antimicrobial, antifertility, and anti-inflammatory effects. They also repel insects. Curcumin may color cosmeceuticals claiming to be free of artificial ingredients. Tetrahydrocurcumin, a hydrogenated form of curcumin, is only off-white in color. It is also added to cosmeceuticals to protect the formulation and impact the skin. This antioxidant appears to be superior to tocopherol.

Five human studies have found curcumin to be safe and have found definite anti-inflammatory effects. It inhibits lipoxygenase, cyclooxygenase, leukotrienes, thromboxane, prostaglandins, nitric oxide, tumor necrosis factor, and interleukin-12. Curcumin has been documented to inhibit collagenase, elastase, and hyaluronidase.<sup>24</sup>

Clinical studies demonstrating the effects on parameters of photoaging are lacking, but when combined with another herb, curcumin effectively treated scabies.<sup>25</sup>

### *Date Palm (Phoenix dactylifera)*

This food stuff is an Asian medicine therapy for inflamed wounds. The active compounds include 50% sugars, such as saccharose; 10% fatty oils; oligomeric proanthocyanidins (OPC); piperidine derivatives, including pipercolic acid; and phytohormones. It has no reported health hazards.<sup>4</sup>

A placebo-controlled trial with 5% date versus placebo in 10 patients was applied to the eyelid area twice daily for 5 weeks. A statistically significant reduction in wrinkle surface (27.6%) and wrinkle depth was achieved. Six of the participants said that visual improvement occurred.<sup>26</sup>

### *German Chamomile*

*Matricaria recutita* functions as an antiallergic, antimicrobial, anti-inflammatory, antioxidant analgesic and was approved by the German Commission E for inflammatory mucocutaneous diseases and wound and burn therapy. The major components of German chamomile include the primary anti-inflammatory agents: alpha-bisabolol, chamazulene, levomenol, and matricine. Other active compounds include bisaboloxides; farnesenes; choline; glycosides; flavonoids, such as apigenin and rutin; tannins; hydroxycoumarins, such as umbelliferone; mucilages; saccharides; fatty acids; and salicylates.<sup>23,27</sup>

Chamazulene inhibits leukotriene B<sub>4</sub> synthesis via inhibition of lipoxygenase and cyclooxygenase, lipid peroxidation, leukocyte infiltration, and histamine release. Levomenol is an anti-inflammatory hydrating agent that diminishes the signs of photodamage and reduces pruritis. Apigenin inhibits adhesion molecules. Bisabolol promotes granulation tissue.<sup>23,27</sup>

Clinical studies showed that topical chamomile cream was superior to 0.5% hydrocortisone in treating dermatitis and sunburn and statistically significantly decreased the wound area and healing time.<sup>2</sup> This herb is administered as an oil for infusion, tea, ointment, gel, wash, gargle, or capsule.<sup>4</sup>

Chamomile is a member of the Compositae family and has a significant risk of contact sensitization, conjunctivitis, angioedema, and anaphylaxis. It also has an additive anticoagulant effect to warfarin.<sup>4</sup>

### *Grape Seed (Vitis vinifera)/PYC/OPCs*

The pharmacologic activity of grape seed extract, along with French maritime pinebark (*Pinus pinaster*) extract, primarily resides in the potent antioxidant proanthocyanidins. These are the two richest natural sources and the most commercially viable. Other rich natural sources include green and black tea, red wine, red apple, red cabbage, black currant, sangre de drago, bilberry, blackberry, blueberry, strawberry, black cherry, cranberry, peanut skins, almonds, cocoa, parsley, onions, legumes, hawthorn, and witch hazel bark.<sup>4,23</sup> The standardized pinebark extract is patent-protected PYC, which has been the generic term for proanthocyanidins. These polyphenolic bioflavonoids are also known as procyanidins, procyanidiol oligomers, leucoanthocyanidins, condensed tannins, and OPCs.<sup>28,29</sup> OPCs consist of dimers of catechins and oligomers of epicatechin and catechin and their gallic acid esters. These compounds are scavengers of both reactive oxygen and nitrogen species.<sup>23,28</sup> Grape seed also includes other therapeutic compounds, including flavonoids, such as kaempferol and quercetin glucosides; stilbenes, such as resveratrol and viniferins; fruit acids;

tocopherols; essential fatty acids; and phenylacrylic acids, such as caffeoyl and feruloylsuccinic acid. Resveratrol is a potent antioxidant that inhibits angiogenesis and carcinogenesis, is antiviral against herpes, and has phytoestrogen activity.<sup>23</sup> PYC also contains monomeric epicatechin and catechin.<sup>4,28,30</sup>

Grape seed applied topically improved cutaneous photoprotection to UVB, inhibits histamine synthesis, promotes wound healing, reduces apoptosis induced by chemotherapy, reduces vascular engorgement, is cytotoxic to adenocarcinoma, and inhibits *Streptococcus*. Grape seed protects deoxyribonucleic acid (DNA) against oxidation more effectively than vitamins C and E and stabilizes collagen and elastin by inhibiting matrix metalloproteinases. It treats chronic venous insufficiency (CVI) and postoperative edema in clinical studies. All of these functions of grape seed strongly suggest that it should improve photoaged skin and protect against further damage. Grape seed has been used for centuries in Asia to treat a variety of cutaneous conditions.<sup>4,23,28-30</sup>

PYC increases nitric oxide levels, stimulates T- and B-cell function, and inhibits nuclear receptor transcription factors nuclear factor  $\kappa$ B (NF- $\kappa$ B) and activating protein (AP)-1 and the adhesion molecule intercellular adhesion molecule 1, as well as interferon- $\gamma$ . It recycles vitamins C and E.<sup>23,30</sup>

Topically applied PYC reduces sunburn, immunosuppression, and tumor formation by ultraviolet light while raising the minimal erythema dose in mice.<sup>31,32</sup> PYC administered orally reduced the area of severity of melasma within 30 days and the signs and symptoms of CVI by 60 days.<sup>33,34</sup>

A topical formulation consisting of grape seed, jojoba, lavender, rosemary, and thyme was used to treat alopecia areata. After 7 months of daily use, statistically significant improvement in hair regrowth occurred (44% vs 15% for placebo).<sup>35</sup> It has been used in antiaging creams for several years.<sup>23</sup> No controlled clinical studies evaluating these herbs for treatment of photoaging have been published.

### *Horse Chestnut* (*Aesculus hippocastanum*)

This herb is approved by the German Commission E for CVI therapy. In homeopathy, horse chestnut treats hemorrhoids. The mechanisms of action include inhibition of elastase and hyaluronase, decreasing capillary permeability, inhibiting leukocyte activation, and inducing vasoconstriction. The active compounds in the seeds of this herb contain 50% polysaccharides and oligosaccharides, other triterpene saponins including aescin, the most active component, fatty oils, and flavonoids, including quercetin and OPCs.<sup>4,23,36</sup>

Leg circumference, heaviness, and pain were statistically significantly reduced in multiple CVI trials with oral therapy. Topically applied horse chestnut reduced the symptoms of CVI in one trial and hemorrhoids in another.<sup>36</sup> Photoaging clinical studies are lacking.

The health risks of horse chestnut include hepatotoxicity, renal toxicity, urticaria, anaphylaxis, and mucocutaneous irritant dermatitis. It may also interact with salicylates and warfarin. This herb is administered as a tea, a tincture for infusion, a gel, or an ointment.<sup>4</sup>

### *Pomegranate* (*Punica granatum*)

This herb was used in ancient Egypt for inflammation of the skin, mucosa, and joints. *Punica granatum* may contain a more potent antioxidant mixture than grape seed extract, PYC, red wine, or green tea. The major constituents are tannins (25–28%), including punicalagin; polyphenols, such as ellagic acid; ascorbic acid; niacin; potassium; and piperidine alkaloids.<sup>4,23</sup> Pomegranate functions as an astringent that also inhibits NF- $\kappa$ B.<sup>37</sup> It has documented antimicrobial activity for gram-negative bacteria, *Saccharomyces* fungus, parasites, and viruses.<sup>38</sup>

There are no health hazards reported with pomegranate. It is administered as a decoction.<sup>4</sup> Topical and oral administration of this herb induced photoprotection to UVB in a human clinical trial.<sup>39</sup>

### *Soy* (*Glycine soja*)

This antioxidant, antiproliferative, antiangiogenic extract is used to treat hyperhidrosis in Asian medicine.<sup>23</sup> Epidemiologic studies indicating much lower malignancy and cardiac disease rates in people eating a diet high in soy resulted in thorough investigations revealing multiple medicinal uses. The major components of soy are phospholipids (45–60%), such as phosphatidyl choline, and essential fatty oils (30–35%). The minor components include the most active compounds, such as isoflavones, saponins, essential amino acids, phytosterols, calcium, potassium, iron, and the proteases soybean trypsin inhibitor and Bowman-Birk inhibitor. The most potent isoflavones are the phytoestrogens genistein and daidzein.<sup>4,23,40</sup> Topical estrogens have been shown to increase skin thickness and promote collagen synthesis; thus, soy phytoestrogen stimulation of human fibroblast collagen synthesis is expected. Genistein is the most potent antioxidant; it inhibits lipid peroxidation and chemical- and UVB-induced carcinogenesis. The two protease inhibitors lighten pigmented lesions and reduce unwanted facial and body hair in human clinical trials.<sup>40</sup>

Soy products have rarely caused dermatitis and pruritis, as well as asthma and gastrointestinal symptoms.<sup>4,23</sup>

### *Tea Tree* (*Melaleuca alternifolia*)

This essential oil has become one of the most commonly used nonprescription remedies for mucocutaneous disorders. TTO's active compounds include terpinenes, such as cineole. The monoterpene terpinen is the major sensitizing

compound in TTO and has become one of the most common contact allergens. The terpene alcohols, such as terpinin-4-ol, are the major constituents, comprising 40% of TTO. They reduce histamine-induced edema and wheal volume in type I hypersensitivity reactions. TTO does not have antioxidant activity, nor does it suppress neutrophil superoxide.<sup>4</sup> Its wide antimicrobial spectrum includes *Propionibacterium acnes*, *Escherichia coli*, *S. aureus*, herpes simplex, *Candida albicans*, *Trichophyton dermatophytes*, and *Sarcoptes scabiei*.<sup>41,42</sup>

Multiple double-blinded clinical trials have documented that TTO effectively treats acne and fungal or yeast infections. TTO failed to effectively treat atopic dermatitis and CVI.<sup>4,23,42</sup>

TTO is cytolytic to epithelial cells and fibroblasts, so it should not be used for burns. Photodamaged TTO is a stronger sensitizer and has induced erythema multiforme with topical application. Thus, the use of TTO in cosmeceuticals for sun-exposed tissue is not scientifically sound.<sup>42</sup>

#### Teas: Black, Green, Oolong, and White (*Camellia sinensis*)

All true teas are derived from *Camellia sinensis*. Black tea is the most processed (fermented), with white tea recently supplanting green tea as the least processed; oolong is partially fermented. Green tea contains 8 to 12% polyphenols and 2 to 4% caffeine. White tea is a more potent antioxidant and is more effective than green tea in inhibiting bacterial dysplastic mutations.<sup>4,23,43</sup> Green tea decreases melanoma cells in tissue culture and squamous cell carcinoma cell formation with topical and oral administration in mice. It also increases keratinocyte cell differentiation, improving wound healing. This tea inhibits *Streptococcus* species and *E. coli*. It also inhibits bradykinin and prostaglandins in animals.<sup>44</sup> Black tea has a much lower content of catechins than green tea but a higher content of other flavonoids, such as kaempferol and theaflavin. The largest catechin and most active antioxidant in any tea is epigallocatechin gallate (EGCG). Green tea has the highest concentration of EGCG.<sup>4,44</sup>

Topical green tea applied to human skin provided photoprotection beginning at 24 hours and lasting 48 to 72 hours. It reduced the number of sunburn cells by 66% when applied 30 minutes prior to UVB. When applied at 1 to 10% concentrations, a dose-response inhibition of ultraviolet-induced erythema occurred.<sup>45</sup> This extract prevented psoralen ultraviolet A photodamage with pre- and post-treatment by reducing erythema, hyperplasia, and hyperkeratosis.<sup>46</sup> Green tea is used to soothe sunburn, reduce baggy eyelids, and produce hemostasis. Black tea extracts applied before and after ultraviolet light challenge decreased signs of cutaneous photodamage, carcinogenesis, and inflammation in human and mouse skin.<sup>23</sup> Oral administration of black and oolong teas, such as green tea, sup-

pressed both type I and IV allergic reactions in the skin.<sup>47,48</sup> Oral oolong tea effectively treated atopic dermatitis.<sup>49</sup>

A recent double-blinded trial of 51 patients treated for 12 weeks with topical green tea extract containing 5.5 to 8.5% EGCG did not reduce the number of actinic keratoses on forearms compared with placebo.<sup>50</sup>

The major adverse reactions are gastrointestinal upset, constipation, irritability, and, very rarely, hepatotoxicity, delirium, and seizures. Caution should be used during pregnancy and lactation with excessive consumption (more than four cups per day).<sup>23</sup>

### Summary

Although there is a sharp increase in the use of botanicals in cosmeceuticals, there is a paucity of human clinical studies and often a lack of sound scientific rationale. Proof that the cosmeceutical formulation has any objective effectiveness is also usually lacking. The most significant human cosmeceutical data have been generated with formulations containing green and black tea, soy, pomegranate, date, and a grape seed-based mixture. Cosmeceutical formulations with the highest risk of reactions contain tea tree oil, comfrey, and German chamomile.

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## Commentary

Botanicals are of great interest to the dermatologist and the consumer. From a dermatologic standpoint, topical botanicals are a source of contact dermatitis, whereas oral botanicals can interfere with blood clotting and create postsurgical complications. From a consumer standpoint, the idea of topical and oral natural products inducing improvement in the growth and functioning of the skin, hair, and nails is enormously appealing. Dr. Thornfeldt has taken a systematic evaluative approach to the cataloging of those botanicals of dermatologic significance. His knowledge should help the dermatologist in obtaining a better understanding of the source and effect of plant derivatives.

It is noteworthy, however, to remember that most botanical extracts are just extracts. What does this imply? This means that they are just one fraction of a plant-derived material that has been processed to meet the needs of the cosmetic formulator.

Ground-up leaves and twigs are not appealing in a skin cream. The botanical must be processed such that it is a white powder that can be easily stirred into a moisturizer formulation. It must be white because few consumers want to put a gray-pink cream on their face. It must be a powder because these are the easiest to disperse. The powder must be very fine because a gritty moisturizer is not acceptable to most consumers. So what does this mean? This means that everything from rosemary to lavender to aloe to chamomile to jojoba to soy must be distilled down to a fine white powder. What happens when all botanical ingredients are transformed into a fine white powder? Perhaps one might say that they now are not truly botanicals but chemical extracts of one sort or another derived from a plant source. It is possible that our natural botanicals have now become unnatural chemicals!

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