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Herbs in Cosmeceuticals: Are They Safe and Effective?

Carl Thornfeldt
Episciences, Inc., Boise, and CT Derm, Fruitland, Idaho, and Oregon Health Sciences University, Portland, Oregon, U.S.A.

BACKGROUND

Botanicals used for medicinal, flavoring, or fragrances are known as herbs (1,2). The guiding principle of herbal medicine is the naturally occurring mixture of active compounds in plants is more effective and safer than individual molecules and man-made 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 treatment of signs and symptoms of disease while improving total "body condition" than reversing the disease etiology.

The foundation of modern pharmacologic medicine is rooted in ethnobotanical traditions utilizing 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 (1).

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 nonprescription 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 (3).

Botanical sales in 2004 exceeded $4 and one-third billion, growing by one-third over only six years. Noni/Morinda was the largest selling botanical in 2004 with sales of nearly $220 million. Now about 70 different herbs are formulated into cosmeceuticals. Botanical product growth has flourished to now consume 25% of all health- and lifestyle-related dollars (4). Thus dermatologists must have a working knowledge of botanicals, especially the most common ones, to provide optimal preventive medical care.

Herbal medicine plays a vital role in current healthcare by: (i) providing alternatives to prescription medications, (ii) enhancing therapeutic effects of other prescriptives, (iii) protecting against adverse reactions to allopathic therapy, and (iv) providing treatment for diseases which there is no current prescription therapy or only poorly effective or high-risk therapy. Herbal and other alternative medical strategies are utilized by over half of the population and especially by those suffering chronic diseases such as psoriasis and those

with less hope for cure such as human immunodeficiency virus (HIV) and terminal diseases (5,6). Extensive public use of complementary and alternative medicine resulted in the National Institute of Health establishing the Office of Alternative Medicine in the United States in 1995 (1).

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 practioners are concerned about the well-known side effects of hepatotoxicity and contact dermatitis with oral and topical Chinese herbal medicinal and preparations, respectively (7).

Many allopathic physicians believe the myth that double-blinded, placebo-controlled studies do not exist for ancient and herbal medicines. Yet, there have been many such studies conducted throughout Asia and India including studies investigating mechanisms of action of the medicinal botanicals (7).

The understanding of the function, metabolism, and interaction of these herbal medicines is often lacking. The specific scientific issues include documenting: (i) complete characterization of the multiple active compounds in each plant source, (ii) activity and synergistic or additive interaction of each of these compounds and their metabolites, (iii) interaction of these active components with food, nutrients, nutritional supplements, and other medicines, and (iv) how the potential toxicity of specific compounds is blunted (2). For example, there are the castor bean in the source of ricin, one of the most poisonous compounds known to man, and azelaic acid, a nontoxic prescription dermatological medicine.

PROCESSING BOTANICALS

Botanicals must undergo a significant amount of processing prior to incorporation into a cosmeceutical which usually significantly affects the biologic activity of the herb. The most important factor for biologic activity is the source of the plant material because each plant part may contain hundreds of different chemicals, ions 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 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, compress, or poultice (2,8). These terms are defined in Table 1 (9).

The concentration of the herb, its extract, and the active molecules affect therapeutic activity. Usually in cosmeceuticals the medicinal botanicals are added in very small, sub-therapeutic amounts for the marketing story. Most synthetic pharmaceuticals, utilize a very low concentration to provide the desired effect. Few herbs are that potent, thus higher doses ($>1\%$) are needed. Herbal efficacy is challenged by the trans-stratum corneum delivery of mucocutaneous surfaces which is usually difficult due to the

Table 1 Definitions

Antiphlogistic	Preventing and/or relieving inflammation
Astringent	Arrests secretions, contracts tissue, and controls bleeding
Comminuted	Whole plant or portion broken into multiple pieces
Decoction	Liquid extract produced by simmering the plant part in water for over 20 minutes
Elixir	Sweetened alcohol extract
Essential oil	Concentrated oil from the whole plant, usually volatile, and fragrant
Fomentation	Liquid extract soaked cloth
Galenic	Crude plant remedies
Herb	Botanical used for medicine, flavoring, or fragrance
Infusion	Liquid extracts combined in hot water
Mucilage	Botanicals that swell with exposure to water for soothing application
Poultice	Liquid extract combined with powdered herb applied directly to lesions while mass is moist
Rubefacient	Substance that causes cutaneous erythema by counter-irritant effects
Tea	Dried whole or parts of plant simmered in hot water usually 5–10 minutes
Tincture	Alcoholic solution of whole or portion of plant or extract

herb's concentration and multiple active compounds with different solubility, polarity, and therapeutic concentration as well as reactivity of different mucocutaneous receptors.

These complex biologic science and formulation issues indicate 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.

REGULATORY CLIMATE

Medicinal botanicals used in cosmeceuticals are considered food additives or dietary supplements by the United States 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 restricted by FDA's over-the-counter monograph requirements. Thus, no standards of herbal potency, concentration in the marketed product, safety, nor efficacy studies exist.

The German Regulatory Authority for herbs is the "Commission E." It is the best expert consensus for weighing the quality of clinical evidence and systemic and topical safety to identify reasonably effective uses of over 300 botanicals (3).

The Physician's Desk Reference for Herbal Medicines, 3rd ed. (2004), by Thomson PDR, Montvale, NJ, published an exhaustive literature review conducted by the respected PhytoPharm U.S. Institute of Phytopharmaceuticals for about 400 more herbs with regard to their use and adverse reactions (3).

ADVERSE REACTIONS

A news magazine in 2001 revealed over 2900 adverse events requiring medical care which were attributed to herbs the previous year. In addition, 104 deaths were attributed primarily to ephedra, St. John's Wort, gingko, and ginseng (10). In 2003 the FDA removed

Ephedra and Ma Huang (*Ephedra sinica*) from the market due to 155 deaths directly attributed to it (11).

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 positive patch test to tea tree oil (TTO) and all these had positive reactions to one or more of 12 other natural compounds including lavender (*Lavandula angustifolia*) (12). Severe cutaneous reactions including angioedema/urticaria, exfoliative erythroderma, linear IgA bullous dermatosis, lupus erythematosus, malignancies, pemphigus, Steven's Johnson syndrome, Sweet's syndrome, ulcerative stomatitis, and vasculitis have all been reported. Ten additional herbs have induced fatal reactions including aristolochia, arnica, cayenne, comfrey, henna, kava kava, mistletoe, rue, senna, and yohimbine. Other severe reactions include anaphylaxis, coma, rhabdomyolysis, and shock (3,13). Herbs known to pose dermatologic surgery dangers include St. John's Wort, gingko, ginseng, garlic, echinacea, kava kava, and valerian (14). See mucocutaneous and severe complications in Table 2.

Even simple plants contain multiple reactive and interactive compounds, but natural medicine advocates and media frequently do not warn the public of the importance of interactions between different herbs and with over-the-counter and prescription drugs. Moreover, 70% of patients fail to disclose their use of herbal products preoperatively. Interactions with medical consequences probably are under-reported (14). There are many herb/food, herb/drug, and herb/herb interactions as in combinations of caution in Table 3 (3).

The medicinal botanicals of proven and potential dermatologic significance are listed by therapeutic uses in Table 4 (3). Multple 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. Green and black tea, soy, pomegranate, and date have published human clinical trials for signs of photoaging as the only active. Avocado and black cohosh are included with two other actives in different topical formulations treating photoaging. Other herbs with published human studies treating dermatologic conditions with topical formulations include almond, allantoin and comfrey, aloe, anise, bitter orange, black nightshade, black seed, camptotheca, cayenne, curcumin, date palm, echinacea, german chamomile, horse chestnut, lemon balm, neem, oat, onion, oregon grape, pomegranate, St. John's wort, tea tree, oolong tea, and western medicinal herbal mixtures. Borage, evening primrose, gotu kola, grape seed, ginko biloba, horse chestnut, black tea, and Chinese herbal mixtures have been documented to treat dermatologic conditions when administered orally.

The second group consists of herbs used in current cosmeceuticals with a scientific rationale supported only by animal, in vivo or in vitro studies, and/or proven efficacy in human systemic disease but without clinical data with topical application. These include apple, arnica, cactus pear, eucommia, ginseng, hibiscus, jojoba, licorice, milk thistle, myrtle, olive oil, papaya, prickly pear, rosemary, sandalwood, sarsaparilla, saw palmetto, spearmint, peppermint, wheat germ, and white birch.

The third group consists of herbs approved for therapy of a cutaneous condition by the German Commission E which are currently or potentially will be incorporated into cosmeceuticals. These include agrimony, bittersweet nightshade, butcher's broom, cajuput, chaste tree, English plantain, fenugreek, flax, heartsease, horsetail, jambolan, lavender, marigold, oak, oat, pansy flower, Peruvian balsam, pineapple, poplar, sage, sesame seed, shepherd's purse, sweet clover, walnut, and white nettle. (*text continued on page 328*)

Table 2 Mucocutaneous and Serious Complications

Acne	Chaste Tree (*Vitex agnus-castus*)
Alopecia	St. John's Wort (*Hypericum perforatum*)
Anaphylaxis	Caraway (*Carum carvi*), Cayenne (*Capsicum annuum*), Echinacea (*Echinacea angustifolia*), Flax linseed (*Linum usitatissimum*), German Chamomile (*Matricaria recutita*), Garlic (*Allium sativum*), Horse Chestnut (*Aesculus hippocastanum*), Mistletoe (*Phoradendron species*), Willow Bark (*Salix alba*)
Burning	Cowhage (*Mucuna pruniens*)
Carcinogenic	Alkanet (*Alkanna tinctoria*), Aloe (*Aloe barbadensis; Aloe capensis: Aloe vera*), Alpine Ragwort (*Senecio nemorensis*), Areca Nut (*Areca catechu*), Basil (*Ocimum basilicum*), Bergamot (*Citrus aurantium*), Cascara Sagrada (*Rhamnus purshiana*), Coca (*Erythroxylum coca*), Colt's Foot (*Tussilago farfara*), Comfrey (*Symphytum officinale*), Cypress Spurge (*Euphorbia cyparissias*), Dusty Miller (*Senecio aureus*), Forget-me-not (*Myosotis arvensis*), Golden Ragwort (*Senecio aureus*), Groundsel (*Senecio vulgaris*), Hemp Agrimony (*Eupatorium cannabinum*), Jalap (*Ipomoea purga*), Madder (*Rubia tinctorum*), Morning Glory (*Ipomoea hederacea*), Petasites (*Petasites hybridus*), Ragwort (*Senecio jacobaea*), Red Clover (*Trifolium pratense*), Rue (*Ruta species*), Sassafras (*Sassafras albidum*), Senna (*Cassia species*)
Contact Blistering	American Liverwort (*Hepatica nobailis*), Arnica (*Arnica montana*), Bergamot (*Citrus aurantium*), Bitter Orange (*Citrus aurantium*), Black Mustard (*Brassica nigra*), Bulbous Buttercup (*Ranunculus bulbosus*), Buttercup (*Ranunculus acris*), Cashew (*Anacardium occidentale*), Cayenne (*Capsicum annuum*), Clematis (*Clematis recta*), Cypress Spurge (*Euphorbia cyparissias*), Garlic (*Allium sativum*), Gingko (*Ginko biloba*), Globe Flower (*Trollius europaeus*), Henna (*Lawsonia inermis*), Juniper (*Juniperus species*), Marsh Marigold (*Caltha palustris*), Mezereon (*Daphne mezereum*), Pasque Flower (*Pulsatilla pratensis*), Poison Ivy, Oak, Sumac (*Rhus toxicodendron*) Poisonous Buttercup (*Ranunculus sceleratus*), Rue (*Ruta species*), Savin Tops (*Juniperus sabina*), Senna (*Cassia species*), Tea Tree (*Melaleuca alternifolia [IgA linear dermatosis]*), Traveller's Joy (*Clematis vitalba*), White Bryony (*Bryonia alba*), Wood Anemone (*Anemone nemorosa*)
Conjunctivitis	Black Mustard (*Brassica nigra*), Cypress Spurge (*Euphorbia cyparissias*), German Chamomile (*Matricaria recutita*), Goa Powder (*Andira araroba*), Psyllium (*Plantago ovata*), Psyllium Seed (*Plantago afra*)
Cutaneous, Nonspecific	American Hellebore (*Veratrum viride*), American Liverwort (*Hepatica nobilis*), Arnica (*Arnica montana*), Artichoke (*Cynara scolymus*), Asarum (*Asarum europaeum*), Birch (*Betula species*), Black Bryony (*Tamus communis*), Blessed Thistle (*Cincus benedictus*), Boneset (*Eupatorium perfoliatum*), Bulbous Buttercup (*Ranunculus bulbosus*), Burdock (*Arctium lappa*), Buttercup (*Ranunculus acris*), Camphor Tree (*Cinnamomum camphora*),

(Continued)

Table 2 Mucocutaneous and Serious Complications (*Continued*)

	Cashew (*Anacardium occidentale*), Castor Oil Plant (*Ricinus communis*), Chaste Tree (*Vitex agnus-castus*), Chaulmoogra (*Hydnocarpus species*), Chicory (*Cichorium intybus*), Chinese Cinnamon (*Cinnamomum aromaticum*), Chinese Olive (*Canarium species*), Cinnamon (*Cinnamomum verum*), Clematis (*Clematis recta*), Clove (*Syzygium aromaticum*), Cowhage (*Mucuna pruriens*), Croton Seeds (*Croton tiglium*), Cypress Spurge (*Euphorbia cyparissias*), Elecampane (*Inula helenium*), English Ivy (*Hedera helix*), English Lavender (*Lavandula angustifolia*), Feverfew (*Tanacetum parthenium*), Ginkgo (*Ginko biloba*), Globe Flower (*Trollius europaeus*), Goa Powder (*Andira araroba*), Guaiac (*Guaiacum officinale*), Hemp Agrimony (*Eupatorium cannabinum*), Hops (*Humulus lupulus*), Hydrangea (*Hydrangea arborescens*), Indian Squill (*Urginea indica*), Jack-in-the-Pulpit (*Arisaema atrorubens*), Lesser Celandine (*Ranunculus ficaria*), Marsh Marigold (*Caltha palustris*), Mayapple (*Podophyllum peltatum*), Mugwort (*Artemisia vulgaris*), Nasturtium (*Tropaeolum majus*), Nerve Root (*Cypripedium calceolus*), Night-Blooming Cereus (*Selenicereus grandiflorus*), Orris (*Iris species*), Ox-eye Daisy (*Chrysanthemum leucanthemum*), Pasque Flower (*Pulsatilla pratensis*), Peppermint (*Menthe piperita*), Pipsissewa (*Chimaphila umbellate*), Poisonous Buttercup (*Ranunculus sceleratus*), Poplar (*Populus species*), Poppyseed (*Papaver somniferum*), Savin Tops (*Juniperus sabina*), Saw Palmetto (*Serenoa repens*), Scotch Pine (*Pinus species*), Soapwort (*Saponaria officinalis*), Spikenard (*Aralia racemosa*), Spurge (*Euphorbia resinifera*), Squill (*Urginea maritima*), Stavesacre (*Delphinium staphisagria*), Stillingia (*Stillingia sylvatica*), Tansy (*Tanacetum vulgare*), Tea Tree (*Melaleuca alternifolia*), Traveller's Joy (*Clematis vitalba*), White Bryony (*Bryonia alba*), White Mustard (*Sinapis alba*)
Cutaneous Yellowing	Kava Kava (*Piper methysticum*)
Death	Aristolochia (*Aristolochia species*), Arnica (*Arnica montana*), Cayenne (*Capsicum annuum*), Comfrey (*Symphytum officinale*), Henna (*Lawsonia inermis*), Kava Kava (*Piper methysticum*), Mistletoe (*Phoradendron species*), Rue (*Ruta species*), Senna (*Cassia species*), Yohimbine (*Pausinystalia yohimbe*)
Dermatitis	Bergamot (*Citrus aurantium*), Bitter Orange (*Citrus aurantium*) Bloodroot (*Sanguinaria canadensis*), Camphor Tree (*Cinnamomum camphora*) Caraway (*Carum carvi*), Cayenne (*Capsicum annuum*), Garlic (*Allium sativum*), German Chamomile (*Matricaria recutita*), Ginger (*Zingiber officinale*), Gingko (*Ginko biloba*), Hawthorn (*Crataegus species*), Henna (*Lawsonia inermis*), Horse Chestnut (*Aesculus hippocastanum*), Juniper (*Juniperus species*), Kava Kava (*Piper methysticum*), Lavender (*Lavandula*), Licorice (*Glycyrrhiza glabra*), Onion (*Allium cepa*) Peppermint (*Mentha piperita*), Quinine (*Cinchona pubescens*) Rue (*Ruta species*), Squill (*Urginea maritima*), Stavesacre (*Delphinium staphisagria*) Tea Tree (*Melaleuca alternifolia*), Turmeric (*Curcuma domestica/longa*), Yarrow (*Achillea millefolium*), Yohimbine (*Pausinystalia yohimbe*)
Dermatitis, Allergic Contact	Black Mustard (*Brassica nigra*), German Chamomile (*Matricaria recutita*), Parsley (*Petroselinum crispum*), Poison Ivy, Oak, Sumac (*Rhus toxicodendron*), Rosemary (*Rosmarinus officinalis*), Tea Tree (*Melaleuca alternifolia*)
Dermatitis, Contact Irritant	Boxwood (*Buxus sempervirens*), Cajuput (*Melaleuca leucadendra*), Copaiba Balsam (*Copaifera langsdorffi*), Feverfew (*Tanacetum parthenium*), Lesser Celandine (*Ranundulus ficaria*), Nutmeg (*Myristica fragrans*)

Dermopathy—Pellagra-like	Kava Kava (*Piper methysticum*)
Dyspigmentation, Hair	Trailing Arbutus (*Epigae repens*)
Dyspigmentation, Skin	Bergamot (*Citrus aurantium*), Bitter Orange (*Citrus aurantium*), Cayenne (*Capsicum species*), Henna (*Lawsonia inermis*), Trailing Arbutus (*Epigae repens*)
Dyspigmentation, Teeth	Cayenne (*Capsicum annuum*)
Edematous	Aloe (*Aloe barbadensis: Aloe capensis: Aloe vera*), Asa Foetida (*Ferula foetida*)—lips, Bitter Orange (*Citrus aurantium*), Buckthorn (*Rhamnus catharticus*), Butterbur (*Petasites hybridus*), Cascara Sagrada (*Rhamnus purshiana*), Chinese Rhubarb (*Rheum palmatum*), Cypress Spurge (*Euphorbia cyparissias*)—eyelid, Ergot (*Claviceps purpurea*)—local, Flax Linseed (*Linum usitatissimum*)—eyelid, Frangula (*Rhamnus frangula*), Ginseng (*Panax species*), Henna (*Lawsonia inermis*), Juniper (*Juniperus species*), Licorice (*Glycyrrhiza glabra*), Mezereon (*Daphne mezereum*), Mistletoe (*Phoradenfron species*)—lip, Pagoda Tree (*Sophora japonica*)—face, Phelloden-dron (*Phelldendron species*), Rue (*Ruta species*), Senna (*Cassia species*)
Erythematous	Bergamot (*Citrus aurantium*), Bitter Orange (*Citrus aurantium*), Butterbur (*Petasites hybridus*), Cashew (*Anacardium occidentale*), Flax Linseed (*Linum usitatissimum*), Gingko (*Ginko biloba*), Henbane (*Hyoscyamus niger*), Henna (*Lawsonia inermis*), Horse Chestnut (*Aesculus hippocastanum*)—facial, Juniper (*Juniperus species*), Mandrake (*Mandragora officinarum*), Mezereon (*Daphne mezereum*), Mistletoe (*Phoradendron species*), Poison Ivy (*Rhus toxicodendron*), Rue (*Ruta species*), Stavesacre (*Delphinium staphisagria*), Yohimbe Bark (*Pausinystalia yohimbe*)
Erythema Multiforme	Henna (*Lawsonia inermis*), Tea Tree (*Melaleuca alternifolia*)
Erythema Nodosum	Echinacea (*Echinacea angustifolia*), Mistletoe (*Phoradendron species*)
Erythroderma, Exfoliative	St. John's Wort (*Hypericum perforatum*), Yohimbine (*Pausinystalia yohimbe*)
Fasciculation	Horse Chestnut (*Aesculus hippocastanum*), Poppyseed (*Papaver somniferum*), Wormseed (*Artemisia cina*)
Glossodynia	Asarum (*Asarum europaeum*), Black Hellebore (*Helleborus niger*), Celandine (*Chelidonium majus*), Croton Seeds (*Croton tiglium*), Cypress Spurge (*Euphorbia cyparissias*), Monkshood (*Aconitum napellus*), Mountain Laurel (*Kalmia latifolia*), Night-Blooming Cereus (*Selenicereus grandifloras*), Peppermint (*Mentha piperita*)
Halitosis	Garlic (*Allium sativum*)
High Morbidity	Blue Cohosh (*Caulophyllum thalictroides*)—shock, Gingko (*Ginko biloba*)—coma, Licorice (*Glycyrrhiza glabra*)—rhabdomyolysis
Hypesthesia	Cowage (*Mucuna pruriens*), Croton Seeds (*Croton tiglium*), Cypress Spurge (*Euphorbia cyparissias*), Garlic (*Allium sativum*), Ginseng (*Panax species*), Monkshood (*Aconitum napellus*), Peppermint (*Menta piperita*)—anal, Tea Tree (*Melaleuca alternifolia*), Tree of Heaven (*Ailanthus altissima*)
Hypohidrosis	Henbane (*Hyoscyamus niger*)

(Continued)

Table 2 Mucocutaneous and Serious Complications (*Continued*)

Infection, Predisposition	White Bryony (*Bryonia alba*)
Jaundice	Bishop's Weed (*Ammi visnaga*), Black Cohosh (*Cimicifuga racemosa*), Germander (*Teucrium chamaedrys*)
Keloid	Henna (*Lawsonia inermis*)
Keratosis	Bloodroot (*Sanguinaria canadensis*)
Lichenoid	Henna (*Lawsonia inermis*), Peppermint (*Mentha piperita*)
Leukoplakia	Bloodroot (*Sanguinaria canadensis*)
Lupus Erythematosis	Yohimbine (*Pausinystalia yohimbe*)
Mastitis / Mastodynia / Gynecomastia	Black Cohosh (*Cimicifuga racemosa*), Dong Quai (*Angelica sinensis*), Ginseng (*Panax species*)
Mucositis / Stomatitis	American Liverwort (*Hepatica nobilis*), Arum (*Arum maculatum*), Bitter Apple (*Citrullus colocynthis*), Bulbous Buttercup (*Ranunculus bulbosus*), Buttercup (*Ranunculus acris*), Clematis (*Clematis recta*), Elecampane (*Inula helenium*), Gingko (*Ginko biloba*), Globe Flower (*Trollius europaeus*), Green Hellebore (*Helleborous viridis*), Hedge-Hyssop (*Gratiola officinalis*), Horse Chestnut (*Aesculus hippocastanum*), Horseradish (*Armoracia rusticana*), Marsh Marigold (*Caltha palistris*), Mezereon (*Daphne mezereum*), Orris (*Iris species*), Peppermint (*Mentha piperita*), Poisonous Buttercup (*Ranunculus sceleratus*), Poke (*Phytolacca americana*), Spurge (*Euphorbia resinifera*), Traveller's Joy (*Clematis vitalba*), White Bryony (*Bryonia alba*)
Paresthesia	Echinacea (*Echinacea angustifolia*), St. John's Wort (*Hypericum perforatum*), Mountain Laurel (*Kalmia latifolia*)
Pemphigus	Garlic (*Allium sativum*)
Photoreactions	Angelica (*Angelica archangelica*), Bergamot (*Citrus aurantium*), Bishop's Weed (*Ammi visnaga*), Bitter Orange (*Citrus aurantium*), Burning Bush (*Dictamnus albus*), Celery (*Apium graveolens*), Contrayerva (*Dorstenia contrayerva*), Dill (*Anethum graveolens*), Dong Quai (*Angelica sinensis*), Haronga (*Haronga madagascariensis*), Henna (*Lawsonia inermis*), Hogweed (*Heracleum spondylium*), Kava Kava (*Piper methysticum*), Lovage (*Levisticum officinale*), Masterwort (*Peucedanum ostruthium*), Parsley (*Petroselinum crispum*), Parsnip (*Pastinaca sativa*), Pimpinella (*Pimpinella major*), Rue (*Ruta graveolens*), St. John's Wort (*Hypericum perforatum*), Tolu Balsam (*Myroxylon balsamum*), Wafer Ash (*Ptelea trifoliate*), Yarrow (*Achillea millefolium*)
Pruritis	Arnica (*Arnica montana*), Black Cohosh (*Cimicifuga racemosa*), Chaste Tree (*Vitex agnus-castus*), Cowhage (*Mucuna pruriens*), Cypress Spurge (*Euphorbia cyparissias*), Dan-Shen (*Salvia miltiorrhiza*), Ergot (*Claviceps purpurea*), Feverfew (*Tanacetum parthenium*), Gingko (*Ginko biloba*), Ginseng (*Panax species*), Henna (*Lawsonia inermis*), Horse Chestnut (*Aesculus hippocastanum*), Kava Kava (*Piper metaysticum*), Mistletoe (*Phoradendron species*), Night Blooming Cereus (*Selenicereus grandiflorus*), Poppyseed (*Papaver somniferum*), Quinine (*Cinchona pubescens*), Sandalwood (*Santalum album*), Senna (*Cassia species*), Stavesacre (*Delphinium staphisagria*), St. John's Wort (*Hypericum perforatum*), Tea Tree (*Melaleuca alternifolia*)
Psoriasis	Henna (*Lawsonia inermis*)

Purpura / Hemorrhage / Bleeding	Garlic (*Allium sativum*), Ginger (*Zingiber officinale*), Gingko (*Ginko biloba*), Ginseng (*Panax species*), Horse Chestnut (*Aesculus hippocastanum*), Phellodendron (*Phellodendron species*), Saw Palmetto (*Serenoa repens*), St. John's Wort (*Hypericum perforatum*), Tolu Balsam (*Myroxylon balsamum*)
Pustular	Bitter Orange (*Citrus aurantium*), Black Bryony (*Tamus communis*), Chaste Tree (*Vitex agnus-castus*), Goa Powder (*Andira araroba*)
Sialorrhea	Areca Nut (*Areca catechu*), Black Hellebore (*Helleborus niger*), Daffodil (*Narcissus pseudonarcissus*), Echinacea (*Echinacea angustifolia*), Jaborandi (*Pilocarpus microphyllus*), Kousso (*Hagenia abyssinica*), Mezereon (*Daphne mezereum*), Mountain Laurel (*Kalmia latifolia*), Quebracho (*Aspidosperma quebrachoblanco*), Stavesacre (*Delphinium staphisagria*)
Stomatitis, Ulcerative	Feverfew (*Tanacetum parthenium*), Mezereon (*Daphne mezereum*), Tolu Balsam (*Myroxylon balsamum*)
Sweet's Syndrome	Arnica (*Arnica montana*), Cayenne (*Capsicum species*)
Toxic Epidermal Necrolysis / Necrosis / Ulcers	Arnica (*Arnica montana*), Black Mustard (*Brassica nigra*), Cayenne (*Capsicum annuum*), European Mistletoe (*Viscum album*), Ginseng (*Panax species*), Mezereon (*Daphne mezereum*), Savin Tops (*Juniperus sabina*), White Bryony (*Bryonia alba*)
Urticaria / Angioedema	American Pawpaw (*Asimina triloba*), Black Bryony (*Tamus communis*), Caraway (*Carum carvi*), Chaste Tree (*Vitex agnus-castus*), Echinacea (*Echinacea angustifolia*), European Mistletoe (*Viscum album*), Feverfew (*Tanacetum parthenium*), Garlic (*Allium sativum*), Henna (*Lawsonia inermis*), Milk Thistle (*Silybum marianum*), Psyllium (*Planatgo ovata*), Psyllium Seed (*Plantago afra*), Stinging Nettle (*Urtica dioica*), Tolu Balsam (*Myroxylon balsamum*), Yarrow (*Achillea millefolium*)
Vasculitis / Petechiae	Black Cohosh (*Cimicifuga racemosa*), Gingko (*Ginko biloba*)
Xerostomia	Chaste Tree (*Vitex agnus-castus*), Henbane (*Hyoscyamus niger*), Mandrake (*Mandragora officinarum*), St. John's Wort (*Hypericum perforatum*), Yellow Jessamine (*Gelsemium sempervirens*)
Xerosis	Kava Kava (*Piper methysticum*)

Table 3 Combination Cautions of Discussed Herbs

Aloe	Antiarrhythmics (aloe-induced hypokalemia may affect cardiac rhythm), digitalis glycosides (increases effect), corticosteroids, thiazide diuretics, and licorice (increased potassium loss)
Arnica	Anticoagulant, antiplatelet, heparin, salicylates, thrombolytic drugs, and warfarin (increased effect)
Cayenne	Same as above
Chaste Tree	Amantadine, dopamine D1 antagonists, levodopa, pergolide mesylate, pramipexole, and ropinirole (enhance dopaminergic adverse effects). Dopamine D2 antagonists (decreased effectiveness)
Curcumin	Anticoagulant, antiplatelet, heparin, thrombolytic drugs (increase effect)
Echinacea Angustifolia	Corticosteroids, immunosuppressants (interferes with effectiveness)
Evening Primrose	Anticonvulsants including phenothiazines (may lower seizure threshold and decrease effectiveness) anticoagulant, antiplatelet, heparin, and thrombolytic drugs (decrease effectiveness)
Fenugreek	Hypoglycemic drugs (may have an additive hypoglycemic effect)
Flax	Absorption of other drugs may be delayed when taken simultaneously
German Chamomile	Alcohol, benzodiazepines (may increase sedative effect), anticoagulants, and warfarin (increase effect)
Gingko	MAO inhibitors (potentiate effect), anticonvulsants (precipitate seizures), insulin (alters need), anticoagulant, antiplatelet, heparin, thrombolytic, and NSAID drugs (increase effect), nicardipine (reduce hypotensive effect), nifedipine, and papaverine (increase effect), SSRI (precipitate hypomania), thiazide diuretics (increase blood pressure)
Ginseng	Hypoglycemic drugs (increases effect), loop diuretics (increases diuretic resistance), MAO inhibitors (combination increases chance for headache, tremors, mania), insulin (reduces effect), estrogen (increases effect), albendazole (alters effectiveness), anticoagulants (decreases INR), nifedipine (increase effect), opiates (decrease effect)
Green Tea	Alkaline drugs (decrease absorption)
Horse Chestnut	Anticoagulant drugs (additive effect)
Licorice	Aloe, buckthorn, antiarrhythmics, digitalis glycoside, laxatives (increase hypokalemia, increase toxicity), glucocorticoids (potentiates), loop, and thiazide diuretics (additive hypokalemia), anticoagulant, antiplatelet, heparin, thrombolytic drugs, (increase effect), antihypentensives (decrease effect), antidiabetic insulin (reduce effect), MAO inhibitors (increase toxicity), potassium (decrease), testosterone (reduce), oral contraceptive (increase toxicity)

Milk Thistle (Silymarin)	Haloperidol phenothiazines (decrease lipid peroxidation), phentolamine mesylate, yohimbine (antagonize effect)
Oak	Alkaline drugs, alkaloids (absorption reduced)
Papaya	Anticoagulant drugs (additive effect)
Peppermint	CYP450 (increases substrate level)
Pineapple	Anticoagulant, thrombolytic drugs (increase bleeding), tetracycline (increase blood, urine level)
Rue	Hypoglycemic drugs (additive effect)
Saw Palmetto	Alpha-adrenergic blockers (additive effect), androgens (antagonizes), iron (complexes increasing toxicity), warfarin (increase effect)
St. John's Wort	Increased effectiveness: antidiabetic Reduced effectiveness: amioradone, anticoagulants, barbiturates, benzodiaze-pines, beta blockers, caffeine, calcium channel blockers, clozapine, chlorzoxazone, cyclophosphamide, cyclosporine, digoxin, etoposide, imatinib mesylate, indinavir, irinotecan, iron, methadone, nonnucleoside reverse transcriptase inhibitors, paclitexal, phenytoin, protease inhibitors, reserpine, sirilimus, statins, tacrolimus, tamoxifen, theophylline Increased toxicity: acetretin (birth defects), aminolevulinic acid, tetracycline, sulfonamide, thiazides (photosensitivity), buspirone, MAOI, nefazodone, nortryptiline, SSRI, trazadone, tricyclic antidepressants, venlafaxine (increase serotonin syndrome[hypertension, hyperthesmia, myoclonus, mental alterations, coma]), loperamide, gingko, opiates (sedation), oral contraceptives (breakthrough bleeding), tyramine, sympathomimetics Alters effect: carbamazepine
Soy	Iron (reduced absorption), levothyroxine (decrease effect), tamoxifen (decrease effect), warfarin (reduce effect)
White Willow	Alcohol, barbiturates (enhance toxicity), antiplatelet, NSAID, salicylates (additive effect), carbonic anhydrase inhibitors (potentiate effect)

Table 4 Therapeutic Uses [a]

Acne	Bittersweet Nightshade (*Solanum dulcamara*), Duckweed (*Lemna minor*), Eucalyptus (*Eucalyptus globulus*), German Chamomile (*Matricaria recutita*), Heartsease (*Viola tricolor*), Tea Tree (*Melaleuca alternifolia*)
Alopecia	Arnica (*Arnica montana*), Black Bryony (*Tamus communis*), Boxwood (*Buxus sempervirens*), Cashew (*Anacardium occidentale*), Horsetail (*Equisetum arvense*), Maidenhair (*Adiantum capillus-veneris*), Nasturtium (*Tropaeolum majus*), Oriental Arborvitae (*Thuja orientalis*), Stavesacre (*Delphinium staphisagria*)
Alopecia Areata	Birch (*Betula species*), Burr Marigold (*Bidens tripartita*)
Aphthous Stomatitis	Common Stonecrop (*Sedum acre*), Water Dock (*Rumex aquaticus*)
Bites	Behen (*Moringa oleifera*), Bistort (*Persicaria bistorta*), Black Cohosh (*Cimicifuga racemosa*), Calotropis (*Calotropis procera*), Cane-Reed (*Costus speciosa*), Cotton (*Gossypium hirsutum*), Echinacea (*Echinacea angustifolia*), Great Burnet (*Sanguisorba officinalis*), Matico (*Piper elongatum*), Picrorhiza (*Picrorhiza kurroa*), Plantain (*Musa paradisiaca*), Purple Gromwell (*Lithospermum erytrorhizon*), Quassia (*Picrasma excelsa*), Rauwolfia (*Rauwolfia serpentine*), Red Sandalwood (*Pterocarpus santalinus*), Scarlet Pimpernel (*Anagallis arvensis*), Tea Tree (*Melaleuca alternifolia*), Turmeric (*Curcuma domestica/longa*), Wormseed Oil (*Chenopodium ambrosioides*)
Bitter taste	Chinese thoroughwax (*Bupleurum chinese*)
Bleeding	Agrimony (*Agrimonia eupatoria*), Brooklime (*Veronica beccabunga*), Cane Reed (*Costus speciosa*), Catechu (*Acacia catechu*), Elephant Ears (*Bergenia crassifolia*), Eucalyptus (*Eucalyptus globules*), European Mistletoe (*Viscum album*), Groundsel (*Senecio vulgaris*), Henbane (*Hyoscyamus niger*), Horsetail (*Equisetum arvense*), Lesser Celandine (*Ranunculus ficaria*), Matico (*Piper elongatum*), New Jersey Tea (*Ceanothus americanus*), Periwinkle (*Vinca minor*), Purple Loosestrife (*Lythrum salicaria*), Sage (*Salvia officinalis*), Scotch Broom (*Cytisus scoparius*), Shepherd's Purse (*Capsella bursa-pastoris*)
Bruises / Contusion	Basil (*Ocimum basilium*), Beth Root (*Trillium erectum*), Bittersweet Nightshade (*Solanum nigrum*), Black Bryony (*Tamus communis*), Black Currant (*Ribes nigrum*), Black Nightshade (*Solanum nigrum*), Cajuput (*Melaleuca leucadendra*), Calotropis (*Calotropis procera*), Comfrey (*Symphytum officinale*), Cane-Reed (*Costus speciosa*) German Ipecac (*Cynanchum vincetoxicum*), Horse Chestnut (*Aesculus hippocastanum*), Onion (*Allium cepa*), Rue (*Ruta graveolens*), Smartweed (*Persicaria hydropiper*), Solomon's Seal (*Polygonatum multiflorum*), Spikenard (*Aralia racemosa*), Tansy (*Tanacetum vulgare*), Tolu Balsam (*Myroxylon balsamum*), Turmeric (*Curcuma domestica/longa*), Vervain (*Verbena officinalis*), Wild Daisy (*Bellis perennis*), White Fir (*Abies alba*)
Burns	Hibiscus (*Hibiscus sabdariffa*), Tea Tree (*Melaleuca alternifolia*)
Candidiasis	Cornflower (*Centaurea cyanus*)
Carcinoma, squamous cell prevention of palliaiton	Green and White Tea Catechins (*Camellia sinensis*), Congorosa (*Maytenus ilicifolia*), Spurge (*Euphorbia resinifera*)

Cheilitis, actinic	Areca Nut (*Areca catechu*), Condurango (*Marsdenia condurango*)
Dermatitis	Behen (*Moringa oleifera*), Bilberry (*Vaccinium myrtillus*), Birch (*Betula species*), Bittersweet Nightshade (*Solanum dulcamara*), Borage Oil (*Borage officinalis*), Boxwood (*Buxus sempervirens*), Carline Thistle (*Carlina acaulis*), Celadine (*Chelidonium majus*), Evening Primrose Oil (*Oenthera biennis*), Heartsease (*Viola tricolor*), Henna (*Lawsonia inermis*), Licorice (*Glycyrrhiza glabra*), Marigold (*Calendula officinalis*), Mezereon (*Daphne mezereum*), Mountain Grape (*Mahonia aquifolium*), Oats (*Avena sativa*), Peanut (*Arachis hypogaea*), Quillaja (*Quillaja saponaria*), Stinging Nettle (*Urtica dioica*), Teazle (*Dipsacus silvertris*), Winter's Bark (*Drimys winteri*)
Fissure, Anal	Aloe (*A. barbadensis, A. capensis, A. vera*), Buckthorn (*Rhamnus catharticus*), Cascara Sagrada (*Rhamnus purshiana*), Chinese Rhubarb (*Rheum palmatum*), European Peony (*Paeonia officinalis*), Field Scabious (*Knautia arvensis*), Frangula (*Rhamnus fragula*), Manna (*Fraxinus ornus*)
Furunculosis / Abcess	American White Pond Lily (*Nymphaea odorata*), Ammmoniac Gum (*Dorema ammoniacum*), Arnica (*Arnica montana*), Behen (*Moringa oleifera*), Bistort (*Persicaria bistorta*), Bittersweet Nightshade (*Solanum dulcamara*), Black Nightshade (*Solanum nigrum*), Bog Bean (*Menyanthes trifoliata*), Burdock (*Arctium lappa*), Calotropis (*Calotropis procera*), Castor Oil Plant (*Ricinus communis*), Chaulmoogra (*Hydnocarpus species*), Corydalis (*Corydalis cava*), Croton Seeds (*Croton tiglium*), Digitalis (*Digitalis purpurea*), Dogwood (*Cornus florida*), Echinacea (*Echinacea angustifolia*), German Chamomile (*Matricaria recutita*), Great Burnet (*Sanguisorba officinalis*), Ground Ivy (*Glechoma hederacea*), Hibiscus (*Hibiscus sabdariffa*), Larch (*Larix decidua*), Licorice (*Glycyrrhiza glabra*), Marshmallow (*Althaea officinalis*), Myrrh (*Commiphora molmol*), Onion (*Allium cepa*), Plumbago (*Plumbago zeylanica*), Psyllium (*Plantago ovata*), Red-Rooted Sage (*Salvia miltiorrhiza*) Solomon's Seal (*Polygonatum multiflorum*), Vervain (*Verbena officinalis*), White Lily (*Lilium candidum*), White Nettle (*Lamium album*), Wild Indigo (*Baptisia tinctoria*)
Halitosis	Clove (*Syzygium aromaticum*), Coriander (*Coriandrum sativum*), Juniper (*Juniperus communis*)
Hyperhidrosis / Excessive Lacrimation	Arjun Tree (*Terminalia arjuna*), Asiatic Dogwood (*Cornus officinalis*), Belladonna (*Atropa belladonna*), Coral Root (*Corallorhiza odontorhiza*), Japanese Atractylodes (*Atractylodes japonica*), Knotweed (*Polygonum aviculare*), Lycium Bark (*Lycium chinense*), Oak Gall (*Quercus infectoria*), Rehmannia (*Rehmannia glutinosa*), Rice (*Oryza sativa*), Rose (*Rosa centifolia*), Safflower (*Carthamus tinctorius*), Sage (*Salvia officinalis*), Sarsaparilla (*Smilax species*), Schisandra (*Schisandra chinensis*), Soybean (*Glycine soja*), Walnut (*Juglans regia*)
Hyperpigmentation	Wild Carrot (*Daucus carota*), Wormwood (*Artemisia absinthium*)
Hyposalivation	Lemonwood (*Schisandra sphenanthera*)
Ichthyosis / Hyperkeratosis	Burdock (*Arctium lappa*), Cashew (*Amacardium occidentale*), Cypress Spurge (*Euphorbia cyparissias*), English Ivy (*Hedera helix*), Garlic (*Allium sativum*), Peanut (*Arachis hypogaea*)
Infection, Herpes	Goldenseal (*Hydrastis canadensis*), Hibiscus (*Hibiscus sabdariffa*), Mezereon (*Daphne mezereum*), Mountain Laurel (*Kalmia katifolia*), Scarlet Pimpernel (*Anagallis arvensis*), Thuja (*Thuja occidentalis*)

(Continued)

Table 4 Therapeutic Uses (*Continued*)

Infection, Viral	Astragalus (*Astragalus species*), Behen (*Moringa oleifera*), Black Cohosh (*Cimicifuga racemosa*), Cat's Claw (*Unicaria tomentosa*), Coriander (*Coriandrum sativum*), Duckweed (*Lemna minor*), Echinacea (*Echinacea angustifolia*), Eucalyptus (*Eucalyptus globules*), Pasque Flower (*Pulsatilla pratensis*)
Infections, Fungal	Aloe (*Aloe barbadensis; Aloe capensis; Aloe vera*), Beet (*Beta vulgaris*), Henna (*Lawsonia inermis*), Onion (*Allium cepa*), Mountain Laurel (*Kalmia latifolia*), Poke (*Phytolacca americana*), Turmeric (*Curcuma domestica/longa*)
Infections, Bacterial / Cellulitis / Erysipelas / Impetigo / Scarlatina	Anemarrhena (*Anemarrhena asphodeloides*), American Pawpaw (*Asimina triloba*), Black Nightshade (*Solanum nigrum*), Burning Bush (*Dictamnus albus*), Cashew (*Anacardium occidentale*), Coconut Palm (*Cocos nucifera*), Corydalis (*Corydalis cava*), Duckweed (*Lemna minor*), Elecampane (*Inula helenium*), English Ivy (*Hedera helix*), Eucalyptus (*Eucalyptus globules*), Goa Powder (*Andira araroba*), Ground Ivy (*Glechoma hederacea*), Heartsease (*Viola tricolor*), Jack-in-the-Pulpit (*Arisaema atrorubens*), Kamala (*Mallotus philippinensis*), Linden (*Tilia species*), Oak Gall (*Qeurcus infectoria*), Oats (*Avena sativa*), Pasque Flower (*Pulsatilla pratensis*), Pitcher Plant (*Sarracenia purpurea*), Psyllium (*Plantago ovata*), Purple Gromwell (*Lithospermum erytrorhizon*), Tea Tree (*Melaleuca alternifolia*), Teazle (*Dipsacus silvestris*), Thuja (*Thuja occidentalis*), Turmeric (*Curcuma domestica/longa*), Virola (*Virola theiodora*), Wild Indigo (*Baptisia tinctoria*)
Inflammation	Agrimony (*Agrimonia eupatoria*), Arnica (*Arnica montana*), Bear's Garlic (*Allium ursinum*), Behen (*Moringa oleifera*), Bittersweet Nightshade (*Solanum dulcamara*), Black Nightshade (*Solanum nigrum*), Bladderwort (*Utricularia vulgaris*), Boxwood (*Buxus sempervirens*), Broad Bean (*Vicia faba*), Burning Bush (*Dictamnus albus*), Cashew (*Anacardium occidentale*), Castor Oil Plant (*Ricinus communis*), Chaulmoogra (*Hydnocarpus species*), Chickweed (*Stellaria media*), Chicory (*Cichorium intybus*), Club Moss (*Lycopodium clavatum*), Common Stonecrop (*Sedum acre*), Congorosa (*Maytenus ilicifolia*), Cornflower (*Centaurea cyanus*), Dandelion (*Taraxacum officinale*), English Ivy (*Dedera helix*), English Plantain (*Plantago lanceolata*), European Elder (*Sambucus nigra*), European Water Hemlock (*Cicuta virosa*), Evening Primrose (*Oenothera biennis*), Fenugreek (*Trigonella foenum-graecum*), Field Scabious (*Knautia arvensis*), Flax (*Linum usitatissimum*), Fumitory (*Fumaria officinalis*), German Chamomile (*Matricaria recutita*), Haronga (*Haronga madagascariensis*), Heartsease (*Viola tricolor*), Henna (*Lawsonia inermis*), Herb Robert (*Geranium robertianum*), Hibiscus (*Hibiscus sabdariffa*), Horse Chesnut (*Aesculus hippocastanum*), Houseleek (*Sempervivum tectorum*), Indian Nettle (*Acalypha indica*), Jambolan (*Syzygium cumini*), Japanese Mint (*Mentha arvensis piperascens*), Labrador Tea (*Ledum latifolium*), Lady's Mantle (*Alchemilla vulgaris*), Lycium bark (*Lycium chinense*), Marigold (*Calendula officinalis*), Marshmallow (*Althaea officinalis*), Mezereon (*Daphne mezereum*), Moneywart (*Lysimachia nummularia*), Monkshood (*Aconitum napellus*), Mullein (*Verbascum densiflorum*), Oak (*Quercus robar*), Oak Gall (*Quercus infectoria*), Oats (*Avena sativa*), Olive (*Olea europaea*), Pasque Flower (*Pulsatilla pratensis*), Peanut

	(*Arachis hypogaea*), Periwinkle (*Vinca minor*), Purple Gromwell (*Lithospermum erytrorhizon*), Purple Loosestrife (*Lythrum salicaria*), Quinine (*Circhona pubescens*), Red Clover (*Trifolium pratense*), Rosemary (*Rosmarinus officinalis*), Rue (*Ruta graveolens*), Saw Palmetto (*Serenoa repens*), Scotch Pine (*Oinus species*), Soapwart (*Saponaria officinalis*), Spurge (*Euphorbia resinifera*), St. John's Wort (*Hypericum perforatum*), Tolu Balsam (*Myroxylon balsamum*), Turmeric (*Curcuma domestica/longa*), Walnut (*Juglans regia*), White Lily (*Lilium candidum*), White Nettle (*Lamium album*), Witch Hazel (*Hamamelis virginiana*), Wormseed Oil (*Chenopodium ambrosioides*)
Keloid / Hypertrophic	Henbane (*Hyoscyamus niger*), Onion (*Allium cepa*)
Leprosy	Betel Nut (*Piper betle*), Black Nightshade (*Solanum nigrum*), Calotropis (*Calotropis procera*), Cashew (*Anacardium occidentale*), Chaulmoogra (*Hydnocarpus species*), Coriander (*Coriandrum sativum*), Cumin (*Cuminum cyminum*), Giant Milkweed (*Calotropis gigantea*), Gotu Kolu (*Centella asiatica*), Henna (*Lawsonia inermis*), Hwema Bark (*Corynanthe pachyceras*), Jasmine (*Jasminum officinale*), Kamala (*Mallotus philippinensis*), Lemongrass (*Cymbopogon citrates*), Lily-of-the-Valley (*Convallaria majalis*), Luffa (*Luffa aegyptica*), Neem (*Antelaea azadirachta*), Northern Prickly Ash (*Zanthoxylum americanum*), Storax (*Liquidambar orientalis*), Turmeric (*Curcuma domestica/longa*)
Mastitis / Mastodynia	Adrue (*Cyperus articulatus*), Bugleweed (*Lycopus virginicus*), Chaste Tree (*Vitex agnus-castus*), Dandelion (*Taraxacum officinale*), Pipsissewa (*Chimaphalia umbellata*)
Miliaria	Speedwell (*Veronica officinalis*)
Mucocutaneous pain	Black Currant (*Ribes nigrum*), Bladderwrack (*Fucus vesiculosus*), Comfrey (*Symphytum officinale*), Echinacea (*Echinacea angustifolia*), Houseleek (*Sempervivum tectorum*), Indian Nettle (*Acalyphia indica*), Marshmallow (*Althaea officinalis*), Onion (*Allium cepa*), Poplar (*Populus species*), Quince (*Cydonia oblongata*), Reed Herb (*Phragmites communis*), Rue (*Ruta graveolens*), Tobacco (*Nicotiana tabacum*), White Fir (*Abies alba*), Wild Indigo (*Baptisia tinctoria*), Wild Thyme (*Thymus serpyllum*), Wormwood (*Artemisia absinthium*)
Mucocutaneous Pruritus	Butcher's Broom (*Ruscus aculeatus*), Buckwheat (*Fagopyrum esculentum*), Cabbage (*Brassica oleracea*), Cashew (*Anacardium occidentale*), Chaulmoogra (*Hydnocarpus species*), Club Moss (*Lycopodium clavatum*), Evening Primrose (*Oenothera biennis*), Fumitory (*Fumaria officinalis*), Golden Shower Tree (*Cassia fistula*), Gotu Kola (*Centella asiatica*), Heartsease (*Viola tricolor*), Houseleek (*Sempervivum tectorum*), Jasmine (*Jasminum officinale*), Knotweed (*Polygonum aviculare*), Plantain (*Musa paradisiaca*), Poison Ivy (*Rhus toxicodendron*), Sarsaparilla (*Smilax species*), Scarlet Pimpernel (*Anagallis arvensis*), Scotch Pines (*Pinus species*), Speedwell (*Veronica officinalis*), Storax (*Liquidambar orientalis*), Sweet Gale (*Myrica gale*), Thyme (*Thymus vulgaris*), Turmeric (*Curcuma domestica longa*) Vervain (*Verbena officinalis*), Wheat (*Triticum aestivum*), Wild Thyme (*Thymus serpyllum*)
Photodermatosis	Wild Carrot (*Daucus carota*)
Pruritis, Anii	Field Scabious (*Knautia arvensis*), Mullein (*Verbascum densiflorum*)

(Continued)

Table 4 Therapeutic Uses (*Continued*)

Psoriasis	Agrimony (*Agrimonia eupatoria*), Black Nightshade (*Solanum nigrum*), Burdock (*Arctium lappa*), Cashew (*Anacardium occidentale*), Chaulmoogra (*Hydnocarpus species*), Goa Powder (*Andira araroba*), Hogweed (*Heracleum sphondylium*), Mountain Grape (*Mahonia aquifolium*), Mountain Laurel (*Kalmia latifolia*), Olive (*Olea europea*), Pasque Flower (*Pulsatilla pratensis*), Red Clover (*Trifolium pratense*), Sarsaparilla (*Smilax species*), Sunflower (*Helianthus annuus*)
Radiation Dermatitis	Sea Buckthorn (*Hippophaë rhamnoides*)
Scabies / Pediculosis	Angelica (*Andelica archangelica*), Black Catnip (*Phyllanthus amarus*), Black Pepper (*Piper nigrum*), Bog Bean (*Menyanthes trifoliata*), Burning Bush (*Dictamnus albus*), Carambola (*Averrhoa carambola*), Celandine (*Chelidonium majus*), Chaulmoogra (*Hydnocarpus species*), Field Scabious (*Knautia arvensis*), Fish Berry (*Anamirta cocculus*), Gotu Kola (*Centella asiatica*), Grape (*Vitis vinifera*), Ground Ivy (*Glechoma hederacea*), Henna (*Lawsonia inermis*), Lycium Berries (*Lycium barbarum*), Morning Glory (*Ipomoea hederacea*), Oleander (*Nerium oleander*), Picrorhiza (*Picrorhiza kurroa*), Plantain (*Musa paradisiaca*), Plumbago (*Plumbago zeylanica*), Poisonous Buttercup (*Ranunculus sceleratus*), Pyrethrum (*Chrysanthemum cinerariifolium*), Quassia (*Picrasma exselsa*), Safflower (*Carthamus tinctorius*), Smartweed (*Perisicaria hydropiper*), Stavesacre (*Delphinium staphisagria*)
Scrofulosis	Bistort (*Persicaria bistorta*), Coriander (*Coriandrum sativum*), English Ivy (*Hedera helix*), Ground Ivy (*Glechoma hederacea*), Oregano (*Origanum vulgare*), Stavesacre (*Delphinium staphisagria*)
Seborrhea	Stavesacre (*Delphinium staphisagria*)
Sjogren's Syndrome	Borage Oil (*Borago officinalis*), Evening Primrose Oil (*Oenthera biennis*)
Skin Care	Almond (*Prunus dulcis*), Avocado (*Persea americana*), Jojoba (*Simmondsia chinesis*), Peanut (*Arachis hypogaea*), Sorb Apple (*Sorbus domestica*)
Snakebite	Calotropis (*Calotropis procera*), Cane Reed (*Costus speciosa*), Cashew (*Anacardium occidentale*), Contrayerva (*Dorstenia contrayerva*), Cotton (*Gossypium hirsutum*), Echinacea (*Echinacea angustifolia*), German Ipecac (*Cynanchum vincetoxicum*), Muskmallow (*Abelmoschus moschatus*), Rauwolfia (*Rauwolfia serpentine*), Red Sandalwood (*Pterocarpus santalinus*), Scotch Broom (*Cytisus scoparius*)
Stomatitis / Gingivitis	Acacia (*Acacia arabica*), Agrimony (*Agrimonia eupatoria*), Amaranth (*Amaranthus hypochondriacus*), American Pawpaw (*Asimina triloba*), Anise (*Pimpinella anisum*), Arnica (*Arnica montana*), Basil (*Ocimum basilicum*), Bilberry (*Vaccinium myrtillus*), Black Currant (*Ribes nigrum*), Black Pepper (*Piper nigrum*), Blackberry (*Rubas fruticosus*), Bladderwort (*Utricularia vulgaris*), Bugle (*Ajuga reptans*), Catechu (*Acacia catechu*), Cayenne (*Capsicum annuum*), Cinquefoil (*Potentilla erecta*), Cleavers (*Galium aparine*), Clove (*Syzygium aromaticum*), Coffee (*Coffea arabica*), Colt's Foot (*Tussilago farfara*), Comfrey (*Symphytun officinale*), Echinacea Purpurea (*Echinacea purpurea*), English Chamomile (*Chamaemelum nobile*), English Plantain (*Plantago lanceolata*), Eucalyptus (*Eucalyptus globulus*),

	European Five-Finger Grass (*Potentilla reptans*), European Golden Rod (*Solidago virgaurea*), Gambir (*Uncaria species*), German Chamomile (*Matricaria recutita*), Herb Robert (*Geranium robertianum*), Hollyhock (*Alcea rosea*), High Mallow (*Malva sylvestris*), Houseleek (*Sempervivum tectorum*), Iceland Moss (*Cetraria islandica*), Jack-in-the-Pulpit (*Arisaema atrorubens*), Jambolan (*Syzygium cumini*), Japanese Mint (*Mentha arvensis piperascens*), Knotweed (*Polygonum aviculare*), Lady's Mantle (*Alchemilla vulgaris*), Larch (*Larix decidua*), Lesser Galangal (*Alpina officinarum*), Marigold (*Calendula officinalis*), Marshmallow (*Althaea officinalis*), Myrrh (*Commiphora molmol*), Oak (*Quercus robar*), Oak Gall (*Quercus infectoria*), Onion (*Allium cepa*), Peppermint (*Mentha piperita*), Pimpinella (*Pimpinella major*), Potentilla (*Potentilla anserina*), Rhatany (*Krameria triandra*), Rose (*Rosa centifolia*), Rue (*Ruta graveolens*), Sage (*Salvia officinalis*), Scotch Pine (*Pinus species*), Self-Heal (*Prunella vulgaris*), Sloe (*Prunus spinosa*), Speedwell (*Veronica officinalis*), Spruce (*Picea species*), Strawberry (*Fragaria vesca*), Sweet Violet (*Viola odorata*), Tamarind (*Tamarindus indica*), Tea Tree (*Melaleuca alternifolia*), Thyme (*Thymus vulgaris*), Tomato (*Lycopersicon esculeutum*), Tropical Almond (*Terminalis chebula*), Turmeric (*Curcuma domestica/longa*), Usnea (*Usnea species*), White Nettle (*Lamium album*), Wild Indigo (*Baptisia tinctoria*), Willow Herb (*Epilobium angustifolium*)
Styes	Eyebright (*Euphrasia officinalis*)
Syphilis / T. Pallidum Infections	Brazilian Pepper Tree (*Schinus terebinthifolius*), Calotropis (*Calotropis procera*), Dill (*Anethum graveolens*), Giant Milkweed (*Calotropis gigantea*), Gotu Kola (*Centella asiatica*), Guaiac (*Guaiacum officinale*), Indian-Hemp (*Apocynum cannabinum*), Kava Kava (*Piper methysticum*), New Jersey Tea (*Ceanothus americanus*), Poke (*Phytolacca americana*), Sassafras (*Sassafras albidum*), Stillingia (*Stillingia sylvatica*)
Ulcers, Skin / Decubitus, Leg, Vascular	American Adder's Tongue (*Erythronium americanum*), Ash (*Fraxinus excelsior*), Bilberry (*Vaccinium myrtillus*), Bittersweet Nightshade (*Solanum dulcamara*), Black Nightshade (*Solanum nigrum*), Burdock (*Arctium lappa*), Calotropis (*Calotropis procera*), Cashew (*Anacardium occidentale*), Castor Oil Plant (*Ricinus communis*), Catechu (*Acacia catechu*), Cleavers (*Galium aparine*), Clematis (*Clematis recta*), Congorosa (*Maytenus ilicifolia*), Digitalis (*Digitalis purpurea*), Echinacea (*Echinacea angustifolia*), English Adder's Tongue (*Ophioglossum vulgatum*), English Ivy (*Hedera helix*), Field Scabious (*Knautia arvensis*), Frostwort (*Helianthemum canadense*), Ground Ivy (*Glechoma hederacea*), Henna (*Lawsonia inermis*), Indian Nettle (*Acaltpha indica*), Lady's Mantle (*Alchemilla vulgaris*), Linden (*Tilia species*), Marigold (*Calendula officinalis*), Martagon (*Lilium martagon*), Myrrh (*Commiphora molmol*), Ox-Eye Daisy (*Chrysanthemum leucanthemum*), Periwinkle (*Vinca minor*), Petasites (*Petasites hybridus*), Quinine (*Cinchona pubescens*), Southern Bayberry (*Myrica cerifera*), Scurvy Grass (*Cochlearia officinalis*), Storax (*Liquidambar orientalis*), Tea Tree (*Melaleuca alternifolia*), Tolu Balsam (*Myroxylon balsamum*), Turmeric (*Curcuma domestica/longa*), Wild Indigo (*Baptisia tinctoria*), Yellow Lupin (*Lupinus leteus*)

(Continued)

Table 4 Therapeutic Uses (*Continued*)

Venous Insufficiency / Varicosities / Venous Stasis / Lymphedema	Ammoniac Gum (*Dorema ammoniacum*), Beth Root (*Trillium erectum*), Buckwheat (*Fagopyrum esculentum*), Butcher's Broom (*Ruscus aculeatus*), Clematis (*Clematis recta*), Club Moss (*Lycopodium clavatum*), Echinacea (*Echinacea angustifolia*), Figwort (*Scrophularia nodosa*), Garlic (*Allium sativum*), Gotu Kola (*Centella asiatica*), Grape (*Vitis vinifera*), Great Burnet (*Sanguisorba officinalis*), Horse Chestnut (*Aesculus hippocastanum*), Lemon Verbena (*Aloysia triphylla*), Marigold (*Calendula officinalis*), Pimpinella (*Pimpinella major*), Purple Loosestrife (*Lythrum salicaria*), Rue (*Ruta graveolens*), Smartweed (*Persicaria hydropiper*), Sweet Clover (*Melilotus officinalis*), Sweet Woodruff (*Galium odoratum*), Witch Hazel (*Hamamelis virginiana*), Yarrow (*Achillea millefolium*)
Warts / Condyloma acuminata	Behen (*Moringa oleifera*), Bittersweet Nightshade (*Solanum dulcamara*), Broad Bean (*Vicia faba*), Calotropis (*Calotropis procera*), Cashew (*Anacardium occidentale*), Celandine (*Chelidonium majus*), Common Stonecrop (*Sedum acre*), Cypress Spurge (*Euphoria cyparissias*), Garlic (*Allium sativum*), Giant Milkweed (*Calotropis gigantean*), Houseleek (*Sempervivum tectorum*), Indian-Hemp (*Apocynum cannabinum*), Mayapple (*Podophyllum peltatum*), Oats (*Avena sativa*), Onion (*Allium cepa*), Savin Tops (*Juniperus sabina*), Scarlet Pimpernel (*Anagallis arvensis*), Spurge (*Euphorbia resinifera*), Sundew (*Drosera ramentacea*)
Wound Care	Agrimony (*Agrimonia eupatoria*), Alkanet (*Alkanna tinctoria*), American White Pond Lily (*Nymphaea odorata*), Ammoniac Gum (*Dorema ammoniacum*), Ash (*Fraxinus excelsior*), Basil (*Ocimum basilicum*), Behen (*Moringa oleifera*), Beth Root (*Trillium erectum*), Birthwort (*Aristolochia clematitis*), Bistort (*Persicaria bistorta*), Black Catnip (*Phyllanthus amarus*), Black Currant (*Ribes nigrum*), Black Nightshade (*Solanum nigrum*), Bladderwort (*Utricularia vulgaris*), Blessed Thistle (*Cnicus benedictus*), Brazillian Pepper Tree (*Schinus terebinthifolius*), Broad Bean (*Vicia faba*), Bugle (*Ajuga reptans*), Burning Bush (*Dictamnus albus*), Cajuput (*Melaleuca leucadendra*), Carline Thistle (*Carlina acaulis*), Cascara Sagrada (*Rhamnus purshiana*), Cat's Claw (*Unicaria tomentosa*), Catechu (*Acacia catechu*), Chickweed (*Stellaria media*), Cinnamon (*Cinnamomum verum*), Cinquefoil (*Potenilla erecta*), Clematis (*Clematis recta*), Club Moss (*Lycopodium clavatum*), Coconut Palm (*Cocos nucifera*), Coffee (*Coffea arabica*), Cola (*Cola acuminata*), Common Kidney Vetch (*Anthyllis vulneraria*), Common Stonecrop (*Sedum acre*), Congorosa (*Maytenus ilicifolia*), Corydalis (*Corydalis cava*), Costus (*Saussurea costus*), Date Palm (*Phoenix dactylifera*), Digitalis (*Digitalis purpurea*), Dogwood (*Cornus florida*), Echinacea (*Echinacea angustifolia and purpurea*), Elm Bark (*Ulmus minor*), English Ivy (*Hedera helix*), English Plantain (*Plantago lanceolata*), English Lavendar (*Lavandula angustifolia*), Eucalyptus (*Eucalyptus globulus*), European Goldenrod (*Solidago virgaurea*), Fenugreek (*Trigonella foenum-graecum*), Feverfew (*Tanacetum parthenium*), Galbanum (*Ferula gummosa*), German Chamomile (*Matricaria recutita*), Goldenseal (*Hydrastis canadensis*), Gotu Kola (*Centella asiatica*), Goutweed (*Aegopodium podagraria*), Great Burnet (*Sanguisorba officinalis*), Ground Ivy (*Glechoma hederacea*), Heather (*Calluna vulgaris*), Henna (*Lawsonia inermis*), High Mallow (*Malva sylvestris*), Horehound (*Marrubium vulgare*), Horsetail (*Equisetum arvense*), Hound's Tongue (*Cynoglossum officinale*), Houseleek (*Sempervivum tectorum*),

	Iceland Moss (*Cetraria islandica*), Indian Nettle (*Acalypha indica*), Jambolan (*Syzygium cumini*), Jujube (*Zyzyphus jujube*), Lady's Bedstraw (*Galium verum*), Lesser Celandine (*Ranunculus ficaria*), Licorice (*Glycyrrhiza glabra*), Loosestrife (*Lysimachia vulgaris*), Lungwort (*Pulmonaria officinalis*), Male Fern (*Dryopteris fili-max*), Marigold (*Calendula officinalis*), Marsh Marigold (*Caltha palustris*), Marshmallow (*Althaea officinalis*), Moneywort (*Lysimachia nummularia*), Monkshood (*Aconitum napellus*), Mouse Ear (*Pilosella officinarum*), Mullein (*Verbascum densiflorum*), Myrrh (*Commiphora molmol*), Nasturtium (*Tropaelum majus*), Oak Gall (*Quercus infectoria*), Onion (*Allium cepa*), Ox-Eye Daisy (*Chrysanthemum leucanthemum*), Petasites (*Pentasites hybridus*), Peruvian Balsam (*Myroxylon balsamum*), Pimpinella (*Pimpinella major*), Pineapple (*Ananas comosus*), Poplar (*Populus species*), Poley (*Teucrium polium*), Quinine (*Cinchona pubescens*), Rauwolfia (*Rawolfia serpentina*), Rose (*Rosa centifolia*), Rosemary (*Rosemary officinalis*), Safflower (*Carthamus tinctorius*), Scarlet Pimpernel (*Anagallis arvensis*), Sea Buckthorn (*Hippophaë rhamnoides*), Shepherd's Purse (*Capsella bursa-pastoris*), Slippery Elm (*Ulmus rubra*), Smartweed (*Persicaria hydropiper*), Speedwell (*Veronica officinalis*), Spikenard (*Aralia racemosa*), Squill (*Urginea maritima*), St. John's Wort (*Hypericum perforatum*), Storax (*Liquidambar orientalis*), Sunflower (*Helianthus annuus*), Tansy (*Tanacetum vulgare*), Teazle (*Dipsacus silvestris*), Thyme (*Thymus vulgaris*), Tolu Balsam (*Myroxylon balsamum*), Traveller's Joy (*Clematis vitalba*), Tropical Almond (*Terminalia chebula*), Turmeric (*Curcuma domestica/longa*), Vervain (*Verbena officinalis*), Virola (*Virola theiodora*), Water Dock (*Rumex aquaticus*), Water Germander (*Teucrium scordium*), White Fir (*Abies alba*), White Lily (*Lilium candidum*), White Nettle (*Lamium album*), White Willow (*Salix nigra*), Wild Daisy (*Bellis perennis*), Wild Indigo (*Baptisia tinctoria*), Willow Herb (*Epilobium angustifolium*), Witch Hazel (*Hamamelis virginiana*), Wood Sage (*Teucrium scorodonia*), Woodsorrel (*Oxalis acetosella*), Wormwood (*Artemisia absinthium*), Woundwort (*Stachys palustris*), Yarrow (*Achillea millefolium*), Yellow Toadflax (*Linaria vulgaris*), Zedoary (*Curcuma zedoaria*)
Xerosis	Marigold (*Calendula officinalis*), Mountain Grape (*Mahonia aquifolium*)

[a] These herbs are approved by the German Commission E. for this indication.

SPECIFIC HERBS

Allantoin and Comfrey (*Symphytum officinale*)

Comfrey is approved by the Commission E to treat blunt injuries due to the activity of triterpene saponins, tannins, and silicic acid as well as allantoin (3).

Allantoin has been extracted from the comfrey root and leaves but is now commercially manufactured. Allantoin is an antipholgistic, antioxidant, and soothing keratolytic that has 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% (15). 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 (3).

Comfrey contains hepatotoxic pyrriolizidine alkaloids which have resulted in deaths with oral consumption. It is carcinogenic and contraindicated in pregnancy and lactation (3).

Allantoin formulated with onion (*Allium cepa*) extract in a proprietary topical formulation improved the signs and symptoms of scars and keloids (16,17). 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, glucommamman 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 (3). The hydroxyanthraquinone emodin inhibits neuroectodermal tumors such as Merkel cell carcinoma (18). Acetylated mannans and lectins appear to have immunomodulatory effects. Aloe is antibacterial to *Staphylococcus aureus*, *Helicobacter pylori*, and dermatophyte fungus. It is viricidal to herpes simplex and varicella zoster and is clinically effective in treating genital herpes. This herb inhibits thromboxane vasconstriction. Aloe inhibits photoimmunosuppression of UVB and inhibits cyclooxygenase for anti-inflammatory effects. It also increases collagen biosynthesis and degradation in granulation tissue (3). The antineoplasia effect is improved with melatonin and ascorbic acid. 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 (19,20).

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. It is contraindicted in pregnancy and lactation (3,18).

Anise (*Pimpinella anisum*)

Commission E has approved this herb for mucocutaneous inflammation. The galenic formulations consist of 30% fatty oil, 20% proteins, 4% volatile oils of which 94% is anethole, caffeic acids such as chlorogenic acid, and flavonoids. This herb has antibacterial, antiviral, antiphlogistic, insect repellant, and estrogenic functionalities. Anise is administered as oil or infusion. It has very rarely produced sensitization (3).

A recent blinded clinical trial in 119 children with scabies documented efficacy of 92% cure, identical to the mix of prescriptives used as the control. The anise formulation also included coconut oil and ylang ylang, an essential aromatic oil (21).

Avocado (*Persea americana*)

The oil from this food heals wounds, treats sclerosis and has long been used in products for skin aging. The oil primarily consists of monosaturated lipids (22).

Bitter Orange (*Citrus aurantium*)

Although this herb has no dermatologic indications in Asian, homeopathic or Commission E, it has been evaluated in clinical trials for cutaneous disease and has been added to multiple cosmeceuticals. The active compounds include flavonoids, triterpenoid bitter principles (limonoids), furocoumarins, methyl anthranilate, and volatile oils including limonene, nerol, and linalool. Bitter orange may cause sensitization, phototoxicity, and hyperpigmentation. It is administered as a tonic, tea, tincture, or galenic drops (3).

A blinded, three-arm trial of 65 patients suffering from tinea corporis was conducted. One arm used a poultice of 100% of this herb applied once daily for three weeks while another arm used 25% emulsion three times daily for four weeks and both were compared to imidizole twice daily for four weeks. At two weeks, 93% of the 100% bitter orange poultice were clinically cured and 80% were cured with the emulsion of this herb while none were cured with the imidizole (23).

Black Cohosh (*Cimicifuga racemosa*)

This North American herb is primarily prescribed to reduce menopause symptoms. It is also known as an insect repellant, to treat acne and warts and improve skin appearance. This herb contains salicylic acid, tannins, long-chain fatty acids, glycosides and phytoestrogens (22).

Black Nightshade (*Solanum nigrum*)

This herb is used in Asian medicine for abcess, furuncle, erysipelas, leprosy, psoriasis, wound, ulcer, and hemorrhoid but is not approved by Commission E for any indication. The active compounds include steroid alkaloid glycosides, alkaloids such as solasonine, and steroid saponins including tigogenin. The major clinical effect is anesthetic/analgesic, but recent studies focus on the anti-infective effects. The nightshades have no reported health hazards. They are administered as liquid extract or tinctures (22).

Two blinded comparative studies tested this herb and *Solanum chrysotrichum* to document clinical antifungal efficacy. The first compared *Solanum nigrum* to nystatin in 100 patients suffering from vaginal candidiasis. This herbal product cured the same number of patients in 25 days with treatment twice daily as nyststin did in 15 days (24). The other study consisted of the 28 patients suffering from tinea pedis who were treated twice daily for four weeks. The test products were 2% micronazole and 5% *Solanum chrysotrichum* each applied to one foot. The herb cure rate was 45% vs. no cure for micronazole (25).

Black Seed (*Nigella sativa*)

This herb has traditionally been a hemorrhoid, skin condition, and cancer treatment and has an immune stimulant effect. Its active compounds include nigellone and thymoquinone. Black seed has antioxidant, antiphlogistic, antibacterial, and antihelminthic effects (22).

Four clinical studies documented efficacy of this herb for treatment of atopic dermatitis and asthma when administered orally. The score of subjective symptomotology in each study decreased with a $p < 0.05$ significantly (26).

Cayenne (*Capsicum species*)

This spicy pepper extract uniquely depletes substance P of the peripheral C nerves. It is approved by the FDA for treatment of pruritis and pain. The active compounds are primarily amides of vanillylamine with fatty acids known as capsaicinoids. Other active compounds include anti-inflammatory carotenoids such as capsantain, flavonoids including apiin, steroid saponins, and volatile oils. Capsaicin rarely has induced anaphylaxis, death, and ulceration. Burning during the first few applications is common (2). It is now available as nonprescription products (3).

Two other human trials documented significant resolution of visible psoriatic lesions with six weeks of use four times daily (27,28). Other clinical studies document efficacy for chilblains, post herpetic neuralgia, and pruritis (3).

Camptotheca acuminata Decne

This herb is one of the few Chinese herbal products with a single botanical applied topically reported in the English medical literature. Many combinations of Chinese herbs administered as teas have documented effectiveness for dermatitis and psoriasis. Topically applied *Camptotheca acuminata* Decne was equally effective as 1% hydrocortisone in treating psoriasis but suffered a 12% incidence of allergic contact dermatitis (29).

Chinese medicine herbs must be used cautiously because in Taiwan 40% were adulterated with corticosteroids, nonsteroidal anti-inflammatories, and/or central nervous system medicines. Over 50% of the Chinese herbal medicines have two or more of these synthetics (30).

Curcumin Derived from Turmeric (*Curcuma domestica/longa*)

This herb is not approved for dermatologic conditions but is used in Asian medicine for cutaneous inflammation, bruising, bites, pruritis, wounds, fungal infections, and ulcers. Its active compounds include volatile oils, such as tumerone, which provides the unique aroma, 4% curcuminoids, heptanoids, and 30–40% starch. This extract provides the yellow color and much of the flavor for curry in foods (3). These molecules provide antioxidant, antitumor, antimicrobial, antifertility, anti-inflammatory, and insect repellent effects. Curcumin may color cosmeceuticals claiming to be free of artificial ingredients. Tetrahydrocurcumin is an off-white color that protects cosmeceutical formulations with antioxidant effect that appears superior to tocopherol. Curcumin is contraindicated in pregnancy due to abortifacient effect.

Clinical studies demonstrating any impact upon parameters of photoaging are lacking. A paste containing curcumin and neem (*Antelaea azadirachta*) clinically cured 97% of 814 children afflicted with scabies within 15 days (31).

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, leukoanthocyanidins, phytohormones, and piperidine derivatives including pipecolic acid. It has no reported health hazards (3).

A placebo-controlled trial with 5% date versus placebo in 10 patients was applied to the eye lid twice daily for five weeks. Statistically significant reduction in wrinkle surface (27.6%) and wrinkle depth was achieved. Six of the participants said visual improvement occurred (32).

Echinacea (*Echinacea angustifolia*, *E. purpurea*, *E. pallida*)

This medicinal botanical has the largest domestic sales volume. It is among the most useful herbs for dermatologic treatment and prevention of skin diseases. *E. angustifolia* was originally used by the Sioux Native Americans for the treatment of snake bites and war wounds because if its antiseptic and analgesic properties (2). Echinacea is known to the public because of its clinically documented immunostimulating effects in treating and aborting respiratory viral infections (3). All three Echinacea species stimulate immunity, protect collagen, and have antioxidant activity. They are also cytotoxic to multiple bacteria and viruses, *E. purpurea* is approved by Commission E for treatment of mucosal inflammation, wounds, burns, and to prevent infection. It is formulated in several cosmeceuticals. *E. angustifolia* is approved for viral therapy and prophylaxis. Unproven therapies include abcesses, ulcers, and measles. An *E. purpurea* formulation did not effectively treat recurrent genital herpes simplex (33).

Of all three species the two most active compounds in the above ground plant include the immunostimulating polysaccharides, echinacin, and inulin. Echinicin has an anti-inflammatory effect similar to corticosteroids but maintains collagen and ground substance integrity. It also stimulates wound healing. Inulin is a potent stimulator of the alternative complement pathyway, viral neutralization, bacterial destruction, and leukocyte chemotaxis. Other active compounds in Echinacea include caffeic and ferulic acid derivatives such as chlorogenic acid, echinoside, flavonoids including rutin, pyrrolizidane alkaloids, alkamides, polyenes, and volatile oils. The roots additionally contain immunostimulating glycoproteins that function like interferon (IFN). *E. purpurea* also contains pyrrolizidane alkaloids and glycoproteins which are lacking in *E. pallida* and *E. angustifolia*. In vitro studies suggest this herb protects against cutaneous ultraviolet light damage (2).

Echinacea species adversely effect fertility and pregnancy. They must not be combined with immunosuppressants. Echinacea is administered as comminuted herb for juice, decoction, tea, and tincture (3).

Garlic (*Allium sativa*)

Homeopathy employs garlic for mucosal inflammation. The biologic activity is primarily due to alkylcysteine sulfoxides, particularly alliins which are converted to allicin then dried resulting in oligosulfides and ajoene. These thiosulfinates are the major active components. Others include fructosans and saponins. Garlic is a proven oral and topical broad spectrum antimicrobial against gram-positive and gram-negatives with potency comparable to many antibiotics (3). The anti-yeast activity is comparable to nystatin and antifungal activity compares to seven other medicines including gentian violet. Garlic has antiviral activity against influenza B and herpes hominis I (11). This herb inhibits carcinogeneisis and cancer cell growth. Garlic tablets stimulate natural killer T cells to fight cancer, viral, and certain bacteria as well as enhance glutathione in cells. Ajoene inhibits clotting and bleeding times and platelet aggregation yet enhances fibirinolysis by inhibiting thromboxane, adenosine diphosphate, and collagen release. Garlic is also a major source of vitamins A, B-1, and C. Virtually odorless garlic based products are being marketed (3).

The adverse reactions due to topical garlic are contact irritant and allergic dermatitis and the distinctive halitosis (13). Avoid garlic while breastfeeding. Orally administered garlic increases bleeding during surgery especially if administered with other anticoagulants. It is administered in capsules, tablets, powder, and oil. A 0.4% ajoene cream successfully cleared all 34 patients of tinea pedis with 14 days of therapy (34).

German Chamomile (*Matricaria recutita*)

Matricaria recutita functions as an anti-allergic, antimicrobial, anti-inflammatory, antioxidant analgesic approved by Commission E for inflammatory mucocutaneous diseases, 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, rutin, tannins, hydroxycoumarins such umbelliferone, mucilages, saccharides, fatty acids, and salicylates (3,35).

Chamazulene inhibits leukotriene B4 synthesis via inhibition of lipoxygenase and cyclo-oxygenase, 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 (35).

Clinical studies showed topical chamomile cream was superior to 0.5% hydrocortisone in treating dermatitis and sunburn and statistically significantly decreased wound area and healing time (29). In another trial, it was not as effective as 0.25% hydrocortisone in treating dermatitis. This herb is administered as oil for infusion, tea, ointment, gel, wash, gargle, or capsule.

Chamomile is a compositae that has a significant risk of contact sensitization, conjunctivitis, angioedema, and anaphylaxis. It also has an additive anticoagulant effect to warfarin (3).

Gingko (*Ginko biloba*)

The efficacy of this herb for human dementia and peripheral occlusive arterial disease therapy are well documented. The mechanisms of action include antioxidant, stimulating fibroblasts, prevent lipid peroxidation, stabilize membranes, reduce neutrophil infiltration, and protect against ischemia. The major active compounds include proanthocyanidins which comprise 8–12%, biflavonoids such as gingkgetin, flavonoids including kaempferol, and trilactonic diterpenes such as ginkolide and sesquiterpene bilabolids (36,37).

The major health hazard encompasses spontaneous hemorrhage including intracranial. Others include adverse effects on oocytes and cutaneous allergic reactions. Gingko is administered as liquid extract for infusion and powder for tablets and capsules (3).

One double-blind, placebo-controlled study documented reduction in the frequency of attacks of Raynaud's disease with ingestion (38). Another double-blind, placebo controlled trial with 40 mg thrice daily halted vitiligo progression in 20 of 47 patients and produced marked improvement in 10 (39).

Grape Seed (*Vitis vinifera*) / Pycnogenol / OPCs

The pharmacologic activity of grape seed extract (GS) along with French maritime pinebark (Pinus pinaster) extract primarily resides in the potent antioxidant proanthocyanidins. These are the two richest natural sources and 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 (3,22). The standardized pinebark extract is patent protected Pycnogenal (PYC), which has been the generic term for proanthocyanidins. These polyphenolic bioflavonoids are also known as procyanidins, procyandiol oligomers, leukoanthocyanidins, condensed tannins, and oligomeric proanthocyanidins (OPCs). 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. GS 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. Resveratol is a potent antioxidant which inhibits angiogenesis and carcinogenesis, is antiviral against herpes, and has phytoestrogen activity. PYC also contains monomeric epicatechin and catechin (3,22,40).

GS 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. GS protects DNA against oxidation more effectively than vitamins C and E and stabilizes collagen and elastin by inhibiting MMPs. It treats chronic venous insufficiency (CVI) and postoperative edema in clinical studies. All these functions of GS strongly suggest is should improve photoaged skin and protect against further damage. GS has been used for centuries in Asia to treat a variety of cutaneous conditions (3,22,40).

PYC increases nitric oxide levels, stimulates T and B cell function, inhibits nuclear receptor transcription factors nuclear factor-kappa B (NF-kappa B) and AP-1 and the adhesion molecule ICAM-1 as well as IFN-gamma. It recycles both vitamins C and E. Topically applied PYC reduces sunburn, immunosupression, and tumor formation by UV light while raising the minimal erythema dose in mice (22,29). PYC administered orally reduced the area of severity of melasma within 30 days and the signs and symptoms of CVI by 60 days (29).

A topical formulation consisting of grape seed, jojoba, lavender, rosemary, and thyme was to treat alopecia areata. After seven months of daily use, statistically significant improvement in hair re-growth occurred (44% vs. 15% for placebo) (41). It has been used in anti-aging creams for several years (22). No controlled clinical studies evaluating these herbs for treatment of photoaging have been published.

Horse Chestnut (*Aesculus hippocastanum*)

This herb is approved by German Commission E for CVI, lupus and ulcer therapy. In homeopathy horse chestnut treats hemorrhoids. The mechanisms of action include inhibition of elastase and hyaluronase primarily by aesin, a triterpene saponin which has anti-exudative effects by decreasing capillary permeability, inhibits leukocyte activation, and induces vasoncontriction. The active compounds in seeds of this herb contain 50% polysaccharides and oligosaccharides, other triterpene saponins, fatty oils, sterols and flavonoids including quercetin and OPCs (3,22).

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 (42). Photoaging clinical studies are lacking.

The health risks of horse chestnut include hepatotoxicity, renal toxicity, urticaria, anaphylaxis, and mucocutaneous irritant and allergic dermatitis. It may also interact with salicylates and warfarin. This herb is administered as tea, tincture for infusion, gel, or ointments (3,22).

Lemon Balm (*Melissa officinalis*)

This herb has antibacterial, antiviral, antioxidant, and anti-hormonal effects. The active compounds include volatile oils such as citronellal, glycosides, caffeic acids such as rosmaric acid, triperpene acids including ursolic acid, and flavonoids such as cynaroside. Lemon balm has one reported case of contact irritation. It is administered as powder, tea, and infusion (22).

A 1% cream applied five times a day in 116 patients in a double-blinded trial for Herpes Simplex documented complete clearing by day 8 in 96%. Lesion size and healing time were statistically significantly superior to placebo (43).

Milk Thistle (*Silybum marianum*)

The extract of this herb is silymarin which consists of three flavonoids: silybin (about 75%), silydianin, and silychristine. Silymarin has potent antioxidant, antiphlogistic, antiangiogenic, and antitumor activities. A 92% reduction in UVB-induced murine skin tumors was produced with topical silymarin (44). Topical silybin decreased the formation of pyrimidine dimers and UVB-induced apotosis was enhanced in mice (45). It also inhibits cyclooxygenase-2 (46). Other active molecules in milk thistle include fatty oil which accounts for 20–30% flavonoids including apigenin and quercetin, steroids such as beta-sitosterol, fumaric acid, and polyynes. This herb is administered as a comminuted drug for liquid extracts and tinctures for infusion. No allergic reactions have been reported (3).

Neem (*Antelaea azadirachta*)

This medicinal botanical is used in Asian medicine to treat inflammatory diseases, infestations, wounds and leprosy. It has documented anti-inflammatory, antihelminthic, antipyretic, antiphlogistic, and insecticide activity due to its triterpenes, tannins, and volatile oils. Neem is administered as a decoction, tincture or ointment. It was formulated in a paste with curcumin to treat 814 children with scabies. A 97% cure rate was achieved within 15 days (22,29,31).

Onion (*Allium cepa*)

This herb is approved for mucosal inflammation therapy and to reduce the tendency toward infection. In Asian medicine it treats wounds fungal, bacterial, and helminthic infections. The active compounds include alliins (alkylcysteine sulphoxides), polysaccharides, saccharose, flavonoids, and steroid saponins. In addition to anti-inflammatory effects, this herb inhibits gram-negative bacteria and thrombocytes and has anti-allergic effects. Onion rarely produces contact irritant reactions.

This herb effectively modulates scars and keloid formation in two human trials when formulated with allantoin (16,17). In a study for treatment of patchy alopecia areata of 23 patients, re-growth of terminal coarse hairs started after two weeks of treatment with crude onion juice. At six weeks, the hair re-growth was observed in 20 patients. The tap-water-treated control group experienced hair re-growth in only two patients at eight weeks of treatment ($p < 0.0001$) versus the onion juice group (47).

Oregon Grape (*Mahonia aquifolium*)

This herb is traditionally used for psoriasis therapy and disinfectant. The active molecules are isoquinoline alkaloids such as berberine and oxyacanthine which are antibacterial,

antihelmintic, and immunostimulating. It can induce pruritis, contact irritant and allergic dermatitis. This herb is administered in powder, cream, and ointment (22).

Two psoriasis clinical studies have been reported. The open study documented improvement in psoriasis symptoms and quality of life (48). The blinded study found oregon grape ointment to be superior to placebo in less than half of the patients (49).

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 grapeseed, Pycnogenol, blueberry, cranberry red wine, or green tea. The major constituents are tannins (25–28%), including punicalagin, polyphenols such as ellagic acid, ascorbic acid, niacin, potassium, piperidine alkaloids and phytoestrogens. Pomegranate functions as an astringent that also inhibits NF-kappa B. It has documented antimicrobial activity for gram-negative bacteria, saccharomyces fungus, parasites, and viruses (22). Topical and oral administration of this herb induced photoprotection to UVB in a human clinical trial (50).

Topically applied, pomegranate can induce contact urticaria/angiodema and conjuctivitis. It is administered as a decoction (3,22).

Soy (*Glycine soja*)

This antioxidant, antiproliferative, antiangiogenic phytoestrogenic extract is used to treat hyperhidrosis in Asian medicine (22). 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-Burke inhibitor. The most potent isoflavones are the phytoestrogens genistein and daidzein. Topical estrogens have been shown to increase skin thickness and promote collagen synthesis; thus, soy phytoestrogen stimulatation of human fibroblast collagen synthesis is expected. Genistein, the most potent antioxidant, 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 (3,51,52).

Soy products have rarely caused dermatitis and pruritis as well as asthma and gastrointestinal symptoms (3,22).

St. John's Wort (*Hypericum perforatum*)

This widely used herb is popular due to its sedative, anxiolytic, and antidepressant action. St. John's Wort is approved for wound healing, burns, and cutaneous inflammation. Asian medicine employs it for dermatitis topical therapy. This herb has antistaphylococcal, anti-inflammatory, antineoplastic, antioxidant activity yet stimulates wound healing and T lymphocytes. The active compounds include flavonoids such as quercetin, catechins, oligomeric procyanidines, xanthones, anthracenes including hypericin, and caffeic acids such as chlorogenic acid. This herb is administered by powders, liquid, tincture, and tea (3). St. John's Wort induces multiple health hazards including dangerous ones such as mutagenicity to oocytes. It interacts with many major systemic drugs including beta-blockers, anticoagulants, calcium channel blockers,

immunosuppressives, anti-hypertensives, antibiotics, contraceptives, statins, SSRI, analgesics, and photosensitizers (13,22).

Human clinical trials from Russia support its wound healing effectiveness (2). In a 21-patient, blinded, clinical trial of mild to moderate atopic dermatitis the improvement of the intensity of the eczematous lesions by 1.5% hypericum-cream was significantly superior to the vehicle at all clinical visits ($p < 0.05$) (53).

Tea Tree (*Melaleuca alternifolia*)

This essential oil has become one of the most commonly used nonprescription remedies for mucocutaneous disorders. TTO active compounds include terpinenes such as cineole. The monoterpene terpinen is the major sensitizing compound in TTO which has become one of the most common contact allergens. The terpene alcohols such as terpin in -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. Its wide antimicrobial spectrum includes *Propionobacterium acnes*, *Escherichia coli*, *Staphylococcus aureus*, Herpes simplex, *Candida albicans*, *Trichophyton dermatophytes* and *Sarcoptes scabeii* (3,54,55).

Multiple double-blinded clinical trials document that TTO effectively treats acne and fungal/yeast infections. TTO failed to effectively treat atopic dermatitis and CVI (3,22,55).

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 (55).

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 8–12% polyphenols and 2–4% caffeine (10-80 mg/cup). White tea is a more potent antioxidant and more effective than green tea in inhibiting bacterial dysplastic mutations (3,22,56). 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 *Escherichia coli*. It also inhibits bradykinin and prostaglandins in animals (57). 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 (3).

Topical green tea provided photoprotection beginning at 24 hours and lasting 48–72 hours. It reduced the number of sunburn cells by 66% when applied 30 minutes prior to UVB. When applied at 1–10% concentrations, a dose response inhibition of UV-induced erythema occurred (58). This extract prevented psoralen UVA photodamage with pre- and post-treatment by reducing erythema, hyperplasia, and hyperkeratosis (59,60). Green tea is used to soothe sunburn, reduce baggy eyelids, reduce gingivitis and produce hemostasis and prevent UV induced carcinogenesis including oral leukoplekis (2,22). Black tea extracts applied pre- and post-ultraviolet light challenge decreased signs of cutaneous photodamage, carcinogenesis, and inflammation in human and mouse skin (22). Oral administration of black and oolong

teas, like green tea, suppressed both type I and IV allergic reactions in the skin (61). Oral oolong tea effectively treated atopic dermatitis (62).

A recent double-blinded trial of 51 patients treated for 12 weeks with topical green tea extract containing 5.5–8.5% EGCG did not reduce the number of actinic keratoses on forearms compared to placebo (63).

The major adverse reactions are gastrointestinal upset, constipation, irritability, and very rare hepatotoxicity, delirium, and seizures. Caution should be used during pregnancy and lactation with excessive consumption (>3 cups or 300 mg per day) (22).

Western Herbal Mix

This consists of grape seed, jojoba, lavender, rosemary, and thyme. It was massaged into the scalp of 86 patients suffering from alopecia areata. After seven months of daily use statistically significant improvement in hair re-growth occurred (44% western herbal mix vs. 15%) for placebo (64).

Witch Hazel (*Hamamelis virginiana*)

The bark and leaf of this herb yield galenic formulations with 5–12% tannins, catechins including EGCG, OPCs, flavonoids such as quercitrin, and volatile oils. Astringent, antiphlogistic, and hemostatic effects result from these potent active compounds. Witch hazel is approved by Commission E and in homeopathy for mucocutaneous inflammation, wound, burn, venous insufficiency, and hemorrhoid therapy. Contact irritant dermatitis is rarely reported. Hepatotoxicity possibly occurs with chronic ingestion. It is administered in various topical formulations via extract of comminuted drugs, steam distillate, decoction or tea, gels, and ointments (3).

Witch hazel is formulated into acne and vein cosmeceuticals. Clinical studies document this herb is less effective than 1% hydrocortisone in reducing UV-induced erythema (65). In 36 atopic dermatitis patients, witch hazel significantly reduced inflammation and pruritis (66).

Scientifically Rational Herbs

There are a number of well-known, commonly used medicinal botanicals incorporated into many cosmeceuticals that have not been studied in any dermatologic human trials but have demonstrated biologic effects in nondermatologic diseases, in vitro, in vivo, or animal models. The lack of FDA regulation allows companies to formulate these herbs into skin care products and market them. Cosmeceuticals that lack human clinical data, contain herbs with only in vitro scientific data, contain subtherapeutic concentrations, lack documented delivery systems for the herbal molecules, and lack proof of chemical stability of the formulation should be viewed with great skepticism by clinicians.

Apple (*Malus domestica*)

Extracts of this foodstuff has been used for years in cosmeceuticals for fruit acids particularly malic, ascorbic acid, and pectin. Other active compounds include tannins such as quercetin and caffeic acids such as quinic acid. Procyanidin B-2 is a protein kinase C inhibiting tannin recently demonstrated to promote hair cell growth and anagen induction in vitro (67).

Arnica (*Arnica montana*)

Arnica, of the compositae family, is approved for treating inflammation of cutaneous and muscosal surfaces and blunt injury and reducing the risk of developing infection. This herb functions as an analgesic, antidandruff, antiseptic, anti-inflammatory, and antiphlogistic but is an immunostimulant. The major active compounds include sesquiterpene lactone esters including helenalin, flavonoids, including flavonol glycosides, polyynes, volatile oils such as thymol, free fatty acids, caffeic acids such as chlorogenic acid, and hydroxycumarines.

Extract, tincture, and powder of arnica are administered topically as infusion, poultice, gel, plaster, oil, and ointment. The health hazards are primarily contact allergic and irritant dermatitis, but erosions and necrosis occur rarely (3). One death and one case of Sweet's syndrome have been reported. The literary giant Johann Wolfgang von Goethe ingested arnica tea to relieve angina in the 19th century (29). It is controversial regarding its safety with oral administration although it is used in cosmetic surgery (unpublished). One author suggests it should not be administered orally and another states the FDA considers arnica to be unsafe (13,22).

Cactus Pear (*Opuntia ficus-indica*)

This herb decreases oxidative damage to lipids and improves antioxidant status in healthy humans after oral supplementation. Vitamin C at a comparable dosage orally also enhances overall antioxidant defense but does not significantly decrease body oxidative stress (68).

Eucommia Ulmoides Oliver (EUOL)

This Chinese herb contains geniposidic acid which statistically significantly increased stratum corneum turnover in aging mice (69).

Ginseng (*Eleutherococcous senticosus*, *Panax ginseng*, *P. quinquefolius*)

The most potent species is Siberian ginseng which is *Eleutherococcus senticosus*. *Panax ginseng* is also from the Orient while *Panax quinquefolius* grows in America. This is a widely used oral herb that has recently entered cosmeceutical products without dermatologic studies or historical use in mucocutaneous disorders.

The major active ingredients of *Panax ginseng* are triterpene and steroid saponins known as ginsenosides, polysaccharides, aglycones, and polyynes. Eleutherococcus also contains steroid glycosides, hydroxycoumarins, phenylacrylic acids, and lignans (3). These actives all contribute to antioxidant, anti-inflammatory, anti-platelet, antitumor, and antiviral effects. Protein synthesis is also enhanced. The efficacy of oral ginsengs against systemic viruses is documented. Red ginseng applied topically appeared to inhibit chemically induced skin tumors in mice (29).

Ginseng is contraindicated in pregnancy, lactation, cardiac disease, and diabetes. Unfortunately 25% of 133 patients using ginseng for two years developed skin reactions. These also indicate ginseng abuse syndrome. Topical application to the face has induced postmenopausal vaginal bleeding. This herb increases effects of antidiabetic and anti-coagulant drugs, estrogen, and MAO inhibitors. It is administered as a powder for infusion (3).

Hibiscus (*Hibiscus sabdariffa*)

This is an Asian medicine for cutaneous inflammation and edema, carbuncle, scalding, and herpes zoster therapy. The active compounds include fruit acids (15–30%),

anthocyanidins, flavonoids, and mucilages. It is administered as tea. Hibiscus has no reported health hazards (3).

Jojoba (*Simmondsia chinensis*)

The galenic formulations of this herb are used in many products as an antioxidant thickener and to exfoliate skin for treatment of acne, psoriasis, sunburn, chapped skin, hair restorer and wounds although it is not approved for any cutaneous indication. The wax esters consist of 20–22 carbon atom length fatty acids arranged in waxy globules, alcohols, and 14% erucic acid. Health hazards include rare contact dermatitis and systemic toxicity (3,22).

Licorice (*Glycyrrhiza glabra and G. uralensis*)

The extracts of this herb are incorporated into cosmeceuticals to improve skin brightness but are used in Asian medicine for wounds and carbuncle therapy. The active components consist of triterpene saponins such as glycyrrhizin (3–15%), flavonoids including licoricidin, isoflavones such as glabridin, hydroxycoumarins including glycycoumarin, cumestans such as glycynol, sterols such as beta-sitosterol, and volatile oils including eugenol. Glycyrrhizin inhibit replication of varicella zoster, hepatitis B, cytomegalovirus, and HIV and stimulates IFN production. It is also anti-estrogenic, antistaphylococcal, antiprotozoal, anti-fungal, anti-yeast, antioxidant, anti-inflammatory, antiplatelet, anti-thrombin, anti-cancer and sebostatic effects. Glabridin is anti-inflammatory, antioxidant, and inhibits tyrosinase reducing UVB-induced erythema and pigmentation (3).

Licorice is administered by comminuted drug, powder, juice, decoction, and tea for infusions. This herb is contraindicated in pregnancy, lactation, hepato-, and renal toxicity and cardiac disease. It may induce rhabdomyolysis, pseudoaldosteronism, and hypokalemic alkylosis. Licorice interacts adversely with anti-arrythmic, antihypertensive, anticoagulant, and antidiabetic drugs, contraceptives, diuretics, laxatives, MAO inhibitors, and corticosteroid drugs (13,22).

Myrtle (*Myrtus communis*)

Cosmeceuticals incorporate this herb to calm the skin. The active compounds include monoterpenes and sesquiterpenes such as cineol and pinene. Tannins, acylphloruglucinols, and volatile oils are present. Antibacterial, fungicidal, and antiseptic effects result from the active molecules. It is administered as infusion. This herb is contraindicated in children and infants due to potential of including glottal spasm when used on the face. It should also be avoided in pregnancy and lactation (3).

Noni (*Morinda citrifolia*)

In 2003 and 2004 Noni was the largest selling single herb in the U.S. It has no reliable published clinical research. Noni's unproven uses are for many systemic diseases including diabetes, infections, fever, arthritis and wounds.

The active ingredients are iridoids including asperulosid. Topically, it is an emoltient used to reduce signs of skin aging. The active ingredients are iridoids including asperulosid, retinol, ascorbic acid, ursolic and linoleic acids (3,22).

Olive (*Olea europaea*)

The ancient Greeks had many uses for this plant and its by products. Olive oil has traditionally been used to treat burns, dermatitis, psoriasis, rosacea, and xerosis. The major components include 56–83% oleic acid, 8–20% palmitic acid, and 4–20% linoleic acid. Steroids including B-sitosterol and tocopherols are present. Extra virgin oil also has a significant amount of polar polyphenols which provide antioxidant effect and contribute to the anti-inflammatory function of olive oil. When applied to murine skin following UVB exposure, significantly fewer tumors developed. This herb is a weak irritant. An increasing number of cosmeceuticals incorporate olive oil into the formulation (70,71).

Papaya (*Carica papaya*)

This foodstuff enhances resolution of bruises and wounds. It is also used for cosmeceuticals to modify the appearance of scars. The juice from the unripened fruit is primarily papain, a mixture of proteinases, lipases, and phosphatases that additionally have anti-ulcerative, antimicrobial, and antihelminthic effects. This herb also contains polyketide alkaloids such as carpane, glucosinolates, saponins, and ficin. Papaya galenic extracts interact with warfarin, induce bleeding, and contact reactions. It is contraindicated in pregnancy. It has no reported health hazards (3).

Prickly Pear (*Opuntia streptacantha*)

The juice of this medicinal botanical soothes cutaneous wounds, burns, and dermatitis due to its mucilages consisting of mucopolysaccharides, sucrose, lignans, and fruit acids. It also is an antiviral against herpes simplex and HIV. This herb is administered as a powder or galenic for a variety of topical formulations. Prickly pear has no reported health hazards (22).

Pumpkin (*Cucurbita pepo*)

The German Commission E approved this herb for prostate therapy. Folk medicine uses pumpkin for helminthic infections. Pumpkin seeds comprise fatty oils (about 50% of total weight) including linoleic acid (55% of fatty oils) and oleic acid (25%). This extract is also rich in gamma-tocopherol, carotenoids including lutein, sterols, and the amino acid curcurbitin which is antihelminthic active (22). Pumpkin seed is antiphlogistic, antioxidant, and antihelminthic. This herb has no reliable published studies for any topical preparations or dermatologic disease (3,22).

There are no photoaging studies despite its use in cosmeceutical chemical peels and other products for nearly a decade.

The reported adverse reactions include gastrointestinal distress.

Rosemary (*Rosmarinus officinalis*)

This medicinal botanical soothes mucocutaneous tissue leading to its formulation into cosmeceuticals. It also has antimicrobial, antiviral, and antioxidant effects. Rosemary applied topically inhibited chemically induced murine epithelial tumors. The active components include flavonoids, triterpenes such as ursolic acid, diterpenes including carnosolic acid, and volatile oils in addition to caffeic and rosmarinic acids.

This herb is contraindicated in pregnancy and has a mild risk of sensitization (3).

Sandalwood (*Santalum album*)

This herb is an Asian therapy for heatstroke and sunstroke and for urethral inflammation in homeopathy. Preliminary data suggests it may be chemopreventive for cutaneous malignancy (57). The antiseptic and therapeutic effects result from tannins, resins, and volatile oils. Sandalwood is administered as oil. It has minimal potential for sensitization. It is contraindicated in pregnancy (3).

Sarsaparilla (*Smilax medica*)

This herb is a homeopathic remedy for pruritic and inflammatory cutaneous diseases including psoriasis, leprosy and syphilis. The active molecules include steroid saponins such as sarsasapogenin, phytosterols including beta-sitosterol, and quercetin. This preferred flavoring agent of the Old West is also an antiseptic and antipruritic. Sarsaparilla can induce asthma and renal failure. It is administered as a powder, decoction, and liquid extract (3,22).

Saw Palmetto (*Serenoa repens*)

This medicinal botanical has documented anti-androgenic, anti-estrogenic, anti-inflammatory, and anti-exudative effects. An unproven use is eczema therapy. Its major components are sitosterols and their glucosides, flavonoids, free fatty acids, and polysaccharides. Multiple blinded human trails document effectiveness in treating prostate disease. This compound has been introduced in at least two cosmeceuticals for photoaging and three for hair growth because of its documented inhibition of 5-alpha reductase. It is contraindicated in pregnancy and lactation and interacts with warfarin. This herb is administered in galenic formulations from comminuted herb (3).

Sesame (*Sesamum orientale*)

This herb is used in folk medicine to treat crusts and as a massage oil. The active ingredients are nearly completely fatty oils including linoleic and loeic acid (35-50% each), palmitic acid (10%), lignans, and sterols (3).

The lignan sesamine is immunosuppressive in vitro. No clinical studies have been published. It has limited risk of sensitization.

Spearmint (*Mentha spicata*)

The distinctive aroma is due to carvone which comprises 40–80% of the extracts of this herb. Other active compounds include caffeic acids such as rosmaric acid, flavonoids including thymonin, and volatile oils. These molecules provide spearmint with antimicrobial and insecticide activity (72).

This herb applied topically produced a statistically significant decrease in oxidative damage and tumor promotion as it decreased thymidine uptake. It is used for mucocutaneous inflammation, arthritis, neurogenic pain, urticaria and pruritis (22).

Wheat Germ (*Triticum aestivum*)

The oil of this medicinal botanical is used in cosmeceuticals to dissolve dirt and makeup and as a skin protectant. The active components include 60–75% triacylglycerols, 50–65%

linoleic acid, 15–22% oleic acid, 7–18% palmitic acid, and 9–14% phospholipids. Wheat germ oil also contains other active compounds including glycolipids, sterol esters, tocopherol, tocotrienols, and carotenoids. It has minimal risk of sensitization. This oil is administered orally or topically (3).

White Birch (*Betulae folium*)

This herb is included in cosmeceuticals to decrease fine lines because of its relatively high concentration of ascorbic acid, OPCs, and flavonoids including hyperoside and quercetin. Other actives include caffeic acids, such as chlorogenic acid, D-glucosides, monoterpene glucosides, and sesquiterpene oxides. This herb is used to treat hair loss and dandruff. White birch is administered as comminuted herb for tea and topicals. There are no reports of sensitization but use with caution in people with renal failure (3).

German Commission E Approved Herbs

Herbs approved by the German Commission E for treatment of mucocutaneous indications not previously discussed are listed alphabetically below. Familiarity with these medicinal botanicals is important because these herbs should be among the most likely candidates for incorporation into future cosmeceuticals. Several have very recently been formulated into novel cosmeceuticals due to the confidence in their known biologic activity, mechanisms of action, and relative safety. Human clinical trials are needed to document any cutaneous efficacy with these formulations just as in the previous group of botanicals.

Agrimony (*Agrimonia eupatoria*)

This herb is approved for treatment of inflammation of cutaneous and mucosal tissues. Asian medicine uses it for hemostyptic effects. Agrimony acts as an astringent due to the active compounds being catechin tannins. This herb is administered by decoction for poultice. There are no reported health risks with agrimony (3).

Bittersweet Nightshade (*Solanum dulcamara*)

This herb is approved to treat warts, acne, dermatitis, and furuncles. It is homeopathy for skin infection. The active compounds include steroid alkaloid glycosides and steroid saponins. The glycosides account for the stimulation of phagocytosis, hemolytic, cytotoxic, antiviral, anticholinergic, anesthetic, and desensitizing effect. The saponins promote resorption of the glycosides. Bittersweet nightshade is administered as decoction and tea for compress and rinse. This medicinal botanical is contraindicated in pregnancy and lactation (3).

Butcher's Broom (*Ruscus aculeatus*)

This medicinal botanical is approved to treat venous conditions including venous insufficiency and hemorroids. The therapeutic activity is due to increasing venous tone while reversing inflammation. The major active compounds include steroid saponins ruscine and ruscoside which comprise 5% of the extract by weight. The other group of active compounds include benzofuranes including euparone. These extracts are orally administered as capsules with only rare gastrointestional adverse reactions reported (3).

Cajuput (*Melaleuca leucadendra*)

This herb is approved to treat wounds and burns and reverse a tendency toward infection. The antimicrobial and rubefacient effects are produced by cineol, terpineol, and other sesquiterpenes and phenones. Cajuput is administered as oil but must not be applied to the face of infants or children due to potential glottalspasm or bronchospasm. Contact allergic reactions rarely occur. This herb must not be ingested (3).

Chaste Tree (*Vitex agnus-castus*)

Known as Vitex, this medicinal botanical is approved for treating premenstrual acne with oral administration. The active compounds include flavonoids such as casticin, glycosides, fatty, and volatile oils. It suppresses follicle-stimulating and luteinizing hormone levels to increase progesterone and reduce estrogen levels. The main adverse effects are gastrointestinal tract distress and allergic eruptions (29).

English Plantain (*Plantago lanceolata*)

The extracts of this herb are approved to treat cutaneous and mucosal inflammation. The active compounds include mucilages such as glucomannans, monoterpenes including aucubin, flavonoids such as apigenine glucoside, caffeic acids including chlorogenic acid, hydroxycoumarins such as aesculetin, silicic acid, tannins, and saponins. Therapeutic effects include acceleration of hemostasis and enhanced epithelialization and are bactericidal. Monoterpenes and saponins account for most of these effects. There are no health hazards reported with English plantain. It is administered as a liquid extract, juice, or tea for lozenge or infusion (3).

Fenugreek (*Trigonella foenum-graecum*)

This herb is approved to treat inflammatory cutaneous diseases. It acts as soothing emollient via its major active compounds mucilages including mannogalactans which account for 25–45% of the extract. Proteins comprise another 25–30% of the extract, while steroid saponins including trigofoenosides and foenugracein account for about 15%. Trigonelline, sterols, volatile oils, and flavonoids such as orientin and vitexin are the other active compounds. Topical sensitization is rare. Fenugreek must not be administered during pregnancy (3).

Flax (*Linum usitatissimum*)

This medicinal botanical is approved to treat inflammatory cutaneous disorders. Asian medicine employs flax to treat superficial infections. This herb functions as a soothing anti-inflammatory emollient due to the linolenic, linoleic, and oleic acids which combined comprise 30–45% of the extract weight. Proteins account for another 20–27% of the extract while mucilages comprise about 10%. Antioxidant, antimycotic, and estrogenic effects result from lignans, whose most abundant source is flax. Cyanogenic glycosides and phenylpropanes are the other active compounds in this extract.

The adverse cutaneous reactions have only been reported to linseed, the oil extracted from flax. They include irritation, erythema, eyelid edema, and one case of an anaphylaxis (3,13,22). Flax is administered as a cracked or ground seed, powder, linseed oil, or a poultice.

Heartsease (*Viola tricolor*)

Heartsease is approved for treatment of cutaneous inflammation and sehorrheic dermatitis in infants. Homeopathy employs it for eczema therapy. The active compounds function as soothing anti-inflammatory emollients. Mucilages account for 10% of the extract by weight. Other actives include tannins, salicylic acid (0.3%) and other phenolics, flavonoids including rutin, saponins, and vitexin, and hydroxycoumarins such as umbelliferone. This herb has no reported health hazards.

Heartsease is administered by powder, decoction or tea for infusion, bath additive, ointment, and shampoo (3).

Horsetail (*Equisetum arvense*)

This herb is approved for treatment of wounds and burns. The major active compound is the astringent silicic acid which comprises 5.0–7.7% of the extract by weight. Flavonoids such as apigenin glucoside contribute to the astringent effect. Other actives are caffeic acids including chlorogenic acid and pyridine alkaloids such as nicotine. Horsetail should not be used in patients with cardiac or renal compromise even topically (13). The liquid extract is administered as a decoction or tea for infusion or compress (3).

Jambolan (*Syzygium cumini*)

The extract of the bark of Jambolan is approved for treatment of cutaneous and mucosal inflammatory diseases but the seed extract is not. It has similar use in Asian medicine. The therapeutic effect is as an astringent primarily due to the tannins such as ellagic acid. Other active compounds include sterols such as beta-sitosterol, triterpenes including eugenin, and flavonoids such as myricetin and kaempferol. There are no reported health hazards with Jambolan. It is administered as a powder or decoction for a gargle, infusion, or compress (22).

Lavender (*Lavandula angustifolia, L. officinalis*)

Lavandula officinalis was used by the ancient Greeks for its fragrant essential oil. English lavender (*Lavandula angustifolia*) is approved for balneotherapy for circulatory disorders. Tannins comprise 13% of this extract by weight. Other active compounds include volatile oils of which linalool and linoyl acetate comprise 90%, and hydroxycoumarins such as umbelliferone, caffeic acids including rosmaric acid, flavonoids, and triterpenoids are the active molecules. Lavender oil inhibits mast cell degranulation and has antimicrobial and antiphlogistic effects (73).

Lavender has weak sensitization potential but cross reacts rarely with TTO (13). It is administered as a liquid extract for tea, infusion, poultice, bath additive, or other topical formulations (3).

Marigold (*Calendula officinalis*)

The flower of this medicinal botanical is approved to treat wounds, burns, and mucosal inflammation. The above ground parts of the Marigold plant are not approved for therapy. This herb is homeopathy for frostbite, burns, and poorly healing wounds. The therapeutic mechanisms include antimicrobial activity to *Staphylococcus aureus*, *Klebsiella pneumoniae*, Candida species, and HIV. Acceleration of granulation tissue, angiogenesis, and epithelialization of wounds are additional therapeutic effects. Faradiol is a terpene alcohol extracted from Marigold with anti-inflammatory effect equivalent to indomethacin

in two animal studies. The major active compounds include polysaccharides such as arabinogalactans which comprise 15% of the extract by weight and triterpene saponin glycosides which comprise 2-10%. Other active compounds include flavonoids such as quercetin glycoside, hydroxycoumarins including scopoletin, volatile oils such as cadinol, and carotinoids including lutein and zeaxanthine.

A very low risk of sensitization (0.2%) is the only health hazard. Marigold flower is administered as a liquid extract, powder, tincture, tea, or decoction for infusion, oil, gel, ointment, solution, and shampoo (3).

Oak (*Quercus robar*)

This herb is approved for treatment of cutaneous and mucosal inflammatory disorders due to its astringent, antiviral, antihelminthic, and antiphlogistic effects. All of the therapeutic activity resides in the multiple tannins which account for 12–16% of the extract by weight. The catechin tannins include monomeric and dimeric catechins, oligomeric proanthocyanidin, and leucocyanidins (3).

The only health hazard occurs with whole body baths for "widespread open" wounds or dermatitis if the patient has cardiac insufficiency stages III and IV and hypertomia stage IV. Oak is administered as powder or tea as a bath additive (22).

Oat (*Avena sativa*)

Oat straw is approved for treatment of cutaneous inflammation, pruritis, varicella and warts. The oat herb and fruit are not approved for therapy. The active compounds include oligosaccharides and polysaccharides including beta-glucan, silicic acid, steroid saponins such as avencoside, amino acids such as avenic acid, and flavonoids including vitexin, apigenin and tocotrienols. The anti-inflammatory effect results from several of these actives. Beta-glucan inhibits prostaglandin biosythesis yet stimulates cell-mediated immunity which provides antiviral and antitumor functionality.

There are no reported health hazards with oat straw. It is administered as decoction, tea, or tincture for bath additive and other topicals (3,22).

Peruvian Balsam (*Myroxylon balsamum*)

This resinous herb is from scorched tree trunks while Tolu balsam is a resin from incised tree trunks of the same plant. Peruvian balsam is approved for treatment of wounds, burns, and hemorrhoids while Tolu balsam treats mucosal inflammation by homeopathy.

Balsams treat wounds as an antiseptic and promoting granulation. Peruvian balsam is also antiparasitic especially for scabies due to benzyl benzoate and benzyl cinnomoate which combined comprise 50–75% by weight. Resins consisting of cinnamic ester polymers comprise another 20–30%. Volatile oils such as nerolidol are other active compound extracted from this herb. There are significant mucocutaneous reactions to both balsams including allergic contact dermatitis, contact urticaria, oral ulcers, purpura, angioedema, photosensitivity, and phototoxicity. Renal failure with widespread topical use has been reported (3,22).

Pineapple (*Ananas comosus*)

This foodstuff is also approved for therapy of wounds and burns. The activity is due to a mixture of five cysteine proteinases known as bromelain. These enzymes stimulate wound

healing by providing fibrinolytic and proteolytic activity while inhibiting thrombocyte aggregation. Bromolain also has anti-inflammatory and antineoplastic effects. The health hazards of pineapple consist of contact allergic and irritant reactions. Pineapple extract is administered as tablets or granules or in compounded topical formulations (3).

Poplar (*Populus species*)

Poplar leaf buds, but not the bark, and leaves, are approved to treat wounds, burns, and hemorrhoids due to the antiphlogistic, antibacterial, analgesic, and wound healing effects. The active compounds are primarily salicylic acid glycosides and esters such as salicin and populin. Flavonoids including propolis and chrysin, zinc lignans, and the volatile oil caryophyllene are the other active compounds.

This herb is contraindicated in hypersensitivity to salicylates, peruvian balsam, and propolis. The cutaneous health hazards consist of allergic and irritant contact dermatitis. Poplar leaf buds are administered as topical semisolid extracts (3).

Sage (*Salvia officinalis*)

This flavoring and medicinal botanical is approved to treat excessive perspiration, burns, and wounds. Its most frequent use in homeopathy is also for excessive perspiration. The active compounds are caffeic acids such as chlorogenic acid, triterpenes including ursolic acid, diterpenes such as carnosolic acid, volatile oils including thujone and camphor and flavonoids such as apigenin- and luteolin-7-glucosides. These active compounds provide astringent, secretolytic, antiperspirant, fungistatic, virostatic, and bactericidal effects.

This herb is contraindicated in pregnancy but has no other health hazards. It is administered via juice, tincture, and distillate for infusion, gargle, rinse, compress, and poultice (3).

Shepherd's Purse (*Capsella bursa-pastoris*)

This herb is approved for treatment of burns and wounds. It is homeopathy for mucosal bleeding. The active compounds consist of caffeic acids such as chlorogenic acid, flavonoids including rutin, glucosinolates, sinigrin, and cardioactive steroids. Shepherd's purse is contraindicated in pregnancy and used with caution in widespread cutaneous lesions. It is administered by tea for infusion (3).

Sweet Clover (*Melilotus officinalis*)

Hemorrhoids, venous conditions including insufficiency, and blunt injuries are approved indications for this herb. It has antiphlogistic, anti-exudative, and anti-edematous effects while it improves venous reflux, lymphatic kinetics, and wound healing. The active compounds include free coumarins including melilotol, hydroxycoumarins such as umbelliferone, flavonoids including kaempferol glycosides, triterpene saponins such as melilotigenin, and volatile oils (3).

Oral administration may lead to hepatoxicity. No cutaneous sensitization or irritation has been reported, but red clover (*Trifolium pratense*) is a mutagen (13). Sweet clover is administered as a comminuted herb for galenic formulation for infusion, poultice, ointment, suppository, and herbal sachet (3).

Walnut (*Juglans regia*)

This foodstuff is approved for treatment of excessive perspiration and cutaneous inflammation, including abcesses, acne, dermatitis and ulcers. Asian medicine employs it as an antihelminthic and aphrodisiac. The active compounds include tannins such as galloylglucose, flavonoids such as hyperoside, and the naphthalene juglone which accounts for the staining effect. The therapeutic effects with include astringent, antibacterial, antiviral and fungistatic (3).

Juglone is mutagenic inducing leukoplakia and tongue carcinoma (3,22). No other health hazards are reported. Walnut is administered by decoction for infusion.

White Nettle (*Lamium album*)

Treatment for cutaneous and mucosal inflammation is among the approved indications for this herb. It is used in Asian medicine to treat carbuncles and inflamed wounds. White nettle functions as an astringent and emollient due to the active mucilages, flavonoids including kaempferol glycosides, caffeic acids such as chlorogenic acid, triterpene saponins, and monoterpenes including lamalbide.

There are no reported health hazards. This herb is administered by tea for infusion, bath additive, poultice, compress, and rinse (3).

SUMMARY

There are multiple herbs currently incorporated into cosmeceuticals with valid scientific rationale and supported with human clinical studies or have documented biologic activity by in vitro, in vivo, or animal studies. Cosmeceuticals containing these herbs may currently be or potentially will be valuable contributions to dermatology and skin care if clinical efficacy can be confirmed by controlled human clinical trials conducted by third-party researchers with the finished marketed product. The cosmeceutical only has scientific integrity if the herbal components are stable, of therapeutic concentrations, and can be adequately delivered across human stratum correum.

ACKNOWLEDGMENTS

I greatly appreciate the assistance of Sheena Beavers, David Talford PA-C, Charity Burkheimer, and Elisha Andrews in this manuscript.

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Topical Anti-inflammatories

Bryan B. Fuller and Dustin R. Smith
Department of Biochemistry and Molecular Biology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, U.S.A.

INTRODUCTION

Inflammatory skin diseases are extremely common dermatological problems that present in a variety of forms, from occasional rashes accompanied by skin itching and redness to more chronic conditions such as atopic dermatitis, rosacea, seborrheic dermatitis, and psoriasis. Combined, these conditions affect over 35 million Americans who annually spend over $2 billion to treat their symptoms. This chapter will provide an overview of the inflammation process, review current drug, over-the-counter (OTC), and cosmetic topical treatments for several inflammatory diseases, discuss research approaches that can be used to identify new anti-inflammatory compounds to treat various aspects of inflammation, and finally, provide an overview of how topical formulations containing novel anti-inflammatory compounds can be developed and characterized.

BIOLOGY OF SKIN INFLAMMATION

Skin inflammation, which is characterized by redness, swelling, heat, itching, and pain, can exist in either an acute or chronic form with acute disease frequently progressing to a more chronic condition. Acute inflammation can result from exposure to UV radiation (UVR), ionizing radiation, allergens, or to contact with chemical irritants (soaps, hair dyes, etc.). Assuming that the triggering stimulus is eliminated, this type of inflammation is typically resolved within one to two weeks with little accompanying tissue destruction. A chronic inflammatory condition, however, can last a lifetime, and cause considerable damage to the skin. Some of the cellular and biochemical events which occur in the skin in response to a triggering stimuli (e.g., UVR, chemical, or antigen) and which lead to an inflammatory response are shown in Figure 1. Within minutes of exposure of skin to an insult there is a rapid release of inflammatory mediators from keratinocytes and fibroblasts and from afferent neurons. In response to a triggering stimulus, keratinocytes produce a number of inflammatory mediators including PGE-2 and TNF-alpha as well as the cytokines, IL-1, IL-6, and IL-8. Dermal fibroblasts also respond to the insult and to IL-1 produced by keratinocytes by increasing production and secretion of cytokines including IL-1, IL-6, IL-8 as well as PGE-2. One of the principal actions of PGE-2 produced and secreted by both keratinocytes and fibroblasts is to increase vasodilation and vascular

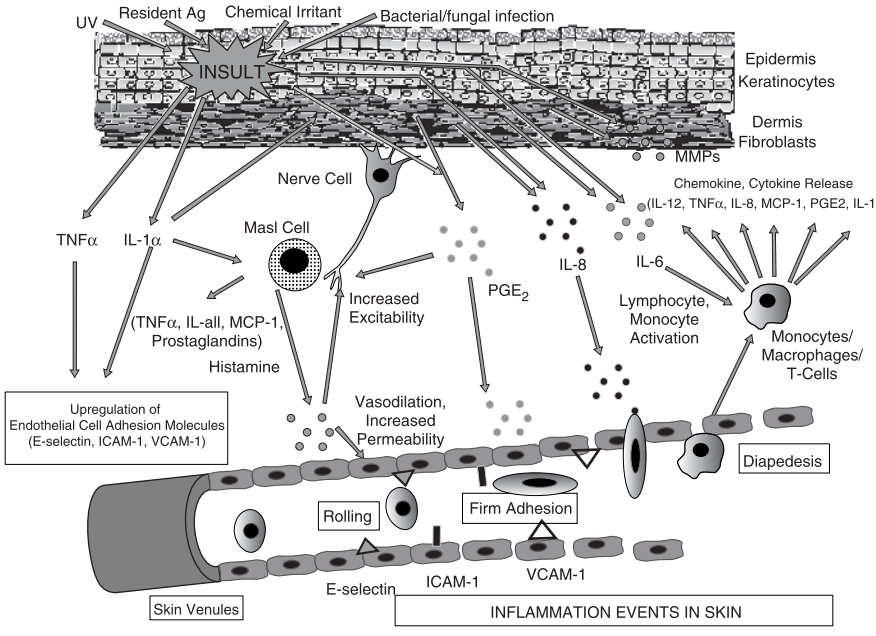

Figure 1 Diagram of cellular events which occur during a cutaneous inflammatory response.

permeability. In addition, PGE-2 aids in the degranulation of mast cells and increases the sensitivity of afferent neuronal endings. The increased sensitivity of nerve endings by prostaglandins and cytokines results in the release of neuropeptides, including substance P and calcitonin gene related peptide (CGRP) (1). Neuron depolarization also increases resulting in the sensation of pain. Substance P and CGRP released by neurons, along with PGE-2, cause degranulation and release of histamine from mast cells, and they also stimulate the cell to produce a variety of inflammatory cytokines. If IgE is bound to its receptor on mast cells, exposure of skin to an IgE specific antigen can also trigger the degranulation and activation of the mast cell (2,3). Increased vasodilation and vascular permeability by PGE-2 and histamine leads to increased blood flow and extravasation of fluid from blood vessels. This causes visible redness and swelling in the inflamed area. The increased production of inflammatory mediators by keratinocytes and fibroblasts, particularly TNF-alpha and IL-1, leads to the expression of intracellular adhesion molecules, such as VCAM and ICAM, on endothelial cells of the blood vessels (4). These proteins, as well as P and E selectin, serve as anchoring elements for monocytes and neutrophils passing through the blood. The attachment of these leukocytes to the adhesion molecules slows their movement through the bloodstream and finally causes their firm adhesion to the endothelial wall (5). In the presence of chemokines, particularly IL-8 produced and released by both keratinocytes and fibroblasts, the adherent leukocytes undergo chemotaxis and migrate from the blood vessel out into the skin where they act to scavenge the area of debris and also produce additional inflammatory mediators. The initial acute response occurs within minutes of the insult to the skin and involves the production of inflammatory mediators, the degranulation of mast cells, and the vasodilation of blood vessels (6). The subsequent movement of neutrophils and monocytes into the "wounded" area typically takes up to 48 hours to occur. If the triggering stimulus is eliminated, inflammatory mediator production by keratinocytes,

fibroblasts, and mast cells ceases, the influx of leukocytes to the "wounded" area decreases and inflammation subsides.

In contrast to acute inflammation which typically resolves in one to two weeks, chronic inflammation results from a sustained immune cell mediated inflammatory response within the skin itself and is long-lasting. Antigen presenting cells (APCs) in the skin, called Langerhans cells in the epidermis and dendritic cells (DCs) in the dermis, can be activated by innate mechanisms and by exposure to the inflammatory cytokines, IL-1 and TNF-alpha, produced by fibroblasts and keratinocytes in response to a triggering stimulus. The activated APCs bind to and transport skin antigens (allergens) through the lymphatics during which time they undergo a maturation process. This maturation step allows the APCs to efficiently present the antigen to T-lymphocytes. This presentation, in turn, triggers the maturation of a specific subset of naïve T-lymphocytes into memory cells and the activation of resident antigen specific T-lymphocytes. The skin-homing T-lymphocytes, which express a cell surface epitope, termed cutaneous lymphocyte antigen (CLA), migrate to the involved area of skin, and adhere to endothelial cell walls initially through an interaction between the CLA expressed on the surface of the T-lymphocyte and E-selectin expressed on endothelial cells (7). Other specific receptors on T-lymphocytes, which aid in the binding and chemotaxis of these cells into the skin, include CCR4 and LFA1 (8). Once T-lymphocyes have migrated into the skin from the circulation, they not only undergo proliferation, but also produce and secrete a wide range of inflammatory mediators as well as matrix-eroding enzymes, such as matrix metalloproteinase-1 (MMP-1; collagenase). Cytokines produced by T-lymphocytes can stimulate fibroblasts and keratinocytes to produce additional cytokines and chemokines, and can also induce the expression of a variety of tissue-destructive enzymes by fibroblasts, including MMP-1 (collagen), MMP-3 (stomelysin-1) and MMP-9 (gelatinase B). As long as the antigen or insult stimulus persists in the skin, the inflammatory response will continue, resulting in significant and serious tissue destruction (9).

Inflammatory processes in the skin, particularly those triggered by long-term exposure to solar radiation, not only cause the more obvious symptoms of redness, swelling, and itching, but also trigger molecular pathways that escalate the aging process. Actinic aging, or photoaging, that occurs following prolonged exposure of the skin to ultraviolet (UV) light from the sun results in increased cytokine production with attendant activation of genes in both keratinocytes and fibroblasts that cause erosion of the normal skin structure. Matrix metalloproteinases (MMPs), which break down the skin extracellular matrix causing sagging and wrinkling, are stimulated in sun-exposed skin. Furthermore, dermal fibroblast synthesis and assembly of collagen, which is required to maintain and restore the extracellular matrix, is inhibited while elastin production is over- stimulated, leading to elastosis. It is now widely accepted that sun-exposed skin in most individuals remains in a constant state of low level UV-induced inflammation, and that this "smoldering" inflammation is responsible for the signs of skin aging that appear in middle age (10–12).

PRESCRIPTION AND OVER-THE-COUNTER TREATMENTS FOR INFLAMMATION AND MECHANISM OF ACTION

Steroids

Given the complexity of the inflammatory process in skin, developing topical products that can effectively resolve the myriad of inflammatory disease states that exist is challenging. By far the most effective and commonly used prescription drugs for treating inflammation are the corticosteroids, particularly the glucocorticoid related steroids. They are very

effective for many forms of eczema, including atopic dermatitis, allergic contact dermatitis, seborrheic dermatitis (in concert with an anti-fungal agent), and have some utility in ameliorating the symptoms of psoriasis. They are not particularly effective, however, in treating acute inflammation, like UVR-induced sunburn, which is not primarily an immune cell driven inflammatory response. Corticosteroids can be used topically or orally. Topical corticosteroids have been classified into groups based on potency. For example, the corticosteroid clobetasol proprionate is ranked as a very potent steroid, while betametasone diproprionate and fluocinolone acetonide can range from potent to moderately potent. OTC topicals containing hydrocortisone are, of course, the least potent (13). Although newer methods are being studied, topical steroid potency is still determined using the MacKenzie vasoconstrictor assay established over 40 years ago. In this assay, a topical steroid is applied to the forearm and the extent and duration of skin blanching due to vasoconstriction assessed by visual examination and rated on a scale of 0 (normal skin, no blanching) to 4 (intense blanching). Although subject to variability, the assay has proved to be a reliable estimate of corticosteroid potency (14).

Given the efficacy of corticosteroids in treating many different types of skin inflammation as well as efficacy in treating autoimmune-based inflammatory diseases such as rheumatoid arthritis, asthma, lupus erythematosus, and allergic rhinitis, considerable research has been directed toward understanding their mechanism of action.

Corticosteroids act on target cells by binding to the glucocorticoid receptor present primarily in the cytosol. This binding "activates" the receptor, resulting in its translocation to the nucleus. The steroid hormone receptor complex then binds, as a homodimer, to DNA regulatory elements along the promoter regions of specific genes. This binding usually results in the up-regulation of gene activity but can also cause transcriptional repression of the target gene (15). The effectiveness of corticosteroids as inhibitors of inflammation stems from the ability of the steroid activated glucocorticoid receptor complex to interfere with the activation of genes regulated, principally, by two transcription factors, NF-kappa B and AP-1 (16,17). These two transcription factors are primarily responsible for the transcriptional activation of a wide variety of pro-inflammatory genes including those for cytokines IL-1, IL-2, IL-3, IL-4, IL-6, IL-11, IL-12, and IL-13, TNF-alpha, and GM-CSF, the chemokine genes IL-8, RANTES, MCP-1, the adhesion molecules ICAM-1, VCAM-1, and E-selectin, the rate-limiting enzyme for PGE-2 production, COX-2, and the matrix-metalloproteinase genes, including MMP-1 (18).

A diagram showing the signaling pathway in cells that leads to the activation of either NF-kappa B or AP-1 and, thus, to the activation of inflammatory genes is shown in Figure 2. Briefly, when a surface receptor on a target cell binds a specific ligand, such as a hormone or cytokine, the receptor is "activated" and this in turn leads to the activation of a signal cascade within the cell. The signaling pathway involves a variety of kinases which are sequentially activated. In the case of the NF-kappa B activation pathway, one of these kinases, IKK, when activated, phosphorylates the protein IkB. This protein, in its unphosphorylated state, binds to NF-kappa B in the cytosol and prevents NF-kappa B from translocating to the nucleus and activating target genes. When IkB is phosphorylated by IKK, it dissociates from NF-kappa B and is degraded. Once freed from the IKB, NF-kappa B can translocate to the nucleus where it binds to the promoter region of specific genes and activates them (19).

As mentioned above, while many inflammatory genes are activated by NF-kappa B, others are regulated by the transcription factor AP-1. This transcription factor is a dimer consisting of either a Jun-Fos heterodimer or a Jun-Jun homodimer. For most cytokine genes, only the Jun-Fos heterodimer functions as a transcriptional activator. As is shown in Figure 2, binding of a ligand such as IL-1 or TNF-alpha to its receptor activates a signaling

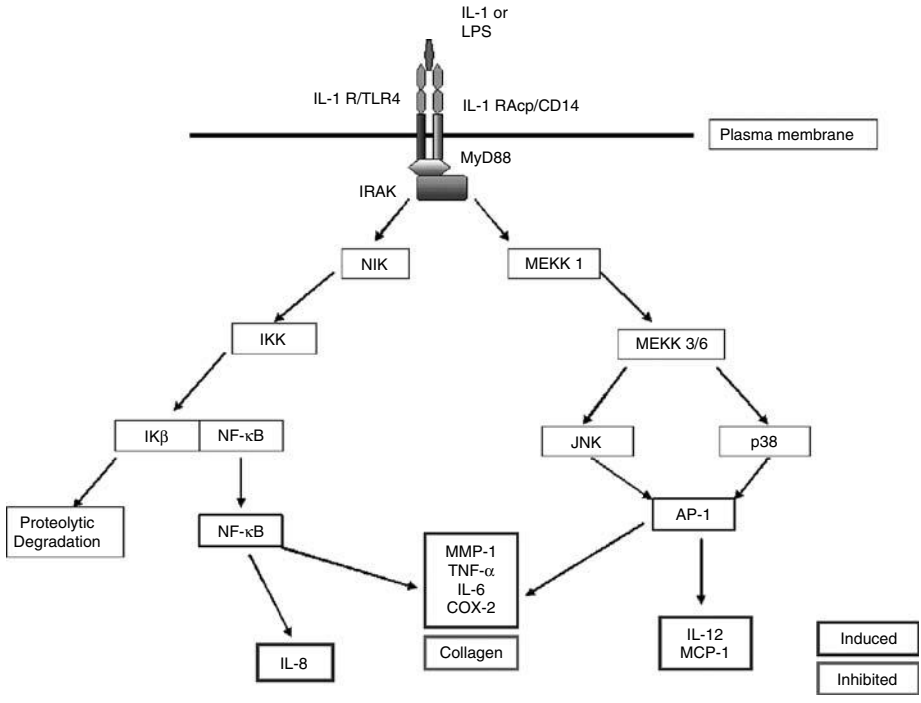

Figure 2 Intracellular signaling cascade leading to the activation of inflammatory genes.

cascade that involves sequential activation of a variety of kinases, some of which are members of the MAP kinase family. Either one of two members of this family, JNK (c-Jun N-terminal kinase) or p38 map kinase, when activated by this signaling cascade, phosphorylates, and activates c-Jun and this forms a dimer with the Fos protein to form the functional transcription factor. The Jun-Fos heterodimer will only form if Jun is first phosphoryated by JNK. The Jun-Fos heterodimer forms the AP-1 complex that activates inflammatory target genes (16).

While some genes are regulated only by either NF-kappa B or AP-1 other inflammatory genes have both an NF-kappa B and AP-1 binding site in their promoter regions and, thus can be regulated by either or both transcription factors. Recent data suggests that the control of gene activity by either AP-1 or NF-kappa B depends on both the placement of the transcription factor binding site along the promoter region of the gene and on the level of expression of the transcription factor. To some extent the transcription factor binding site that is closest to the start of transcription plays a predominant role in regulating the activity of the gene. Thus, for example, the MCP-1 gene is strongly regulated by the AP-1 site that lies close to the transcription start site even though there are three NF-kappa B binding sites in the promoter of this gene. Examples of the placement of NF-kappa B and AP-1 transcription factor binding sites in the promoter regions of some inflammatory genes are shown in Figure 3.

As mentioned above, the anti-inflammatory activity of corticosteroids comes from their ability to repress either the activation or activity of the NF-kappa B and AP-1 transcription factors thereby suppressing transcription of genes coding for inflammatory mediators. In the case of NF-kappa B, the actual mechanism of action of the glucocorticoid receptor complex in repressing inflammatory genes activated by this transcription factor is not well understood, but evidence suggests a couple of likely possibilities. One mechanism

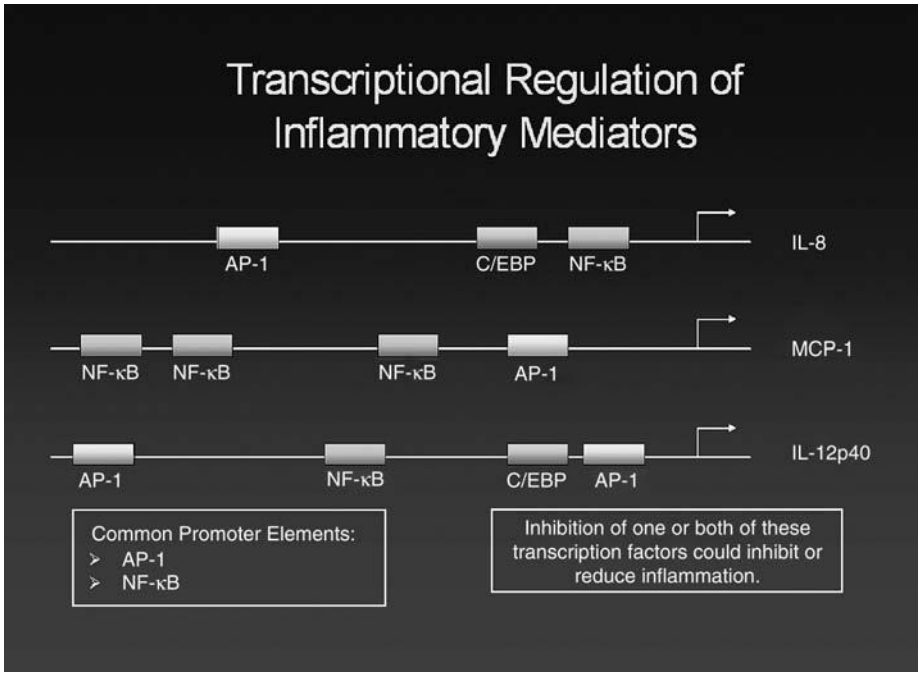

Figure 3 Diagram of transcriptional elements that regulate the activation of inflammatory genes.

involves the steroid activated glucocorticoid receptor up-regulation of the gene coding for IKB. This produces a cellular excess of this protein which then complexes to and inactivates NF-kappa B, preventing its translocation to the nucleus.

Other data suggests that the glucocorticoid receptor does not block the translocation of NF-kappa B but rather inhibits either binding of the transcription factor to its regulatory site in the promoter region of target genes or alternatively interferes with NF-kappa B's ability to activate the target gene after binding the promoter region (19–22). Regardless of which specific mechanism is correct, the end result of corticosteroid activation of the glucocorticoid receptor is the repression of NF-kappa B activity and a down-regulation of inflammatory gene activity. In regard to the suppression of the AP-1 stimulation of genes, recent evidence suggests that glucocorticoids block AP-1 phosphorylation and activation by two mechanisms. First, glucocorticoids can suppress AP-1 activity by physically interacting with the Jun component of the dimer, thereby blocking its binding to fos and preventing the formation of an active complex. Secondly, recent studies show that glucocorticoids stimulate the transcription of the MAPK phosphatase-1 gene thereby increasing its abundance in the cell and blocking the phosphorylation of Jun (16).

While the glucocorticoids have been shown to be extremely effective in suppressing the activation of pro-inflammatory genes because of their ability to block NF-kappa B and AP-1 functioning, steroids produce a variety of undesirable side effects. First, due to their potent inhibition of genes involved in an immune cell driven inflammatory response, they have an overall immune suppressive effect. Prolonged use of glucocorticoids leads to a reduction in B- and T-lymphocyte populations, and a reduced ability to fight skin infections. Further, steroids adversely affect the ability of dermal fibroblasts to synthesize collagen and at high doses they reduce the proliferation rate of these cells. Consequently, long-term use of topical steroids can lead to skin thinning and a decrease in the dermal matrix. Other potential negative side effects caused by prolonged use of steroids include

altered carbohydrate metabolism, suppression of the hypothalamic-pituitary-adrenal axis, increased osteoporosis, and increased risk of developing cataracts.

Due to the undesirable side effects which limits the length of time steroids can be used to treat inflammatory diseases, non-steroidal topical therapeutics have been developed to treat inflammation. One group of drugs, the non-steroidal anti-inflammatory drugs (NSAIDs) have been used for many years as oral drugs to control inflammatory responses.

Non-steroidal Anti-inflammatory Drugs (NSAIDS)

The most well-known of all the NSAIDS, aspirin, has been used for over 100 years to control various forms of inflammation and today Americans consume over 80 billion tablets of aspirin a year. NSAIDS are available in OTC and prescription forms. Common OTC forms are ibuprofen, naproxen, aspirin, and acetaminophen. Those available with a prescription include celecoxib (Celbrex®), diclofenac (Votaren®), etodolac (Lodine®), indomethacin (Indocid®), ketoprofen (Orudis®) and Rofecoxib (Vioxx®) to name a few. While many topical forms of NSAIDs including Voltaren Emulgel®, Indocid® (indomethacin), Nidol® (nimesulide), Feldene gel® (piroxicam), Oruvail® (ketoprofen), and Pennsaid® (diclofenac) are available in Europe and elsewhere without prescription, in the U.S. none are available as either OTC or prescription drugs (23). One topical prescription NSAID that has received FDA approval in the U.S. is Solareze® (diclofenac) which is indicated for the treatment of actinic keratoses (24). Perhaps due the availability of topical NSAIDS in Europe but not in the U.S., a number of non-FDA approved topical NSAID products have now emerged for sale without a prescription on various Web sites. These include such products as ProzRelief® (12% ibuprofen) and IbuCream (10% ibuprofen).

When one examines the published data on the efficacy of topical NSAIDS in treating various inflammatory symptoms, the results show considerable disparity. A statistical analysis of clinical data from a wide number of trials with various topical NSAID preparations for treating inflammation associated with arthritis concluded that while relief from symptoms was higher in the NSAID group versus the placebo group for the first two weeks, after that time, there was no measurable difference between the two treatment groups (25). Many other reports, however, do suggest that topical NSAID treatment for joint pain provides relief beyond that observed with the placebo group (26,27). A very recent clinical study with over 200 patients suffering from knee osteoarthritis found that the topical application of diclofenac provided significantly more effective relief from pain and stiffness than the vehicle control group (28). In another recent study, the product, Nidol®, which contains 2% of the COX-2 inhibitor, nimesulide, was found to be significantly more effective than topical diclofenac in reducing the pain of shoulder periarthritis (29). Considering that few studies have yet to evaluate topical formulations containing newer NSAIDs, including the specific COX-2 inhibitors, and considering that few topical formulations for NSAIDs have been developed and optimized, there is a considerable amount of research to be carried out to fully assess the efficacy of topical NSAIDs in treating inflammation (30,31). Certainly, it seems likely that a topical preparation of a potent NSAID that delivers adequate levels of an effective COX inhibitor through the skin would likely be effective in treating a variety of inflammatory conditions in which PGE-2 is indicated as a causative factor. Such products would be preferred over the use of oral dosing because of minimal risk topically applied NSAIDs present for stomach irritation.

The mechanism of action of NSAIDs involves the inhibition of prostaglandin production, particularly PGE-2. The common target for NSAIDS is the enzyme

cyclooxygenase (COX), which exists in two forms, COX-1, and COX-2. While most older versions of NSAIDS including aspirin, ibuprofen, and acetaminophen are not selective inhibitors of any particular form of COX, newer drugs have been designed to target primarily COX-2. The effort to design COX-2 specific inhibitors stems from findings that COX-1 plays a protective role in preserving the stomach lining, and thus, NSAIDs that target both COX-1 and COX-2 can erode the stomach lining and cause ulcer formation when taken orally (32,33). This deleterious side effect would however, likely be significantly reduced with topically applied NSAIDS. If so, COX inhibitors, whether specific for COX-2 or not, could be used with equal effectiveness in treating symptoms of inflammation.

Perhaps one of the most obvious and effective uses of a topical NSAID would be to treat the symptoms associated with sunburn. This type of inflammation is primarily driven by the UVR-induced production of PGE-2, which, as mentioned above, causes vasodilation, enhances sensitivity of nerve endings, causes histamine release from mast cells, and stimulates the production of additional inflammatory mediators in fibroblasts. By blocking or reducing the UVR-induced production of PGE-2 from keratinocytes and fibroblasts it should be possible to minimize the onset and progression of a sunburn. Thus, it seems likely that the topical use of a COX inhibitor might be able to not only slow the progression of a sunburn but decrease the magnitude of the UVR induced erythema. At present in the U.S. there are no topical prescription or OTC drugs that either effectively prevent the onset of sunburn (other than sunscreens that simply block UVR at the skin's surface) or eliminate existing erythema resulting from a sunburn. Topical steroids have been shown to reduce the onset of erythema resulting from a minimal erythema dose (MED) of 2 but are ineffective at higher MED values (34). Further, they cannot reverse existing UVR-induced erythema.

Studies with topical NSAIDs have shown that these are effective in both retarding the onset of UVR-induced erythema and decreasing the magnitude of the sunburn response. Topical indomethacin (1%) if administered immediately after sun exposure is more effective than steroids, being able to block the onset of sunburn produced by a 6 MED dose of UVB radiation (34). Further, topical application of the COX-2 inhibitor, celecoxib, after UVB irradiation of skin reduced erythema, edema, PGE-2 levels, the number of sunburn cells, and dermal infiltration of neutrophils (35). The topical NSAID, diflofenac (branded Solareze®), which is approved for use in the U.S. to treat actinic keratoses, has been shown to reduce sunburn symptoms when applied within four hours of the initial onset of sunburn (36). It is quite likely that other NSAIDS would be similarly effective in reducing the intensity of a sunburn if applied topically, and may also show the same efficacy as topical diclofenac in treating actinic keratoses. Interestingly, several studies implicate PGE-2 as a causative factor in skin cancer, and results from mouse experiments show that topical application of a PGE-2 inhibitor lowers the UVB-induced number of papillomas detectable 12 weeks after UVB dosing (37–40).

Immunomodulators

A newer type of NSAIDS is represented by the immunomodulators. Two anti-inflammatory drugs that have received FDA approval for topical use are the immunomodulators, Tacrolimus and the related drug Pimecrolimus. These drugs, along with cyclosporine, which exerts its effects through the same mechanism of action, had their origin as immunosuppressive agents used to prevent organ rejection after transplant surgery (41). Although cyclosporine has been used fairly successfully for years as an oral therapeutic for psoriasis, attempts to show that a topical formulation of it is efficacious for this disease have been unsuccessful. Both Pimecrolimus and Tacrolimus have been

approved for topical use in treating atopic dermatitis, but not for psoriasis. However, clinical studies show that systemically delivered Tacrolimus, like cyclosporine, is an effective therapeutic for psoriasis. As is the case with the glucocorticoids, the immunomodulators inhibit the production of inflammatory mediators but unlike the corticosteroids, both Tacrolimus and Pimecrolimus are more cell specific in that they target primarily mast cells and T-lymphocytes. The drugs have fewer inhibitory effects on Langerhans cells/DC, fibroblasts, and keratinocytes (42). Thus, the skin thinning complications seen with topical corticosteroids are eliminated (43,44).

Tacrolimus, Pimecrolimus, and cyclosporine all repress inflammatory genes in target cells through a common mechanism that involves the repression of activity of a ubiquitous calcium-activated phosphatase, calcineurin, that is involved in the activation of specific inflammatory genes (45). When specific receptors on T-cells bind to an antigen, this binding activates the receptor causing an increase in intracellular calcium. The increased calcium causes the activation of calmodulin which then binds to the calcium-dependent enzyme calcineurin and activates it. The activated calcineurin enzyme is a phosphatase, which can dephosphorylate the cytosolic subunit of a transcription factor, nuclear factor of activated T-cells, cytosol (NFATc). The dephosphorylation of the cytosolic NFAT subunit allows it to translocate to the nucleus where it forms a complex with the nuclear subunit of NFAT (NFATn) whose synthesis was induced by the signaling cascade initiated by the antigen binding to the T-cell surface receptor. Once the NFAT dimer has formed in the nucleus, it can bind to the promoter region of several inflammatory genes including those for IL-2, IL-3, IL-4, and TNF-alpha (46,47). A diagrammatic representation of calcineurin activation is shown in Figure 4.

When the drugs Tacrolimus, pimecrolimus, or cyclosporine enter the cell they bind to a cytosol protein, either FKBP for Tacrolimus or Pimecrolimus or Cyclophilin for cyclosporine. Once formed, this complex is able to bind to and inactivate calcineurin.

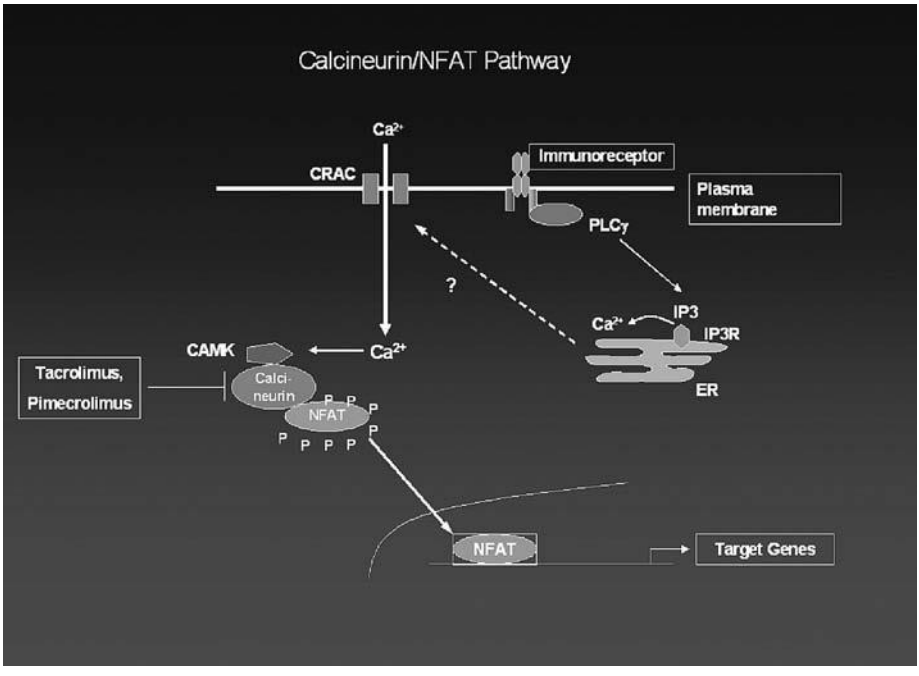

Figure 4 Diagram of calcineurin and NFAT activation.

The now inactive calcineurin can no longer dephosphorylate NFATc, which results in the transcription factor remaining unactivated and in the cytosol. Thus, the NFATn protein in the nucleus has no binding partner and cannot bind to and activate inflammatory genes (46). One of the genes in T-cells that is inhibited by Tacrolimus is the IL-2 gene, which is necessary for full T-cell activation. Thus, in the presence of these immunomodulators, T-lymphocytes do not differentiate in response to antigen stmulation. In addition to their inhibitory effect on inflammatory gene regulation, these immunomodulators inhibit the degranulation of mast cells, a property which may help explain their efficacy in treating some of the symptoms of atopic dermatitis.

While Tacrolimus and other calcineurin inhibitors are much more specific than corticosteroids in terms of the types of cells they act on, they still inhibit a wide variety of inflammatory genes by inactivating calcineurin and blocking NFAT activation. Another class of immunomodulators, called biologic response modifiers (BRM) or simply "biologics" because they are made from living organisms, have been developed over the past five years (48–50). These are essentially "designer" drugs because they target a specific event or mediator involved in inflammation. Anti-inflammatory drugs in this category include the TNF-alpha inhibitors, Enbrel (etanercept), Remicade (infliximab), and Humira (adalimumab) (51–53). Of these Enbrel has received FDA approval for psorasiatic arthritis and more recently for severe psoriasis. Remicade and Humira have been approved for arthritis and approval for psoriasis is pending. Enbrel is a fusion protein containing the extracellular TNF-alpha binding region of the TNF-alpha receptor.It is injected twice a week by the patient at home. Remicade is a humanized monoclonal antibody to TNF-alpha and is injected intravenously. A second and third dose at two weeks and six weeks after initial dosing is recommended for arthritis (54). Humira is another anti-TNF monoclonal antibody designed to bind TNF-alpha, thereby preventing its attachment to and activation of target cells. Humira is injected every other week by the patient at home.

In addition to the TNF-alpha blockers other BRM drugs that suppress immune responses through different mechanisms have been approved for use in treating various forms of inflammation (55). Two of these, Raptiva (Efalizumab) and Amevive (Alefacept) have been approved as injectables for treating arthritis. Amevive, the first FDA approved drug for psoriasis, is a dimeric fusion protein containing the CD-2 binding site of the leukocyte antigen, LFA-3. When injected (once a week) Amevive binds to the CD2 binding site on T-lymphocytes thereby preventing binding between the LFA-3 antigen present on APC and the CD2 binding site on T-lymphocytes. Thus, the lymphocytes are not activated by antigen presentation. Another "humanized," "biologic" therapeutic which is injected weekly is the monoclonal antibody, called Raptiva, which binds to CD11a, which is part of the LFA-1 protein expressed on leukocytes. By occupying this binding site Raptiva prevents the leukocytes from binding an adhesion molecule, ICAM, which is present on endothelial cells. By preventing the adhesion of T-lymphocytes to the blood vessel wall, Raptiva prevents the activation of T-lymphocytes as well as their movement into the skin, thereby reducing the level of T-cell mediated inflammation. CD11a is also expressed on the surface of B-lymphocytes, monocytes, neutrophils, natural killer cells, and other leukocytes. Thus, Raptiva has the potential to down-regulate responses by other immune cells further reducing inflammatory responses (52).

These new protein-based "biologic" immunomodulators, although effective and useful for treating various dermatological conditions, are, however, not without side effects. Because of their potent immunosuppressive effects, particularly on T-lymphocytes, the risk of infection among patients taking these medications is elevated (56–58). Enbrel, for example, has been found, in post-marketing use, to cause serious infections, sepsis, and even fatalities in patients predisposed to infections, and this warning is now included with

the drug information. Further, as is the case with all of protein-based biological response modifier drugs, none are capable of being delivered topically because of their size.

Given the myriad of immune driven events which occur in skin in response to exposure to antigens or other external stimuli, it is easy to see why immunomodulators and biologics are effective in treating inflammatory diseases such as atopic dermatitis and psoriasis. In the case of Tacrolimus and Pimecrolimus, by blocking the calcineurin pathway, these drugs can suppress the activity of the TNF-alpha and IL-2 genes in T-lymphocytes, thus preventing the activation of these lymphocytes as well as preventing their binding to adhesion proteins along the endothelium. Further, recent studies have shown that the calcineruin/NFAT pathway is active in epidermal keratinocytes and inhibited by either cyclosporine or Tacrolimus (47). Since keratinocytes produce a variety of inflammatory mediators such as IL-1 and TNF-alpha which, in turn, exert effects on a number of cells including fibroblasts (up-regulate PGE-2, cytokines), mast cells (degranulation) and endothelial cells (increased expression of adhesion moledule, ICAM, and VCAM, an inhibitory effect on IL-1 and TNF-alpha production would slow the production of inflammatory mediators and suppress the movement of immune cells into the skin. Similarly, the BRMs can be expected to be effective treatments for atopic dermatitis, and psoriasis based on their designed function of either blocking TNF-alpha action or T-lymphocyte activation. However, as mentioned these drugs can only be used by injection and not applied topically.

Other Anti-inflammatory OTC and Prescription Drugs

There are a large number of FDA approved topical drugs that are useful for treating various types of inflammatory dermatological conditions but which are not steroids, NSAIDs, or immunomodulators. One well-known example of this class is the antibacterial/anti-protozoal drug, metronidazole, which is used to treat rosacea, a skin disease that affects 14 million Americans (59,60). Rosacea is sometimes characterized mistakenly as adult-acne because patients present with a reddened face and acne-like symptoms. Individuals with this disease experience redness, pain, and itching on the face, chest, back, and as the disease progresses small blood vessels and small papules appear. Severe rosacea involves the ocular area and causes disfigurement to the nose, termed, rhinophyma. The causes of rosacea are not known, although there appears to be some genetic predisposition for the disease. Metronidazole (sold under the trade name Metrogel®) has been shown to be effective in alleviating some of these symptoms and, although the mechanism of action is unknown, efficacy is not thought to be related solely to its antimicrobial activity. Rosacea is also treated with the oral antibiotic tetracycline, but again, the mechanism of action is not known. Other topical non-steroidal, non-NSAID treatments for rosacea include azaleic acid, sodium sulfacetamide, and Accutane (61). While somewhat effective none of these products resolve all of the redness and other symptoms of rosacea.

Other non-steroidal, non-NSAID topical products used to treat inflammatory conditions such as eczema, psoriasis, and seborrheic dermatitis include coal tar, tazarotene (a retinoid derivative), anthralin, and even the simple OTC keratolyic compound, salicylic acid. However, for most inflammatory conditions the most effective treatments are still the corticosteroids, the immune modulators and recently the "biologics."

ANTI-INFLAMMATORY COSMECEUTICAL "ACTIVES"

The demand for effective non-prescription topical products to treat inflammatory diseases such as eczema, atopic dermatitis, seborrheic dermatitis, and even psoriasis has led to the

introduction of products based on either novel synthetic chemicals or on botanical "actives" which claim to be effective anti-inflammatory compounds. Some of the many purported botanical anti-inflammatory "active" ingredients in cosmeceutical products include bee pollen, curry extract, calendula extract, chamomile, jewelweed, green tea extract, geranium essential oil, aloe, bilberry, tea tree oil, lavender essential oil, boswellia, and willow bark, to mention only a few. Given the abundance of botanicals which claim anti-inflammatory activity, is there any scientific evidence to suggest that any actually have inhibitory effects on the production or action of inflammatory mediators in the skin? The answer is yes for a few botanically derived ingredients. Clearly the botanically derived substance most widely studied for its anti-inflammatory activity is curcumin, the active ingredient in turmeric, the root used in curry dishes. A large number of scientific studies published in peer-reviewed scientific journals over the past 5–10 years have shown remarkable and potent anti-inflammatory activities of curcumin (62). In fact, given curcumin's broad inhibitory effects on the production of inflammatory mediators by a wide number of cell types including immune cells, the compound could be classified as an immune suppressor or at the very least an immune modulator. Curcumin is effective in blocking both AP-1 and NF-kappa B driven inflammatory genes including COX-2, IL-8, IL-1, IL-12, and TNF-alpha (63). An example of the potency of curcumin in blocking IL-1 induced inflammatory gene expression in human fibroblasts is shown in Figure 5. Note that curcumin at concentrations below 10 μM can suppress the IL-1 induced increase in PGE-2 and IL-8. The compound is also very effective in blocking TNF-alpha production in normal human fibroblasts.

Although the mechanism of action of curcumin in suppressing the expression of inflammatory genes is not completely understood, it appears that at least one mechanism involves a block of the intracellular signaling pathway that leads to AP-1 and NF-kappa B activation (64). Recent evidence suggests that this blockade occurs near the start of the signaling pathway, that is, at the activated receptor, e.g., the IL-1 activated receptor (65).

Another plant derived "active" that has been shown through rigorous scientific studies to have anti-inflammatory activity is quercetin, a flavonoid derived from several plants and fruits, including apples. Its efficacy as an antioxidant and anti-inflammatory seems to provide some substantiation for the old expression, "an apple a day keeps the doctor away." Recent studies have shown that quercetin, like curcumin, can block NF-kappa B driven genes and thus prevent the production of a variety of inflammatory mediators (66,67). Other plant derived compounds that have been scientifically shown to

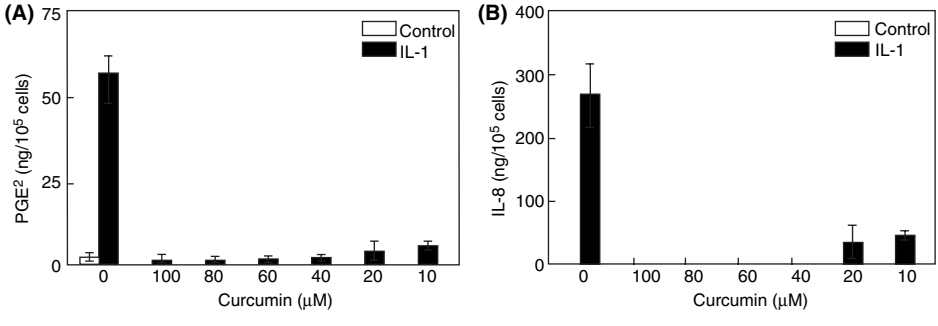

Figure 5 Effect of curcumin on inflammatory mediator production. Cultured dermal fibroblasts were treated with IL-1 and curcumin for 24 hours. Cell culture media was removed and assayed for the production of (**A**) PGE_2 and (**B**) IL-8.

have anti-inflammatory activities, at least in cell culture model systems, include resveratrol, derived from grapes, boswellic acid, derived from Boswellia, the polyphenol Epigallocatechin gallate, derived from green tea, and bisabolol, derived from Chamomile. All of these compounds have been shown to exert some anti-inflammatory effect on cells in culture, either inhibiting the production of PGE-2, cytokines, chemokines, adhesion molecules, or other molecules involved in the inflammatory process.

BIOLOGICAL SCREENING ASSAYS TO IDENTIFY NOVEL ANTI-INFLAMMATORY COMPOUNDS

The search for novel anti-inflammatory compounds that can be successfully formulated into either prescription or cosmetic topical products that show efficacy in treating dermatological conditions requires the availability of appropriate skin cell culture-based assays. Clearly, the cell types needed for such studies must include, at a minimum, normal human keratinocyte and fibroblast cell strains. In addition, because chronic skin inflammatory disease involves the activity of immune cells, cultures of human monocytes and T-lymphocytes should also be incorporated into the screening strategy. Finally, when one considers the important role that adhesion molecules, expressed on the surface of endothelial cells, play in directing leukocytes into the skin, being able to assess the effect of putative anti-inflammatory compounds on adhesion molecule expression in cultured endothelial cells would add an additional important screening capability.

Once the cell culture models have been established, the appropriate screening assays must be selected. These screens should focus on the effect that a potential anti-inflammatory molecule has on the expression of one or more key inflammatory mediators. Due to the fact that one of the most common activators of skin inflammation is sunlight, specifically UVB radiation, the determination of a compound's ability to block the induction of pro-inflammatory PGE-2 by UVR in both keratinocytes and fibroblasts represents a logical first step in the screening process. In addition, because skin inflammation is often triggered by contact with chemical irritants or allergens, the use of tetradecanoylphorbol acetate (TPA), which is a potent "irritant" stimulator of inflammatory mediators in skin, provides an additional model for the analysis of anti-inflammatory activities of test compounds. Finally, because IL-1 is one of the most important mediators and propagators of inflammation and is rapidly induced by an inflammatory stimulus, such as UVR, determining the ability of a potential anti-inflammatory compound to block either the production or action of IL-1 is a critically important initial screening study (68–70).

ELISA-Based Screening

To carry out initial screening experiments, cultured cells are first treated with the potential anti-inflammatory molecule followed by treatment with the inducing agent (ex. IL-1, UVR, TPA), which up-regulates the expression of inflammatory mediators. After a period of time (six to 24 hours), the media is removed and tested for the production of a particular inflammatory mediator using an enzyme-linked immunosorbent assay (ELISA). The ELISA method is based on the recognition of a particular antigen, such as some inflammatory mediator of interest, by a specific antibody, called the capture antibody. While there are many different forms of this assay, one of the simplest variations, the "sandwich assay," is shown in Figure 6. In this assay, the capture antibody is typically bound to a well in a plastic plate. When the media containing the inflammatory mediator of interest is added to the well, the bound capture antibody binds to the antigen. After binding, the well

is then washed and an additional antibody, called the detection antibody, is added to the well. The detection antibody also binds to the antigen, but in addition this antibody contains a "tag" (for example, an enzyme that reacts with a colorless substrate to produce a colored product) which allows for the amount of bound antigen to be quantified. Thus, if the culture media being tested contains a high amount of the antigen being measured, e.g., IL-1, then a high amount of detection antibody will bind, and a pronounced color reaction will occur when substrate is added. If, however, the anti-inflammatory compound blocks the production of the inflammatory mediator, for example, IL-1, then when the culture medium is added to the assay well, there will be little antigen to bind the capture antibody, and consequently very little detection antibody will bind. The result is very little color formation when the substrate is added.

The advantage of ELISA methods is that they are rapid, can accommodate a large number of samples simultaneously, require very little material for assay (a few microliters of culture medium), are very sensitive (pmole range), and are cost-effective. Commercial ELISA-based assays are available for most cytokines and chemokines, and thus, media from cell cultures can be assayed simultaneously for a variety of inflammatory mediators.

Figure 7 shows a flow chart of a screening strategy designed to identify anti-infammatory compounds. As is shown, all putative anti-inflammatory compounds are first screened for the ability to block the IL-1, TPA, or UVR induction of PGE-2, one of the most important inflammatory mediators produced in skin. Although there are exceptions, typically if a candidate anti-inflammatory compound cannot inhibit signaling pathways leading to increased PGE-2 production, it is unlikely to block the production of other inflammatory mediators. Compounds that effectively block PGE-2 production at a concentration of 100 μm or less are then subjected to more demanding dose-response studies and are tested for their ability to block additional inflammatory cytokines and chemokines. For these screening assays, it is important that, where possible, only primary cell strains of human fibroblasts and keratinocytes be used since the use of normal cells increases the probability that results from in vitro studies will be predictive of effects of a given compound when applied topically. Unfortunately, when screening protocols are used for leukocytes, it is difficult to obtain enough normal cells for such studies, and thus, permanent T-lymphocytes and monocyte cell lines are used.

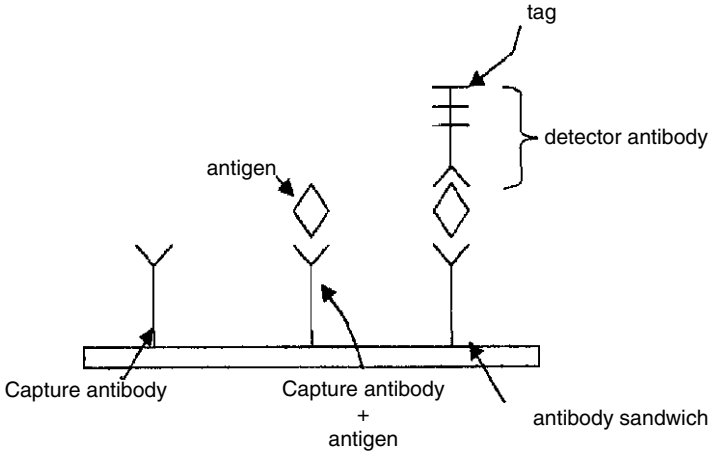

Figure 6 Sequence of steps for enzyme-linked immunosorbent assay.

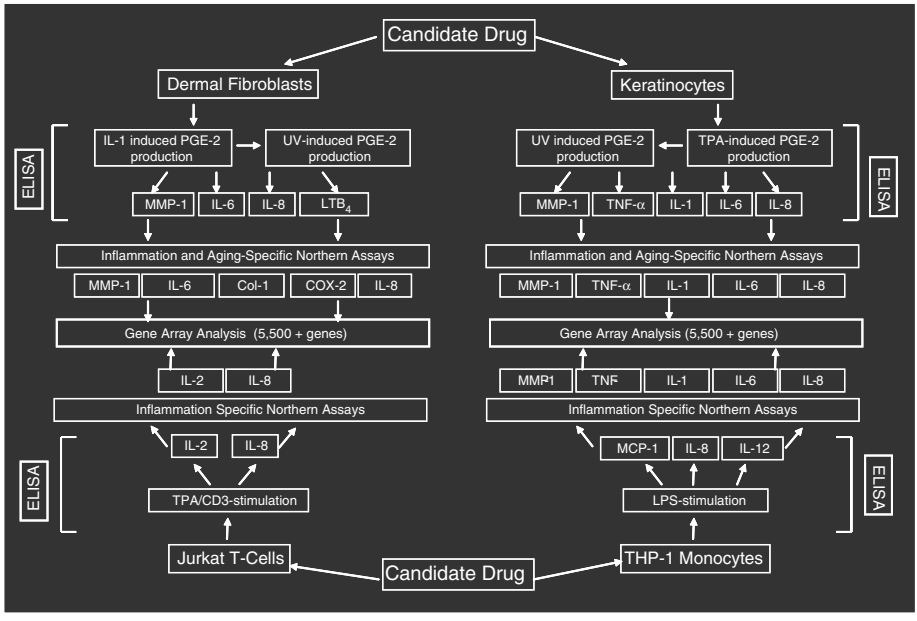

Figure 7 Screening strategy for assessment of anti-inflammatory activity of a candidate drug.

The results of studies with one putative anti-inflammatory compound are shown in Table 1. The compound was found to effectively inhibit the expression of several inflammatory mediators produced in skin cells in response to various stimuli including UVR, TPA, and IL-1. The table lists the concentration of this particular compound that is effective at inhibiting the induction of an inflammatory mediator by 50% (IC_{50}).

Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR)

While ELISAs are an excellent method for obtaining information on the ability of a given compound to inhibit a wide variety of inflammatory mediators, it cannot determine HOW the anti-inflammatory compound is working. For example, if a compound is identified that inhibits PGE-2 production in keratinocytes, is the compound acting as a direct COX-2 inhibitor, as do most NSAIDS, or is it acting at the gene level to inhibit the activation of the COX-2 gene or other genes necessary for PGE-2 production? The method of reverse transcriptase-polymerase chain reaction (RT-PCR) is commonly used to quickly assess the expression levels of a particular gene, and thus can determine if an anti-inflammatory compound has any suppressive (or stimulatory) effect on a particular gene (71). The method uses the enzyme reverse transcriptase to reverse transcribe mRNA isolated from experimental tissue or cultured cells into complementary DNA (cDNA). This cDNA is then denatured and incubated with DNA primers that hybridize (anneal) specifically to the cDNA of interest. Once the primers are attached to the cDNA, a new DNA strand is produced by enzymatic extension of the hybridized primers followed by denaturing the newly formed double-stranded DNA. This process of primer annealing, extension, and strand separation is repeated as much as 40 times and this results in the logarithmic amplification of a specific region of the gene of interest (Fig. 8). The amplified products are then separated by gel electrophoresis, stained with the fluorescent DNA binding dye ethidium bromide, and visualized under UV light. By quantitating the intensity of the

Table 1 Screening Strategy for Assessment of Anti-inflammatory Activity of a Candidate Drug

Human dermal fibroblasts IC_{50} (μM)		
Inflammatory mediator	Stimulus—UVR 50 mJ	Stimulus—IL-1α 100 pg/ml
PGE-2	5	0.01
IL-6	Not tested	50
IL-8	10	50
TNF-α	Not tested	Not Tested
MMP-1	50	10
Human epidermal keratinocytes (% Inhibition-100 μM)		
Inflammatory mediator	Stimulus—UVR 75 mJ	Stimulus—TPA 32 nM
PGE-2	100	100
IL-6	100	100
IL-8	100	100
TNF-α	100	100
MMP-1	100	100

fluorescence of the amplified PCR products, which, in turn, is proportional to the amount of DNA product made, it is possible to determine the relative abundance of a particular mRNA, and thus to determine what effect any compound had on the activity of the inflammatory mediator gene.

Gene Arrays

The use of ELISA, RT-PCR, and Northern and Western blot analyses are very useful in identifying specific inflammatory mediators which are inhibited by anti-inflammatory compounds. However, when one is designing topical formulations for treating an inflammatory skin condition, it is not only necessary to identify the inflammatory mediators that can be inhibited by topical application of a lotion or gel containing a given

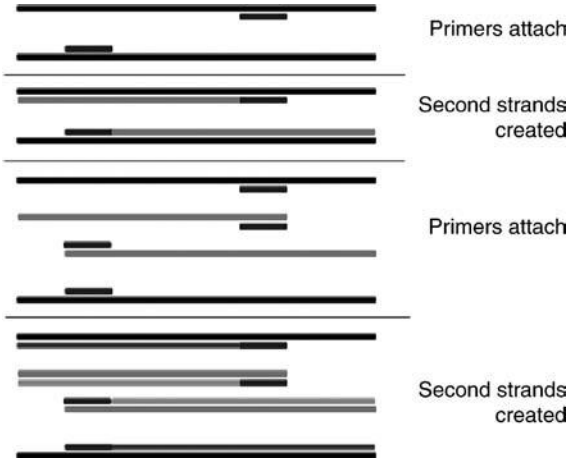

Figure 8 Diagram of the polymerase chain reaction (PCR) showing how gene sequences are amplified.

anti-inflammatory compound, but it is also important to have some knowledge of what beneficial genes and proteins may be *inhibited* by the topical product. For example, although corticosteroids are potent anti-inflammatory agents when used topically, they have negative side effects including the inhibition of collagen production in the skin, the reduction of the immune response to a point where a risk of skin infections increases, and at high doses, inhibition of fibroblast proliferation. Thus, to develop an effective and safe topical anti-inflammatory product that does not damage skin structure and function, it is important to determine what potentially beneficial genes in keratinocytes, fibroblasts, and immune cells, for example, IL-10, collagen III, or tissue inhibitor of metalloproteinase (TIMP), may be suppressed by the anti-inflammatory compound. One of the most effective methods for screening anti-inflammatory compounds for both their positive and negative effects on gene expression is the use of gene array technology (72). With this technique it is possible to assess the expression level of hundreds to thousands of genes simultaneously. Gene arrays are membrane filters or glass slides to which are bound small pieces of known and/or unknown (EST-expressed sequence tags) human genes. A typical nylon gene array filter may contain as few as fifty or as many as 5000 different gene sequences on a single filter, and some arrays have even been designed with specific tissues or diseases in mind, such as inflammation. The sequence of steps involved in a gene array analysis is shown in Figure 9. The first step involves isolating mRNA from untreated cells (control group) and from cells exposed to some experimental condition (experimental group). After hybridization, any unbound cDNA is washed away and the hybridized cDNA is detected and quantified. Since the location and identity of each gene on the filter is known, by comparing the quantified spots on the array produced from the control group to those spots produced from the experimental group, one can determine if a particular gene in the experimental group is up-regulated or down-regulated compared to the control

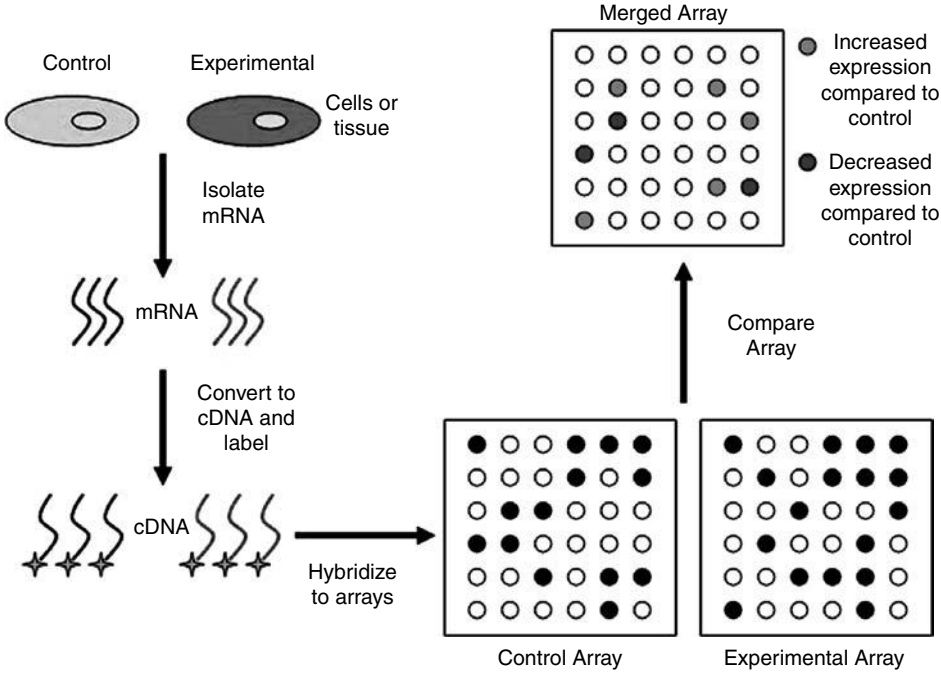

Figure 9 Steps involved in gene array analysis.

group. Given the complexity of gene arrays, a computer software program is used to aid in the quantification and analysis of the large amount of data that is obtained. The software produces an "overlay" image of the filters from both the control and experimental groups, calculates the difference in expression level for each gene between the two groups, and then converts this relative expression data into a color image. For example, a gene that is up-regulated in the experimental group compared to the control group is shown as a green spot on the computer generated image, while a gene that is down-regulated in the experimental group is shown as a red spot. By using this method the effect of any compound on the expression of genes that code for pro- and anti-inflammatory mediators as well as other genes expressed in epidermal and dermal cells can be rapidly determined. An example of the use of this technology is shown in Figure 10. In this experiment human fibroblasts were treated with quercetin and the effect of this compound on the expression of inflammatory and dermal matrix altering genes determined. The cDNA array images from untreated (A) or quercetin (B) treated fibroblasts captured by the phosphoimager were merged and colorized by the computer software to yield the image in panel C. Genes that were down-regulated in quercetin treated fibroblasts relative to those in untreated cells are displayed by the software as either red or yellow while those genes up-regulated by quercetin are displayed as green. In this study, quercetin was found to lower the expression of MCP-1 and collagenase (MMP-1) while up-regulating a gene that blocks MMP activity (TIMP-1). Table 2 shows the results of an array analysis of genes that are up- and down-regulated by quercetin in TPA-treated keratinocytes. Note that quercetin up-regulates genes that are play a role in protecting the dermal matrix and down-regulates matrix destroying genes.

DEVELOPMENT OF EFFECTIVE TOPICAL FORMULATIONS

Although screening assays are critical for identifying new anti-inflammatory compounds, unless these compounds can be formulated into a topical product that delivers the compound across the stratum corneum and down to the target cells in the epidemis and/or dermis, the product will be ineffective. The steps to developing an effective topical product involve: (i) assessing likelihood of skin penetration from molecular weight and log P values, (ii) determining solubility and stability of the anti-inflammatory compound in acceptable formulation solvents, (iii) preparing prototype formulations that are physically stable and which maintain biological activity of the compound, (iv) testing the prototype formulation by Franz cell percutaneous absorption analysis to determine the rate and quantity of compound that can penetrate into human skin, and (v) subjecting the formulation to placebo-controlled clinical studies to determine topical efficacy in a patient population.

The stratum corneum is an effective barrier against entry of foreign objects into the skin, and this includes most proteins, peptides, and even small molecules. Thus, the development of topical products which allow penetration of compounds into the skin is not a trivial undertaking. Typically, unenhanced formulations may "deliver" 0.1% to 1% of a "biologically active" compound across the stratum corneum. Even formulations that are engineered to optimize delivery of a given compound may result in, at best, 10% of the applied dose moving across the stratum corneum and down into the skin. In addition, if the molecule to be delivered into the skin is highly hydrophobic, it will likely pass easily into the stratum corneum but not move into the more aqueous environment of the epidermis (73). Thus, a significant percentage of the active compound in the product will never diffuse through the skin to reach the target cells. To aid in formulation development of a given "active" compound, the use of log P values has become popular to predict efficacy in skin

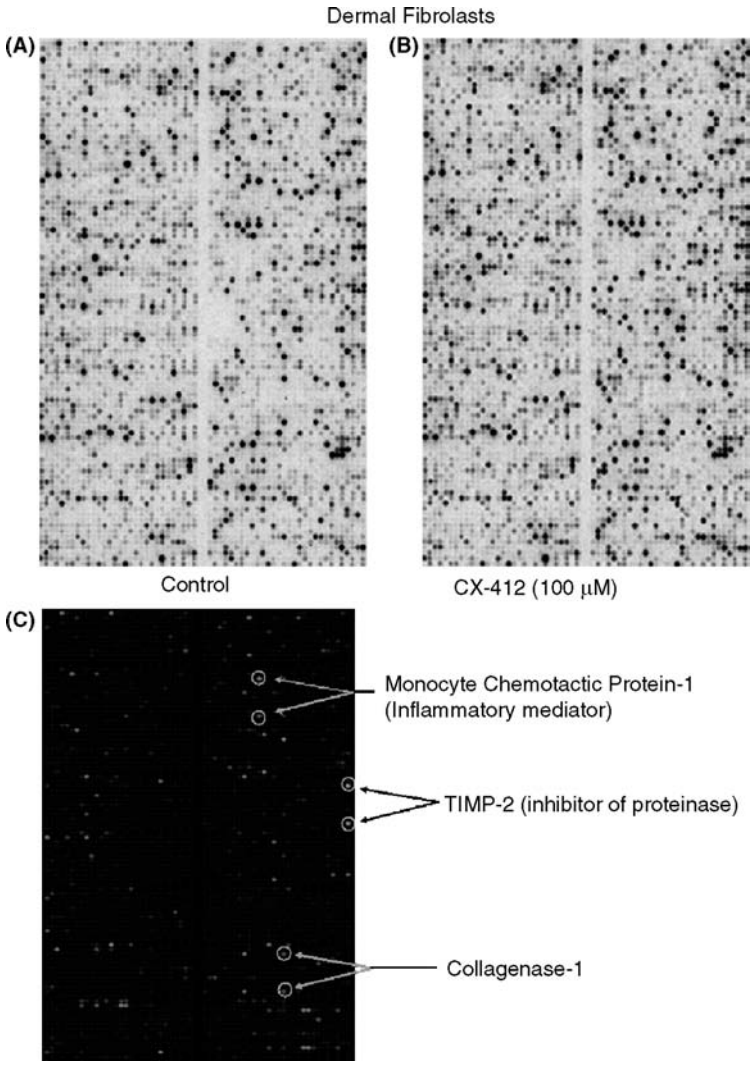

Figure 10 Gene array filters showing hybridization signals (black dots) from (**A**) untreated and (**B**) quercetin treated fibroblasts were "merged" and colorized by software analysis to show genes that are upregulated or downregulated (shown here in gray scale) by this compound. (**C**) In the merged image, arrows point to 2 genes, MCP-1 and MMP-1, that are downregulated in fibroblasts treated with quercetin and one gene, TIMP-1, that is upregulated by this compound.

penetration of a given molecule. Log P measurements show the degree to which a given compound will partition between water and octanol (or other non-miscible solvent). For example, a compound that has a Log P of 1 will prefer an organic solvent to an aqueous one by a factor of 10. A compound with a log P of 0 has an equal affinity for water or an organic solvent. From a topical formulation perspective, compounds that have a logP of around 2.5 will likely have a fairly high probability of skin penetration from a suitable formulation (74). In addition to log P values, the ability of any compound to penetrate the stratum corneum depends on its size. Compounds with molecular weights above 1000 are not going to easily move through the stratum corneum regardless of their log P value. Two other factors that influence skin penetration of any compound from a formulation are the solubility and

Table 2 Effects of Quercetin on Gene Expression in TPA-Treated Human Epidermal Keratinocytes Determined by Integriderm Dermarray™

Upregulated	*Downregulated*
Tissue inhibitor of metalloproteinases-2 (TIMP-2)	Collagenase-1 (MMP-1)
Tissue inhibitor of metalloproteinases-3 (TIMP-3)	Stromelysin-2 (MMP-10)
Serine proteinase inhibitor	MTI-MMP (MMP-14)
Proliferating cell nuclear antigen	ADAM 9
Metallothionein	Urokinase-type plasminogen activator (uPA)
Keratin 6	Plasminogen activator inhibitor I (PAI-1)
Keratin 14	Plasminogen activator inhibitor II (PAI-2)
Keratin 16	Monocyte chemotactic protein-1
	RANTES
	Envoplakin
	Interleukin-8
	Cystatin
	Involucrin
	Small proline rich protein-1

concentration of the compound in the formulation. Those formulations that contain a near-saturated (or even super-saturated) concentration of a compound will deliver more of the compound into the skin. Conversely, the more soluble a compound is in the formulation the less potential it will have for leaving the formulation and entering the skin. To increase the movement of compounds into the skin, a number of penetration enhancers may be used. These are solvents that temporarily disrupt the integrity of the stratum corneum allowing molecules to penetrate this layer of skin. Although over 300 penetration enhancers are known, ony a few are used routinely for topical formulation development. Common enhancers used in cosmetic formulations include simple alcohols, propylene glycol, oleic acid, ethoxydiglycol, polyolprepolymer-2 (and PP-14 and PP-15), some terpenoids, cyclodextrins, urea, and sodium lauryl sulfate to name a few (75,76).

Percutaneous Absorption Analysis

Once a compound's size, log P value, and solubility properties in various acceptable formulation solvents have been determined, the next step in formulation development involves either measuring the penetration through skin of the compound dissolved in a single solvent or its skin penetration from simple formulations. Regardless of which approach is taken, measuring a compound's "flux" through skin requires the use of some type of diffusion cell. The most common apparatus for measuring the penetration of topical formulations through skin is the Franz diffusion cell, shown in Figure 11. The unit consists of an upper chamber into which the test formulation is applied and the lower reservoir chamber which is filled with buffer. A piece of human skin (animal skin or a synthetic membrane is sometimes used) is mounted in between the two chambers and held in place with a clamp. The formulation to be tested is applied to the stratum corneum surface of the mounted skin and at various times, samples of the lower reservoir buffer are removed and assayed for the presence of the anti-inflammatory compound in the

formulation. For compounds that are not made radioactive, the presence of the compound in the lower chamber of the Franz cell is typically determined by high-performance liquid dramatography (HPLC) analysis. In order to obtain results which more accurately reflect the rate of skin penetration that will be obtained in vivo, human skin, either dermatomed or full thickness, should be used. The use of Franz diffusion cell analysis to measure percutaneous absorption of anti-inflammatory compounds from topical formulations provides information needed to optimize the formulation prior to initiating clinical studies. Based on dose-response studies in cell culture systems, it is possible to predict what level of skin penetration a given anti-inflammatory compound likely needs to attain to show efficacy in vivo. Formulations can be modified and re-tested by Franz cell analysis until the predicted "flux rate" of compound into the skin is achieved.

It is useful to keep in mind that, as a general rule, compounds which show efficacy in blocking inflammatory mediators in cell culture systems with IC_{50} values of less than 100 uM (preferably 10 uM) have a reasonable chance of being efficacious when applied topically, assuming the flux rate of the compound from the formulation is optimized. However, topical formulations containing anti-inflammatory compounds that are only effective in cell culture at concentrations higher than 100 uM have a low probability of being good anti-inflammatory products because of the difficulty of delivering enough of the compound into the skin and to the target cells over a long enough period of time to be effective. In our laboratory, compounds with anti-inflammatory IC_{50} values higher than 100 uM are not considered for product development.

Another consideration when developing topical formulations concerns "residence time" of the active ingredient. To effectively treat inflammatory conditions, a topical formulation must not only deliver enough of the active ingredient into the skin to be effective, but should also deliver the active continuously over many hours. Typically a topical product is applied to the affected area twice a day, once in the morning and once in the evening. Thus, the time between applications can be as much as 12 hours. If the topical formulation delivers a high level of the anti-inflammatory compound into the skin for a short period of time, for example one hour, the compound is going to reach the target cells at a high enough concentration to begin to inhibit inflammation, but after an hour the concentration falls as the active continues to traverse the skin and dissipate into the capillary beds. When one considers that only about 1–2 ml of any topical product is

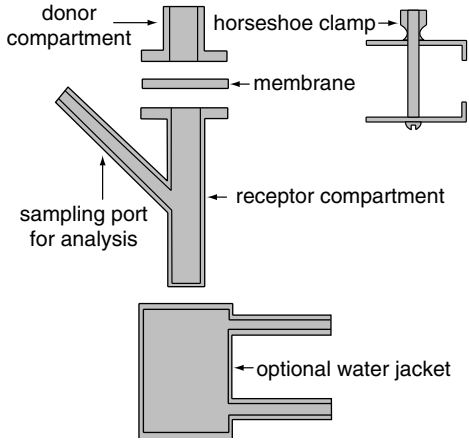

Figure 11 Diagram of Franz diffusion chamber.

applied to 100 cm^2 of skin, developing formulations that deliver enough of the active into the skin continuously over a 12-hour period is not a trivial undertaking. Obviously, if the bioactive compound is effective at nanomolar levels, the product can be designed as an "unenhanced" formulation, which will result in a slower rate of skin penetration and theorectically provide a longer residence time or "depot" of drug needed to affect cell functioning for a 12-hour period. Further, if the water solubility of the active compound is low, it is likely to be retained in the stratum corneum, and only move into the edidermis slowly at a low concentration. If the compound's bioactivity is in the nanomolar range this low rate of movement into the epidermis will be ideal for maintaining a high residence time in the skin.

Assessment of Anti-inflammatory Activity by UVR Clinical Study

Although careful and thorough analysis of the biological activities of a given anti-inflammatory compound using a variety of cell culture models can provide information on which inflammatory conditions a given compound is likely to be effective in treating, and although skin penetration studies will aid in the development of a formulation that theoretically delivers adequate levels of the compound into the skin, of course the only way to know if the topical formulation is truly effective in treating inflammatory conditions is to conduct clinical studies. In this regard, there are several different approaches to designing and implementing a clinical study. The least scientifically credible study design is one in which no placebo is run, where there is no blinding of either the clinical investigator or patients, and where the efficacy of a product formulation is simply determined comparing some parameter (redness, tone, skin roughness, etc.) at the end of the treatment period to baseline readings determined at the beginning of the study. In order to determine the efficacy of a novel anti-inflammatory compound in a formulation, it is necessary to conduct clinical studies under blinded, placebo-controlled conditions, where the efficacy of the formulation containing the anti-inflammatory "active" is statistically compared to the placebo group.

One of the easiest and quickest clinical studies to conduct to assess the potential anti-inflammatory activity of a topical formulation is a UVR erythema study. In this protocol, the patient is exposed to a 3 MED dose of UVB radiation from a light source that irradiates a small area (20 mm diameter) of skin. Multiple areas on the inner arm are irradiated. Immediately after irradiation, one spot is left untreated while a second spot is treated with the topical formulation containing the anti-inflammatory compound. The third irradiated area is treated with a "vehicle" lotion that is identical to the treatment lotion but does not contain the putative anti-inflammatory compound. For these studies it is important that the skin is not pre-treated with the test lotions. The reason for this is that if the putative anti-inflammatory compound in the formulation absorbs UV light, then applying the product before irradiation may result in protection from erythema simply because of the UV absorbing properties of the compound. At hourly intervals after irradiation, surface spectrophotometric measurements and photographs of the treated areas are taken to quantify the level of erythema. Clinical photographs of one patient from a study conducted on a novel anti-inflammatory compound developed in our laboratory are shown in Figure 12. The photograph shows that even 24 hours after irradiation and after a single application of an anti-inflammatory formulation, the area treated with this formulation has markedly less erythema than the area treated with the vehicle formulation (the exact formulation but without the anti-inflammatory compound).

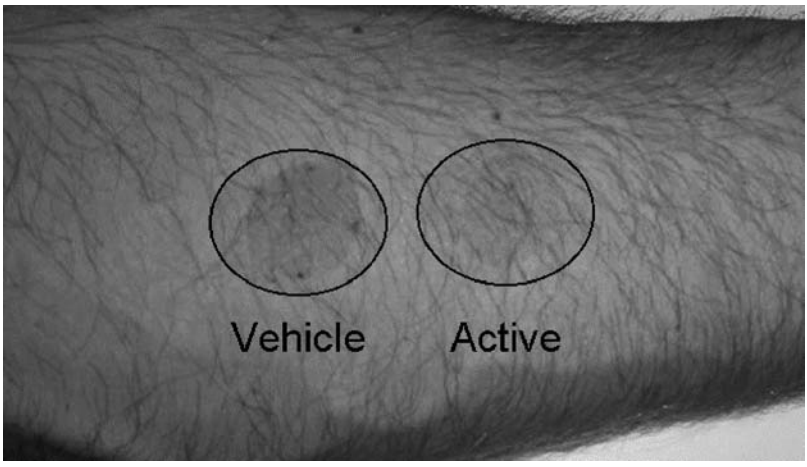

Figure 12 Effect of anti-inflammatory topical formulation on UVB radiation-induced sunburn 24 hours post-irradiation.

CONCLUSIONS

By using multiple cell culture-based inflammatory mediator assays to identify the anti-inflammatory capabilities of a given compound, followed by the development of topical formulations that are analyzed by Franz cell percutaneous absorption analysis to ensure that adequate amounts of the compound are being delivered into the skin, it is possible to develop novel topical anti-inflammatory products that have a very high probability of being effective treatments for a variety of inflammatory skin conditions. There are a number of botanically derived compounds which have been shown to have excellent anti-inflammatory activity, and results of screening assays in our laboratory suggest that perhaps as many as 50 fairly common botanically derived compounds could be developed into topical anti-inflammatory products that would effectively lower the level of many inflammatory cytokines and chemokines in the skin including PGE-2, IL-1, TNF-alpha, MCP-1, IL-12, and IL-8. Further, these compounds can not only block the *production* of cytokines but can also suppress the ability of a target cell to *respond* to a given cytokine or chemokine. When one considers the known deleterious side effects that have been reported for the anti-inflammatory steroids and recently for the newer class of oral or injectable anti-inflammatory immunomodulator drugs, it seems that the development of topical anti-inflammatory products that are less immunosuppressive and which are delivered directly to the affected areas of the skin instead of systemically might represent a safer approach. Such products could be designed to reduce or "reset" cytokine and chemokine levels in affected areas of the skin to a more non-inflamed "ground state." Such a product would reduce the inflammatory response but yet leave the immune system intact to fight infection and to conduct surveillance. From our research it appears very likely that a number of botanically based compounds could be formulated into topical products to meet this goal.

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