Botanicals in Dermatology
An Evidence-Based Review

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Abstract

Botanical extracts and single compounds are increasingly used in cosmetics but also in over-the-counter drugs and food supplements. The focus of the present review is on controlled clinical trials with botanicals in the treatment of acne, inflammatory skin diseases, skin infections, UV-induced skin damage, skin cancer, alopecia, vitiligo, and wounds. Studies with botanical cosmetics and drugs are discussed, as well as studies with botanical food supplements. Experimental research on botanicals was considered to a limited extent when it seemed promising for clinical use in the near future.
In acne therapy, *Mahonia*, tea tree oil, and *Saccharomyces* may have the potential to become standard treatments. *Mahonia, Hypericum, Glycyrrhiza* and some traditional Chinese medicines appear promising for atopic dermatitis. Some plant-derived substances like dithranol and methoxsalen (8-methoxypsoralen) [in combination with UVA] are already accepted as standard treatments in psoriasis; *Mahonia* and *Capsicum* (capsaicin) are the next candidates suggested by present evidence. Oral administration and topical application of antioxidant plant extracts (green and black tea, carotenoids, coffee, and many flavonoids from fruits and vegetables) can protect skin from UV-induced erythema, early aging, and irradiation-induced cancer. Hair loss and vitiligo are also traditional fields of application for botanicals.

According to the number and quality of clinical trials with botanicals, the best evidence exists for the treatment of inflammatory skin diseases, i.e. atopic dermatitis and psoriasis. However, many more controlled clinical studies are needed to determine the efficacy and risks of plant-derived products in dermatology. Safety aspects, especially related to sensitization and photodermatitis, have to be taken into account. Therefore, clinicians should not only be informed of the beneficial effects but also the specific adverse effects of botanicals used for dermatologic disorders and cosmetic purposes.

The term ‘botanicals’ subsumes numerous preparations derived from herbs, spices, roots, stems, and other materials of botanical origin. Botanicals are used for therapeutic or cosmetic purposes in the form of fresh plants, dried, or extracted plant material. Botanical medicine is also referred to as herbal medicine, phytotherapy, or phytomedicine. The use of plant extracts and herbs has its origin in ancient times, with the earliest records originating from ancient China and Egypt. However, the use of botanicals in dermatology is widely based on personal experience and tradition, and relatively sparse scientific data are available with regard to the efficacy of botanical extracts in controlled clinical trials.[1]

An increasing number of patients and consumers are asking for plant-based therapeutic products as complementary dermatologic therapy. Botanical therapies are often considered as therapeutic alternatives, as agents of safer choice than conventional therapy, or sometimes even as the only effective therapeutic way left to treat a certain skin disorder. The cosmetic industry is taking a good profit of this trend by introducing plant extracts from herbs, flowers, fruits, and seed oleates into their products, promising a gentler, more organic approach to beauty. Botanical-based cosmetics are greatly accepted by the consumers because they are said to possess the ability to detoxify, hydrate, strengthen, stimulate, relax, and balance the skin and hair. These products with active compounds are collectively referred to as ‘cosmeceuticals.’[2] Moreover, some specific ingredients of botanicals such as antioxidants, taken orally on a daily basis, may be efficient in preventing the skin from aging by displaying photoprotective effects. These supplements are referred to as ‘nutraceuticals,’ a portmanteau of nutrition and pharmaceutical.

Botanical cosmeceuticals are largely unregulated and therefore often lack pharmaceutical quality and evidence of safety and efficacy. In the US, botanical extracts are often distributed as dietary supplements without regulatory requirements for standardization, safety, and efficacy.[3] In contrast, in Germany a regulatory authority known as Commission E has conducted an extensive review of more than 300 botanicals with established traditional use.[4] The level of scientific evidence, reporting of adverse events, and toxicologic data were evaluated and resulted in positive or negative plant monographs. The Commission E monographs together with the European Scientific Cooperative on Phytotherapy (ESGCP) monographs and the monographs of the American Botanical Council (ABC) are often used as a basis for decision making by regulatory authorities in European countries and in the US.[4]

This article mainly reviews the results of controlled clinical studies on botanicals used in dermatology. Plant-derived single compounds already established in dermatologic therapy, such as dithranol, salicylates, or podophyllotoxin, are also discussed (table I). In the following sections, the botanicals are discussed under the dermatologic indications in which they have been studied or would be primarily indicated according to their mode of action (table II).

The published literature was searched between December 2007 and March 2010 in the PubMed database. Keywords such as ‘botanicals,’ ‘phytomedicine,’ ‘phytotherapy,’ ‘herbal therapy,’

<table>
<thead>
<tr>
<th>Table I. Plant-derived compounds already established in dermatology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compound</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Dithranol (anthralin)</td>
</tr>
<tr>
<td>Methoxsalen (8-methoxypsoralen)</td>
</tr>
<tr>
<td>Podophyllin</td>
</tr>
<tr>
<td>Salicylates</td>
</tr>
<tr>
<td>Tannins</td>
</tr>
<tr>
<td>Mode of action</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Antimicrobial</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Anti-proliferative</td>
</tr>
<tr>
<td>Wound healing</td>
</tr>
<tr>
<td>Photoprotective</td>
</tr>
</tbody>
</table>

and 'herbal medicine' were entered, combined with 'dermatology' and 'skin.' This combination yielded hits for a few specific skin disorders: 'acne,' 'rosacea,' 'atopic dermatitis,' 'psoriasis,' 'chronic venous insufficiency,' 'skin infections,' 'alopecia,' 'vitiligo,' 'wounds,' and 'skin cancer' but also 'UV-protection' and 'sunscreen.' To give examples, 137 hits were found for the combination of 'herbal therapy' and 'atopic dermatitis,' 107 hits for 'herbal therapy' and 'psoriasis,' and 264 hits for 'herbal therapy' and 'skin infections.' Altogether, 1263 articles were found for all searches. Additionally, 'related articles' proposed by PubMed for the selected citations were systematically searched. From these hits all clinical studies were considered, no matter what quality the study was. However, to provide the reader with information on the quality of the studies, each study was classified according to the levels of evidence (LOE) A–D suggested by the UK National Health Service. In brief, LOE-A is assigned to consistent randomized, controlled clinical trials and cohort studies; LOE-B is assigned to consistent retrospective cohorts, exploratory cohorts, outcomes research, case-control studies, or extrapoloations from LOE-A studies; LOE-C is assigned to case series studies or extrapolations from LOE-B studies; and LOE-D is assigned to expert opinions without explicit critical appraisal, or based on physiology, bench research, or first principles. Whenever possible, the LOE was indicated for each study in squared brackets, e.g. [LOE-A].

1. Acne

Traditional phytopharmaceuticals play an adjuvant role in acne therapy in Europe, in addition to or in combination with intensive cosmetic care. A large number of herbs with anti-inflammatory, antihistiodric, and/or antibacterial compounds are used for washing or steambaths. Examples are chamomile (Matricaria recutita), marigold (Calendula officinalis), and wheat bran (Triticum aestivum). After cleaning, creams or aqueous decoctions with astringent compounds like tannins are applied topically. Witch hazel (Hamamelis virginiana) bark extract is most commonly used since it is considered to be very safe in topical administration. Other tannin-containing plants include white oak bark (Quercus alba), English walnut leaf (Juglans regia), agrimony (Agrimonia eupatoria), goldenrod (Solidago virgaurea), jambolan bark (Syzygium cuminum), Labrador tea (Ledum latifolium), lady’s mantle (Alchemilla mollis), lavendar (Lavandula angustifolia), mullein (Verbascum thapsus), rhatany (Krameria triandra), Chinese rhubarb (Rheum palmatum), St John’s wort (Hypericum perforatum), and yellow dock (Rumex crispus) [LOE-D]. Other herbs traditionally used topically or as depurative teas are daisy (Bellis perennis), pansy (Viola tricolor), quitch (Elymus repens), and dandelion (Taraxacum officinale). [LOE-D] Horsetail (Equisetum spp.) tea is recommended because of its high content of silicic acid, and topical application of yellow milk from fresh leaves of aloe (Aloe ferox) for its anthranoids [LOE-D].

Vitex (Vitex agnus-castus) taken orally has been shown to be effective in the treatment of premenstrual acne [LOE-D]. The whole fruit extract increases progesterone levels and decreases estrogen levels by acting upon follicle-stimulating hormone and luteinizing hormone levels in the pituitary gland, and decreases exceedingly high premenstrual prolactin levels via dopaminergic mechanisms. The German Commission E has recommended an intake of 40 mg/day for the treatment of acne. The agent should not be taken by pregnant or nursing women and adverse effects, such as gastrointestinal tract upset and skin rashes, are reported.

Besides the traditionally used antiacne botanicals, several herbs have been investigated for antimicrobial activities to evaluate their potential as herbal therapies for acne. Propionibacterium acnes, an anaerobic pathogen, plays an important role in the pathogenesis of acne and seems to initiate the inflammatory process by triggering the release of reactive oxygen species and proinflammatory cytokines [LOE-D]. Interestingly, the pronounced antibacterial effect of licorice (Glycyrrhiza glabra) against P. acnes in vitro is not associated with induction of bacterial resistance [LOE-D]. A recent screening of plant extracts for antimicrobial activity against bacteria and yeasts with dermatologic relevance revealed a strong inhibitory effect on P. acnes of usnic acid, the major
constituent of beard lichen (*Usnea barbata*). Bacterial growth was inhibited at concentrations from 1 μg/mL upwards. Moreover, *U. barbata* displays antioxidative and broad antimicrobial properties, making it a promising agent for the treatment of acne[^12] [LOE-D]. A 4-week open-label clinical trial compared essential oil from basil (*Ocimum gratissimum*) in four different concentrations (0.5–5%) and in four different bases with placebo and standard therapy (benzoyl peroxide 10%).[^13] *O. gratissimum* essential oil 2% in hydrophilic (alcohol or cetomacrogol) bases reduced lesions faster than standard therapy and was well tolerated, while the 5% concentration was also highly effective but irritating. Although 126 students were included in the patient population, the number of treatment groups was too high for valid statistical proof of efficacy[^13] [LOE-B]. Because of their antimicrobial effects, the German Commission E has also approved topically administered bittersweet nightshade (*Solamum dulcamara*) and systemically administered brewer's yeast (*Saccharomyces cerevisiae*) in the treatment of acne[^8] [LOE-D]. Topical duckweed (*Lemma minor*) is used in China to treat acne[^6] [LOE-D].

Oregon grape root (*Mahonia aquifolium* or *Berberis aquifolium*) is used for chronic skin eruptions or rashes associated with pustules in Western traditional medicine as well as in the Japanese Kampo medicines (Japanese traditional herbal medicines based on combinations of a number of individual medicinal plants). The main constituents of the crude *Mahonia* extract are the two protoberberine alkaloids berberine and jatrohrrizine, which display antimicrobial activity against various strains of coagulase-negative staphylococci, *P. acnes*, and *Candida* spp. *in vitro*[^14] [LOE-D]. It has been recently shown in an animal model that berberine 100 μmol/L suppresses sebaceous gland lipogenesis by 63%[^15] [LOE-D]. The alkaloid berberine is a bitter substance that displays antiapoptogenic and anti-inflammatory effects on 3T3-L1 adipocytes, and the antiapoptogenic effect seems to be due to the downregulation of adipogenic enzymes and transcription factors[^16] [LOE-D]. However, the exact mode of action of berberine and berberine-rich botanicals in acne is unknown.

The volatile oil of tea tree (*Melaleuca alternifolia*), a traditional herbal remedy of the Australian aborigines for bruises and skin infections, might also be beneficial in the treatment of acne. Besides its well known antimicrobial properties, tea tree oil displays anti-inflammatory activities by reducing histamine-induced inflammation of the skin[^17] [LOE-D]. In a 3-month, single-blind clinical trial with 124 patients, both tea tree oil 5% and benzoyl peroxide 5% ameliorated acne, although the onset of action was slower for tea tree oil; however, fewer patients in the tea tree oil group reported skin discomfort[^18] [LOE-B]. While a placebo group was missing in this older report, recently a 45-day randomized, double-blind, placebo-controlled study with 60 patients has proven the efficacy of topical tea tree oil 5% gel in mild to moderate acne vulgaris.[^19] Tea tree oil gel was 3.55-fold more effective than placebo in terms of the total acne lesions count and 5.75-fold more effective in the acne severity index[^19] [LOE-A]. Although the study provided no evidence for differences in adverse effects and tolerability, the sensitizing potential of tea tree oil and oxidised monoterpens should be taken into account when using tea tree oil for the treatment of acne[^20] [LOE-C].

Gluconolactone is formed from a polyhydroxy acid synthesized by *Saccharomyces bulderi*[^21] [LOE-D]. The results of a 150-patient, double-blind clinical study with topical application of gluconolactone 14% solution demonstrated a clearance of inflamed acne lesions that was significantly superior to placebo and comparable to benzoyl peroxide 5% but with fewer adverse effects[^22] [LOE-A].

### 1.1 Summary

Traditional herbal treatment in combination with cosmetic care is a well established basis of acne therapy. Some botanicals, especially Oregon grape root, tea tree oil, *Saccharomyces*, and perhaps basil may have the potential to replace standard chemical therapy in mild to moderate cases because of their good efficacy and higher tolerability. Further valid, controlled clinical studies that also consider optimization of pharmaceutical preparations are needed.

### 2. Inflammatory Skin Diseases

#### 2.1 Atopic Dermatitis

Traditional herbal treatment of atopic dermatitis (AD) has to consider the actual stage of the disease. Acute, oozing eczema is covered (but not occluded) with cold wet packs made from oak bark (*Quercus* spp.), witch hazel (*H. virginiana*), black tea (*Camellia sinensis*), or chamomile (*M. recutita*) decoctions. In subacute stages and intervals, ointments or creams with anti-inflammatory and antipruritic drugs like balloon vine (*Cardiospermum halicacabum*), bittersweet (*S. dulcamara*), witch hazel (*H. virginiana*), or oat straw are recommended. Oils from borage (*Borago officinalis*) or evening primrose (*Oenothera biennis*) are rich in γ-linolenic acid and used for systemic and topical application. Bacterial superinfections are treated topically with chamomile tea or oil from St John's wort (*H. perforatum*)[^23,24] [LOE-D].

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[^12]: Reuter et al.
[^13]: Reuter et al.
[^14]: Reuter et al.
[^15]: Reuter et al.
[^16]: Reuter et al.
[^17]: Reuter et al.
[^18]: Reuter et al.
[^19]: Reuter et al.
[^20]: Reuter et al.
[^21]: Reuter et al.
[^22]: Reuter et al.
[^23]: Reuter et al.
[^24]: Reuter et al.
2.1.1 Topical Application

For most of these traditionally used herbal treatments there is limited evidence from clinical studies (an overview of clinical studies in AD is given in Table III). A randomized, partially double-blind study was carried out as a half-side comparison of a cream containing chamomile (M. recutita) extract from the variety 'Manzana' versus hydrocortisone 0.5% cream and the vehicle cream as placebo in 7 patients with medium-degree AD. After 2 weeks of treatment the chamomile cream displayed only a marginal superiority compared with hydrocortisone 0.5% and was not superior to placebo[25] [LOE-A].

Since bacterial colonization plays a role in the pathogenesis of AD, antimicrobial activity of a medical skin care product for AD would be beneficial. Recently, the antimicrobial property of a distillate of witch hazel (H. virginiana) and urea, formulated as a topical dermatologic preparation that contains both active ingredients, has been investigated in vivo by using the simple occlusion test in 15 healthy volunteers. The test revealed a significant antimicrobial activity of the product[46] [LOE-C]. Thus, formulations containing Hamamelis distillate have mainly anti-inflammatory, hydrating, and barrier-stabilizing effects, which may be beneficial in AD maintenance therapy. However, Hamamelis is not efficient enough to treat severe AD, as shown in a randomized, double-blind, paired trial in patients with moderately severe AD. Seventy-two patients were treated with a Hamamelis distillate cream compared with the corresponding drug-free vehicle and hydrocortisone 0.5% cream over a period of 14 days. The Hamamelis preparation was not superior to the vehicle[47] [LOE-A].

In contrast, both antimicrobial activity and therapeutic efficacy have been demonstrated for St John's wort (H. perforatum) extract[23,47]. A medical skin care product in the form of a cream distributed in European countries was tested in a randomized, double-blind, placebo-controlled, half-side comparison study in 28 patients with AD. The efficacy of the Hypericum cream was significantly superior to its vehicle. The skin tolerance and cosmetic acceptability of the Hypericum cream was excellent[27] [LOE-A]. In addition to antimicrobial activity, one possible mode of action of St John's wort and its major metabolite hyperforin might be inhibition of the antigen-presenting capacity of epidermal Langerhans cells[48] [LOE-D].

Another placebo-controlled study with only seven AD patients was performed with Shiunko, a typical Japanese Kampo drug made from herbal extracts. The clinical effectiveness and the changes in bacterial species and cell numbers on the skin were evaluated in test areas treated with Shiunko, salt water, or petrolatum. Bacterial counts were reduced with Shiunko in four of seven patients (57%) compared with one of seven patients (14%) treated with petrolatum or salt water[28] [LOE-B].

No effect superior to placebo could be demonstrated in the following trials: a randomized, double-blind, placebo-controlled trial with 53 patients with mild to intermediate AD using cream containing sea buckthorn (Hippophae rhamnoides) 20% and 10%[29] [LOE-A]; a randomized, double-blind, placebo-controlled study with 20 AD patients using an ointment containing black seed (Nigella sativa) oil 15%[30] [LOE-A]; and a randomized, double-blind, placebo-controlled, parallel-group trial with 151 AD patients including children investigating the efficacy and tolerability of oral high-dosage treatment with borage oil, which contains a high concentration of γ-linolenic acid[31] [LOE-A].

Besides displaying antimicrobial activity due to berberine and other constituents, Oregon grape root (Mahonia aquifolium) inhibits proinflammatory cytokines. A cream containing Mahonia extract ('psorberine') 10% has recently been evaluated in an open-label trial in 42 adult AD patients treated three times daily over a period of 12 weeks. There was a significant improvement of the Eczema Area and Severity Index score[32] [LOE-B].

An open-label, non-controlled study of 27 children with AD was conducted with an over-the-counter herbal ointment containing 5% of homeopathic mother tinctures of each of the botanicals Oregon grape root (M. aquifolium), pansi (Viola tricolor hortensis), and goth kola (Centella asiatica). Within the 2- to 4-week observation period, the symptoms resolved completely in 22% of the patients, with an additional 60% reporting marked improvement[33] [LOE-B]. In a previously conducted randomized, double-blind, clinically vehicle-controlled, half-side comparison with 88 adult patients with mild to moderate AD, the same ointment was superior to the vehicle after 4 weeks of treatment. However, a subanalysis indicated that the cream might be effective under conditions of cold and dry weather[34] [LOE-A].

Glycyrrhetinic acid, as the most important compound from licorice, has been shown to possess pronounced anti-inflammatory activity in tetracyclonolpborbol acetate-induced mouse ear edema[49] [LOE-D]. A standardized extract of licorice (G. glabra) in the form of a 1% and 2% gel has been investigated in the treatment of AD. In a double-blind, vehicle-controlled phase II trial, 2% licorice gel was more effective than 1% gel and the vehicle in reducing the scores for erythema, edema, and itching after 2 weeks of treatment (90 patients; 30 in each group)[33] [LOE-A].

A new phytotherapeutic cream available in pharmacies for the treatment of AD contains glycyrrhetinic acid 2%, an extract of the leaves of grape vine (Vitis vinifera), allantoin, and telmesteine (3-ethylhydrogen-3,4-thiazolidine-dicarboxylate). In a small
Table III. Overview of clinical studies with botanicals for atopic dermatitis (AD)

<table>
<thead>
<tr>
<th>Botanicals</th>
<th>Patients (n)</th>
<th>Placebo-controlled</th>
<th>Study endpoints</th>
<th>Route of administration</th>
<th>Treatment phase</th>
<th>Results</th>
<th>Reference/LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chamomile (<em>Matricaria recutita</em>)</td>
<td>72</td>
<td>+</td>
<td>Itch, erythema, scaling</td>
<td>Topical</td>
<td>2 wk</td>
<td>Not superior to placebo</td>
<td>[25]/LOE-A</td>
</tr>
<tr>
<td>Witch hazel (<em>Hamamelis virginiana</em>)</td>
<td>72</td>
<td>+</td>
<td>Itch, erythema, scaling</td>
<td>Topical</td>
<td>2 wk</td>
<td>Not superior to placebo</td>
<td>[26]/LOE-A</td>
</tr>
<tr>
<td>St John's wort (<em>Hypericum perforatum</em>)</td>
<td>28</td>
<td>+</td>
<td>SCORAD</td>
<td>Topical</td>
<td>4 wk</td>
<td>AD improved</td>
<td>[27]/LOE-A</td>
</tr>
<tr>
<td>Shiunko (Japanese Kamp medicine)</td>
<td>7</td>
<td>+</td>
<td>Bacterial species</td>
<td>Topical</td>
<td>3 wk</td>
<td>Bacterial isolates ↓</td>
<td>[28]/LOE-B</td>
</tr>
<tr>
<td>Sea buckthorn (<em>Hippophae rhamnoides</em>)</td>
<td>53</td>
<td>+</td>
<td>SCORAD, TEWL, skin hydration</td>
<td>Topical</td>
<td>4 wk</td>
<td>Not superior to placebo</td>
<td>[29]/LOE-A</td>
</tr>
<tr>
<td>Black seed (<em>Nigella sativa</em>) oil</td>
<td>20</td>
<td>+</td>
<td>SCORAD</td>
<td>Topical</td>
<td>4 wk</td>
<td>Not superior to placebo</td>
<td>[30]/LOE-A</td>
</tr>
<tr>
<td>Borage (<em>Borago officinalis</em>) oil</td>
<td>151</td>
<td>+</td>
<td>SASSAD score</td>
<td>Oral 2–4 capsules two times daily</td>
<td>12 wk</td>
<td>Not superior to placebo</td>
<td>[31]/LOE-A</td>
</tr>
<tr>
<td>Oregon grape root (<em>Mahonia aquifolium</em>)</td>
<td>42 adults</td>
<td>–</td>
<td>EASI</td>
<td>Topical</td>
<td>12 wk</td>
<td>AD improved</td>
<td>[32]/LOE-B</td>
</tr>
<tr>
<td>Oregon grape root (<em>M. aquifolium</em>), <em>pansy</em> (<em>Viola tricolor</em>), gotu kola (<em>Centella asiatica</em>)</td>
<td>27 children</td>
<td>–</td>
<td>Itch, erythema</td>
<td>Topical</td>
<td>4 wk</td>
<td>AD improved</td>
<td>[33]/LOE-B</td>
</tr>
<tr>
<td>LC118 (Lactic acid bacteria)</td>
<td>88 adults</td>
<td>+</td>
<td>Itch, erythema</td>
<td>Topical</td>
<td>4 wk</td>
<td>AD improved but not significantly</td>
<td>[34]/LOE-A</td>
</tr>
<tr>
<td>Licorice (<em>Glycyrrhiza glabra</em>)</td>
<td>90</td>
<td>+</td>
<td>Edema, itch, erythema</td>
<td>Topical 1%, 2%</td>
<td>2 wk</td>
<td>AD improved</td>
<td>[35]/LOE-A</td>
</tr>
<tr>
<td>Licorice (<em>G. glabra</em>), <em>Vitis vinifera</em>, allantoin, and telmestine</td>
<td>218 adults</td>
<td>+</td>
<td>EASI, BSA, itch, TEWL, itch, erythema</td>
<td>Topical</td>
<td>50 d</td>
<td>AD improved</td>
<td>[36]/LOE-A</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>+</td>
<td>EASI, itch, TEWL, itch, erythema</td>
<td>Topical</td>
<td>72 h</td>
<td>TEWL ↓, erythema ↓</td>
<td>[37]/LOE-A</td>
</tr>
<tr>
<td></td>
<td>30 adults</td>
<td>+</td>
<td>EASI, itch, TEWL, itch, erythema</td>
<td>Topical</td>
<td>5 wk</td>
<td>AD improved</td>
<td>[38]/LOE-A</td>
</tr>
<tr>
<td></td>
<td>142 children</td>
<td>+</td>
<td>Global assessment, EASI</td>
<td>Topical</td>
<td>3 wk</td>
<td>AD improved</td>
<td>[39]/LOE-A</td>
</tr>
<tr>
<td>Oolong tea</td>
<td>121</td>
<td>–</td>
<td>Itch, clinical signs</td>
<td>Oral three times daily</td>
<td>6 mo</td>
<td>AD improved</td>
<td>[40]/LOE-B</td>
</tr>
<tr>
<td>Diet and Hochu-ekki-to (Japanese Kamp medicine)</td>
<td>95</td>
<td>–</td>
<td>Skin symptoms</td>
<td>Oral granules</td>
<td>6 mo</td>
<td>AD improved</td>
<td>[41]/LOE-C</td>
</tr>
<tr>
<td>Hochu-ekki-to (Japanese Kamp medicine)</td>
<td>10</td>
<td>–</td>
<td>Skin symptoms, eosinophils, IgE</td>
<td>Oral 7.5 g granules daily</td>
<td>3 mo</td>
<td>AD improved, IgE ↓, eosinophils ↓</td>
<td>[42]/LOE-D</td>
</tr>
<tr>
<td>Traditional Chinese herbal medicine</td>
<td>85 children</td>
<td>+</td>
<td>SCORAD, CDLQI</td>
<td>Oral 3 capsules two times daily</td>
<td>12 wk</td>
<td>Quality of life improved, AD not superior to placebo</td>
<td>[43]/LOE-A</td>
</tr>
<tr>
<td></td>
<td>40 adults</td>
<td>+</td>
<td>Erythema, surface damage</td>
<td>Oral decoction daily</td>
<td>5 mo</td>
<td>AD improved</td>
<td>[44]/LOE-A</td>
</tr>
<tr>
<td></td>
<td>49 adults</td>
<td>+</td>
<td>Skin symptoms</td>
<td>Oral decoction daily</td>
<td>2 wk</td>
<td>Not superior to placebo</td>
<td>[45]/LOE-A</td>
</tr>
</tbody>
</table>

BSA = affected body surface area; CDLQI = Children's Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; LOE = level of evidence according to the Centre for Evidence Based Medicine[5]; SASSAD = six area, six sign, atopic dermatitis score; SCORAD = SCORing of Atopic Dermatitis score; TEWL = transepidermal water loss; + indicates yes; – indicates no; ↓ indicates decreased.
randomized, double-blind, vehicle-controlled trial with 20 subjects, this cream was superior to the vehicle in improving the sodium lauryl sulfate-induced irritant contact dermatitis as measured by parameters such as the transepidermal water loss and blood flow (cited in Abramovits et al. 2013) [LOE-A]. A European, randomized, double-blind, vehicle-controlled, 5-week study of 30 adult AD patients with mild to moderate AD revealed that this cream is safe and effective in the treatment of AD [38] [LOE-A]. This study was followed by a randomized, multicenter, vehicle-controlled clinical study over a period of 50 days with 218 adult AD patients in the US, which confirmed the results of the pilot study, demonstrating highly significant superiority over placebo in all test parameters [36] [LOE-A]. The efficacy of the same ointment was assessed in 132 children aged 6 months to 12 years in a randomized, vehicle-controlled study. The ointment was applied three times daily to the affected areas. After 22 days the test preparation was statistically more effective than vehicle cream in all endpoints tested [39] [LOE-A].

2.1.2 Oral Administration

Oolong tea, a variety of black tea (C. sinensis) orally administered (1000 mL divided into three serving sizes per day), seems to be effective in the treatment of recalcitrant AD [40]. In an open-label study conducted over a period of 6 months with 121 patients, 63% of the subjects showed moderate to marked improvement of the skin after 1 month of treatment. Good treatment response was still observed in 54% of the patients after 6 months. The therapeutic efficacy of oolong tea in AD is attributed to the anti-allergic properties of the oolong tea polyphenols [40] [LOE-B].

Japanese Kampo medicines have been investigated for efficacy and safety in 95 patients with recalcitrant AD [41] [LOE-C]. The most commonly used Kampo formula was Hochu-ekki-to containing Astragalus root (Astragalus membranaceus), licorice (G. glabra), jujube (Ziziphus zizyphus), ginseng (Panax ginseng), white Atractylodes rhizome (Atractylodes macrocephala), fresh ginger (Zingiber officinale), and Chinese Angelica root (Angelica sinensis). Since Kampo medicines are individually formulated for each patient it was not possible to choose a defined Hochu-ekki-to formula as treatment for all types of AD in a randomized controlled study. The outcome of the study with 95 AD patients showed a slight (38% of the patients) to moderate (35% of the patients) or marked (20% of the patients) on the suppression of AD. The formula was ineffective in 4% of the patients [41] [LOE-C].

Japanese herbal medicine is thought to be useful as an alternative therapy for intractable AD in association with diet. It has been shown that increased blood eosinophil counts in patients with recalcitrant AD decreased significantly and the serum IgE levels also showed a tendency to decrease after administration of Hochu-ekki-to [42] [LOE-D].

Traditional Chinese herbal medicines (TCHMs) have been used to treat AD for many years and their efficacy has attracted public attention. Several clinical trials have demonstrated the efficacy of TCHMs. Recently, a randomized, double-blind, placebo-controlled trial of 85 children with AD has been conducted with twice-daily dosing of three capsules of either TCHM or placebo for 12 weeks. The daily dose corresponded to 9 g of a herbal formula consisting of Lonicerae flos (jinyinhua) 2 g, Menthae herba (Bohe) 1 g, Moutan cortex (Danpi) 2 g, Atractylodis rhizoma (Cangzhu) 2 g, and Phellodendri cortex (Huangbai) 2 g. The results of this study suggested that the TCHM concoction is efficacious in improving quality of life and reducing topical corticosteroid use in children with moderate to severe AD. However, there was no significant difference in the improvement of symptoms as determined by the SCORing of Atopic Dermatitis (SCORAD) score [43] [LOE-A]. Another double-blind, crossover, placebo-controlled trial investigated a formulation of ten orally administered Chinese medicinal plant extracts (Clematis armandii, Dictamnus dasycarpus, G. glabra, Ledebouriella sesloides, Lophatherum gracile, Rehmannia glutinosa, Paonia lactiflora, Potentilla chinensis, Tribulus terrestris, and Schizonepeta tenuifolia) in 40 adult patients [44]. Patients had to drink 200 mL of a freshly prepared decoction once a day, corresponding to 10 g of this blend or to a placebo blend of plants not expected to be helpful for AD. The extent and severity of erythema and surface damage was significantly reduced with the medicinal plant extract compared with placebo. A subjective improvement in itching and sleep was noted during the treatment phase [44] [LOE-A]. The symptoms were significantly improved and stabilized during the 1-year follow-up [50] [LOE-A].

A randomized, double-blind, placebo-controlled trial with 49 patients could not demonstrate that oral administration of a tri-herbal combination of Siberian ginseng (Eleutherococcus senticosus), yarrow (Achillea millefolium), and white deadnettle (Lamium album) in addition to topical treatments has an advantage over placebo in the treatment of AD [45] [LOE-A].

2.1.3 Summary

Good scientific data are scarce for most traditionally used botanical treatments of AD, but their application seems justified by long-term clinical experience and theoretical considerations based on their active ingredients. However, their efficacy depends on good knowledge of drug quality, adequate
preparation, and correct application. Therefore, it would be desirable for more standardized preparations to be developed and clinically proven. Of the plant species reported here, St John's wort, Oregon grape root, licorice, and some traditional Chinese medicines clearly warrant further study.

2.2 Psoriasis

2.2.1 Plant-Derived Standard Therapies

Standard psoriasis therapy includes topical preparations containing salicylic acid, originally derived from white willow bark (Salix alba) [see table I]. Salicylic acid is ubiquitously found in plants where it functions as a phenolic phytohormone. Salicylic acid-containing preparations have exfoliative effects on hyperkeratotic skin lesions and are, therefore, beneficial to 'prepare' psoriatic skin for an anti-inflammatory treatment.

One of the most important topical psoriasis treatments is dithranol (in Germany: cignolin, in the US: anthralin). Nowadays synthetically manufactured, dithranol was derived in former days from chrysarobin, a constituent of the bark of the araroba tree (Andira araroba) or goa tree found in the rain forests of the Amazon. Dithranol inhibits the release of proinflammatory cytokines and the growth of keratinocytes. Recently, a randomized multicenter study with 106 patients revealed that topical dithranol, although difficult to use in an outpatient setting, is superior to other established topical psoriasis drugs such as the vitamin D3 analog calcipotriene (calcipotriol) in a day-care setting [61] [LOE-A].

The abnormal growth of keratinocytes is also inhibited by psoralen in combination with UVA irradiation (PUVA). The most potent psoralen is methoxsalen (8-methoxypsoralen or 8-MOP, a furocoumarin from Armoracia ruthaeae and Moraceae [63] [LOE-D]. While PUVA was widely used as a systemic therapy in the US and Europe, various studies have recently confirmed the antipsoriatic efficacy of methoxsalen as a bath additive or cream in combination with phototherapy for the topical treatment of psoriasis [63,64] [LOE-A].

Traditional oral treatment of psoriasis with depurative teas has no scientific evidence. The following antipsoriatic drugs are all applied topically.

2.2.2 Topical Application

Oregon grape root (M. aquifolium or B. aquifolium) is not only used for the treatment of acne but also for psoriasis. A monograph on three open-label clinical trials using M. aquifolium cream and a review of earlier clinical data with M. aquifolium for the treatment of plaque psoriasis have indicated that this botanical is a safe and possibly effective treatment for patients with mild to moderate psoriasis [55] [LOE-B]. A recent randomized, double-blind, placebo-controlled study in 200 patients yielded statistical proof for the efficacy and safety of a topical Mahonia 10% cream standardized to berberine 0.1% in the treatment of psoriasis, with improvement in the Psoriasis Area and Severity Index (PASI) as well as in the Quality of Life Index [56] [LOE-A] (table IV).

Avocado oil combined with vitamin B12 in a cream has been shown in a randomized, prospective, clinical trial to be equally beneficial as calcipotriene in the topical treatment of psoriasis without any adverse effects, especially with regard to long-term treatment [57] [LOE-A].

A double-blind, placebo-controlled clinical trial with 197 patients has shown that capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide), the main ingredient in cayenne pepper (Capsicum frutescens), applied as a 0.025% cream four times daily for 6 weeks, significantly decreases symptoms in psoriasis. The psoriasis severity score combined from scaling, thickness, erythema, and pruritus was different between treatment groups from week 4 to week 6 (p = 0.03) [58] [LOE-A]. These observations have already been established in a previous double-blind, placebo-controlled study in 44 patients during a 6-week treatment with topical capsaicin in moderate and severe psoriasis vulgaris; there was no difference in efficacy between 0.01% and 0.025% capsaicin cream but significant superiority of both to placebo [59] [LOE-A]. Transient burning at the site of application was the most frequent adverse effect reported in both trials. However, capsaicin is contraindicated on injured skin and should not be used on the face. Moreover, the duration of application should be limited.

The efficacy of bitter melon (Momordica charantia), another botanical that has been traditionally used for the treatment of psoriasis [60] [LOE-D], has not been proven yet in controlled clinical studies.

Aloe vera (Aloe barbadensis) is utilized as an ingredient in a myriad of health and cosmetic products, principally due to its valuable moisturizing emollient effects. Scientific literature yields conflicting reports on the efficacy of aloe vera in the treatment of psoriasis. A randomized, double-blind, placebo-controlled study with 60 patients treated with aloe vera extract 0.5% in a hydrophilic cream three times daily for up to 4 weeks showed the cream to be more effective than placebo without any adverse effects. Only 2 of 30 patients in the placebo group, but 25 of 30 in the treatment group, were rated as cured after 4 weeks, and the PASI score decreased from 8.9 to 8.2 in the placebo group, and from 9.7 to 2.2 under active treatment [60] [LOE-A]. In contrast, another double-blind, placebo-controlled study with 41 patients with slight to moderate psoriasis showed only a modest effect of a
Table IV. Overview of clinical studies with botanicals for psoriasis

<table>
<thead>
<tr>
<th>Botanicals</th>
<th>Patients (n)</th>
<th>Control</th>
<th>Study endpoints</th>
<th>Route of administration</th>
<th>Treatment phase (wk)</th>
<th>Results</th>
<th>Reference/LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oregon grape root 10% (Mahonia aquifolium)</td>
<td>200</td>
<td>Placebo</td>
<td>PASI, QLI</td>
<td>Topical</td>
<td>12</td>
<td>Superior to placebo</td>
<td>[56]/LOE-A</td>
</tr>
<tr>
<td>Avocado (Persea americana) and vitamin B12</td>
<td>13</td>
<td>Calcipotriene (calcipotriol), half-side</td>
<td>PASI, 20 MHz sonography</td>
<td>Topical</td>
<td>12</td>
<td>Slower, but finally equal efficacy with avocado</td>
<td>[57]/LOE-A</td>
</tr>
<tr>
<td>Capsaicin (from Capsicum frutescens)</td>
<td>197</td>
<td>Placebo</td>
<td>Combined psoriasis index</td>
<td>Topical</td>
<td>6</td>
<td>Superior to placebo (p = 0.03)</td>
<td>[58]/LOE-A</td>
</tr>
<tr>
<td>Aloe vera (Aloe barbadensis)</td>
<td>44</td>
<td>Placebo, half-side</td>
<td>Scaling, erythema, overall improvement</td>
<td>Topical</td>
<td>6</td>
<td>Superior to placebo</td>
<td>[59]/LOE-A</td>
</tr>
<tr>
<td>Kukui nut oil (Aleurites moluccana)</td>
<td>60</td>
<td>Placebo, half-side</td>
<td>Score from erythema, infiltration, desquamation</td>
<td>Topical</td>
<td>4</td>
<td>Not superior to placebo</td>
<td>[61]/LOE-A</td>
</tr>
<tr>
<td>New Pulian ointment (Radix Scutellariae, Cortex Phellodendri)</td>
<td>30</td>
<td>Mineral oil placebo</td>
<td>PASI, GSPS, plus development of one defined lesion</td>
<td>Topical</td>
<td>12</td>
<td>Not superior to placebo</td>
<td>[62]/LOE-A</td>
</tr>
<tr>
<td>Indigo naturalis 20% (Baphicacanthus cusia)</td>
<td>108</td>
<td>Vehicle</td>
<td>PASI</td>
<td>Topical</td>
<td>4</td>
<td>Superior to vehicle</td>
<td>[63]/LOE-A</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>Vehicle</td>
<td>Score from erythema, infiltration, desquamation</td>
<td>Topical</td>
<td>8</td>
<td>Superior to vehicle</td>
<td>[64]/LOE-B</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>Vehicle</td>
<td>Score from erythema, infiltration, desquamation</td>
<td>Topical</td>
<td>12</td>
<td>Superior to vehicle</td>
<td>[65]/LOE-A</td>
</tr>
</tbody>
</table>

GSPS = Global Severity of Psoriasis Scale; LOE = level of evidence according to the Centre for Evidence Based Medicine[6]; PASI = Psoriasis Area and Severity Index; QLI = Quality of Life Index.

Commercial, aloin-free aloe vera gel that was not superior to placebo. However, the high response rate of the placebo gel indicated a possible effect of the placebo in its own right, which could have made the aloe vera gel appear less effective[61] [LOE-A]. The difference may also be due to the presence or absence of aloe, belonging to the anthranoids, which are known to have beneficial effects on psoriasis.

A double-blind, placebo-controlled, pilot study with 30 patients was conducted to determine the effectiveness of the oil of the kukui nut tree (Aleurites moluccana) as a topical treatment for psoriasis. No significant beneficial effect of the oil could be demonstrated [LOE-A], although anecdotal reports existed from psoriasis patients visiting Hawaii who seemed to benefit from topical kukui nut oil[62].

In the treatment of psoriasis, TCHMs are commonly used. Randomized controlled clinical trials to assess the efficacy of Chinese herbs are difficult to undertake because TCHMs, similar to Japanese Kampo medicines, consist of a mixture of herbs individually formulated for oral intake by the patient. The specific combination utilized is often changed over time according to the clinical status of the patient. Therefore, scientific literature yields little with regard to controlled clinical trials to substantiate the effects of those herbal mixtures. However, a great number of uncontrolled studies have been performed with TCHMs in psoriasis. In these trials, a total of 174 Chinese herbs have been used. The ten most commonly used herbs are Rhenania glutinosa, A. sinensis, Salvia miltiorrhiza, D. dasyacarpus, Smilax glabra, Oldenlandia diffusa, Lithospermum erythrorhizon, P. lactiflora, Carthamus tinctorius, and Glycyrrhiza uralensis. Most of the key actions of these botanicals that are relevant to reducing psoriatic symptoms reflect anti-inflammatory activities, modulation of cytokine production, or inhibition of angiogenesis[67] [LOE-D]. More experimental studies are needed to elucidate the exact mode of action of the specific herbs.
One recent TCHM study investigated the effect of a new Pu- lian ointment (NPLO), consisting of two primary herbs, Radix Scutellariae (Huang Qin) and Cortex Phellodendri (Huang Bai). NPLO was applied twice daily in 108 psoriasis patients in addition to individual TCHM oral formulations. The effect of NPLO was assessed in a randomized, single-blind, vehicle-controlled study. After 4 weeks the NPLO was significantly superior (45% clearing) to the vehicle (12% clearing)[63] [LOE-A].

Indigo naturalis (Qing Dai) is a blue powder that is extracted from the stems and leaves of the plant Baphicacanthus cusia. In a prospective, non-randomized, half-side comparison study, indigo naturalis 20% ointment was compared with vehicle in 14 patients with chronic plaque psoriasis. After 8 weeks, marked improvement was seen in 80% of the plaques treated with indigo naturalis, whereas no improvement was seen with the vehicle[64] [LOE-B]. In a subsequent randomized, vehicle-controlled, observer-blind, intra-patient comparison study with 42 patients, these findings were confirmed (about 74% clearing of the indigo-ointment treated lesions)[65] [LOE-A].

India madder root (Rubia cordifolia) is a Chinese herb with antiproliferative properties. There is evidence that induction of apoptosis of keratinocytes is the underlying mechanism for the observed antiproliferative action of Radix Rubiae. Experimental results suggest that this drug is a promising source from which a herb-based topical agent could be developed for the treatment of psoriasis[68] [LOE-D].

2.2.3 Summary

There are some promising herbal treatments for psoriasis, which is a difficult-to-treat and chronic disease requiring a number of well tolerated alternatives for individual therapy. In addition to the well-established plant-derived molecules, Oregon grape root and capsicain are interesting candidates, and it is definitely reasonable to conduct more controlled clinical trials to substantiate the positive effects of TCHM in the treatment of psoriasis. However, psoriasis will require combination rather than monotherapy, and tolerability and cosmetic effects of botanical formulations are nearly as important as their therapeutic potency.

3. Infectious Skin Diseases

3.1 Bacterial Infections

Numerous botanical compounds exhibit antimicrobial activities against microbes with dermatologic relevance in vitro. However, the clinical evidence for their efficacy is poor and, therefore, antiseptic, antimycotic or antibacterial treatment using synthetic compounds is still the treatment of choice. Plant-derived antimicrobial therapeutics are used in an adjuvant manner or in mild cases of bacterial infections. For example, tea tree oil (M. alternifolia) is not only effective in the topical therapy of acne as mentioned in section 1. It functions as a topical antiseptic with an efficacy superior to that of phenol and displays broad-spectrum antimicrobial activity in vitro against Gram-negative bacteria such as Escherichia coli, Gram-positive bacteria such as Staphylococcus aureus, and also against the yeast Candida albicans[69] [LOE-D]. Disruption of plasma membrane barriers for ions and small molecules is discussed as a mode of action, monoterpenes being the active compounds.

Hyperforin, a major compound from St John's wort (H. perforatum), is highly effective against a panel of Gram-positive bacteria, including multi-resistant S. aureus strains[70] [LOE-D].

Coriander oil (Coriandrum sativum) is another topical plant-derived agent with distinct antibacterial efficacy and good skin tolerance[71] [LOE-D]. It is highly effective against E. coli and other bacteria and fungi in vitro[72-74] [LOE-D]. Some isolated compounds (long chain alcohols and aldehydes) may be very effective, but their combined effects in the crude oils are difficult to predict. Dodecenal from coriander had a minimum bactericidal concentration of 6.25 µg/mL against Salmonella choleraesuis[75]. The strength and spectrum of coriander oil fractions often exceeded those determined in the crude oil, but mixing of single fractions could result in additive, synergistic, or antagonistic effects.

Recently, a topical lipolotion containing coriander oil 0.5% has also been shown to inhibit UVB-induced erythema in humans to a significantly greater extent than placebo, but less than hydrocortisone 1%[76] [LOE-A], making it an interesting treatment for inflammatory skin diseases with bacterial colonization.

Various plant extracts and isolated compounds have been screened for antimicrobial effects on bacteria and yeasts with dermatologic relevance. Olibanum (Boswellia serrata), beard lichen (U. barbata), rosemary (Rosmarinus officinalis), sage (Salvia officinalis), and others inhibit the growth of several Gram-positive bacteria such as S. aureus (including methicillin-resistant strains), P. acnes, and Corynebacterium spp.[12] [LOE-D]. Japanese Kampo formulations also possess antibacterial properties directed towards P. acnes, Staphylococcus epidermidis, and S. aureus[77] [LOE-D].

3.2 Fungal Infections

Numerous botanicals, especially essential oils, exhibit antifungal activities in vitro. The essential oil of snow gum (Eucalyptus pauciflora) has been shown to possess strong antifungal properties against a broad spectrum of human pathogenic
fungi including *Epidermophyton, Microsporum,* and *Trichophyton* species. Within a non-vehicle-controlled clinical study, the *Eucalyptus pauceflora* essential oil formulated into an ointment was applied topically twice a day for 3 weeks to 50 patients with tinea pedis, tinea corporis, or tinea cruris.\(^{[77]}\) After the second week of treatment, all patients were negative for fungal infection as was confirmed by microscopic evaluation of the scraping from the infected area after staining with 10% potassium hydroxide (KOH). After 3 weeks of treatment, 60% of the patients recovered completely as proven by microscopic evaluation and clinical signs such as erythema, scaling, itching, maceration, vesication, and pustulation, and the remaining 40% showed significant improvement of the clinical signs of tinea without any adverse effects. No KOH-negative cases had relapsed at re-examination of the patients 2 months after the end of the treatment\(^{[77]}\) [LOE-B].

Another traditional antifungal plant is garlic (*Allium sativum*). Garlic contains the biologically active ingredient ajene, a trisulfur compound that has been demonstrated to possess antifungal properties. In an uncontrolled clinical study of 34 patients with tinea pedis, the use of an ajene 0.4% cream resulted in a complete clinical and mycologic cure in 79% of the patients after 7 days of treatment.\(^{[78]}\) The remaining 21% of patients achieved complete healing after an additional 7 days of treatment. All patients were evaluated for recurrence of mycotic infections 90 days after the end of treatment, yielding negative mycologic cultures\(^{[78]}\) [LOE-B].

### 3.3 Viral Infections

Numerous botanicals exhibit antiviral properties *in vitro*. Only a few have been studied *in vivo* so far. Lemon balm (*Melissa officinalis*) extract formulated into a cream was investigated in a randomized, double-blind, placebo-controlled trial in 66 patients with recurrent herpes simplex labialis.\(^{[79]}\) The cream was used four times daily over a period of 5 days on the affected area. Lemon balm treatment resulted in significantly faster healing time, prevented the infection spreading, and relieved blistering and pain better than placebo\(^{[79]}\) [LOE-A]. A well established dermatologic therapy of condylomata acuminata, which are caused by human papilloma viruses, is podophyllotoxin, extracted from the root of American mayapple (*Podophyllum peltatum*). Recently, in a randomized, double-blind study, 97 patients with recurrent condylomata acuminata were treated with a podophyllotoxin solid lipid nanoparticle gel and a standard podophyllotoxin gel.\(^{[80]}\) The condyloma clearance rate in patients receiving podophyllotoxin solid lipid nanoparticle gel was 97.1%, similar to that with the routine preparation (90.6%), but the nanoparticle preparation significantly reduced the recurrence rate and adverse effects. It was concluded that podophyllotoxin delivered via a solid lipid nanoparticle gel can effectively clear condylomata acuminata and reduce the recurrence rate with only mild, tolerable adverse effects\(^{[80]}\) [LOE-A]. Recently, an ointment containing a standardized green tea extract with a high content of epigallocatechin gallate (Polyphenon E™; Mitsui Norin Co. Ltd, Tokyo, Japan) has been shown to be effective in the treatment of condylomata acuminata. To date three randomized, vehicle-controlled, multicenter clinical studies with 1508 patients have been published. In these studies, patients with external genital or perianal warts were treated with Polyphenon E™ 10% or 15% ointment compared with the vehicle over a period of 16 weeks or until complete clearance. The clearance rates with both Polyphenon E™ concentrations were >50% compared with about 30% with the vehicle. The adverse effects and recurrence rates were low with all treatments.\(^{[81,82]}\) [LOE-A].

An extract of arborvitaes (*Thuja occidentalis*) in the form of a tincture has traditionally been used as a topical treatment of common verruca vulgaris. Similarly, the application of fresh juice from greater celandine (*Chelidonium majus*) is said to be beneficial in the treatment of warts\(^{[52]}\) [LOE-D]. Traditional systemic botanical treatment of warts includes immunostimulating plant extracts from purple coneflowers (*Echinacea purpurea*) or Siberian ginseng (*Eleutherococcus senticosus*) administered orally over a period of 8 weeks\(^{[52]}\) [LOE-D]. However, the efficacy of these traditional therapies has not been proven in controlled clinical trials so far.

### 3.4 Summary

There are effective botanicals for the topical treatment of bacterial, fungal, and viral infections of the skin. They can be used as adjuvants to other therapeutic measures, or alone in mild to moderate cases. Especially when essential oils are used, possible contact sensitizations should be kept in mind. An important aspect is that garlic or aromatic herbs may be available when modern medicine is not, and this does not only apply to the Third World but also to catastrophes in industrial nations, which we are experiencing again and again. Some of these treatments are old household remedies that should not be forgotten.

### 4. UV-Induced Skin Damage and Non-Melanoma Skin Cancer

Photoaging and the development of skin cancer are of increasing importance since changes in lifestyle have led to a
significant increase in the individual cumulative UV doses. This trend is likely to continue in the future. Therefore, the adverse effects of UV irradiation on the skin have become a major human health concern. New prevention strategies have to be developed to reduce UV exposure and delay photoaging processes, aiming at reducing the incidence of skin cancer. Within this context, topically as well as orally administered botanicals are of interest. Basically, all botanicals that have been shown to possess antioxidant properties can be considered to be beneficial in the prevention of photocarcinogenesis.\[83\] It is suggested that routine consumption of those botanicals may provide protection against many harmful effects of UV irradiation. In combination with sunscreens or skin care lotions they may provide an effective strategy for reducing UV-induced skin diseases.\[83\]

UV-induced skin damage can be classified into three clinical stages. The acute stage of skin damage is sunburn, characterized by clinical signs of inflammation such as erythema, pain, and swelling, and histologically by sunburn cells. In chronically UV-exposed skin the elastic and collagenous fibers are rarified and precancerous skin conditions such as actinic keratoses are present. Finally, in long-term, UV-exposed skin, non-melanoma skin cancer such as squamous cell carcinoma and basal cell carcinoma may eventually develop. The mechanisms, prevention, and therapy have been reviewed extensively by Yaar and Gilchrest.\[84\] Various botanicals have been reported to help prevent photocarcinogenesis by displaying anticarcinogenic and antiinflammatory activities because of their antioxidative and anti-inflammatory properties.\[83\]

4.1 Protection from Acute Erythema

The extract of the tropical cabbage palm fern (CPF) \[Phlebodium aureum or Polypodium leucotomos\] is a plant-derived product that has been studied \textit{in vitro} as well as \textit{in vivo}. A clinical study in 21 healthy subjects exposed to UV irradiation before and after administration of CPF demonstrated that CPF, orally administered as well as topically used, displays significant photoprotective properties by preventing sunburn and psoralen-induced phototoxic reactions, and immunohistochemically revealed photoprotection of epidermal Langerhans cells\[86\] [LOE-B]. In a recent small study with ten subjects, it was shown that CPF is an effective protector against PUVA-induced skin phototoxicity and protects the skin from damaging effects of PUVA as evidenced by histology.\[87\] [LOE-C]. Another trial with nine volunteers assessed erythema reactions after UV irradiation without CPF and after oral administration of CPF. The clinical and histologic results revealed that the oral CPF extract decreased UV-induced skin damage\[88\] [LOE-C]. One possible molecular mechanism for this protection seems to be the inhibition of UV-induced photoisomerization of transurocanic acid, a common photoreceptor located in the stratum corneum. The CPF extract also blocks its photodecomposition in the presence of oxidizing reagents such as hydrogen peroxide and titanium dioxide. Additionally, it was shown that CPF protects human fibroblasts from UV-induced death \textit{in vitro}\[89\] [LOE-D].

Topical application of anti-inflammatory plant extracts immediately after irradiation can reduce symptoms of sunburn. In 40 human volunteers, an ointment containing 2% extract of sage (\textit{S. officinalis}) rich in phenolic diterpenes inhibited UV-induced erythema \textit{in vivo} to a similar extent as did hydrocortisone 1%\[90\] [LOE-A]. Anti-inflammatory efficacy in a UVB erythema test could also be demonstrated for a topical preparation containing 10% of a distillate from witch hazel (\textit{H. virginiana})\[91\] [LOE-A].

Dietary supplements that provide moderate protection against UV-induced erythema are carotenoids such as β-carotene or lycopene. In a placebo-controlled, parallel-group study design, 36 volunteers received β-carotene, a carotenoid mix, or placebo for 12 weeks.\[92\] Carotenoid levels in serum and skin of the palm, as well as erythema intensity before and 24 hours after irradiation with a solar light simulator were measured at baseline and after 6 and 12 weeks of treatment. The results showed that long-term supplementation for 12 weeks with a carotenoid mix ameliorated UV-induced erythema in humans. The effect was comparable to a daily supplementation with 24 mg of β-carotene alone.\[92\] [LOE-A]. Within a study of 36 healthy volunteers, the photoprotective effect of synthetic lycopene in comparison with a tomato extract and a drink containing the tomato extract in a solubilized form was evaluated.\[93\] With these different carotenoid sources, the volunteers ingested similar amounts of lycopene (about 10 mg/day). After 12 weeks of supplementation, significant increases in lycopene serum levels and total skin carotenoids were observed in all groups. The induced erythema at weeks 0, 4, and 12 was most decreased at week 12, with a protective effect most pronounced in the group consuming the solubilized tomato extract (48% after 12 weeks)\[93\] [LOE-B].

4.2 Effects of Long-Term Oral Administration on Skin Aging and Cancer Prevention

Green tea extract (manufactured from \textit{C. sinensis}) with a high content of oligomeric proanthocyanidins is another UV damage-preventing agent. It mainly contains catechin and epicatechin
derivatives, with epigallocatechin gallate being the most important compound. It is able to scavenge free radicals and acts as a potent antioxidant. The anticarcinogenic properties of green tea have been thoroughly investigated in vitro as well as in vivo. Recently, a review of numerous studies with green tea has concluded that both oral consumption and topical application of green tea protects against inflammation and chemical- and UV-induced carcinogenesis[94] [LOE-A]. Various cytokines involved in the inflammation process in the beginning of skin tumor development are inhibited by green tea extract. Moreover, biochemical markers of chemical carcinogenesis as well as UV-induced oxidative stress are counteracted by green tea extract. In addition, UV-induced immunosuppression is prevented by green tea[94] [LOE-D]. Also, it has been shown that green tea protects against PUVA-induced photochemical damage to the skin[93] [LOE-D]. The in vitro photoprotective effects of tea polyphenols and caffeine as a component of tea have recently been evaluated within some reviews[96-98] [LOE-D]. However, tea polyphenols have yet to be evaluated in clinical intervention trials in humans.

Black tea (fermented C. sinensis) may also play a role in UV protection and chemoprevention due to theaflavins[99] [LOE-D]. It has been shown that theaflavins are equally effective antioxidants as are catechins in green tea[100] [LOE-D].

The extract of the fruits of the coffee plant (Coffea arabica) has been shown to exhibit antioxidant activity mediated by potent antioxidant polyphenols, especially chlorogenic acid, condensed proanthocyanidins, quinic acid, and ferulic acid[101] [LOE-D]. Because of these antioxidants, the extract might be valuable for photoprotection and chemoprevention. In a clinical study, 30 patients with actinic damage of the skin used a skin care system containing this extract.[102] Twenty patients had full face application of the test product, and ten patients had half-side application with the other side covered with a placebo cream. Compared with placebo, the test cream was significantly superior in improving fine lines, wrinkles, pigmentation, and overall appearance[102] [LOE-A]. In a double-blind, non-controlled study, 24 women consumed either a high flavonol or low flavonol cocoa powder with epicatechin and catechin as major flavonol monomers, dissolved in water for 12 weeks.[103] UV-induced erythema was significantly decreased in the high flavonol group by 15% and 25% after 6 and 12 weeks of treatment, respectively, whereas no changes occurred in the low flavonol group. The ingestion of high flavonol cocoa led to an increase in blood flow of cutaneous and subcutaneous tissues and to an increase in skin density and skin hydration[103] [LOE-B].

Silymarin, a flavonoid complex isolated from the seeds of milk thistle (Silybum marianum), has been demonstrated to possess anti-inflammatory, antioxidative, and anticarcinogenic properties in vivo in animal models. Experimental data suggest that silymarin may be a promising chemopreventive and pharmacologically safe agent that can be exploited or tested against skin cancer in humans. Moreover, silymarin may favorably supplement sunscreen protection and provide additional antiphotocarcinogenic protection[104] [LOE-D].

Some other interesting dietary botanicals mainly containing antioxidant polyphenols appear as promising UV protection agents. Apigenin, a non-toxic botanical-derived flavonoid occurring in numerous herbs, fruits, and vegetables, curcumin obtained from the tumeric rhizome (Curcuma longa), proanthocyanidins from the seeds of grapes (V. vinifera), and resveratrol, a polyphenol found in numerous plant species including grapes, peanuts, fruits, red wine, and mulberries, have also been shown to possess the ability to protect the skin from harmful UV-induced effects by displaying antimutagenic, antioxidant, free radical scavenging, anti-inflammatory, and anticarcinogenic properties.[83] Other candidates are rosemary (R. officinalis) extract,[105] propolis,[106] a resinous material produced by honeybees from the bud and bark of certain plants and trees; red ginseng,[107] genistein, an isoflavone from soybeans,[108] and pomegranate (Punica granatum)[109] [all LOE-D]. It has also been shown that the pomegranate extract protects human immortalized HaCaT keratinocytes against UVB-induced oxidative stress and markers of photoaging, and might therefore be a useful supplement in skin care products[110] [LOE-D].

4.3 Therapeutic Treatment of Actinic Keratoses

Triterpenes extracted from the outer bark of birches contain more than 80% (volume in volume) betulin. This triterpene extract displays antiproliferative and pro-apoptotic effects in human squamous cell carcinoma cells in vitro.[111] In a prospective non-randomized study it has been shown that an ointment prepared from betulin is an effective treatment (79% responders) of actinic keratoses that represent in situ squamous cell carcinomas[112] [LOE-B]. These results were confirmed in a prospective, randomized study that compared the effect of betulin oleogel with cryosurgery and the combination of both in 45 patients with mild to moderate actinic keratoses[113] [LOE-B]. However, the high response rate of about 80% of the lesions needs to be confirmed in prospective, randomized, placebo-controlled studies with histologic examination.

An extract from the spurge Euphorbia peplus contains the diterpene ester ingenol mebutate that induces necrosis in tumor cells. Two randomized, double-blind, vehicle-controlled, phase II
studies investigated the efficacy and safety of topical ingenol mebutate in actinic keratoses. In both studies, ingenol mebutate gel was highly effective and superior to vehicle, with only two or three applications\cite{114,115} [LOE-A].

4.4 Summary

Many botanicals containing antioxidant flavonoids or other polyphenols can contribute to skin protection from UV irradiation and prevent sunburn, non-melanoma skin cancer, and early skin aging. Acute treatment before or after exposure to UV as well as long-term oral consumption or topical application seems appropriate, depending on the specific drug used. Classical nutrients like green and black tea, fruits, and vegetables contain these antioxidants, which also have beneficial effects in other fields of health protection, but for effective UV protection larger amounts than taken with normal nutrition seem necessary. Botanicals may be used externally as cosmetics or part of sun protection products or internally from food or food supplements. However, as shown previously, the LOE from clinical trials is poor and many more large-scale studies are needed to confirm UV protective effects for specific botanicals.

Betulin and ingenol mebutate appear to be interesting new potential options for therapy of precancerous skin modifications.

5. Hair Loss and Alopecia

There is increasing interest in the cosmetic industry in the development of products containing botanicals to treat or prevent hair loss and alopecia. Some botanical extracts are traditionally used to promote hair growth without scientific support, like birch sap in hair tonics. Garlic (A. sativum) is used topically in India, but is associated with obvious olfactory adverse effects. A single-blinded clinical trial was designed to test the effectiveness of topically applied crude onion juice (Allium cepa), which has many sulfurous ingredients.\cite{116} Sixty-two male and female patients with patchy alopecia areata were treated with fresh onion juice in comparison with tap water, applied twice daily for 2 months. Only 23 patients in the active treatment group and 15 control patients finished the study. However, the use of crude onion juice gave significantly better results with regard to hair regrowth than did tap water\cite{116} [LOE-B].

A standard medication for male androgenic alopecia is finasteride, a potent inhibitor of 5α-reductase, which converts testosterone to dihydrotestosterone. Finasteride was originally developed for the treatment of benign prostatic hyperplasia. Plants containing phytosterols like β-sitosterol or phytosterol glycosides, such as the palm tree saw palmetto (Serenoa repens), are traditionally used for benign prostatic hyperplasia treatment, and the same mechanism is discussed as their mode of action. Therefore, it was intriguing to test botanical 5α-reductase inhibitors in androgenic alopecia. In a randomized, double-blind, placebo-controlled pilot study with 26 male subjects, the effectiveness of a combination of β-sitosterol 50 mg and extract from the berries of saw palmetto 200 mg twice daily in the treatment of androgenic alopecia was determined.\cite{117} Ten patients were treated over 5 months with the active study formula. The blinded investigative staff assessment report showed that 60% of the study subjects were rated as improved at the final visit compared with only 11% of the placebo group\cite{117} [LOE-A]. Because of the small sample size, statistical significance was not the primary aim of the study. The formulation was well tolerated; one patient reported loss of appetite possibly related to active treatment. In contrast to finasteride, the tested botanical 5α-reductase inhibitors have no impact on prostate-specific antigen levels and do not interfere with cancer diagnostics.\cite{118} They are also widely used traditionally by women for a variety of indications without safety problems, so they may also be tested in androgenic alopecia in women.\cite{119}

6. Vitiligo

Treatment of vitiligo by UV exposure combined with oral or topical application of photosensitizing plant extracts goes back to ancient times, 1200–2000 BC, when A. majus was used in Egypt and Psoralea coryllifolia in India for phototherapy.\cite{120} Modern oral methoxsalen PUVA therapy of vitiligo seems to be inferior to standard narrowband UVB therapy,\cite{121} which nevertheless is not fully satisfactory. However, the combination of narrowband UVB therapy with oral administration of CPF (P. aureum or P. leucotomos) extract 250 mg significantly increased repigmentation on neck and hand areas in comparison with placebo plus narrowband UVB, as was recently shown in a randomized, double-blind trial with 50 patients treated twice weekly for 25–26 weeks.\cite{122} The difference was less pronounced on the trunk and extremities\cite{122} [LOE-A]. Another clinical observation of 74 vitiligo patients investigated the therapeutic efficacy of Xiaobai mixture in comparison with a control group treated with PUVA. The therapeutic effect of Xiaobai mixture was better than that of
PUVA\textsuperscript{[123]} Unfortunately, the ingredients of Xiaobai mixture and the LOE are not clear since the full text of this study is only available in Chinese. A recent review of natural health product treatment for vitiligo criticizes the quality of studies performed with plant materials but acknowledges that phenylalanine in combination with phototherapy and oral \textit{Ginkgo biloba} are promising\textsuperscript{[124]}

Oral administration of an extract of gingko (\textit{G. biloba}) 40 mg three times daily over a 6-month period was effective in a double-blind, placebo-controlled trial in 52 patients with limited, slowly spreading vitiligo\textsuperscript{[125]} [LOE-A]. Ginkgo significantly induced cessation of active progression, and 10 of 38 patients compared with 2 of 22 patients in the placebo group showed marked to complete repigmentation. However, no information about a long-term follow-up was available. Antioxidant and immunomodulatory properties of ginkgo may be the underlying mechanisms. Since ginkgo is the most prescribed botanical medicine, this treatment appears to be safe.

7. Wounds, Burns, and Injuries

Widely used traditional European botanicals in wound care are chamomile (\textit{M. recutita}), marigold (\textit{C. officinalis}), and arnica (\textit{Arnica montana}), all applied locally. Aqueous (teas, decoctions) extracts of chamomile or marigold are used as washings or wet packs for fresh wounds. Arnica should never be applied on open wounds and not as an undiluted tincture because of possible sensitization. However, arnica ointments are excellent on later stages of healing wounds for contusions and bruises. Marigold is especially recommended for wounds with bacterial infections. Small, well circumscribed lesions may be treated with the oil of St John’s wort (\textit{H. perforatum}), which is also believed to reduce scars by inhibition of keloid formation. All these drugs have anti-inflammatory and antimicrobial activities. Active compounds are diverse, and complex within each plant. Chamomile contains essential oil with bisabolol and chamazulen as well as saponins and other ingredients; alcoholic extraction yields the most complete blend, which may be transferred to aqueous formulations or ointments\textsuperscript{[126]} [LOE-D].

Marigold (\textit{C. officinalis}) has been topically used for wound treatment since ancient times. It has been shown to display bactericidal, antiseptic, and anti-inflammatory, as well as free radical scavenging properties\textsuperscript{[127]} [LOE-D]. Marigold was approved by the German Commission E as a wound healing agent\textsuperscript{[128]} [LOE-D]. A recent prospective, randomized trial in 254 patients who underwent surgical treatment of breast cancer and received postsurgical radiation therapy compared the effectiveness of a \textit{Calendula} 10% ointment with the standard therapy (trolamine) in the prevention of radiodermatitis\textsuperscript{[129]} Twice-daily application of \textit{Calendula} ointment over the whole period of radiotherapy was significantly superior to trolamine and highly effective in the prevention of acute radiodermatitis\textsuperscript{[129]} [LOE-A].

Diluted alcoholic tinctures from the flowers of arnica (\textit{A. montana}) are applied externally for the treatment of bruises, sprains, inflammation caused by insect bites, gingivitis, and aphthous ulcers, and for the symptomatic treatment of rheumatic complaints\textsuperscript{[130]} [LOE-C]. The secondary metabolites that mediate the anti-inflammatory effects are sesquiterpene lactones of the 10x-methylpropoglucaionoid type such as helela, 11z,13-dihydrohexalen, and their ester derivatives\textsuperscript{[131]} [LOE-D]. It was demonstrated that these compounds mainly exert their anti-inflammatory effect by inhibiting the transcription factor, nuclear factor-κB\textsuperscript{[132,133]} [LOE-D].

Although arnica has a long history in folk medicine and is widely used among consumers, up to now only a few clinical studies with arnica preparations have been carried out. In the field of dermatology, the possible synergism of vein-typical hydrotherapy according to Kneipp and topical arnica treatment was investigated in a randomized, double-blind clinical trial in 100 patients with chronic venous insufficiency\textsuperscript{[134]} [LOE-A]. Both hydrotherapy and combined therapy were found to be successful. However, the combined therapy was significantly superior to the monotherapy.

The gel of aloe vera (\textit{A. barbadensis}) is said to be beneficial in the treatment of chronic wounds and thermal injury\textsuperscript{[135,136]} [LOE-D]. A recently conducted, systematic review of the scientific literature found four clinical trials with 371 patients (including two randomized controlled trials) that supported the efficacy of aloe vera in wound healing of first- to second-degree burns\textsuperscript{[137]} [LOE-A].

Wound healing activity has been demonstrated in animal models for numerous botanical extracts. To name a few, teak (\textit{Tectona grandis})\textsuperscript{[138]} [LOE-D], golden trumpet (\textit{Allamanda cathartica})\textsuperscript{[139]} [LOE-D], vitex (\textit{Vitex trifolia} and \textit{Vitex altissima})\textsuperscript{[140]} [LOE-D], madagascar periwinkle (\textit{Catharanthus roseus})\textsuperscript{[141]} [LOE-D], gotu kola (\textit{C. asiatica})\textsuperscript{[142]} [LOE-D], and sacred basil (\textit{Ocimum sanctum})\textsuperscript{[143]} [LOE-D]. Curcumin obtained from the tumeric rhizome (\textit{C. longa})\textsuperscript{[144]} [LOE-D] as well as Pycnogenol\textsuperscript{TM} (Horphag Research Ltd, Geneva, Switzerland) from French maritime pine bark (\textit{Pinus maritima})\textsuperscript{[145]} [LOE-D] seem to be promising agents in the treatment of wounds. However, the efficacy of these
8. Adverse Effects of Plant Extracts on the Skin

This section is not intended to address each commonly used botanical. It should rather stoke the awareness of clinicians for the eventualities of adverse effects and how they may present.

Virtually all herbal remedies may provoke allergic reactions, and several botanicals hold the risk of photosensitization. The prevalence of contact sensitization against some botanical compounds, such as oxidation products of monoterpenes, terpinene, balsam of Peru, and Compositae plants, is quite high in Europe.[146] Contact sensitization towards cosmetics containing plant extracts as a fragrance is increasingly reported. Such patients should avoid plant extracts in their personal care products.[147] Therefore, clinicians should not only be informed of the beneficial effects of botanicals for dermatologic disorders but also of specific adverse effects that might be caused by the use of herbal remedies.

Botanicals may cause phytodermatitis, which can be classified into non-immunologic, such as toxic or phototoxic dermatitis, and immunologic phytodermatitis, such as immediate-type hypersensitivity, allergic contact dermatitis, or photoallergic dermatitis.[20] An example of toxic phytodermatitis is the irritant phororbol dermatitis caused by the sun spurge (Euphorbia helioscopia).[148] Furocoumarins represent the principal agents responsible for phototoxic phytodermatitis. They comprise psoralens such as 5-methoxypsoralen (5-MOP, bergapten) and methoxsalen (xanthotoxin), which possess a distinct photosensitizing potential. Furocoumarins also occur in burning bush (Dictamnus albus) and garden rue (Ruta graveolens), which belong to the Rutaceae plant family.[149,150] Phototoxic skin reactions to psoralens include the Berloc dermatitis caused by 5-MOP, which is contained in cosmetically used Citrus bergamia (bergamot oil). Dermatitis bullosa praeptens is frequently caused by methoxsalen that mainly occurs in the Apiaceae family (Umbelliferae), which includes plants such as the giant hogweed (Heracleum mantegazzianum)[151] and various vegetables/herbs such as celery, parsnip, and parsley.[152]

Besides toxic and phototoxic phytodermatitis, some botanicals may cause allergic contact dermatitis sensitized to plants or plant products. The Asteraceae A. montana has been classified as a strong allergen according to sensitization studies with guinea pigs.[153] Its sesquiterpene lactones, especially those with an α-methylene-γ-lactone moiety, are the most important allergens responsible for inducing allergic contact dermatitis. In a recent clinical study, 443 patients were patch tested with Compositae mix, sesquiterpene lactone mix, arnica, marigold, and propolis. Other plant species from the Asteraceae family that also contain sesquiterpene lactones, such as tansy (Tanacetum vulgare), feverfew (Tanacetum parthenium), yarrow (A. millefolium), or elecampane (Inula helemont), may also induce sensitization or elicitation of Compositae dermatitis. Chamomile (M. recutita) and marigold (C. officinalis) are different from the mentioned Asteraceae species.[154] As extracts of these plants are frequently used in occupational and cosmetic products, patch testing with additional plant extracts or adjustment of the commercial Compositae mix to regional conditions has been recommended.[155] However, the sensitizing potential of arnica may be underestimated. Recent studies have shown that arnica tinctures and sesquiterpene lactones are only weak contact sensitizers.[156,157] The potent anti-inflammatory effects of sesquiterpene lactones are dominant and fail to overcome immune regulation, which prevents contact hypersensitivity.[156] In essential oils such as peel oil from citrus fruits or tea tree oil from M. alternifolia, the allergens are oxidized degradation products of monoterpenes.[158,159] Tea tree oil has become one of the most common contact allergens. Moreover, tea tree oil and lavender oil have recently been reported to cause prepubertal gynecomastia.[160]

A recent review on the adverse effects of herbal drugs in dermatology summarizes the different sensitizing potential of herbal remedies, such as aloe vera, chamomile, or curcumin, and aromatherapy oils, such as lavender or tea tree oil.[161]

9. Discussion

Botanicals applied to wounds and skin diseases are perhaps the oldest medicines of humankind, and they still have their place in modern medicine. Three mechanisms of botanical medicines are especially important in the modern view: anti-inflammatory, antimicrobial, and antioxidant properties, which are often combined in a single plant extract and may be based on a number of ingredients rather than on single compounds. This combination is relevant for some actual trends in dermatology: the increasing number of inflammatory skin diseases in industrial nations; the emergence of microbial strains resistant to conventional antibacterials; and the increased challenges for the skin from lifestyle and environmentally caused irradiation. Plants
offer a huge range of substances and combinations that may be used for more and more specific and individual therapies. It is worthwhile to search for more valuable botanicals in folk medicines all over the world.

Botanicals are often used in trivial afflictions of the skin as home remedies or in skin care products before professional medical help is necessary. Although not all herbs used traditionally are clinically well documented in a modern sense, drugs like chamomile, marigold, arnica, and others seem well established empirically and supported by pharmacologic understanding of their mechanisms of action. Dermatologists should not try to discredit this use but know about their indications and mode of application, and also about risks and limitations. In acute and serious cases, botanicals may often not be sufficient treatment but are still helpful as adjuvants. For example, astringent and wound healing effects may complement measures to suppress acute inflammation, infection, or pain that require treatment with stronger remedies.

Scientific evidence for clinical efficacy of botanicals is often scarce. A number of controlled clinical trials have been conducted, e.g. in AD, but only very few when a specific plant species is examined, and with limited numbers of patients and not always with positive results. More investigations are necessary to definitely confirm whether Mahonia, Glycyrrhiza, or Hypericum are effective in AD, and whether Mahonia and capsaicin are effective in psoriasis. There is strong evidence for the use of botanicals in UV protection. However, this is only to a minor extent related to medical treatment but rather to diet recommendations and cosmetic care. Nevertheless, plant-derived topical formulations can be used for treatment of sunburns, amelioration of adverse effects in PUVA, or enhancement of efficacy in UVB treatment. Birch extract even seems to be effective in the therapy of precancerous skin deletions caused by long-term irradiation.

UV protection is also important for cosmetic purposes in antiaging treatment. Another field of cosmetic application is cellulite; many products are advertised as effective, but clinical evidence only supports mild short-term improvement up to now. Caffeine and other botanicals may be efficient, but delivery in special formulations seems necessary to reach the relevant tissues. Redness of the face may be a cosmetic problem but is also associated with rosacea; there is preliminary evidence that certain botanical treatments might help in rosacea, but more rigid application of diagnostic criteria is necessary in this field.

Research in phytomedicine is always associated with the search for active principles, and some examples were given where specific molecules have been identified as the (only?) therapeutically meaningful ingredients of a traditionally used plant, which are now accepted as standard therapies in their isolated form. However, many botanicals contain combinations that are probably superior to their isolated components in that they induce different but synergistic mechanisms in the organism. Application of complex natural products raises questions of reproducibility and quality control. Clinical investigations should therefore use well defined, standardized formulations.

10. Conclusion

An increasing number of botanical extracts have been studied in randomized, controlled, clinical trials, i.e. in the treatment of inflammatory skin diseases and chronic venous insufficiency. Plant monographs such as the monographs of the former German Commission E, ESCOP, and ABC provide specific recommendations for the use of various botanicals in dermatology. Botanicals play an important role as home remedies or self-medication of trivial dermatologic disorders, but extracts with anti-inflammatory, antimicrobial, and antioxidant capacities seem especially useful in diseases of high actual and increasing importance such as AD, psoriasis, and infections with resistant microorganisms, where some botanicals might become first-line treatments. Wounds, burns, and acne are examples of applications where the traditional use of botanicals is helpful at least as adjuvant treatments. However, many more controlled clinical studies with well defined botanical extracts and preparations are needed to determine the efficacy and risks of popular plant-derived products in dermatology. Extensive use of botanicals in nutrition supplements and cosmetic care should also be accompanied by research, especially concerning long-term safety and tolerability.

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