

Herbal Therapies from a Clinical and Toxicological Point of View

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herbal therapies, clinical efficacy, safety, need for new regulations

Herbal therapies have been used successfully for the treatment of dermatologic disorders for thousands of years in Europe and Asia. In India ,Ayurvedic medicine dates back to 3000 BC, Chinese medicine to 4000 BC. In younger days alternative medicine based on this knowledge is becoming increasingly popular in the industrial countries. Therefore standardization of herbal preparations and investigation about their clinical use and efficacy is recommended. Further practitioners need more information about the ingredients, the common drug interactions and side effects of herbal remedies. We want to discuss some common herbal preparations historically used for dermatologic conditions and recent studies that support their use. For example green tea extracts have been reported to be beneficial in treating UV-induced photodamage. Tannins are used in the treatment of acne because of their natural adstringent properties. Aloe vera is useful for wound healing. Capsaicin, the main ingredient of cayenne pepper, is effective in the treatment of psoriasis. German chamomile shows positive effects in the treatment of skin inflammation and dermatitis as the atopic eczema. Nevertheless one has to keep in mind that virtually all herbal remedies can cause allergic reactions. Less often they can cause photosensitivity. Ayurvedic medicine sometimes contains arsenic and mercury in relevant amounts. Most of the adverse effects reported are of mild to moderate severity and of transient nature. But dermatologists should be aware that these remedies can cause adverse effects which, at times, may be serious. The knowledge about the mechanisms how these herbs act and the specific indications of herbal remedies will be of great benefit for the patients.

1. Alternative medicine – it is getting “en vogue”

In 2001, \$ 17,8 billion were spent in the United States on dietary supplements. \$ 4,2 billion of it for herbs and other botanical remedies (1). The popularity of these products has increased over the past decade probably stimulated by sharp increases in prices of regular prescriptions and because of media reports of adverse effects of prescription drugs. The Centers for Disease Control and Prevention reported that 29 percent of adults have used complementary and alternative medicine in 1999, in detail with 10 percent ingesting herbal medicines. Women, people with higher levels of education and income, and patients with chronic illnesses turn to complementary and alternative medicine most often. The underlying rationale behind this trend is the common opinion that because an herb is a natural product it is supposed to be safe.

The increasing interest in herbal medicine deserves standardization of these preparations in the same manner as for already existing prescription drugs. This means in detail consistency in the composition and biologic activity and complete declaration of all ingredients.

Rigorous studies of their mechanisms of action, pharmacology and their clinical outcomes investigated by preclinical and early phase trials and subsequently multicenter studies are also essential requirements.

In the past year alone , the Food and Drug Administration (FDA) was compelled to issue warnings about nephrotoxic , hepatotoxic, and carcinogenic effects associated with botanical products

containing kava, comfrey, and aristolochic acid- all herbal remedies, which are widely used in the United States and Europe (2).

In 2001, the FDA received approximately 500 reports of adverse side effects related to dietary supplements. Poison-control centers in the United States received 19,468 reports, up from 6,914 in 1998 (3). It is estimated and worth mentioning that less than 1 percent of adverse effects, caused by dietary supplements, including herbs, are reported to the FDA (4).

The majority of herbal products in the United States are considered dietary supplements and thus are not regulated as medicines and are therefore not subjected to the standards for drugs specified in the Federal Food, Drug, Cosmetic Act (5). Thus, dietary supplements have to meet lower safety standards than food additives and prescription drugs. It is essential for the FDA and for European governments to review the safety of new dietary supplements before their sale and to remove unsafe products from the market. Therefore, new regulations are urgently required. The European commission has recently promulgated a draft directive on the licensing of traditional herbal preparations. This simplified approach allows a premarketing assessment of the quality and safety of a product and facilitates postmarketing surveillance and product recalls.

2. The common use of individual herbs

2.1. Ginkgo

Ginkgo-leaf extracts are used for the treatment of dementia (e.g. Alzheimer's disease), peripheral vascular diseases (e.g. intermittent claudication) and neurosensory problems (e.g. tinnitus). They contain terpenoids (ginkgolides and bilobalide) and flavonoids.

Two long term randomized placebo controlled trials have shown significant, but limited improvements of a well defined extract (containing 6% ginkgolides and bilobalide and 24% flavonoids) in patients with Alzheimer's disease or multiinfarct dementia (6,7).

Placebo controlled trials of ginkgo in patients with claudication intermittent showed no effects of clinical relevance (8,9).

It is also used for heart disease, asthma, vertigo, and tinnitus. Ginkgo promotes vasodilation, therefore it seems to be useful in the treatment of peripheral vascular disorders.

Problems caused by oral administration of ginkgo are possibly headache, nausea, gastric symptoms, diarrhea, or allergic skin reaction. There have been reports of subarachnoid and intracerebral hemorrhage, as well as increased bleeding time. Anaphylaxis like reactions are only seen with intravenous administration.

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

St. John's wort is advocated for depression, anxiety, and nervous unrest (10). The herb contains naphthodianthrones (hypericin and pseudohypericin), phloroglucinols (hyperforin and adhyperforin), phenylpropanes, flavonol derivatives, biflavones, proanthocyanidins, xanthones, and amino acids (11). Which major constituent leads to the reported clinical effects is still under investigation. In the last years hyperforin has focussed to be responsible for most of the clinical efficacy. Systematic reviews suggest that St. John's wort is more efficacious than placebo for the short term treatment of depression that is mild or moderate (12).

Adverse effects reported during the use of St. John's wort include gastrointestinal symptoms, dizziness or confusion, frequent urination, and swelling. Further, there are reports of photosensitivity reactions in users of St. John's wort (13,14). Mania (15), psychotic relapse in patients with schizophrenia (16), serotonin syndrome like events (e.g. anxiety, confusion, hypertension) and hypertensive crisis have also been reported as possible adverse effects (17).

2.3. Aloe vera

Aloe vera reduces burning, itching, and scarring associated with radiation dermatitis(18). It has also shown to accelerate healing of chronic leg ulcers, surgically induced wounds, and frostbite. It has recently been shown to be potential for the treatment of psoriasis (19). Furthermore, bactericidal and antifungal activity has been revealed. The main adverse effect of topical aloe vera gel is allergic contact dermatitis. Taken orally it is considered very safe when used properly.

2.4. Tea Tree Oil

Tea Tree Oil has been widely used topically for the treatment of bactericidal and fungal infections. It shows antimicrobial activity against *Propionibacterium acnes*, *Staphylococcus aureus*, *E. coli*, *Candida albicans*, *Tr. mentagrophytes*, and *Tr. rubrum* (20). In double-blind randomized trials there are conflicting results. In some trials mycologic cure is found to be comparable to clotrimazole, in other trials only symptomatic relief could be postulated (21).

More recently green tea extracts have been reported to be beneficial in treating UV-induced photodamage. In a study by Elmets et al. green tea extracts were applied onto the backs of 6 volunteers. Thirty minutes after the application patients were exposed to twice the minimal erythema dose of UV-radiation from a solar simulator. Green tea extracts resulted in a dose-dependent reduction of UV-induced erythema.

2.5. Chinese Herbal Medicine

In traditional Chinese medicine the body is treated as a whole and the aim of therapy is to restore harmony to the functions of the body. This requires a mixture of various herbs individually formulated for the patient, making randomized controlled trials difficult to undertake. Chinese medicine and traditional Indian (Ayurvedic) medicine worryingly often contains arsenic (22,23) This can lead to serious intoxication and several cases with dermatological side effects have been reported.

2.6. German Chamomile

German chamomile has been used for centuries, internally and externally, for almost all ailments, most notably gastrointestinal tract symptoms, oral or skin inflammation, and dermatitis. Studies have shown that topical chamomile is comparable with 0,25% hydrocortisone in case of contact dermatitis induced by sodium lauryl sulfate (24).

The anti-inflammatory, wound healing, and antimicrobial effects are attributed to a blue essential oil that contains sesquiterpene alcohol, alpha-bisabolol, chamazulene, and flavonoids.

2.7. Tannins

Tannins act as astringents. They are found in several herbs as English walnut leaf, Labrador tea, lavender, mullein, oak bark, rhatany, Chinese rhubarb, St. John's wort, and yellow dock.

In the treatment of dermatitis they reduce permeability and secretion by coagulating surface proteins of cells. Further they are supposed to have antimicrobial properties (24).

2.8. Essential oils

Essential oils have recently been shown to be helpful for patients with alopecia areata (25).

A mixture of essential oils including thyme, rosemary, lavender, and cedarwood in carrier oils; grapeseed; and jojoba (a liquid wax) was massaged into the scalp daily. The control group massaged only the carrier oils into the scalp. Success was evaluated on the basis of sequential photographs, by both a 6-point scale and a computerized analysis of areas of alopecia. Overall, the treatment group had statistically significant improvement over the control group (44% vs 15%). This improvement compares with the success of standard treatment practices used conventionally. There were no adverse effects.

2.9. Ascorbic Acid and Vitamine E

Ascorbic Acid and Vitamine E found increasing use in dermatologic treatment, especially in anti-aging preparations. Several studies have investigated their effects against oxidative stress (26), which is supposed to be a major component for aging of the skin. Topical pretreatment in humans with a combination of Ascorbic Acid and Vitamine E and melatonin provided a statistically enhanced photoprotection against UV-induced erythema (27).

2.10. Arnica

Arnica comes from the dried flowers of *Arnica montana* or other arnica species. It has been used for centuries as an anti-inflammatory aid to rub into sore muscles and joints, bruises, insect bites, boils, inflamed gums, acne eruptions and hemorrhoids. It is also found as an ingredient in many seborrheic dermatitis and psoriasis preparations. External preparations appear to be very safe and effective (28).

2.11. Propolis

Propolis is a resinous material produced by honeybees from the buds and bark of certain plants and trees. It is supposed to have anti-inflammatory, analgesic, and antitumor effects. These properties are thought to be due to the flavinoid and related phenolic acids that are components of propolis. Clerodane diterpenoid, a tumoricidal component was recently isolated (29).

3. Adulteration of botanical preparations and adverse effects

The problem with alternative medicine, as mentioned above, is the lack of standardization and the missing of double-blind placebo controlled trials to prove their efficacy. Inadequately regulated herbal medicines may contain toxic plant material, may be contaminated with heavy metals, or be adulterated with synthetic drugs.

Some impressive examples will underline this problem:

3.1. Chinese Medicine

The most adulteration in herbal creams are corticosteroids. This seems to be a particular problem with Chinese herbal creams. Recently a team of dermatologists from London asked 10 patients to bring in their Chinese herbal creams for analysis (30) and submitted these to chromatographic analysis. Eight out of 11 samples contained dexamethasone at a mean concentration of 456 µg/g of cream. One can easily imagine that such potent topically applied steroids of which patients suppose to use so called safe natural products can cause adverse effects especially because of their inappropriate use.

Another compound often found in Chinese medicine and Traditional Indian medicine is arsenic. The National Skin Center of Singapore reviewed all records of patients with cutaneous lesions related to chronic intake of arsenic seen between 1990 and 1996 (31). The sample consisted of 17 Chinese patients, 14 of whom had taken Chinese herbal remedies contaminated with inorganic arsenic. The most frequent dermatological manifestations were Bowen's disease, arsenical keratosis and squamous cell carcinoma. Such complications have been repeatedly related to the administration of Asian herbal remedies. Between 1972 and 1973 no less than 74 cases were reported in Singapore (32).

3.2. Essential oils

Essential oils used topically for aromatherapy and herbal creams have repeatedly been shown to be responsible for photosensitization. Recently there was one report of a young woman who

took an aromatherapy bath with 6 drops of bergamot and 6 drops of geranium oil. Afterwards she spent half an hour under a sunbed. 48 hours later she suffered of 70% superficial partial thickness burns caused by the photosensitivity of methoxypsoralens which are one component of the essential oils (33).

Eucalyptus oil is used in various dermatological conditions. Eucalyptus oil intoxication is well documented after oral administration of an amount of 30 ml. Additionally there is one case report about a 6 year old child who suffered from pruritus. Its parents applied the oil generously on the body, because of its known anti-itching properties. The child experienced slurred speech, ataxia, muscle weakness and progressed to unconsciousness. It was brought to hospital and made a full recovery (34).

3.3. Tea tree oil

The commercial use of Tea tree oil has considerably increased and with this the number of case reports of allergic contact dermatitis to this essential oil. Even a case of erythema multiforme-like id reaction has recently been published (35).

3.4. Henna

Henna is a herbal preparation often used for hair colouring or as an ingredient in shampoos. The combined use of henna and p-phenylenediamine is highly toxic. Twenty cases were noted in Khartoum over a 2-year period. Hours after the application of the dye mix to the skin, angioneurotic oedema of the face, lips, glottis, pharynx, neck and bronchi occurred, subsequently followed by renal failure (36).

3.5. Echinacea

The benefit of echinacea extract in case of illness caused by a cold was investigated in several studies. Most of them are neither reproducible nor objective. One recent study in the USA proclaimed no positive effects of echinacea compared to placebo (37). Special attention should be called to the higher risk of asthma and anaphylaxis due to echinacea in patients with atopic disorders.

There is also one case report of recurrent erythema nodosum associated with echinacea herbal therapy (38).

3.6. Piper betle

In April 1997 an unusual pigmentary disorder was noticed by dermatologists in Taiwan.

All patients had a history of using facial dressings with steamed leaves of piper betle. The clinical course and histopathologic findings suggest that the evolution of this pigmentary disorder finally leads to confetti-like depigmentation. It may be induced by chemicals in the betle leaves such as phenol, catechol and benzene derivatives, perhaps through inhibition of melanin synthesis or melanocytotoxicity (39).

4. Drug interactions

As Paracelsus stated for all kind of medications the dosage of an herb also distinguishes between a beneficial and a toxic effect. Interactions between herbs and drugs may increase or decrease the pharmacological or toxicological effects of either component. According to an article published by Adriane Fugh-Berman in *Lancet*, January 2000 which reviewed literature sources from 1966 to 1998 for crucial herb-drug interactions, this serious problem will gain further importance in the near future (40). The list of interactions between herbal medicines and prescribed drugs is recently

completed by a publication by Izzo and Ernst in "Drugs" and will demonstrate the necessity of further studies (41).

There are reports of bleeding when warfarin is combined with ginkgo (*Ginkgo biloba*), garlic (*Allium sativum*), dong quai (*Angelica sinensis*) or dashen (*Salvia miltiorrhiza*).

Patients who mix St John's wort (*Hypericum perforatum*) with serotonin-reuptake inhibitors suffered from mild serotonin syndrome. Furthermore St John's wort causes intermenstrual bleeding, delirium or mild serotonin syndrome, respectively, when used concomitantly with oral contraceptives.

A decreased bioavailability of digoxin, theophylline, cyclosporine and phenprocoumon results when St John's wort is combined with these drugs.

Liquorice potentiates the effect of topical or oral corticosteroids.

Decreased blood concentrations of prednisolone were seen when taken in combination with the Chinese herbal product xiao hu tang (sho-saiko-to). Also decreased concentrations of phenytoin when combined with Ayurvedic syrup shankhapushpi have been described.

5. Plant extracts in cosmetic products

With a vogue for natural products in the cosmetic industry, there is also an increase in their use in this field. To examine the prevalence of contact allergy to plants in patients susceptible to cosmetic dermatitis was the aim of one recently performed study which was published by Thomson et al. in the British Journal of Dermatology (42).

Allergic contact dermatitis to cosmetics is a common problem. The prevalence is reported between 2 and 5 % and may be much higher if only those patients with facial dermatitis are considered. In the last years there is an increase use of natural fragrances and plant derived ingredients in cosmetics. If one reviews the literature concerning contact allergies due to plant ingredients one will find a large number of positive reports. Just to give some examples :

lavender, witch hazel, mint water ecoconcentrate, aloe, tea tree oil, rosemary peppermint, geranium, balm mint (*melissa officinalis*), german chamomile, lemon peel, jasmine, eucalyptus, lemongrass, cinnamon, sage are shown to be allergenic in a number of occasions.

In the above mentioned study (42) a total of 29 patients, 27 female, 2 male the mean age was 45 years, with variable cosmetic dermatitis were undergoing patch testing to plant extracts and fragrances. 23 (79%) patients showed a positive reaction to fragrance mix on the standard series and 10 (34%) to Balsam of Peru. 17 (59%) showed a positive reaction to at least one component of the plant series. All these patients also had positive reactions to fragrance mix.

The most common plant allergy seen was to tea tree oil. This was mainly seen in patients who had been using tea tree oil containing products. Tea tree oil is found in many different formulations including ointments, shampoo, mouthwash, soaps, deodorant, sun screen, wart-paint, acne treatments and cosmetics, as well as household products such as fabric softener, detergent and cleansers. Considering such an extended use the development of cases of contact dermatitis is perhaps not surprising.

Positive patch testing was also seen to Compositae species (43,44) in 5 patients and to propolis in one patient. It has to be considered that some plant and fragrance ingredients are taken orally in foods and medical products as well as being used in cosmetics.

It can be concluded that patients with contact allergy to fragrance may also be allergic to plant extracts. Many cosmetic companies do not label plant extracts e.g. essential oils on their products because they were not classed as fragrances but as medical ingredients. So it happens that products which are labelled as fragrance free are containing plant extracts used as perfume ingredients but not labelled on the product. For that reason persons found allergic to fragrance should better avoid cosmetics containing not further defined plant extracts (45).

6. What is to be considered in the future to have save plant extracts containing cosmetic and medical products?

With herbal medicines, what is on the label may not be what is in the bottle. Just because an herb is natural does not mean it is safe and claims for remarkable healing powers are rarely supported by evidence (46).

Because of the numerous cases of contact dermatitis and even worse side effects as erythema multiforme, erythema nodosum, phototoxicity, contact urticaria (47) as well as critical interactions of herbal drugs if mixed with pharmaceutical drugs, there is need for new regulations.

The Department of Dermatology, Mayo Clinic Scottsdale and the Department of Dermatology, Mayo Clinic and Mayo Foundation, Rochester have recently published a topical skin care product data base to facilitate successful antigen avoidance (48). Typical allergen names are often long, difficult to spell and commonly have numerous complex synonyms. Further not all ingredients are labelled on the product. This "Contact Allergen Avoidance Program" (CAAP) enables patients and clinicians to find cosmetic products which does not contain the patients special allergens.

The European Parliament is currently considering measures to ensure that all traditional herbal medicinal products used in member countries have demonstrated efficacy and an acceptable level of safety (49). But it is likely that many proponents of the alternative medicine accompanied by economical forces will oppose these efforts. Therefore, the education of the public and the governments about the critical need for new regulations and safeguards is first to be done.

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