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## Application of medicinal plants in several dermatovenerological entities

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Treatment of skin conditions with medicinal plants has been an ongoing human activity lasting over thousands of years. The use of specific plant species developed regionally, based on local flora. Commonly used medicinal plants for dermatological complaints are: *Phlebodium aureum* (L.) J. Sm., *Ginkgo biloba* L., *Rosmarinus officinalis* L., *Panax ginseng* C.A.Mey., *Allium cepa* L., *Aloe vera* (L.) Burm.f., *Capsicum annuum* L., *Berberis aquifolium* Pursh, *Camellia sinensis* (L.) Kuntze, and *Podophyllum peltatum* L.

The demand for complementary therapeutics is an emerging trend due to the awareness of potential side effects that synthetic drugs might cause. More scientific evidence and better documentation are needed before advising dermatologic patients on herbal medicinal treatment. Standardised extracts and formulations with proven clinical efficacy should be developed for this cause. Here provided review entails the use of herbal medicinal products in the treatment of frequent chronic skin diseases, such as vitiligo, alopecia, psoriasis and genital warts.

**Keywords:** medicinal plants, vitiligo, alopecia, psoriasis, genital warts

### INTRODUCTION

Medicinal plants have been utilized for the treatment of various skin diseases in folk medicine. Species from local flora were used along with certain medicinal plants that were acquired through trade. In the recent years, research on medicinal plants and their bioactive compounds is growing in importance since chronic skin diseases, such as vitiligo, alopecia, psoriasis and genital warts, seem to be fairly resistant to the conventional treatment.

### Vitiligo

Vitiligo is a common autoimmune pigmentation disorder affecting 0.5–4 % of the population. Current treatment options include topical application of corticosteroids, calci-

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neurin inhibitors, vitamin D analogues, phototherapy, laser therapy and surgery (1). Since the treatment results are often slow and unsatisfactory, with possible side effects, there is a great interest in complementary treatment modalities, such as medicinal plants.

*Phlebodium aureum* (L.) J. Sm. (*Polypodium leucatomos* Poir.), *Polypodiaceae*. – Dietary supplement containing *P. aureum* extract has been used for more than 30 years (1). Primary bioactive compounds are phenolic acids (2). When used in combination with narrow band (nb) UVB light (311 nm) or psoralen + UVA (PUVA) therapy, *P. aureum* supplementation may improve re-pigmentation and provide photoprotection (1). The results of a study which compared supplementation with 250 mg of *P. aureum* three times daily in combination with nb-UVB to placebo and nb-UVB, re-pigmentation of head and neck area was achieved in 44 % of patients in *P. aureum* group and in 27 % of patients in the control group. *P. aureum* supplementation prevented oxidative damage, especially in lighter skin type patients with lower baseline antioxidant capacity (3). A similar study was conducted on 57 patients with generalized vitiligo, but the dosage of *P. aureum* was 480 mg daily. Improvement was reported for 47.8 % of the patients in the *P. aureum* and nb-UVB group, and 22 % of patients with nb-UVB alone (4). The randomized study investigated the use of PUVA plus *P. aureum*, in comparison to placebo. More than 50 % of re-pigmentation was reported for the patients in the *P. aureum* group. The threshold of 50 % re-pigmentation was not achieved in the placebo group. Additionally, the immunomodulatory effect was shown by lymphocyte ratio normalization in the *P. aureum* group (5).

*P. aureum* demonstrated photoprotective activity in another study where the severity of erythema, pyrimidine dimer formation and epidermal proliferation were evaluated post-exposure to UV light. Pre-exposure supplementation with an oral dose of 7.5 mg kg<sup>-1</sup> of *P. aureum* decreased the UV light-induced damage (6). The toxicity of oral administrated *P. aureum* was minimal, reported adverse reactions include mild pruritus and gastrointestinal upset (1).

*Ginkgo biloba* L., *Ginkgoaceae*. – *G. biloba* is a medicinal plant originating from Traditional Chinese Medicine shown to inhibit disease progression and augment re-pigmentation in vitiligo (1). The observed benefits are due to the anti-inflammatory, antioxidant and anxiolytic activity of flavonoids and terpene trilactones present in the leaves.

A double-blind study investigated the effects of supplementation with 40 mg kg<sup>-1</sup> of *G. biloba* extract in patients with limited, slow-spreading vitiligo. A significant arrest of active disease was reported, re-pigmentation was achieved in 40 % of treated patients compared with 9 % of patients in the control group. A common side effect is gastrointestinal upset, but care should be taken because there have also been reports of haemorrhage and increased bleeding time (7).

### *Alopecia*

Depending on its acuity and extent, hair loss is an important cause of anxiety.

*Essential oils mixture*. – A double-blind study included 86 patients with alopecia areata to investigate the efficacy of a mixture of essential oils as alopecia areata treatment. Selected essential oils for the mixture were obtained from: *Thymus vulgaris* L., *Lavandula angustifolia* Mill., *Rosmarinus officinalis* L. and *Cedrus atlantica* (Endl.) Manetti ex Carrière.

The mixture was diluted in carrier oil, a combination of grape seed and jojoba oil. Prepared oily mixture was administered daily and massaged into the scalp. The control group followed the same routine using only carrier oil. The treatment group had statistically significant improvement by 44 %, based on expert and computerized analyses of sequential photographs, comparing to the control group with 15 % improvement. There were no adverse effects reported (8).

*Rosmarinus officinalis* L., *Lamiaceae*. – *R. officinalis* is a well-known Mediterranean aromatic plant. The essential oil of *R. officinalis* improves microcirculation surrounding the hair follicle (9). Bioactive compounds of *R. officinalis* are phenolic acids, mainly caffeic and rosmarinic acid, and monoterpenoids like 1,8-cineole (10). A clinical study from 2015 compared the efficacy of rosemary essential oil to minoxidil 2 % solution for the treatment of androgenetic alopecia. Patients used either minoxidil 2 % solution ( $n = 50$ ) or rosemary essential oil ( $n = 50$ ). Significant increase in hair count was reported for both treatments without significant difference between the study groups. Scalp irritation was more frequent in minoxidil 2 % solution group (9).

*Panax ginseng* C. A. Mey., *Araliaceae*. – Ginsenosides are saponin compounds derived from *P. ginseng* with a wide spectrum of biological activity, with the influence on hair-growth being only one of the proposed activities (11). In 2014, a study was conducted in order to assess the efficacy of *P. ginseng* supplementation in treating female pattern alopecia. Group 1 consisted of patients who used topical 3 % minoxidil solution, while group 2 used topical 3 % minoxidil solution and oral *P. ginseng* supplement. An expert panel of dermatologists concluded that group 2 showed significantly better results although the hair density and thickness were improved in both groups (12).

*Allium cepa* L., *Amaryllidaceae*. – Sulphurous and phenolic compounds from onion juice act as irritants, thereby causing mild dermatitis which might provoke hair growth. A study where *A. cepa* juice was used as a treatment for alopecia areata has shown significantly more hair re-growth after six months of the treatment (86.9 %). The control group used only tap water and 13 % of hair re-growth was reported (13).

### *Psoriasis*

Most studied medicinal preparations for the treatment of psoriasis are *Aloe vera* juice, capsaicin, indigo naturalis and *Berberis aquifolium* extracts (14).

*Aloe vera* (L.) Burm.f., *Liliaceae*. – *A. vera* has been used for medicinal purposes for more than 2000 years. Gel-like leaf juice of *A. vera* is a pharmaceutical material with reported anti-inflammatory, antipruritic, and wound healing effects. Bioactive compounds of the juice are phenolics, polysaccharides, organic acids and various other metabolites (15).

A study with a group of patients who were treated with 0.5 % of *A. vera* juice in hydrophilic vehicle showed statistically significant improvement in the *A. vera* group compared to the group treated with hydrophilic vehicle exclusively. The *A. vera* juice caused a decrease in the severity of symptoms in 83.3 % of patients (16).

*Capsicum annuum* L., *Solanaceae*. – The main active ingredient of pepper extracts for topical application is capsaicin which inhibits transcription factors NF- $\kappa$ B and AP-1

activation *in vitro* (17). Substance P could play a role in neurogenic pathophysiology of psoriasis. In psoriatic plaques, substance P-activated inflammatory pathways can cause vasodilation and angiogenesis, followed by keratinocyte hyperproliferation. Capsaicin causes an efflux of substance P from sensory neurons by activating vanilloid receptors and thereby depleting cutaneous substance P (14).

Topically used 0.025 % capsaicin cream has shown to improve symptoms like scaling and erythema in patients with moderate and severe psoriasis after 6 weeks of treatment (18). In another study, with the same dosage and duration of the treatment, along with improvements in scaling and erythema a significant decrease in thickness and pruritus are reported. The application of capsaicin is followed by an intense and short-lasting burning sensation (19).

*Indigo naturalis*. – *Indigo naturalis* is a preparation from Traditional Chinese Medicine usually obtained from plant species *Strobilanthes cusia* (Nees) Kuntze, Acanthaceae, and has long been used as a therapy for psoriasis and other conditions with an inflammatory component. Indirubin was identified as the active compound, besides the anti-inflammatory effect, inhibition of proliferation and promotion of differentiation in epidermal keratinocytes are proposed mechanisms of action (14).

*Indigo naturalis* ointment was studied as a topical therapy in moderate plaque psoriasis. After 8 weeks of randomized, double-blind, placebo-controlled clinical study, the results were quantified through Psoriasis Area Severity Index (PASI). Significant improvement by 75 % (PASI 75) had been achieved in 56.3 % of patients compared to 0.0 % in the placebo group. Additionally, in order to establish the exact mechanism, a biopsy was performed showing the down-regulation of the IL-17 pathway (20). Lin *et al.* (21) reported a reduction of plaque area and significant improvement in symptoms after the treatment with an ointment containing *indigo naturalis*. In another study by Lin *et al.* (22) with the same *indigo* preparation, the PASI 75 was achieved in 74 % of patients in the treated group. Temporary erythema and itching on the application site were noted as adverse effects. Oily extract of *indigo naturalis* was formulated for a clinical study assessing the topical application in nail psoriasis and a significant improvement in the severity of symptoms was quantified with Nail Psoriasis Severity Index (NAPSI) after 12 and 24 weeks of treatments, without adverse effects (23).

*Berberis aquifolium Pursh* (*Mahonia aquifolium (Pursh) Nutt.*), *Berberidaceae*. – *B. aquifolium* use for the treatment of psoriasis is linked to the presence of berberine, an anti-inflammatory alkaloid that reduces keratinocyte hyperproliferation markers typical for psoriasis (14, 24).

The extract of *B. aquifolium* formulated into a cream was tested in a clinical study for the treatment of chronic plaque psoriasis. Improvements in PASI score were significant in comparison to placebo cream (24). In another study, *B. aquifolium* extract was compared to conventional therapeutics calcipotriol and tazarotene; *B. aquifolium* extract was either as effective or better in treating disease symptoms (14).

### *Condyloma accuminata*

*Camellia sinensis (L.) Kuntze, Theaceae*. – *C. sinensis* is a rich source of polyphenols. Epigallocatechin and epigallocatechin gallate are the most abundant polyphenols but the

composition might vary depending on leaf processing method (25). Green tea polyphenols have been shown to possess antioxidant, antiproliferative, proapoptotic, antiviral and antitumor properties (26).

Ointment with green tea extract, comprised of more than 85 % catechins, is a patient-administered therapy for external genital warts. Phase III clinical trials demonstrated significantly higher efficacy and lower recurrence rates compared to other currently available patient-applied treatments. In two identically designed, randomized, double-blind, Phase III trials, a total of 1005 participants (535 men and 470 women) were included to receive 15 % green tea extract ointment, 10 % green tea extract ointment or vehicle. Treatment was applied at 8-hour intervals three times a day for 16 weeks or until complete resolution of all baseline warts was observed. Rates of complete clearance of all warts in both green tea extract ointment groups were significantly superior to vehicle ( $P_s < 0.001$ ). The median time to complete wart clearance in the two trials was 16 weeks and 10 weeks in the 15 % and 10 % green tea extract ointment groups, respectively. In all studies, recurrence rates were low and complete clearance rates were higher in women than in men (27).

*Podophyllum peltatum* L., *Berberidaceae*. – *P. peltatum* has been used for centuries in the treatment of warts and skin cancers by indigenous people of the Americas. Podophyllin is a resin extracted from the root of the *P. peltatum* (28). When treating genital warts, a recent study showed that a combination of cryotherapy and podophyllin therapy is more efficient than cryotherapy alone, shortening the treatment regimen (29). According to a meta-analysis of 9 randomised controlled trials, podophyllotoxin, the main ingredient of podophyllin, in the concentration of 0.5 % caused complete clearance of genital warts in 56.41 % of patients. Burning sensation, pain, pruritus and inflammation might occur on the site of application (28).

## CONCLUSIONS

Medicinal plants have been used for the treatment of skin conditions long before synthetic drugs came on the market. Advantages of synthetic drugs for prescribers are reliable scientific background, quality and stability of the product, which is ensured by legislative means. Although herbal medicinal products can only strive to achieve a quality level comparable to conventional therapy, certain advantages cannot be ignored. Firstly, described medicinal plants have a better safety profile, with the exception of *Ginkgo* – conventional therapeutic for indications other than vitiligo, with well-known side-effects and potential interactions. Secondly, multiple pharmacological targets are modulated with a complex mixture of plant metabolites, thereby providing a possible solution for diseases resistant to conventional therapy.

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