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Cera alba (Beeswax) 7.00 gm	**Powerful Skin Conditioner Which Calms the skin cells Exfoliates & Repair Skin Damages Promotes Skin Regeneration also a LongLasting Protective Barrier against the Environmental Pollutants** *Ref: Beeswax for skin- Journal of Cosmetic Dermatology*
Oil of Syzygium aromaticum (Clove oil) 0.20 gm	**Reduces Redness, Itching, Irritation due to Anti-Inflammatory Properties.** *Ref: use of Clove in Psoriasis - MD Edge – Dermatology*
Oil of Curcuma longa (Turmeric oil) 0.20 gm	**Hydrates Skin, Prevents Dryness, Infections & Scars, Rich in AntiOxidants & Anti-Aging Properties.** *Ref: Use of Curcumin in psoriasis -NIH- PUBMED CENTRAL*
Cinnamomum camphora (Kapoor) 0.50 gm	**Alleviates Pathogenic Systems of Atopic Dermatitis & Eczema & Powerful Anti-Irritant.** *Ref: Uses of Cinnamomum Camphora Leaves -NIH- PUBMED CENTRAL*
Mentha piperita (Peppermint) 0.20 gm	**Boosts Blood Circulation, Rejuvenates & Nourishes Skin, Assists Smooth Skin Turnover, Loosens Dead Skins & Accelerates Skin Regeneration.** *Ref : Effectiveness of topical peppermint oil in symptomatic Treatment -NIH- PUBMED CENTRAL*
Trachyspermum ammi (Ajwain) 0.20 gm	**Prevents Scars, Itching & Skin Boils.** *Ref: Use of Ajwain: Thymol activates TRPM8-mediated Ca2+ influx for its antipruritic effects and alleviates inflammatory response -NIH- PUBMED CENTRAL*
Gandhak (Sulphur) 0.20 gm	**Relieves Pain & Prevent Burning Sensation.** *Ref: Sulfur for skin-NEJ of Medicine - The Treatment of Psoriasis with an Organic Sulphur Compound -vol.213 No 8-page 353*
Suhaga (Borax) 0.20 gm	**Potent Anti-Fungal and has an effective Antiseptic Action on Cuts & Burns.** *Ref: Effectiveness of Borax in psoriasis -NIH- PUBMED CENTRAL*
Cocos nucifera (Coconut oil) q.s	**Rich in Fatty Acids which Soften the Skin & is a Powerful AntiMicrobial, which Reduces Skin Infections & Irritation.** *Ref: Effectiveness of Coconut Oil in Psoriasis- Medical News Today*

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4.1 Use Rogan Hina in Psoriasis

Introduction

Epidermolysis bullosa (EB) is a rare inherited genetic skin disorder with severe skin itching and recurrent blisters and erosion. There is no effective and specific therapy for all types of EB.

Objectives

The aim of this study was to evaluate a topical formulation of henna (Lawsonia inermis Linnaeus) in the management of wounds and the itching sensation in patients with EB.

Methods

This is a pilot single-arm clinical trial. Nine patients with recessive dystrophic EB, with the age range of 5 to 32 years were enrolled in the study. The patients were instructed to apply the topical 1% henna ointment once daily on two erosions and on also two sites with moderate to a severe itching sensation. The total duration of the intervention was 4 weeks with weekly follow-up visits. Patient global impression of improvement, visual analog scale, and clinical global impression of improvement were used for assessing the wound healing process and itching discomfort.

Results

There was a significant improvement in the skin symptoms of epidermolysis bullosa including skin redness, itching, burning, and local warmness ($P < 0.05$). Local pain decreased during the study period, but this was not statistically significant ($P < 0.19$). One patient reported moderate xerosis of skin after continuous usage.

Conclusions

It seems that the topical formulation of henna may be effective in the management of itching, burning, stringing, and cutaneous warmness sensation in patients with EB. Further controlled studies with larger sample sizes are recommended to better evaluate this formulation.

Introduction

Inherited epidermolysis bullosa (EB) is a rare genetic skin disorder that can affect many extracutaneous organs including the gastrointestinal and genitourinary system, eye and etc [1,2]. There are four major types of inherited epidermolysis bullosa; epidermolytic (EB simplex [EBS]), lucidolytic (junctional EB [JEB]), dermolytic (dystrophic EB [DEB]), and Kindler syndrome [3]. The common characteristics of all subtypes of EB are recurrent blistering and erosions (after even minor trauma or traction) of skin and the organs covered by mucous membrane [4].

The pathogenesis of EB is the mutation of the genes which is caused due to dysfunction of collagen type VII that is the main component of the anchoring fibrils located below the lamina densa layer of the epidermal basement membrane zone [2]. EB patients, especially patients with recessive dystrophic EB (RDEB), suffer from severe skin itching and also recurrent blisters and erosion [2,5]. There is no specific therapy for all types of EB, therefore supportive care including wound care, control of infection and itching are very important [6]. Using topical and systemic antibiotics, analgesics, antihistamines are very popular in these patients.

Henna (*Lawsonia Inermis* Linnaeus) is one of the most commonly used medicinal plants in traditional Persian medicine as a treatment for dermatological conditions and improving wound healing [7,8]. There are several studies demonstrating the efficacy of henna on skin disorders such as dermatitis including diaper dermatitis,

bedsore, itch, and et. [9–12]. It has been shown that henna can improve the wound healing process and also has antipruritic effects [13,14]. In addition, some investigations revealed the antimicrobial and antifungal properties of henna. These effects are considered to be due to high concentrations of some components in this plant including carbohydrates, anthraquinones, naphthoquinone derivatives, flavonoid, and phenolic components. [15,16].

Objectives

To the best of our knowledge, there are no studies on the efficacy of henna in the management of wounds and itch in patients with RDEB. The aim of this study was to evaluate the efficacy of henna in the wound healing process and itching complaints in patients with RDEB.

Methods

Study Design

This study was designed as a single-arm, uncontrolled clinical trial. This study was in compliance with the Declaration of Helsinki (1989 revision) [17], and also approved and monitored by the Ethics Committee of Shiraz University of Medical Sciences (License number: IR.SUMS.REC.1398.761). Moreover, the enrolled patients were informed completely about the protocol of the study and signed the written informed consent. The patients were permitted to withdraw from the study at any time of the study. This clinical trial was registered at the Iranian Registry of Clinical Trials (IRCT) by IRCT20150825023753N14 code (http://www.irct.ir/trial/41647).

Sample Size and Study Population

Patients with RDEB were recruited from Faghihi Dermatology Clinic, Shiraz University of Medical Sciences, Shiraz, Iran. Given the rarity of RDEB, the researchers decided to enroll at least seven patients in this pilot study.

Inclusion criteria were patients with RDEB, who signed the written informed consent (themselves or their parents if less than 15 years old) to participate in the study. The exclusion criteria were a positive history of allergic reaction to henna, or glucose-6-phosphate dehydrogenase (G6PD) deficiency, and any other systemic diseases.

Drug Preparation

Henna (*Lawsonia inermis Linnaeus*) leaves were gathered from Shahdad fields (Kerman, Iran) and dried. A botanist at Kerman University of Medical Sciences authenticated the plant and recorded it with a specified voucher number (No: KF-1408). The maceration method five times was conducted to prepare the hydro-ethanolic extraction (30:70). The gathered extract was purified through filtration and concentrated by a vacuum rotary evaporator and dried in an oven 40°C. The ointment containing 1% henna was prepared by dissolving a one-gram fine powder of dried henna extract in the minimum volume of ethanol 40%, then it was dispersed in 99 grams of Eucerin through geometric dilution. The prepared ointment was packed in 50-gram containers for delivery to the patients.

Pharmaceutical Properties of the Ointment

The quality control of the prepared ointment was performed according to WHO guideline [18]. Pharmaceutical characterizations of henna ointment were evaluated as follows [19–23]:

Determination of pH

Some ointment was heated up to the melting point and diluted with a 1:9 dilution ratio (1 unit of drug and 9 units of water) and measured with a pH meter. This procedure was repeated three times and its mean and standard deviation were recorded.

Homogeneity

Homogeneity of the herbal ointment was evaluated for any aggregation by the skin test. In this study, 12 healthy volunteers tested some of the product on the back of their hands and were asked to express their satisfaction with the particle being present in the ointment.

Total Polyphenolic Content

The total phenolic content of the extract and ointment were measured based on the Folin-Ciocalteu method.

Rheological Behaviour

Cone and Plate Brookfield rheometer (Brookfield Engineering Laboratories) at 25°C was performed to evaluate the rheological behaviour of ointment for triplicate.

Spreadability Test

Two horizontal glass plates (10 cm × 10 cm) were conducted to assess the spreadability of the prepared ointment. The spreading diameter of one gram of sample between plates was measured under 25 grams' standard weight shear application three times.

In Vitro Drug Release

Two grams of henna ointment were poured into a 10-kDa semi-permeable dialysis membrane bag. After dispersing, it was immersed in 50 ml of 25 mM phosphate buffer solution (PBS) at 37 ± 0.5 ° C and rotated at 100 rpm. For 24 hours, at a specified interval, 1 ml volume of PBS solution was sampled and replaced with the same volume of PBS. The samples were analyzed by UV spectrophotometer and repeated three times and the amount of active ingredient release was calculated according to the standard curve.

Microbial Control

The microbial and fungal control tests of the product were performed by Barij Essence® Pharmaceutical company (serial number:1521M98; batch number: 9805101) for aerobic microorganisms, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, modals, and yeasts enumeration.

Intervention and Follow-up of the Patients

The patients were instructed to use a fingertip of henna ointment once a day on two erosions and also on two sites with moderate to severe itching for 4 weeks with first, second, and fourth week follow-up visits. Patient global impression of improvement (PGI-I), visual analog scale (VAS), and clinical global impression of improvement (CGI-I) were used to assess the wound healing process and itching discomfort. Furthermore, photographs were taken of all of the patients.

Furthermore, wound improvement response was defined as excellent (90% improvement), good (50%–90% improvement), mild (20%–50% improvement), and fair (less than 20% or worse) according to general appearance.

At the end of the study, patients or their parents (for children participants) were asked to express their opinions about the efficacy of henna ointment in comparison to other used medications.

Statistical Analysis

Statistical Package for Social Sciences, SPSS version 18 (SPSS Inc.), was used for data analysis. According to the low sample size, Freedman test was used for assessment of the effects of henna ointment on the variables of the study. P value equal to or less than 0.05 was considered significant.

Results

Pharmaceutical Characterization

The measured pH of ointment was 6.4 ± 0.3. This ointment displayed rheological thixotropic behavior. The results of the spreadability test showed that the mean diameter for henna ointment was 9 ± 0.8 cm. Folin-Ciocalteu method was used to determine total phenolic contents in terms of Gallic acid equivalent (GAE) in mg/g of the extract. Based on the equation of the calibration curve (y = 0.007x+0.006, R2 = 0.999), the total phenolic content of the extract and ointment were 129.6 ± 1.1 and 0.98 ± 0.18 mg/g of extract, respectively.

The rate of drug substance release is presented in Table 1. As shown in Figure 1, the release of active ingredients of henna ointment follows the Weibull equation (Q=1−exp−tAK) with R2=0.97 so that k (time constant) is equal to 6.92 and A (shape parameter) is equal to 1.03. The prepared product releases half of its active ingredient content up to 4 hours and about 90% of its active ingredient content releases up to 12 hours after application. This release kinetic is consistent with topical products containing ointment-based hydroalcoholic extracts.

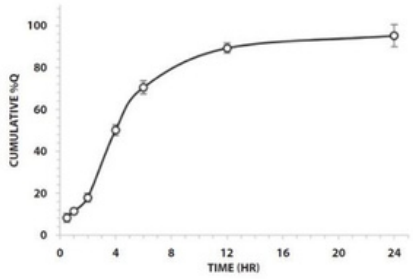


Figure 1

In vitro release of total phenolic compounds from henna ointment performed according to the Folin-Ciocalteau method (mean ± standard deviation, N=3).

Table 1

Mean percentage of release of henna ointment

[a]Time (hours)	Cumulative % Q	Standard deviation
0.5	8.3	2.1
1	11.4	1.2
2	17.9	2.1
4	50.1	2.5
6	70.5	3.1
12	89.3	2.4
24	95.2	5.3

cumulative amount released

Participants Enrolment and Basic Characteristics

A detailed description of the patients enrolment and analysis is given in Figure 2. Nine patients were enrolled in the study. Two patients were lost to follow-up. Finally, 7 out of 9 patients including 3 boys and 4 girls completed the study. The age range of the patients was 5–32 years.

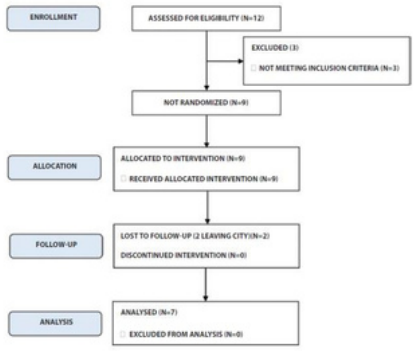
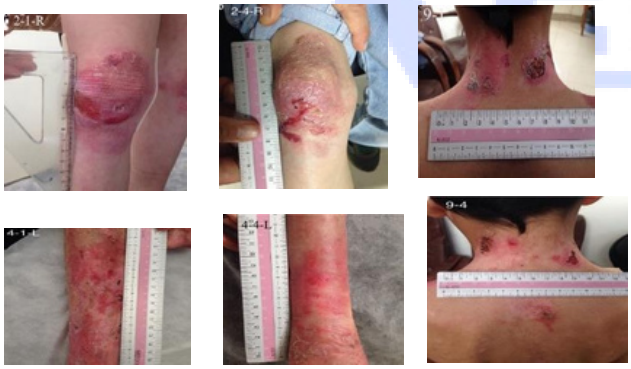


Figure 2

TREND flow chart of efficacy of a topical formulation of henna (*Lawsonia inermis Linnaeus*) on the itch and wound healing in patients with epidermolysis bullosa.

Efficacy Outcomes

The average drug satisfaction rate was reported 74% (min = 50%, and max = 90%) by the patients. For more details, based on PGI-I, 6 patients reported “very much better” and 1 reported “much better” in itching discomfort after using henna ointment. According to CGI-I, the physician concluded that all the patients were “much better” and “very much better” after using henna ointment. There was a significant improvement in the skin symptoms of epidermolysis bullosa including skin redness, itching, burning, and local warmness sensation ($P < 0.05$). Local pain decreased during the study period, but this was not statistically significant ($P < 0.19$) (Table 2). Moreover, Figure 3 shows the photos of 3 patients with RDEB before the treatment and after four weeks of receiving topical 1% henna ointment.



This image shows the patients with recessive dystrophic epidermolysis bullosa(RDEB) who were enrolled in the study before the treatment (A–C) and after four weeks of receiving topical 1% henna ointment (D–F). (A and D) The right knee of a 6-year-old boy with RDEB. (**B and E**) The left forearm of a 32-year-old girl with RDEB. (C and F) The back of a 10-year-old boy with RDEB.

Table 2

Mean of dermatological complaints scores from baseline to weeks 1, 2 and 4 in patients with epidermolysis bullosa who treated with local henna ointment

Weeks					
Outcome measures	Week 0	Week 1	Week 2	Week 4	P[a]
Skin redness (mean ± SD[b])	6.28 ± 1.26	6.14 ± 1.10	3.57 ± 0.68	2.42 ± 0.48	0.003
Itching sensation (mean ± SD)	8.57 ± 0.71	4.71 ± 0.47	3.42 ± 0.86	2.00 ± 0.43	0.001
Skin burning (mean ± SD)	3.57 ± 1.21	2.28 ± 0.77	1.57 ± 0.61	1.00 ± 0.436	0.003
Local warmness sensation (mean ± SD)	5.14 ± 0.98	4.00 ± 0.92	3.14 ± 0.93	2.00 ± 0.75	0.001
Local pain (mean ± SD)	4.71 ± 1.45	4.14 ±1.29	3.57 ± 1.19	2.71 ± 0.74	0.197

[a]P-value;

[b]SD = standard deviation

Qualitative Evaluation of Patients Opinion About Topical Henna Ointment

Five out of 7 patients who participated in the study reported henna as the most effective ointment for their pruritus in comparison to other medications, including corticosteroids, Vaseline, and repair creams. In addition, most patients had a good experience in wound healing effect while using henna ointment, at least as well as conventional medicine such as Mupirocin, MEBO® and *BIAFINE*® topical emulsion.

Side Effects Evaluation

No serious adverse effect was observed. One patient reported moderate xerosis of skin after continuous application of henna after 4 weeks so that he needed to apply larger amounts of emollient medicines.

Conclusions

This study showed that the 1% henna ointment could improve skin redness, itching, burning, and local warmness. But it should be considered that it was a pilot study and further studies with a higher number of cases are necessary to approve these results. Although EB patients suffer from several severe complications related to their disease, there are not enough randomized clinical trials for novel drugs that can manage their complications.

EB is a non-curable hereditary condition with several cutaneous and extracutaneous manifestations. Skin redness (dermatitis), pruritus, burning sensation in the skin, local warmness sensation, repeated ulceration, and pain are the most common cutaneous manifestations and complaints of patients with EB [24]. These manifestations could affect the quality of life in patients with EB and their families [25,26]. Therefore, most of the time patients, their parents, and health care providers try to administer multiple topical medications including natural and herbal remedies to manage or relieve these symptoms [27].

Henna is one of the herbal medications that is used commonly in both traditional and folk medicine for the treatment of skin, hair, and nail diseases, as well as cosmetic problems [7,28,29]. Niazi et al demonstrated that henna ointment could improve the symptoms of contact dermatitis including skin edema, itching, sweating, skin thinning and pain which is consistent with our study [12]. However, unlike our study, skin redness increased due to the use of henna ointment, which may be due to the method of measuring erythema [30].

Keshavarz et al showed that henna had a significant effect in comparison to hydrocortisone ointment in the improvement of diaper rash [10]. Ansari et al revealed that topical Alpha® ointment (containing natural henna) had a significant therapeutic effect on the healing of radiation-induced dermatitis in breast cancer patients [31]. Another study conducted by Yucel *et al*. showed that topical henna had significant effects in the treatment of capecitabine-induced hand-foot syndrome. The authors of this study suggested that these therapeutic effects could be related to anti-inflammatory, antipyretic and analgesic effects of henna [32].

The present study showed that 1% of henna ointment had an acceptable effect on skin characteristics in patients with EB. In fact, all the selected wounds of these patients were improved clinically during to first two weeks of the study. Mourad et al demonstrated that the henna gel had a significant effect on wound healing in *in-vivo* model. The results of this study were confirmed by histological stain assessments [13]. The study of Shiravi et al revealed that henna had anti-inflammatory and anti-bacterial effects in Wistar rats. According to this study, reduction of inflammation, edema, bleeding, and increased collagen formation resulted in acceleration of wound healing, angiogenesis, and vasodilatation in these rats [33].

The mechanisms of wound healing of topical henna are unclear till now, but one recent study suggests that these mechanisms may include reduction of tissue inflammation and increasing cellular glucose uptake, which was mediated by up-regulating the expression of glucose transporter-1 and insulin-like growth factor I. Furthermore, this study showed that topical henna could shorten the inflammatory phase of the wound healing process, accelerate cellular proliferation, raise wound contraction ratio, and caused improvement of revascularization, collagen deposition, and re-epithelialization rate, and promotion of intracytoplasmic carbohydrate storage [34]. According to the knowledge of TPM, *"Ghabz"*, with nearly meaning of "contraction" in conventional medicine, is the common feature of drugs that are effective in wound healing [35,36], as well as henna [29,37], that is in line with the finding of conventional medicine.

The findings of our study showed that topical henna ointment did not relieve pain sensation of the patients with EB. This result may be referred to stimulate pain receptors of the selected sites by pain signals coming from contiguous wounds. This finding was not in line with the other studies. The study of Nesa et al showed remarkable analgesic, anti-inflammatory, and central nervous system (CNS) depressant effects of henna [38]. Hasan Imam et al suggested that the analgesic effect of henna was resulted from alpha amylase enzyme inhibitory and Anti-inflammatory effects of this herbal remedy [39]. The difference in the results may be due to different doses and routes of administration. Moreover, previous analgesic effects are reported in animal model, but our study was on human EB subjects with potential different in pain pathways.

One out of seven patients reported that the skin of the areas in contact with the drug had become drier and flakier.

According to the best of our knowledge, there are some evidences of skin dryness after using topical henna in literature review. However, it is compatible with side effects reported in traditional Persian medicine for henna.

Other reported side effects for topical use of henna are acute allergic contact dermatitis [40], temporary localized hypertrichosis [41], hair and clothing dye allergy [42], vesicular erythema multiforme-like reaction, [43] and hemolysis in patients with G6PD deficiency [44].

Most of the patients were more satisfied with using henna ointment in comparison with conventional medications, especially in the management of pruritus and inflammation, as well as its wound-healing effects. This is the first study investigating the efficacy of herbal medicine in the management of EB complications. Therefore, it was impossible to compare this product with other herbal remedies in EB. But there is a great piece of evidence showing the efficacy of topical usages in dermatological conditions, such as wound, androgenic alopecia, and prevention and treatment of pressure ulcers, dermatitis, and much more [9,11,45–47].

There were several limitations in this study. First, this was a non-controlled single-arm clinical trial; therefore, the results of this study had not been compared with placebo or other medications. We did not administer a second arm for this trial because there is not any standard and defined treatment for EB ulcers and patients usually apply different or multiple medications for controlling the itching sensation and wound healing with different responses. Second, we used a researcher-made checklist for evaluating the patients. Although the face validity and content validity of this questionnaire were acceptable, we could not evaluate the internal validity of the questioner because of a low sample size of the study. Next, because of the rarity of the disease, the sample size of the study was low. Finally, the age range of the patients was wide (5–32 years); therefore, the parents evaluated the efficacy of the drug for children and this can be a probable confounding factor.

According to the results of this pilot study, the topical formulation of henna may be effective in the management of wound, itching, burning, stringing, and cutaneous warmness sensation in patients with EB. In this regard, we suggest further controlled clinical trials with larger sample sizes and longer duration of follow-up to evaluate the efficacy of this herbal medication.

Footnotes

Competing interests: The authors declare that there is conflict of interest, in the way that two individuals listed in authors' list, MMP and ZP, suffer from DEB and they participated in this clinical trial, but they did not have any role in response evaluation of the drug.

Authorship: Conception and design of the work: MN, MMP, MH, NS, MM, ZP; data collection: MN, NS, MM; analysis and interpretation of the data: MN, MH, MM, NS; statistical analysis: MMP, MM; drafting the manuscript: MN, MMP, NS, MM, ZP; critical revision of the manuscript: MMP, MM, NS, MH, Final approval: MN, MMP, MH, NS, MM, ZP

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References

1. Murrell DF. Life with epidermolysis bullosa (EB): Etiology, diagnosis, multidisciplinary care and therapy. J Am Acad *Dermatol.* 2009;61(6):1092–1093. doi: 10.1016/j.jaad.2009.06.011. [CrossRef] [Google Scholar]
2. Fine JD. Epidemiology of Inherited Epidermolysis Bullosa Based on Incidence and Prevalence Estimates From the National Epidermolysis Bullosa Registry. *JAMA dermatol.* 2016;152(11):1231–1238. doi: 10.1001/jamadermatol.2016.2473. [PubMed] [CrossRef] [Google Scholar]
3. Fine JD, Bruckner-Tuderman L, Eady RA, et al. Inherited epidermolysis bullosa: updated recommendations on diagnosis and classification. *J Am Acad Dermatol.* 2014;70(6):1103–1126. doi: 10.1016/j.jaad.2014.01.903. [PubMed] [CrossRef] [Google Scholar]
4. Fine JD. Inherited epidermolysis bullosa. *Orphanet J Rare Dis.* 2010;5(1):12. doi: 10.1186/1750-1172-5-12. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
5. Rizzo C, Anandasabapathy N, Walters RF, et al. Pretibial epidermolysis bullosa. *Dermatology online journal.* 2008 Oct 15;14(10):26. [PubMed] [Google Scholar]
6. El Hachem M, Zambruno G, Bourdon-Lanoy E, et al. Multicentre consensus recommendations for skin care in inherited epidermolysis bullosa. *Orphanet J Rare Dis.* 2014;9:76. doi: 10.1186/1750-1172-9-76. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
7. Aghili Khorasani MH, al-Advieh Makhzan. *Tehran: Tehran University of Medical Sciences.* 2009:341. [Google Scholar]
8. Arzani MA. *Teb-e-Akbari.* Qom, Iran: Jalaledin Publication; 2008. [Google Scholar]
9. Rafiei Z, Mazaheri M, Eghbali-Babadi M, Yazdannik A. The Effect of Henna (Lawsonia Inermis) on Preventing the Development of Pressure Ulcer Grade One in Intensive Care Unit Patients. *Int J Prev Med.* 2019;10:26. doi: 10.4103/ijpvm.IJPVM_286_17. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
10. Keshavarz A, Zeinaloo AA, Mahram M, Mohammadi N, Sadeghpour O, Maleki MR. Efficacy of Traditional Medicine Product Henna and Hydrocortisone on Diaper Dermatitis in Infants. *Iranian Red Crescent medical journal.* 2016 May;18(5):e24809. doi: 10.5812/ircmj.24809. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
11. Rekik DM, Ben Khedir S, Daoud A, Ksouda Moalla K, Rebai T, Sahnoun Z. Wound Healing Effect of Lawsonia inermis. *Skin Pharmacol Physiol.* 2019;32(6):295–306. doi: 10.1159/000501730. [PubMed] [CrossRef] [Google Scholar] 12. Niazi M, Mehrabani M, Namazi MR, et al. Efficacy of a topical formulation of henna (Lawsonia inermis L.) in contact dermatitis in patients using prosthesis: A double-blind randomized placebo-controlled clinical trial. *Complement Ther Med.* 2020:102316. doi: 10.1016/j.ctim.2020.102316. [PubMed] [CrossRef] [Google Scholar]
13. Jridi M, Sellimi S, Lassoued KB, et al. Wound healing activity of cuttlefish gelatin gels and films enriched by henna (Lawsonia inermis) extract. *Colloids Surf A Physicochem Eng Asp.* 2017;512:71–79. doi: 10.1016/j.colsurfa.2016.10.014. [CrossRef] [Google Scholar]
14. Negahdari S, Galehdari H, Kesmati M, Rezaie A, Shariati G. Wound healing activity of extracts and formulations of aloe vera, henna, adiantum capillus-veneris, and myrrh on mouse dermal fibroblast cells. *Int J Prev Med.* 2017;8:18. doi: 10.4103/ijpvm.IJPVM_338_16. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
15. Kulkarni S, Kale V, Velankar K. To study the Photodynamic antimicrobial activity of Henna extract and preparation of topical Gel formulation. *The Journal of Phytopharmacology.* 2018;7(3):242–252. [Google Scholar]
16. Nawasrah A, AlNimr A, Ali A. Antifungal effect of Henna against Candida albicans adhered to acrylic resin as a possible method for prevention of denture stomatitis. *Int J Environ Res Public Health.* 2016;13(5):520. doi: 10.3390/ijerph13050520. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
17. World Medical Association. Declaration of Helsinki: ethical principles for medical research involving human subjects. *Jama.* 2013;310(20):2191–2194. doi: 10.1001/jama.2013.281053. [PubMed] [CrossRef] [Google Scholar]
18. World Health Organization. *Quality control methods for herbal materials: updated edition of Quality control methods for medicinal plant materials, 1998.* WHO; 2011. [Google Scholar]

19. Akhtar N, Khan AB, Muhammad S, et al. Formulation and characterization of a cream containing terminalia chebula extract. *Forsch Komplementmed.* 2012;19(1):20–25. doi: 10.1159/000335823. [PubMed] [CrossRef] [Google Scholar]
20. Moldovan M, Lahmar A, Bogdan C, Părăuan S, Tomuță I, Crișan M. Formulation and evaluation of a water-in-oil cream containing herbal active ingredients and ferulic acid. *Clujul Med.* 2017;90(2):212–219. doi: 10.15386/cjmed-668. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
21. Shriwas S, Choukse R, Dwivedi S. Formulation and evaluation of herbal cream containing hydroalcoholic extract of Ipomea cairica Linn. for the treatment of gynecological disorders. *Acta Scientific Medical Sciences.* 2019;3(8):192–196. doi: 10.31080/ASMS.2019.03.0366. [CrossRef] [Google Scholar]
22. Garg A, Aggarwal D, Garg S, Singla AK. Spreading of semisolid formulations: an update. *Pharmaceutical technology North America.* 2002;26(9):84–105. [Google Scholar]
23. Rover MR, Brown RC. Quantification of total phenols in bio-oil using the Folin–Ciocalteu method. *J Anal Appl Pyrolysis.* 2013;104:366–371. doi: 10.1016/j.jaap.2013.06.011. [CrossRef] [Google Scholar]
24. Bruckner-Tuderman L. Dystrophic epidermolysis bullosa: pathogenesis and clinical features. *Dermatol Clin.* 2010;28(1):107–114. doi: 10.1016/j.det.2009.10.020. [PubMed] [CrossRef] [Google Scholar]
25. Pagliarello C, Tabolli S. Factors affecting quality of life in epidermolysis bullosa. *Expert Rev Pharmacoecon Outcomes Res.* 2010;10(3):329–338. doi: 10.1586/erp.10.28. [PubMed] [CrossRef] [Google Scholar]
26. Chogani F, Parvizi MM, Murrell DF, Handjani F. Assessing the quality of life in the families of patients with epidermolysis bullosa: The mothers as main caregivers. *Int J Womens Dermatol.* 2021;7(5Part B):721–726. doi: 10.1016/j.ijwd.2021.08.007. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
27. Shayegan LH, Levin LE, Galligan ER, et al. Skin cleansing and topical product use in patients with epidermolysis bullosa: Results from a multicenter database. *Pediatr Dermatol.* 2020;37(2):326–332. doi: 10.1111/pde.14102. [PubMed] [CrossRef] [Google Scholar]
28. Al Saif F. Henna beyond skin arts: Literatures review. *Journal of Pakistan Association of Dermatology.* 2016;26(1):58–65. [Google Scholar]
29. Jorjani SE. Zakhireh Kharazmshahi. *Ehyae teb-e-tabiei.* 2012 [Google Scholar]
30. Abdlaty R, Hayward J, Farrell T, Fang Q. Skin erythema and pigmentation: a review of optical assessment techniques. *Photodiagnosis and Photodynamic Therapy.* 2021;33:102127. [PubMed] [Google Scholar]
31. Ansari M, Dehsara F, Mosalaei A, Omidvari S, Ahmadloo N, Mohammadianpanah M. Efficacy of topical alpha ointment (containing natural henna) compared to topical hydrocortisone (1%) in the healing of radiation-induced dermatitis in patients with breast cancer: a randomized controlled clinical trial. *Iran J Med Sci.* 2013;38(4):293–300. [PMC free article] [PubMed] [Google Scholar]
32. Yucel I, Guzin G. Topical henna for capecitabine induced hand–foot syndrome. *I nvest New Drugs.* 2008;26(2):189–192. doi: 10.1007/s10637-007-9082-3. [PubMed] [CrossRef] [Google Scholar]
33. Shiravi AH, Alebooyeh M, Hojati V, Akbari H. The effect of extract of henna leaves (Lawsonia inermis) on skin wound healing in Wistar rats. *Journal of Animal Biology.* 2011;3(4):45–51. [Google Scholar]
34. Daemi A, Farahpour MR, Oryan A, Karimzadeh S, Tajer E. Topical administration of hydroethanolic extract of Lawsonia inermis (henna) accelerates excisional wound healing process by reducing tissue inflammation and amplifying glucose uptake. *Kaohsiung J Med Sci.* 2019;35(1):24–32. doi: 10.1002/kjm2.12005. [PubMed] [CrossRef] [Google Scholar]
35. Parvizi MM, Handjani F, Moein M, et al. Efficacy of cryotherapy plus topical Juniperus excelsa M. Bieb cream versus cryotherapy plus placebo in the treatment of Old World cutaneous leishmaniasis: A triple-blind randomized controlled clinical trial. *PLoS Negl Trop Dis.* 2017;11(10):e0005957. doi: 10.1371/journal.pntd.0005957. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
36. Jowkar F, Godarzi H, Parvizi MM. Can we consider silymarin as a treatment option for vitiligo? A double-blind controlled randomized clinical trial of phototherapy plus oral Silybum marianum product versus phototherapy alone. *J Dermatolog Treat.* 2019:1–5. doi: 10.1080/09546634.2019.1595506. [PubMed] [CrossRef] [Google Scholar]
37. Qarshi IN. *Al-Mujaz fi al-Tibb.* Islamic Heritage Revival Committee, Supreme Council for Islamic Affairs, Ministry of Endowments; 2004. [Google Scholar]
38. Nesa L, Munira S, Mollika S, Islam M. Evaluation of analgesic, anti-inflammatory and CNS depressant activities of methanolic extract of Lawsonia inermis barks in mice. *Avicenna J Phytomed.* 2014;4(4):287–296. [PMC free article] [PubMed] [Google Scholar]
39. Imam H, Mahbub NU, Khan MF, Hana HK, Sarker MMR. Alpha Amylase Enzyme Inhibitory and Anti-inflammatory Effect of Lawsonia inermis. *Pak J Biol Sci.* 2013;16(23):1796–1800. doi: 10.3923/pjbs.2013.1796.1800. [PubMed] [CrossRef] [Google Scholar]

40. Nawaf AM, Joshi A, Nour-Eldin O. Acute allergic contact dermatitis due to para-phenylenediamine after temporary henna painting. *J Dermatol.* 2003;30(11):797–800. doi: 10.1111/j.1346-8138.2003.tb00480.x. [PubMed] [CrossRef] [Google Scholar]
41. del Boz J, Martin T, Samaniego E, Vera A, MorON D, Crespo V. Temporary localized hypertrichosis after henna pseudotattoo. *Pediatr Dermatol.* 2008;25(2):274–275. doi: 10.1111/j.1525-1470.2008.00654.x. [PubMed] [CrossRef] [Google Scholar]
42. Matulich J, Sullivan J. A temporary henna tattoo causing hair and clothing dye allergy. *Contact Dermatitis.* 2005;53(1):33–36. doi: 10.1111/j.0105-1873.2005.00626.x. [PubMed] [CrossRef] [Google Scholar]
43. Sidwell RU, Francis ND, Basarab T, Morar N. Vesicular erythema multiforme-like reaction to para-phenylenediamine in a henna tattoo. *Pediatr Dermatol.* 2008;25(2):201–204. doi: 10.1111/j.1525-1470.2008.00634.x. [PubMed] [CrossRef] [Google Scholar]
44. Lee SWH, Lai NM, Chaiyakunapruk N, Chong DWK. Adverse effects of herbal or dietary supplements in G6PD deficiency: a systematic review. *Br J Clin Pharmacol.* 2017;83(1):172–179. doi: 10.1111/bcp.12976. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
45. Poursadra E, Anvari-Tafti M, Dehghani A, Eghbali-Babadi M, Rafiei Z. Comparing the Effect of Henna Oil and Olive Oil on Pressure Ulcer Grade One in Intensive Care Units Patients. *Adv Biomed Res.* 2019;8:68. doi: 10.4103/abr.abr_207_19. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
46. Vahabi S, Hakemi-Vala M, Gholami S. In vitro Antibacterial Effect of Hydroalcoholic Extract of Lawsonia inermis, Malva sylvestris, and Boswellia serrata on Aggregatibacter actinomycetemcomitans. *Adv Biomed Res.* 2019;8:22. doi: 10.4103/abr.abr_205_18. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
47. Zheng Y, Hu Y, Liu K, Lu Y, Hu Y, Zhou X. [Therapeutic effect of Impatiens balsamina, Lawsonia inermis L. and Henna on androgenetic alopecia in mice]. *Nan Fang Yi Ke Da Xue Xue Bao.* 2019;39(11):1376–1380. doi: 10.12122/j.issn.1673-4254.2019.11.17. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

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4.2 Use Clove Oil in Psoriasis

Cloves (*Syzygium aromaticum*, also known as *Eugenia caryophyllata*) are the aromatic flower buds of a tree in the *Myrtaceae* family native to Indonesia. The essential oil of clove is known to exhibit antioxidant, anti-inflammatory, antimicrobial, antifungal, antiviral, anticancer, cytotoxic, insect repellent, and anaesthetic activities.1,2 It is used topically in herbal medicine to alleviate pain and facilitate healing,3 and has been used in traditional medicine to confer analgesic, anti-inflammatory, antimicrobial, antiviral, and antiseptic activity.4 Cloves also are used in fragrances and for food flavoring.2

The two main constituents of clove oil are eugenol (78%) and beta-caryophyllene (13%). Although clove oil and its primary components are generally recognized as safe, a 2006 *in vitro* study by Prashar et al. found that clove oil and eugenol displayed cytotoxicity toward human fibroblasts and endothelial cells. Clove oil, in concentrations as low as 0.03%, was noted for being exceedingly cytotoxic, with up to 73% of this effect ascribed to eugenol, with beta-
caryophyllene displaying no toxicity.3 In addition to beta-caryophyllene and the phenylpropanoid eugenol, other important constituents of clove essential oil are the phenylpropanoids carvacrol, thymol, and cinnamaldehyde.2

4.3 Use Curcumin in Psoriasis

Abstract

Curcumin is a polyphenol derived from the golden spice turmeric, which is widely used for different purposes, such as culinary spice and alimentary addictive, make - up and, finally, as a natural product for the treatment of different diseases, especially for the chronic inflammatory ones. Recently, curcumin has been proposed as a valid and safe therapeutic option for psoriasis.

Introduction

The traditional medicine, based on the administration of natural and herbal products for the treatment of several human diseases, has been employed by many different cultures throughout history, becoming today a real multi millionary industry, with a recorded cost of USD 10 billion/year.

Among the numerous herbal compounds available for the medical purpose, there is Curcumin, a polyphenol derived from the golden spice turmeric ("Curcuma longa"), of the Zinzigiberaceae family, characterised by many properties.

Since ancient time, Curcumin has been widely used for different purposes, such as culinary spice and alimentary addictive (e.g. ice cream, yogurt, orange juice, biscuits, popcorn, cakes, cereals, sauces, gelatins), make - up and, finally,
as natural product for the treatment of different diseases, especially for the chronic inflammatory ones.

Although, its well - known effectiveness as a therapeutic herb, curcumin pharmacological properties have been scientifically proved only in the last century. Today, it is clear how the wide range of use of curcumin in medicine is the result of its numerous properties, such as antioxidant, anti-inflammatory, anti - proliferative, anti-carcinogenic and anti-microbial ones.

In medicine, curcumin is used for the treatment of different diseases, like rheumatoid arthritis, eye diseases (e.g. chronic anterior uveitis, conjunctivitis), urinary tract infections, menstrual alterations, liver and gastrointestinal disorders (e.g. abdominal pain, inflammatory bowel disease). Furthermore, curcumin is used as adjuvant therapy for the treatment of skin cancers, chicken pox and wound healing.

Even if it may be assumed with diet, curcumin is now formulated into tablets, at a different dosage, often associated to particular adjuvants (e.g. piperine, phospholipids), which lead to improving its absorption and bioavailability.

Curcumin and psoriasis

Psoriasis is a chronic, inflammatory, cell-mediated disease, which involves the skin, and sometimes joints, bones, tendons, ligaments, nails, and mucosal membranes. Although it may represent with different clinical variants, the most
commonly described is the "vulgaris" one, which is characterised by erythematous round or oval lesions, covered by white-silvery scales. Cutaneous lesions are usually localised on the elbows, knees, scalp and lumbar-sacral region in a symmetric pattern, even if they can affect different body areas.

Despite the availability of different topical and systemic therapeutic options for the treatment of psoriasis, none of them provides excellent clinical results without the risk of side effects (TABLE 1)

Table 1

Common antipsoriatic therapies

Drugs	MoA
TOPICAL Corticosteroids	Immunosoppressive; anti-inflammatory; anti- proliferative;
Soothing: urea, allantoin, lanolin	vasocostriction Anti-inflammatory
Keratolytics: salicylic acid 3 - 6%,	↓ cell – to - cell cohesion in the stratum corneum
Alpha - Hydroxy acids (lactic acid, →	
propylene glycol), emollients, Help to remove accumulated scales or hyperkeratosis	
bath	Anti - proliferative effect; anti-inflammatory effect
Anthralin (Dithranol, 1, 8 –	Keratoplastic; anti-acanthotic; photosensitizing (absorption
Dihydroxy – 9 - anthrone)	Tars spectrum of 330-550 nm); vasocostrictive
(coal tars and wood tars)	Normalize the abnormal differentiation of keratinocytes;
Retinoids: tarazotene	antiproliferative affects on keratinocytes; ↓ expression of
Derivatives and analogues of	inflammatory markers on keratinocytes (e.g. HLA - DR,
vitamin D3: calcipotriol, tacalcitol,	ICAM - I)
calcitriol	Regulation of epidermal hyperproliferation; enhancement
Calcineurin inhibitors: Tacrolimus,	of normal keratinisation; immunomodulating; anti-
Pimecrolimus	inflammatory; angiogenesis inhibition Immunosuppression
PHOTOTHERAPY PUVA therapy	UVB, nbUVB, Cell cycle arrest; immunosuppression
excimer laser	Cell cycle arrest; immunosoppression
SYSTEMIC Methotrexate	Acitretin Antiproliferative; anti-inflammatory Normalize the
Cyclosporin A	Fumaric acid esters abnormal differentiation of keratinocytes; antiproliferative
Hydroxyurea	Sulfasalazine affects on keratinocytes Inhibition of CD4 T cells
Mycophenolate mofetil	6 - Immunomodulation Regulation of proliferating cells
Thioguanine	Antiinflammatory Immunomodulator Cell cycle arrest
BIOLOGICS Etanercep, Infliximab, Anti TNFα	
Adalimumab	

In the last years, an increasing number of studies underline the potential use of curcumin in the treatment of psoriasis.

Many are the evidence which supports its therapeutic efficacy. The first one is that curcumin, with its antioxidative property, may reduce the oxidative stress of psoriatic lesions. More recently, two different studies showed how curcumin therapeutic efficacy might also be related to its ability in inhibiting the phosphorylase kinases, which are increased in psoriatic patients. Also interesting are the results, achieved by Varma et Al., about the use of curcumin at 25 and 50 μM concentrations in the treatment of psoriatic - like cells (HaCaT cells), in vitro. The authors showed how curcumin was able to inhibit the proliferation of psoriatic - like cells, by the down-regulation of pro-inflammatory cytokines, such as interleukin - 17, tumour necrosis factor - α, interferon - γ and interleukin - 6. Moreover, curcumin significantly enhanced the skin - barrier function by the up-regulation of involucrin (iNV) and filaggrin (FLG).

Recently, Kang D. et Al. have proved, on mice models, another important effect of curcumin, consisting in the inhibition of the potassium channels (subtypes Kv1.3) expressed on T cells, which seem to be involved in the onset of psoriasis. The anti-inflammatory properties of curcumin, have been confirmed by the finding that mice, showed in their serum a decrease of more than 50% level of inflammatory factors, including TNF - α, IFN - γ, IL - 2, IL - 12, IL - 22 and IL - 23.

No study in vivo have shown side effects of curcumin in the treatment of psoriatic patients, and the U.S. Food and Drug Administration (FDA) has defined curcumin as “generally regarded as safe” (GRAS).

In conclusion, curcumin is a polyphenol derived from the golden spice turmeric (“Curcuma longa”). Because of its numerous properties (e.g. anti - oxidant, anti -proliferative, anti-inflammatory, antiviral, antibacterial and antifungal properties), curcumin has been used for the treatment of different diseases. Recently it has been proposed for the treatment of psoriasis, where its efficacy seems to be the result of different mechanism of actions. Even if different studies, both in vitro and in vivo, have shown its efficacy and safe profile, further placebo-controlled studies are needed before recommending oral curcumin as a valid treatment for psoriasis.

References

1. Garodia P, Ichikawa H, Malani N, et al. From ancient medicine to modern medicine:Ayurvedic concepts of health and their role in inflammation and cancer. J Soc Integr Oncol. 2007;5:25–37. https://doi.org/10.2310/7200.2006.029 PMid:17309811. [PubMed] [Google Scholar]
2. Ammon HP, Wahl MA. Pharmacology of Curcuma longa. Planta Medica. 1991;57(1):1–
7. https://doi.org/10.1055/s-2006-960004 PMid:2062949. [PubMed] [Google Scholar]
3. Gupta SC, Patchva S, Koh W, et al. Discovery of curcumin, a component of golden spice, and its miraculous biological activities. Clin Exp Pharmacol Physiol. 2012;39(3):283–99. https://doi.org/10.1111/j.1440-1681.2011.05648.x PMid:22118895 PMCid:PMC3288651. [PMC free article] [PubMed] [Google Scholar]
4. Oppenheimer A. Turmeric (curcumin) in biliary diseases. Lancet. 1937;229:619–21. https://doi.org/10.1016/S0140-6736(00)98193-5. [Google Scholar]
5. Maheshwari RK, Singh AK, Gaddipati J, et al. Multiple biological activities of curcumin:a short review. Life Sci. 2006;78:2081–2087. https://doi.org/10.1016/j.lfs.2005.12.007 PMid:16413584. [PubMed] [Google Scholar]
6. Kim EJ, Lewis DJ, Dabaja BS, et al. Curcumin for the treatment of tumor - stage mycosis fungoides. Dermatol Ther. 2017;30(4) https://doi.org/10.1111/dth.12511. [PubMed] [Google Scholar]
7. Mills S, Bone K. Principles and Practice of Phytotherapy. Toronto, ON: Churchill Livingstone; 2000. [Google Scholar]
8. Dixit VP, Jain P, Joshi SC. Hypolipidaemic effects of Curcuma longa L. and Nardostachys jatamansi, DC in triton-induced hyperlipidaemic rats. Indian J Physiol Pharmacol. 1988;32:299–304. PMid:3215683. [PubMed] [Google Scholar]
9. Bundy R, Walker AF, Middleton RW, et al. Turmeric extract may improve irritable bowel syndrome symptomology in otherwise healthy adults:A pilot study. J Altern Complement Med. 2004;10:1015–
8. https://doi.org/10.1089/acm.2004.10.1015 PMid:15673996. [PubMed] [Google Scholar]
10. Hanai H, Sugimoto K. Curcumin has bright prospects for the treatment of inflammatory bowel disease. Curr Pharm Des. 2009;15:2087–94. https://doi.org/10.2174/138161209788489177 PMid:19519446. [PubMed] [Google Scholar]
11. Anand P, Kunnumakkara AB, Newman RA, et al. Bioavailability of curcumin:problems and promises. Mol Pharm. 2007;4:807–18. https://doi.org/10.1021/mp700113r PMid:17999464. [PubMed] [Google Scholar]
12. Lotti T, Hercogovaà J, Prignano F. The concept of psoriatic disease:can cutaneous psoriasis any longer be separated by the systemic comorbidities? Dermatol Ther. 2010;23(2):119–22. https://doi.org/10.1111/j.1529-8019.2010.01305.x PMid:20415818. [PubMed] [Google Scholar]
13. Goren A, Salafia A, McCoy J, et al. Novel topical cream delivers safe and effective alternative to traditional psoriasis phototherapy. Dermatol Ther. 2014;27(5):260–3. https://doi.org/10.1111/dth.12132 PMid:24773915. [PubMed] [Google Scholar]
14. Lotti T, Hercogovaà J. Successful treatment of psoriasis with low-dose per os interleukins 4, 10, and 11. Dermatol Ther. 2015;28(1):1–2. https://doi.org/10.1111/dth.12174 PMid:25286191. [PubMed] [Google Scholar]
15. Lotti T. Something new under the sun in the field of psoriasis? Dermatol Ther. 2010;23(2):99–
100. https://doi.org/10.1111/j.1529-8019.2010.01302.x PMid:20415815. [PubMed] [Google Scholar]
16. Farahnik B, Nakamura M, Singh RK, et al. The Patient's Guide to Psoriasis Treatment. Part 2:PUVA Phototherapy. Dermatol Ther (Heidelb) 2016;6(3):315–24. https://doi.org/10.1007/s13555-016-0130-9 PMid:27474030 PMCid:PMC4972736. [PMC free article] [PubMed] [Google Scholar]
17. Fioranelli M, Roccia MG, Lotti T. Risankizumab versus ustekinumab for moderate-to-severe plaque psoriasis. Dermatol Ther. 2017;30(5) https://doi.org/10.1111/dth.12507. [PubMed] [Google Scholar]
18. Barygina V, Becatti M, Soldi G, et al. Altered redox status in the blood of psoriatic patients:involvement of NADPH oxidase and role of anti-TNF-αtherapy. Redox Rep. 2013;18(3):100–
6. https://doi.org/10.1179/1351000213Y.0000000045 PMid:23601139. [PMC free article] [PubMed] [Google Scholar]
19. Reddy S, Aggarwal BB. Curcumin is a non - ompetitive and selective inhibitor of phosphorylase kinase. FEBS Lett. 1994;341(1):19–22. https://doi.org/10.1016/0014-5793(94)80232-7. [PubMed] [Google Scholar]
20. Heng MC, Song MK, Harker J, et al. Drug-induced suppression of phosphorylase kinase activity correlates with resolution of psoriasis as assessed by clinical, histological and immunohistochemical parameters. Br J Dermatol. 2000;143(5):937–49. https://doi.org/10.1046/j.1365-2133.2000.03767.x PMid:11069500. [PubMed] [Google Scholar]
21. Varma SR, Sivaprakasam TO, Mishra A, et al. Imiquimod-induced psoriasis-like inflammation in differentiated Human keratinocytes:Its evaluation using curcumin. *Eyr J Pharmacol.* 2017;813:33–
41. https://doi.org/10.1016/j.ejphar.2017.07.040 PMid:28736282. [PubMed] [Google Scholar]

22. Kang D, Luo L, Jiang W, et al. Curcumin shows excellent therapeutic effect on psoriasis in mouse model. Biochimie. 2016;123:73–80. https://doi.org/10.1016/j.biochi.2016.01.013 PMid:26826458. [PubMed] [Google Scholar]
23. Kurd SK, Smith N, VanVoorhees A, Troxel AB, Badmaev V, Seykora JT, et al. Oral curcumin in the treatment of moderate to severe psoriasis vulgaris:a prospective clinical trial. J A Acad Dermatol. 2008;58(4):625–31. https://doi.org/10.1016/j.jaad.2007.12.035 PMid:18249471 PMCid:PMC4131208. [PMC free article] [PubMed] [Google Scholar]
24. Blumenthal M, Goldberg A, Brinckmann J. Herbal Medicine:Expanded Commission E Monographs. Newton, MA: Integr Med Comm; 2000. pp. 379–84. [Google Scholar]
25. Aggarwal BB, Harikumar KB. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, ulmonary, metabolic, autoimmune and neoplastic diseases. Int J Biochem Cell Biol. 2009;41(1):40–59. https://doi.org/10.1016/j.biocel.2008.06.010 PMid:18662800 PMCid:PMC2637808. [PMCfree article] [PubMed] [Google Scholar]

4.4 Use Kapoor/ Camphora in Psoriasis

Abstract

In this study, we investigated the therapeutic potential of *Cinnamomum camphora* leaves on allergic skin inflammation such as atopic dermatitis. We evaluated the effects of *C. camphora* leaves on human adult low-calcium high-temperature keratinocytes and atopic dermatitis mice. *C. camphora* leaves inhibited Macrophage-derived chemokine (an inflammatory chemokine) production in interferon-γ (10 ng/mL) stimulated Human adult low-calcium high-temperature keratinocytes in a dose dependent manner. *C. camphora* leaves suppressed the phosphorylation of janus kinase signal transducer and activator of transcription 1. *C. camphora* leaves also suppressed the phosphorylation of extracellular signal-regulated kinase 1/2, a central signaling molecule in the inflammation process. These results suggest that *C. camphora* leaves exhibits anti-inflammatory effect via the phosphorylation of signal transducer and activator of transcription 1 and extracellular signal-regulated kinase 1/2. To study the advanced effects of *C. camphora* leaves on atopic dermatitis, we induced experimental atopic dermatitis in mice by applying 2,4-dinitrochlorobenzene. The group treated with *C. camphora* leaves (100 mg/kg) showed remarkable improvement of atopic dermatitis symptoms: reduced serum immunoglobulin E levels, smaller lymph nodes with reduced thickness and length, decreased ear edema, and reduced levels of inflammatory cell infiltration in the ears. Interestingly, the effects of *C. camphora* leaves on atopic dermatitis symptoms were stronger than those of hydrocort cream, a positive control. Taken together, *C. camphora* leaves showed alleviating effects on the inflammatory chemokine production *in vitro* and atopic dermatitis symptoms *in vivo*. These results suggest that *C. camphora* leaves help in the treatment of allergic inflammation such as atopic dermatitis.

Keywords: Atopic dermatitis, *Cinnamomum camphora*, 2,4-Dinitrochlorobenzene, Inflammation, Immunoglobulin E, Signal transducer and activator of transcription 1

INTRODUCTION

Allergic skin inflammation such as atopic dermatitis (AD) is characterized by skin barrier dysfunction, edema, and infiltration of various types of inflammatory cells. AD is a chronic skin disease associated with skin hyper-reactivity, including edema and itching, which affects approximately 10–20% of children and 1–3% of adults worldwide (1). This systemic disorder is characterized by thickening of the papillary dermis, parakeratosis, skin barrier dysfunction, epidermal hyperplasia, severe skin dehydration, and T-cell hyper-proliferation. The skin lesions in AD patients are characterized by the proliferation and infiltration of various inflammatory cells, mainly eosinophils, mast cells, basophils, and T cells (2,3). Mast cells play an important role in the inflammatory process and anaphylactic reactions.

Immunoglobulin (Ig) E is a crucial therapeutic target for AD, as it is the major activator of mast cells, which release histamine, tryptase, and cytokine (4).

Chemokine is a group of factors that control the activity of white blood cells, and serve to control the infiltration of inflammatory cells (5). It is closely related to various pathological processes, such as inflammation, allergy, and infectious diseases. Furthermore, chemokine is also known to be involved in the generation and maturation of immune cells, and differentiation of T cells (5,6). Macrophagederived chemokine (MDC/CCL22) is a typical inflammatory chemokine and a ligand for CC chemokine receptor 4 (CCR4), which is predominantly expressed on Th2 lymphocytes, basophils and natural killer cells (7,8). Previous studies showed that the MDC level is elevated in the serum and skin lesions of patients with AD, suggesting that keratinocyte-generated chemokines are key mediators in the drawing of inflammatory lymphocytes to the skin (9–11).

Interferon (IFN)-γ, one of the multifunctional cytokines that have antiviral, anti-tumor, and immunomodulatory effects, is produced predominantly in T cells and natural killer (NK) cells (12). Upon binding to IFN-γ, the IFN-γ receptors (IFN-γR1 and IFN-γR2) rapidly associate with Janus tyrosine kinases (JAK) 1 and JAK2. JAK1 and JAK2 phosphorylate with one another and then subsequently phosphorylate the IFN-γ receptor, forming a docking moiety for the cytoplasmic transcription factor named signal transducer and activator of transcription (STAT) 1, a member of the STAT protein family (13,14). STAT1 phosphorylation plays a critical role in the IFN-mediated innate immunity to microbial infection, especially inflammatory responses (15,16). IFN-γ also stimulates the activation of p38, extracellular signal regulated kinase 1/2 (ERK1/2), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (17,18).

C. camphora (known as camphor tree) has glossy and waxy leaves and grows in the southern part of Jeju Island in Korea. For a long time, people in Jeju have believed that the unique odor of camphor tree drives away demons. Camphor oil that is extracted from the wood of camphor trees has been used traditionally for the relief of pain and inflammation in joints and muscles for many years (19). Other volatile oil variants (linalool, 1,8-cineole, nerolidol, safrole, and borneol) distilled from camphor trees exhibit the antifungal or molluscicidal activities (20–22). In a previous study, we reported the anti-oxidative and anti-inflammatory effects of *C. camphora* leaves in the cellular levels (23). There are few studies on the other chemical constituents of *C. camphora*. Therefore, in this study, the pharmacological effects of *C. camphora* on the cellular and animal allergic inflammatory events were investigated to determine its therapeutic potential for AD.

MATERIALS AND METHODS

Reagents

C. camphora leaves extract (80% EtOH extract, CCex) was provided from Jeju Biodiversity Research Institute (JBRI- 10135). Human interferon-γ (hIFN-γ: recombinant *E. coli*) was purchased from Gibco (Grand Island, NY, USA), and MDC enzyme linked immunosorbent assay (ELISA) duoset kit was obtained from R&D system (St. Louis, MO, USA). Anti- STAT1 antibody was purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA). Anti-phospho-STAT1 antibody was purchased from Cell signaling (Beverly, MA, USA), and anti-β-actin antibody, Epigallocatechingallate (EGCG) was obtained from Sigma Chemical Co (St. Louis, MO, USA). Dinitrochlorobenzene (DNCB) was purchased from Tokyo Kasei Kogyo (Tokyo, Japan). All other chemicals and reagents were of reagent grade.

Experimental animals

BALB/c mice (female, 7-weeks-old) were purchased from Orient Bio (Orient Bio Inc., Seongnam, Korea) and maintained under pathogen-free conditions in the animal facility of Jeju National University. All animal experiments were approved by the Jeju National University Animal Care and Use Committee.

DNCB application to induce AD

Mice were divided into four groups (n = 8 per group): saline (normal), AD (induction-only), AD + Hydrocort cream, and AD + CCex. Mice were sensitized by applying 1% 2,4-dinitrochlorobenzene (DNCB) or vehicle on their abdomen as the first sensitization (day-7). On day 0, mice were challenged again by applying 0.3% DNCB to the ears on every other day for up to 30 days. Starting on day 12, the mice were treated with hydrocort cream (Green Cross, Yongin, Korea) containing 2mg/g hydrocortisone valerate and CCex (10 and 100 mg/kg) on their ears every other day. The mice were sacrificed on day 31.

Cell culture and cell viability

following the manufacturer's protocol. Briefly, cells were seeded into the wells of a 96-well plate and treated with IFN-γ (10 ng/mL) in the absence or presence of CCex for 24 hr. A solution of 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-*2H* tetrazolium (WST) was added to each well and incubated for 1 hr in an incubator. Then, the absorbance of each well was measured at 450 nm with a VersaMax ELISA microplate reader (Molecular Devices Inc., Sunnyvale, CA, USA).

Enzyme-linked immunosorbent assays (ELISA)

Secretion of the MDC protein into the supernatant of cultured cells was measured by using an ELISA kit (R&D Systems Inc., Minneapolis, MN, USA) according to the manufacturer's instructions. Briefly, HaCaT cells were stimulated with IFN-γ in the presence of CCex for 24 hr. The cell culture medium was transferred to a 96-well culture plate coated with MDC antibody and treated according to the manufacturer's (R&D Systems) instructions. Absorbance at 450 nm was recorded by using the VersaMax ELISA microplate reader (Molecular Devices, Sunnyvale, CA, USA).

Western blot analysis

The cells were washed twice with ice-phosphate buffered saline (PBS). The cells were disrupted in the lysis buffer (iNtRON Biotechnology, Gyeonggi, Korea) for 30 min on ice. Protein of the supernatants was quantified via the Bradford assay (Bio-rad, Herculers, CA, USA). Aliquots of the lysates were separated on a NuPAGE 4–12% bis-Tris gel (Invitrogen, Carlsbad, CA, USA). The proteins were transferred onto a polyvinylidene difluoride (PVDF) membrane using an iBlot gel transfer device (Invitrogen). Then membranes were blocked with 5% non-fat skim milk solution diluted Tween 20-tris buffered saline (TTBS), and the membranes were incubated with primary antibodies diluted in 1% bovine serum albumin (BSA)-TTBS buffer at 4°C overnight. After washing, the membrane was incubated with secondary HRP-linked anti-rabbit or anti-mouse IgG respectively for 90 min at room temperature. After washing again, immune active proteins were determined with WEST-ZOL (plus) western blot detection system (iNtRON Biotechnology) according to the manufacturer's instructions.

Macroscopic edema and histology

In the experimental AD mouse model, DNCB stimulation elicited ear edema, and ear thickness was measured using a Digital Thickness Gauge (Mitutoyo, Kawasaki, Japan). Ear tissues were fixed in 10% formalin, and then embedded in paraffin. Paraffin sections (3 μM each) were stained with by hematoxylin and eosin (H&E).

Statistical analysis

Quantity One version 4.2.1 (Bio-Rad) and Image-Pro plus version 4.5 software (Media Cybernetics, Silver Spring, MD, USA) were used to transform images into numerical values. Student's *t*-test and two-way analysis of variance were used to determine the statistical significance of differences between experimental and control groups. Data are shown as mean ± standard deviation. *P*-values less than 0.05 were considered statistically significant.

RESULTS

Effect of CCex on the MDC production in the IFN-γ-stimulated HaCaT keratinocytes

We first examined the cell cytotoxicity of CCex against HaCaT cells. The cells were treated with different concentrations of CCex (12.5, 25, 50, and 100 μg/mL) for 24 hr. Cell viability was determined using the EZ-cytox-enhanced cell viability assay kit (itsBIO). As shown in Fig. 1A CCex did not exhibit cytotoxicity to HaCaT keratinocytes at the assayed concentrations. Then, we evaluated the inhibitory effect of CCex on inflammatory chemokine (MDC) production in IFN-γ (10 ng/mL)-stimulated HaCaT keratinocytes. Results showed that CCex suppressed the production of MDC by IFN-γ in a concentration-dependent manner (Fig. 1B).

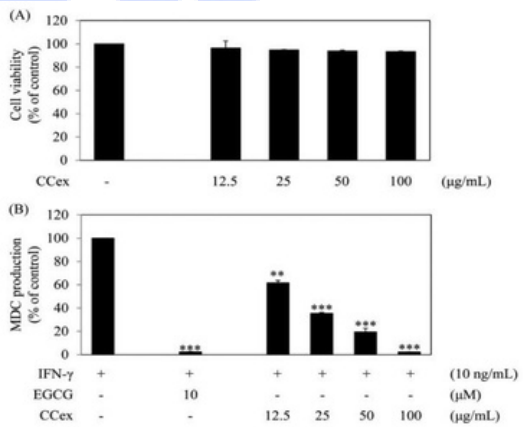

Fig. 1

Effect of CCex on the MDC production in the IFN-γ-stimulated HaCaT keratinocytes. (A) Cells (1.5 x 105 cells/mL) were pre-incubated for 18 hr, and then treated with IFN-γ (10 ng/mL) in the presence or absence of CCex for 24 hr (12.5–100 μg/mL). Cell viability was determined by the WST assay. (B) Cells (1.5 × 105 cells/mL) were pre-incubated for 18 hr and then treated with CCex (12.5–100 μg/mL) in the presence of IFN-γ (10 ng/mL) for 24 hr. The amounts of MDC were measured from the culture supernatants by ELISA. EGCG was used as a positive control. Data are the mean ± SD of three independent experiments. $^{**}p < 0.01$ and $^{***}p < 0.001$ vs. CCex-untreated cells in the presence of IFN-γ.

Effect of CCex on the phosphorylation of STAT1 in IFN-γ-stimulated HaCaT keratinocytes

STAT1 protein is a crucial and specific regulator of IFN-γ-induced signals that control the transcription of target genes, including MDC (13,14,24,25). Therefore, we assayed the effect of CCex on the activation of STAT1 in IFN-γ-treated HaCaT keratinocytes, and detected a high level of phosphorylated STAT1 15 min after cytokine treatment. The pretreatment of cells with CCex for 120 min suppressed STAT1 (tyrosine 701 and serine 727) phosphorylation in a dose dependent manner (Fig. 2).

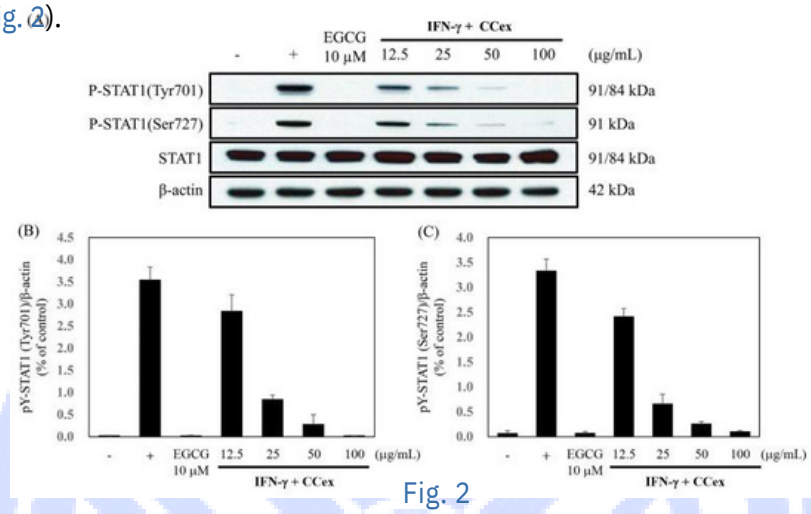

Fig. 2

Effect of CCex on the phosphorylation of STAT1 in IFN-γ-stimulated HaCaT keratinocytes. (A) Cells (5.0 × 105 cells/mL) were pretreated with CCex (12.5–100 μg/mL) for 120min and stimulated with IFN-γ (10 ng/mL) for 120 min. The levels of phosphorylated STAT1 (Tyr701, Ser727) were assessed by Western blotting from whole cell lysates. (B, C) Data represent the density ration of STAT 1 (Tyr701) and STAT1 (Ser727) phosphorylation in IFN-γ-stimulated HaCaT keratinocytes. EGCG was used as a positive control.

Effect of CCex on the phosphorylation of ERK1/2 in IFN-γ-stimulated HaCaT keratinocyte

The mitogen-activated protein kinase (MAPK)s pathway is reportedly involved in the production of inflammatory chemokines, and IFN-γ activates the receptor-associated MAPKs depending on the cell type (17,18). Thus, we investigated the involvement of these signaling kinases in IFN-γ-induced MDC production in HaCaT cells. We first determined the time dependent activation of three MAPKs (ERK1/2, c-jun N-terminal kinase (JNK), and p38) after IFN-γ treatment. IFN-γ induced the phosphorylation of ERK1/2 at 5 min, whereas there was no effect on the phosphorylation of JNK and p38 (data not shown). Then we examined the inhibitory effect of CCex on ERK1/2 activation in IFN-γ-stimulated HaCaT cells. As shown in Fig. 3, CCex suppressed the ERK1/2 phosphorylation at the concentrations of 25, 50, and 100 μg/mL.

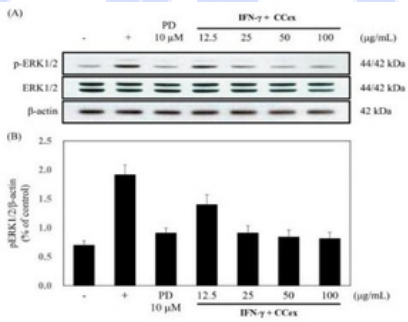

Fig. 3

Effect of CCex on the phosphorylation of ERK1/2 in IFN-γ-stimulated HaCaT keratinocyte. (A) Cells (5.0 × 105 cells/mL) were pretreated with CCex (12.5–100 μg/mL) for 120 min and stimulated with IFN-γ (10 ng/mL) for 5min. The levels of phosphorylated ERK1/2 were assessed by Western blotting from whole cell lysates. (B) Data represent the density ratio of ERK1/2 phosphorylation in IFN-γ-stimulated HaCaT keratinocytes. PD98059 (ERK1/2 inhibitor) was used as a positive control.

CCex decreases serum IgE level

To induce AD experimentally, mice were subjected to initial sensitization with 1% DNCB on the abdomen. They were then resensitized by applying 0.3% DNCB to the ears every other day for up to 31 days. Starting on day 12, the mice were treated with hydrocortisone cream and CCex (10 and 100 mg/kg) on the ears every other day. All mice were sacrificed on day 31 (Fig. 4A). IgE is a crucial therapeutic target for AD, as it is the major activator of mast cells, which release histamine, tryptase, and cytokine (4). Therefore, we measured serum IgE levels in mice with dermatitis by using ELISA method. The CCex-treated group showed significantly decreased levels of IgE ($p < 0.05$) compared with the induction group (Fig. 4B).

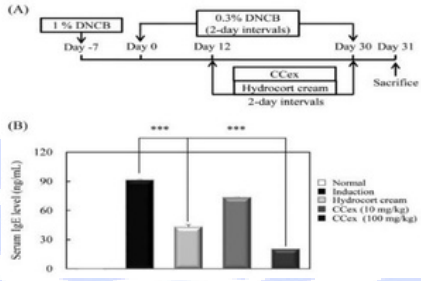

Fig. 4

CCex decreases serum IgE level. (A) Mice were sensitized by applying 1% DNCB or vehicle on their abdomen as the first sensitization (day-7). On day 0, mice were challenged again by applying 0.3% DNCB to the ears on every other day for up to 30 days. Starting on day 12, the mice were treated with hydrocort cream and CCex (10 and 100 mg/kg) on their ears every other day. The mice were sacrificed on day 31. (B) After sacrifice, the IgE in mouse serum was measured by ELISA. Values represent the mean ± SD. ***p< 0.001 compared to mice stimulated with DNCB alone (induction group).

CCex alleviates the development of experimental AD

The skin lesions associated with AD are characterized by infiltration of various inflammatory cells (26,27). Therefore, we determined whether CCex treatment alleviates the inflammatory cell infiltration in the ears of AD mice. We also tested skin swelling as a measure of AD progression. We found that cutaneous edema in CCex - treated mice was reduced on day 29 ($p < 0.05$) compared with that in the induction-only mice (Fig. 5A, 5B). We next examined the effect of CCex on the infiltration of inflammatory cells by H&E staining of ear tissue sections. Epidermal thickness and the degree of inflammatory cell infiltration were significantly lower in the CCex-treated group than in the induction group (Fig. 5C). Lymph node (LN)s play a crucial role in cell-mediated immunity by regulating the activity of T and B cells (28). Therefore, we examined the morphologic changes in the LNs of AD mice. The LNs of mice in the induction-only group were quite swollen, whereas those in CCex-treated mice were smaller (Fig. 5D).

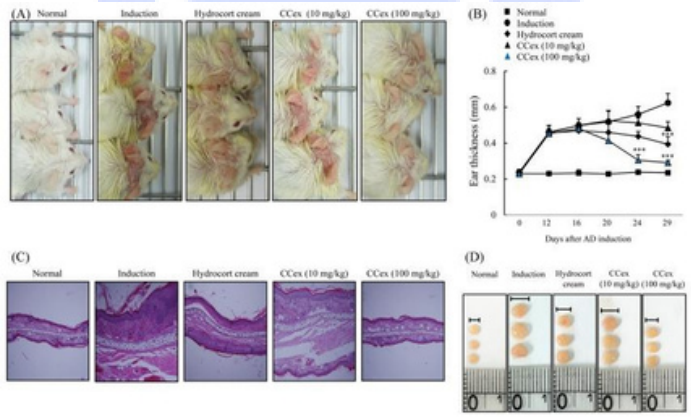

Fig. 5

CCex alleviates the development of experimental AD. (A) Photos of the ears. (B) Ear thickness at indicated days. (C) Paraffin-embeded sections of ear tissue stained with hematoxylin and eosin. (D) Photos of the lymph nodes (LNs). Values represent the mean ± SD. ***p< 0.001 compared to mice stimulated with DNCB alone (induction group).

DISCUSSION

MDC/CCL22 is a key mediator in drawing inflammatory lymphocytes to the skin, and resulting in skin inflammation (9–11). In the present study, *C. camphora* leaves (80% EtOH extract, CCex) potentially inhibited MDC production in IFN-γ-stimulated HaCaT keratinocytes. CCex did not show any effect on the production of interleukin (IL)-6 and tumor necrosis factor (TNF)-α, major inflammatory cytokines in LPS-induced macrophages (data not shown). These results suggest that CCex has effective components acting on skin keratinocytes. Hence, we assayed the inhibitory effects of four available components (camphor, cineole, nerolidol and linalool) of *C. camphora* on MDC production in IFN-γ stimulated HaCaT keratinocytes. All tested components did not show any effect on the MDC production (data not shown).

To identify the mechanism by which CCex inhibits MDC production, we investigated the phosphorylation of intracellular signaling molecules related to immune responses in skin cells. The JAK-STAT signal pathway is induced by IFN-γ, an important mediator of immunity and inflammation. Hald et al reported that Tyr701 and Ser727 expression of STAT1 is increased in psoriatic skin lesion (29). Furthermore, IFN-γ activates the MEK/ERK signal pathway (30,31), and a previous study suggested that ERK1/2 is related to STAT1 activation induced by IFN-γ. In particular, Ser727 phosphorylation of STAT1 was attributed to the inhibition of ERK (32). CCex suppressed the phosphorylation of STAT1 (Tyrosine 701 and Serine 727 residues) in a dose dependent manner. CCex (12.5–100 μg/mL) also suppressed the phosphorylation of ERK1/2, a central signaling molecule in the inflammation process. EGCG, an active ingredient of green tea, is known to be a potent STAT1 inhibitor (33). In the present study, EGCG (10 μM) potentially inhibited STAT1 (Tyr701 and Ser727 residues) phosphorylation after 2 hr treatment and then MDC production after 24 hr treatment. These results suggest that CCex inhibits MDC/CCL22 production via the down-regulation of STAT1 and ERK1/2 pathways in skin inflammation lesions.

While a significant number of natural products are effective at the cellular level, they are often not effective when applied to animal experiments. To study the *in vivo* effects of CCex on AD, we induced experimental AD in mice by applying of DNCB. IgE is a major therapeutic target for AD, and IgE levels are related to the severity of AD and associated with abnormal skin barrier (4,34). In this study, the CCex-treated group showed significantly decreased levels of serum IgE ($p < 0.001$) compared with the induction group. The cutaneous edema in CCex-treated mice was reduced on day 29 ($p < 0.001$) compared with that observed in the induction mice. Furthermore, epidermal thickness and the degree of inflammatory cell infiltration were significantly lower in the CCex-treated group than in the induction group. LNs are located throughout the body and are related to site initiated pathogenic antigens. LNs also act as a secondary lymphoid organ, so that the rare antigen-specific immune cells can increase their contact with their cognate antigen (35,36). Our results showed that the LNs in mice in the induction group were quite swollen, whereas those in CCex-treated mice were smaller. Hence, CCex alleviated the pathologic symptoms in AD mice.

In conclusion, CCex inhibited the production of MDC, a principal chemokine in skin inflammation via down-regulation of STAT1 and ERK1/2 signaling and improved several symptoms (ear edema, serum IgE levels, histological change, lymph node size) in mice AD. These results suggest that *C. camphora* leaves help in the treatment of allergic inflammation such as AD.

REFERENCES

- Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA. New insights into atopic dermatitis. *J Clin Invest.* 2004;113:651–657. doi: 10.1172/JCI21060. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- Li C, Lasse S, Lee P, Nakasaki M, Chen S-W, Yamasaki K, Gallo RL, Jamora C. Development of atopic dermatitis-like skin disease from the chronic loss of epidermal caspase-8. *Proc Natl Acad Sci USA.* 2010;107:22249–22254. doi: 10.1073/pnas.1009751108. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- Nystad W, Røysamb E, Magnus P, Tambs K, Harris JR. A comparison of genetic and environmental variance structures for asthma, hay fever and eczema with symptoms of the same diseases: a study of Norwegian twins. *Int J Epidemiol.* 2005;34:1302–1309. doi: 10.1093/ije/dyi061. [PubMed] [CrossRef] [Google Scholar]
- Levin TA, Ownby DR, Smith PH, Peterson EL, Williams LK, Ford J, Young P, Johnson CC. Relationship between extremely low total serum IgE levels and rhinosinusitis. *Ann Allergy Asthma Immunol.* 2006;97:650–652. doi: 10.1016/S1081-1206(10)61095-2. [PubMed] [CrossRef] [Google Scholar]
- Yoshie O, Imai T, Nomiyama H. Chemokines in immunity. *Adv Immunol.* 2001;78:57–110. doi: 10.1016/S0065-2776(01)78002-9. [PubMed] [CrossRef] [Google Scholar]
- Bäumer W, Seegers U, Braun M, Tschernig T, Kietzmann M. TARC and RANTES, but not CTACK, are induced in two models of allergic contact dermatitis. Effects of cilomilast and diflorasone diacetate on T-cell-attracting chemokines. *Br J Dermatol.* 2004;151:823–830. doi: 10.1111/j.1365-2133.2004.06220.x. [PubMed] [CrossRef] [Google Scholar]

7. Yamashita U, Kuroda E. Regulation of macrophage-derived chemokine (MDC/CCL22) production. *Crit Rev Immunol.* 2002;22:105–114. doi: 10.1615/CritRevImmunol.v22.i2.10. [PubMed] [CrossRef] [Google Scholar]
8. Saeki H, Tamaki K. Thymus and activation regulated chemokine (TARC)/CCL17 and skin diseases. *J Dermatol Sci.* 2006;43:75–84. doi: 10.1016/j.jdermsci.2006.06.002. [PubMed] [CrossRef] [Google Scholar]
9. Shimada Y, Takehara K, Sato S. Both Th2 and Th1 chemokines (TARC/CCL17, MDC/CCL22, and Mig/CXCL9) are elevated in sera from patients with atopic dermatitis. *J Dermatol Sci.* 2004;34:201–208. doi: 10.1016/j.jdermsci.2004.01.001. [PubMed] [CrossRef] [Google Scholar]
10. Jahnz-Rozyk K, Targowski T, Paluchowska E, Owczarek W, Kucharczyk A. Serum thymus and activation-regulated chemokine, macrophage-derived chemokine and eotaxin as markers of severity of atopic dermatitis. *Allergy.* 2005;60:685–688. doi: 10.1111/j.1398-9995.2005.00774.x. [PubMed] [CrossRef] [Google Scholar]
11. Maeda S, Fujiwara S, Omori K, Kawano K, Kurata K, Masuda K, Ohno K, Tsujimoto H. Lesional expression of thymus and activation-regulated chemokine in canine atopic dermatitis. *Vet Immunol Immunopathol.* 2002;88:79–87. doi: 10.1016/S0165-2427(02)00140-X. [PubMed] [CrossRef] [Google Scholar]
12. Farrar MA, Schreiber RD. The molecular cell biology of interferon-gamma and its receptor. *Annu Rev Immunol.* 1993;11:571–611. doi: 10.1146/annurev.iy.11.040193.003035. [PubMed] [CrossRef] [Google Scholar]
13. Best SM, Morris KL, Shannon JG, Robertson SJ, Mitzel DN, Park GS, Boer E, Wolfinbarger JB, Bloom ME. Inhibition of interferon-stimulated JAK-STAT signaling by a tick-borne flavivirus and identification of NS5 as an interferon antagonist. *J Virol.* 2005;79:12828–12839. doi: 10.1128/JVI.79.20.12828-12839.2005. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
14. Ivashkiv LB, Hu X. Signaling by stats. *Arthritis Res Ther.* 2004;6:159–168. doi: 10.1186/ar1197. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
15. Ju SM, Song HY, Lee SJ, Seo WY, Sin DH, Goh AR, Kang Y-H, Kang I-J, Won M-H, Yi J-S. Suppression of thymus- and activation-regulated chemokine (TARC/CCL17) production by 1, 2, 3, 4, 6-penta-O-galloyl-β-d-glucose via blockade of NF-κB and STAT1 activation in the HaCaT cells. *Biochem Biophys Res Commun.* 2009;387:115–120. doi: 10.1016/j.bbrc.2009.06.137. [PubMed] [CrossRef] [Google Scholar]
16. Kang G-J, Kang N-J, Han S-C, Koo D-H, Kang H-K, Yoo B-S, Yoo E-S. The chloroform fraction of carpinus tschonoskii leaves inhibits the production of inflammatory mediators in HaCaT keratinocytes and RAW264. 7 macrophages. *Toxicol Res.* 2012;28:255–262. doi: 10.5487/TR.2012.28.4.255. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
17. Pearson G, Robinson F, Beers Gibson T, Xu B-e, Karandikar M, Berman K, Cobb MH. Mitogen-activated protein (MAP) kinase pathways: regulation and physiological functions. *Endocr Rev.* 2001;22:153–183. [PubMed] [Google Scholar]
18. Madonna S, Scarponi C, De Pità O, Albanesi C. Suppressor of cytokine signaling 1 inhibits IFN-γ inflammatory signaling in human keratinocytes by sustaining ERK1/2 activation. *FASEB J.* 2008;22:3287–3297. doi: 10.1096/fj.08-106831. [PubMed] [CrossRef] [Google Scholar]
19. Hamidpour R, Hamidpour S, Hamidpour M, Shahlari M. Camphor (Cinnamomum camphora), a traditional remedy with the history of treating several diseases. *Int J Case Rep Imag.* 2013;4:86–89. doi: 10.5348/ijcri-2013-02-267-RA-1. [CrossRef] [Google Scholar]
20. Guo S, Geng Z, Zhang W, Liang J, Wang C, Deng Z, Du S. The chemical composition of essential oils from Cinnamomum camphora and their insecticidal activity against the stored product pests. *Int J Mol Sci.* 2016;17:1836. doi: 10.3390/ijms17111836. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
21. Pragadheesh V, Saroj A, Yadav A, Chanotiya C, Alam M, Samad A. Chemical characterization and antifungal activity of Cinnamomum camphora essential oil. *Ind Crops Prod.* 2013;49:628–633. doi: 10.1016/j.indcrop.2013.06.023. [CrossRef] [Google Scholar]
22. Yang F, Long E, Wen J, Cao L, Zhu C, Hu H, Ruan Y, Okanurak K, Hu H, Wei X. Linalool, derived from Cinnamomum camphora (L.) Presl leaf extracts, possesses molluscicidal activity against Oncomelania hupensis and inhibits infection of Schistosoma japonicum. *Parasit Vectors.* 2014;7:407. doi: 10.1186/1756-3305-7-407. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
23. Lee H-J, Hyun E-A, Yoon W-J, Kim B-H, Rhee M-H, Kang H-K, Cho J-Y, Yoo E-S. In vitro anti-inflammatory and anti-oxidative effects of Cinnamomum camphora extracts. *J Ethnopharmacol.* 2006;103:208–216. doi: 10.1016/j.jep.2005.08.009. [PubMed] [CrossRef] [Google Scholar]
24. Kang G-J, Lee H-J, Yoon W-J, Yang E-J, Park S-S, Kang H-K, Park M-H, Yoo E-S. Prunus yedoensis inhibits the inflammatory chemokines, MDC and TARC, by regulating the STAT1-signaling pathway in IFN-γ-stimulated HaCaT human keratinocytes. *Biomol Ther (Seoul)* 2008;16:394–402. doi: 10.4062/biomolther.2008.16.4.394. [CrossRef] [Google Scholar]

25. Ivashkiv LB, Donlin LT. Regulation of type I interferon responses. *Nat Rev Immunol.* 2014;14:36–49. doi: 10.1038/nri3581. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
26. Kim J, Lee J, Shin S, Cho A, Heo Y. Molecular mechanism of atopic dermatitis induction following sensitization and challenge with 2,4-dinitrochlorobenzene in mouse skin tissue. *Toxicol Res.* 2018;34:7–12. doi: 10.5487/TR.2018.34.1.007. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
27. de Vries IJM, Langeveld-Wildschut EG, van Reijsen FC, Bihari IC, Bruijnzeel-Koomen CA, Thepen T. Nonspecific T-cell homing during inflammation in atopic dermatitis: expression of cutaneous lymphocyte-associated antigen and integrin αEβ7 on skin-infiltrating T cells. *J Allergy Clin Immunol.* 1997;100:694–701. doi: 10.1016/S0091-6749(97)70175-1. [PubMed] [CrossRef] [Google Scholar]
28. Debes GF, Bonhagen K, Wolff T, Kretschmer U, Krautwald S, Kamradt T, Hamann A. CC chemokine receptor 7 expression by effector/memory CD4+ T cells depends on antigen specificity and tissue localization during influenza A virus infection. *J Virol.* 2004;78:7528–7535. doi: 10.1128/JVI.78.14.7528-7535.2004. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
29. Hald A, Andrés R, Salskov-Iversen M, Kjellerup R, Iversen L, Johansen C. STAT1 expression and activation is increased in lesional psoriatic skin. *Br J Dermatol.* 2013;168:302–310. doi: 10.1111/bjd.12049. [PubMed] [CrossRef] [Google Scholar]
30. Platanias LC. Mechanisms of type-I-and type-II-interferon-mediated signalling. *Nat Rev Immunol.* 2005;5:375–386. doi: 10.1038/nri1604. [PubMed] [CrossRef] [Google Scholar]
31. Roy SK, Hu J, Meng Q, Xia Y, Shapiro PS, Reddy SP, Platanias LC, Lindner DJ, Johnson PF, Pritchard C. MEKK1 plays a critical role in activating the transcription factor C/EBP-β-dependent gene expression in response to IFN-γ *Proc Natl Acad Sci USA.* 2002;99:7945–7950. doi: 10.1073/pnas.122075799. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
32. Li N, McLaren JE, Michael DR, Clement M, Fielding CA, Ramji DP. ERK is integral to the IFN-γ-mediated activation of STAT1, the expression of key genes implicated in atherosclerosis, and the uptake of modified lipoproteins by human macrophages. *J Immunol.* 2010;185:3041–3048. doi: 10.4049/jimmunol.1000993. [PubMed] [CrossRef] [Google Scholar]
33. Menegazzi M, Tedeschi E, Dussin D, de Prati AC, Cavalieri E, Mariotto S, Suzuki H. Anti-interferon γ action of epigallocatechin-3-gallate mediated by specific inhibition of STAT1 activation. *FASEB J.* 2001;15:1309–1311. doi: 10.1096/fj.00-0519fje. [PubMed] [CrossRef] [Google Scholar]
34. Liu F-T, Goodarzi H, Chen H-Y. IgE, mast cells, and eosinophils in atopic dermatitis. *Clin Rev Allergy Immunol.* 2011;41:298–310. doi: 10.1007/s12016-011-8252-4. [PubMed] [CrossRef] [Google Scholar]
35. Koning JJ, Mebius RE. Interdependence of stromal and immune cells for lymph node function. *Trends Immunol.* 2012;33:264–270. doi: 10.1016/j.it.2011.10.006. [PubMed] [CrossRef] [Google Scholar]
36. Buettner M, Bode U. Lymph node dissection-understanding the immunological function of lymph nodes. *Clin Exp Immunol.* 2012;169:205–212. doi: 10.1111/j.1365-2249.2012.04602.x. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

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4.5 Effectiveness of topical peppermint oil on symptomatic treatment of chronic pruritus (Sat Pudina)

Abstract

Background

Pruritus is one of the commonest skin complaints. Peppermint oil can be effective in reducing the severity of such a condition.

Aim

The aim of this study was to assess the efficacy of topically applied peppermint oil in the treatment of chronic pruritus.

Subjects and methods

Fifty selected subjects diagnosed with chronic pruritus due to hepatic, renal, or diabetic cause were studied and divided
into two groups of 25 patients each. Group I patients were instructed to hydrate the skin and then apply topical peppermint oil, while Group II patients applied petrolatum topically by hand; this application was done on the areas of pruritus, twice daily for 2 weeks. The severity of the itch was assessed and compared before and after the study by the 5-D itch scale (5D-IS). The results were analyzed by SPSS software. Statistical methods such as descriptive analysis,
independent samples *t*-test, paired samples *t*-test, and chi-square test were employed.

Results

There was a significant improvement regarding all studied individual parameters (5-D IS) for the peppermint oil users with no significance among petrolatum users. A comparison of total score of 5-D IS between patients of Group I and patients of Group II favored the improvement following the use of peppermint oil than using placebo (*P*-value <0.05).

Conclusion

The topical treatment of chronic pruritus with peppermint oil is effective, easy to use, safe, cheap, and more acceptable
for those whose topical and systemic treatments tend to be irritating, contraindicated, or less well tolerated.

Keywords: pruritus, peppermint oil, itch

Introduction

Chronic pruritus is defined as an itch persisting for >6 weeks, which can be severe enough to interfere with lifestyle activities.1 Pruritus can be a hallmark of many skin diseases as well as other noncutaneous diseases. Neuropathic,
psychogenic, systemic, and dermatologic disorders constitute the majority of causes of pruritus.

Peppermint (*Mentha piperita*, of the Labiatae or Lamiaceae family), a native herb of Mediterranean Europe that is cultivated in many parts of the world, is a well-known plant that can be used in many forms (ie, oil, leaf, leaf extract, and leaf water).3 Peppermint oil is a hybrid of spearmint (*Mentha spicata*) and water mint (*Mentha aquatica*) and is synonymous with Mentha oil, *M. piperita* oil, and oil of peppermint.4

Records from ancient Egypt, Greece, and Rome show that peppermint has been used medicinally for centuries for gastrointestinal disorders, including irritable bowel syndrome, indigestion, and nausea, as well as cold, headache, and cramps.5

Recently, topical application of peppermint oil has also received much attention. A little has been published on peppermints effect on pruritus or other conditions other than irritable bowel syndrome, for which its use is still controversial.6

The present pilot study aimed to evaluate application of peppermint oil for the treatment of chronic pruritus of renal, hepatic, and diabetic origins.

Subjects and methods

This study was conducted on 50 patients (of both sexes and different ages) attending the outpatient clinic of dermatology, venereology, and andrology in Al-Hussein University Hospital, Cairo, Egypt, and suffering from chronic pruritus, ie, hepatic, renal, and diabetic pruritus, during the period from June 2014 to June 2015. The study was initially approved by the ethical committee of Al-Azhar University. Written informed consent was obtained from all participants before enrollment (Table 1).

Table 1

Age and sex in the studied groups

	Peppermint group (n=25)	**Control group (n=25)**
Mean age ± SD	47.76±8.23	50.76±7.80
Males, n (%)	10 (40)	13 (52)
Females, n (%)	15 (60)	12 (48)

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Abbreviation: SD, standard deviation.

Exclusion criteria

The following patients were excluded from the study:

patients with dermatological diseases that cause pruritus, eg, psoriasis and contact dermatitis;

patients who suffered from acute pruritus (<6 weeks); and

patients with chronic pruritus due to systemic disease other than chronic renal disease, hepatic disease, or diabetes mellitus.

The studied population was divided into two groups: Group I with 25 patients applied 5% of topical crude peppermint oil, while Group II of 25 patients applied topical petrolatum.

Materials

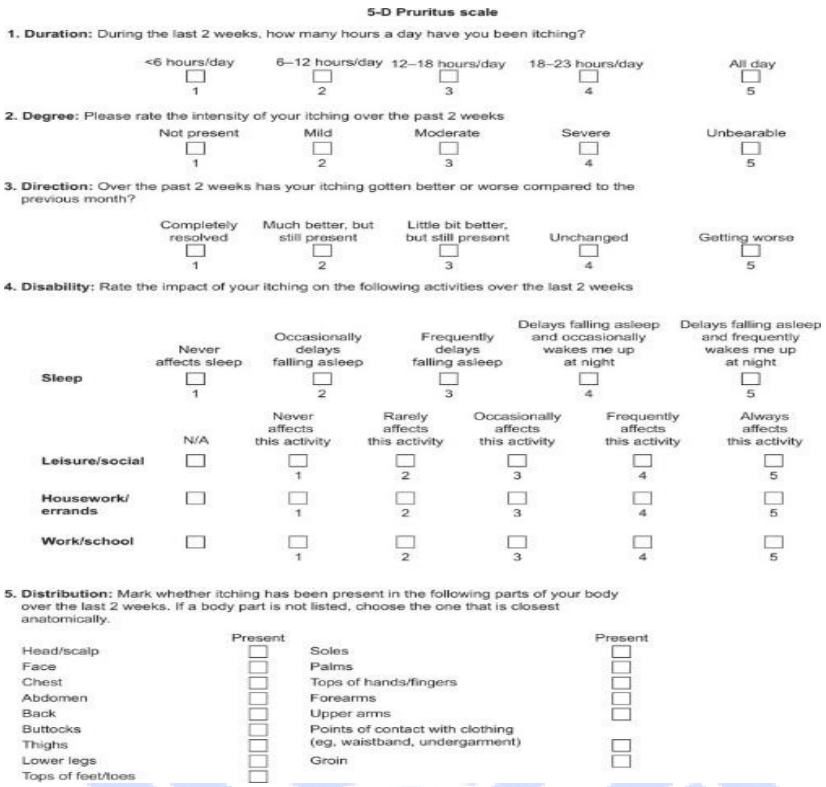
The materials required for this study were as follows:
% crude peppermint oil in petrolatum for Group I patients and
petrolatum base used alone for Group II patients.

Methods

All patients were subjected to an informed verbal consent after explanation of the problem and its medication.
All patients were subjected to the following.

Clinical assessment

The patients were subjected to history taking about their present illness, duration, degree, direction, and distribution of pruritus, in addition to disabilities resulting from pruritus (sleep disorder, social disorder, house work, and work problems); all of these constituted the items of pruritus scale estimation, according to the 5-D itch scale (5-D IS) of assessment of pruritus.7 The distribution domain included 16 items of itch locations (Figure 1):physical examination; general examination: for clinical evidence of renal or hepatic affection, as well as diabetes mellitus; and local examination: to exclude dermatological causes of pruritus and to determine the distribution of pruritus according to the 5-D IS.



5-D Pruritus scale

1. Duration: During the last 2 weeks, how many hours a day have you been itching?

<6 hours/day	6–12 hours/day	12–18 hours/day	18–23 hours/day	All day
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. Degree: Please rate the intensity of your itching over the past 2 weeks

Not present	Mild	Moderate	Severe	Unbearable
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. Direction: Over the past 2 weeks has your itching gotten better or worse compared to the previous month?

Completely resolved	Much better, but still present	Little bit better, but still present	Unchanged	Getting worse
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. Disability: Rate the impact of your itching on the following activities over the last 2 weeks

	Never affects sleep	Occasionally delays falling asleep	Frequently delays falling asleep	Delays falling asleep and occasionally wakes me up at night	Delays falling asleep and frequently wakes me up at night
Sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	N/A	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
Leisure/social	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Housework/ errands	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Work/school	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. Distribution: Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.

	Present		Present
Head/scalp	☐	Soles	☐
Face	☐	Palms	☐
Chest	☐	Tops of hands/fingers	☐
Abdomen	☐	Forearms	☐
Back	☐	Upper arms	☐
Buttocks	☐	Points of contact with clothing (eg, waistband, undergarment)	☐
Thighs	☐	Groin	☐
Lower legs	☐		
Tops of feet/toes	☐		

Figure 1

The 5-D IS.

Abbreviations: 5-D IS, 5-D itch scale; N/A, not applicable.

Diagnosis of chronic pruritus

The diagnosis of chronic pruritus was done as follows:

History: history of pruritus >6 weeks with history of chronic liver diseases, renal diseases, or diabetes.

Clinically: by exclusion of dermatological causes of itching and the presence of involved systemic disease.

Investigations: chosen patients were known hepatic, renal, or diabetic patients (proved by previous investigations of liver functions, kidney functions, and fasting blood glucose).

Patient instructions for drug application

The patients were instructed to hydrate the skin and then apply the preparations (peppermint or petrolatum) topically by hand; this application was done on the areas of pruritus, twice daily for 2 weeks.

Follow-up

Two weeks after the treatment, the patients were evaluated for improvement of itching and its severity, using the 5-D IS of assessment along with the possible recording of side effects such as irritation and burning sensation.

Statistical analysis

Statistical evaluation was done using the SPSS software, and methods such as descriptive analysis, independent samples *t*-test, paired samples *t*-test, and chi-square test were employed. The significance level was set at a *P*-value of <0.05.

Results

Fifty patients were included in this study (26 males and 24 females). According to the cause of chronic pruritus, there were 16 patients with renal diseases, 15 patients with hepatic diseases, and 19 patients with diabetic disease.

The patients were divided into two groups. Group I included 25 patients (10 males and 15 females). The mean age of patients was 47.76±8.23 years with minimum age 32 years and maximum age 66 years. They were subdivided according to the cause of pruritus into three subgroups:

renal: eight patients;

hepatic: seven patients; and

diabetic: ten patients.

They were treated with 5% of topical peppermint oil for 2 weeks.

Group II included 25 patients (13 males and 12 females). The mean age of patients was 50.76±7.80 years with minimum age 29 years and maximum age 64 years. They were subdivided according to the cause of pruritus into three subgroups:

renal: eight patients;

hepatic: eight patients; and

diabetic: nine patients.

They were treated with topical petrolatum as placebo for 2 weeks.

Results of Group I

The average total score of 5-Ds for Group I before and after treatment was 15.18±3.55 and 7.94±3.28, respectively. There was a significant improvement regarding all studied individual parameters (5-D IS), including duration, degree, direction, disability, and distribution domains (*P*-value <0.05; Table 2).

Table 2

Effect of using peppermint oil before and after treatment (n=25)

5-D variables	Before treatment	After treatment	*P*-value
Average duration (hours/day)	2.20±0.76	1.12±0.43	0.000
Average degree	4.64±0.56	2.32±0.80	0.000
Average direction	4.16±0.37	2.20±0.86	0.000
Average disability			
Sleep	2.60±1.22	1.36±0.48	0.000
Social	2.44±0.96	1.32±0.55	0.000
Housework	1.32±1.21	0.76±0.51	0.001
Work	0.64±0.95	0.36±0.48	0.01
Mean average disability	1.75±0.71	0.95±0.30	0.0001
Average distribution	2.43±0.82	1.35±0.89	0.0001
Average total 5-D IS score	15.18±3.55	7.94±3.28	0.0001

All the hepatic, renal, and diabetic patients showed a significant improvement regarding all studied individual parameters (5-D IS), including duration, degree, direction, disability, and distribution domains (*P*-value <0.05), except for the either "work" only or "work" and "housework" domains where there was no significant change before and after treatment (*P*-value >0.05; Tables 3–5).

Table 3

Improvement of patients with renal pruritus in Group I

5-D variables	Before treatment	After treatment	*P*-value
Average duration (hours/day)	2.00±0.75	1.00±0.00	0.007
Average degree	4.50±0.53	1.87±0.33	0.000
Average direction	4.37±0.51	2.12±0.83	0.000
Average disability			
Sleep	2.62±1.3	1.37±0.51	0.01
Social	2.62±0.91	1.50±0.75	0.007

5-D variables Before treatment After treatment	*P*-value
Housework 0.87±1.24 0.50±0.53	0.28
Work 0.00±0.00 0.00±000	–
Mean average disability 1.53±0.49 0.84±0.22	0.001
Average distribution 2.54±0.81 1.13±0.68	0.006
Average total 5-D IS score 14.94±5.66 6.96±4.52	0.001

Table 4

Improvement of patients with hepatic pruritus in Group I

5-D variables Before treatment After treatment	*P*-value
Average duration (hours/day) 2.71±0.75 1.14±0.37	0.000
Average degree 5.00±0.00 2.42±0.53	0.000
Average direction 4.14±0.37 2.14±0.37	0.000
Average disability	
Sleep 3.14±1.34 1.57±0.53	0.005
Social 2.85±1.06 1.28±0.48	0.002
Housework 1.42±1.61 0.85±0.89	0.01
Work 0.42±0.78 0.28±0.48	0.35
Mean average disability 2.45±1.09 1.25±0.48	0.004
Average distribution 2.68±1.96 1.38±0.53	0.003
Average total 5-D IS score 16.98±6.26 8.33±11.4	0.006

Table 5

Improvement of patients with diabetic pruritus in Group I

5-D variables Before treatment After treatment	*P*-value
Average duration (hours/day) 2.00±0.66 1.20±0.57	0.003
Average degree 4.50±0.70 2.60±1.07	0.000
Average direction 4.00±0.00 2.30±1.15	0.001
Average disability	
Sleep 2.20±1.03 1.20±0.42	0.01
Social 2.00±0.81 1.20±0.42	0.01
Housework 1.60±0.84 0.90±1.30	0.01
Work 1.30±1.05 0.70±0.48	0.02
Mean average disability 2.22±1.96 1.25±1.15	0.038
Average distribution 2.19±2.21 1.50±3.91	0.45

5-D variables Before treatment After treatment *P*-value

Average total 5-D IS score 14.91±5.31 8.85±7.89 0.002

Comparison of total score of 5-D IS among Group I indicated that improvement among patients had no correlation with gender (*P*-value <0.05). However, when comparing between male and female patients regarding the total score of the 5-D IS before treatment, there was a small but a significant difference (*P*-value <0.05), same as with

comparison
after the treatment.

Results of Group II

The average total score of the 5-Ds for Group II before and after treatment was 14.54±2.09 and 13.47±3.73, respectively. There was no significant improvement in the duration, direction, disability, and distribution domains (*P*-value >0.05), while there was a significant improvement among the degree of itch and among the social and sleep items of the disability domain (Table 6).

Table 6

Effect of using petrolatum before and after treatment (n=25)

5-D variables Before treatment After treatment *P*-value

Average duration (hours/day) 2.16±0.68 2.04±0.78 0.26

Average degree 4.72±0.54 4.24±1.09 0.01

Average direction 4.00±0.00 3.72±0.93 0.14

Average disability

Sleep 2.04±0.84 1.80±0.91 0.05

Social 2.36±1.25 2.24±1.26 0.08

Housework 1.00±0.91 0.96±0.88 0.32

Work 0.52±0.91 0.48±0.87 0.32

Mean average disability 1.47±1.14 1.36±1.21 0.74

Average distribution 2.19±1.93 2.11±2.40 0.90

Average total 5-D IS score 14.54±2.09 13.47±3.73 0.22

All the hepatic, renal, and diabetic patients showed no significant improvement regarding all studied individual parameters (5-D IS) to all the studied individual parameters (5-D IS), including duration, degree, direction, disability, and distribution domains (*P*-value >0.05). Comparison of the total score of the 5-D IS with regard to gender among Group II indicated that the absence of improvement among patients had no correlation with gender (*P*-value >0.05); however, when comparing male and female patients regarding the total score of the 5-D IS before treatment, there was a small but a significant difference (*P*-value >0.05).

Discussion

A wide range of herbal remedies was proposed for use in pruritus. Tannins, chamomile, camphor, menthol, aloe vera, oatmeal, and others are traditionally considered of low risk and good value in treating pruritus, but there are no controlled studies to determine such effects.[8]

Peppermint is thought to alleviate the sensation of itch by activating A-delta fibers and *k*-opioid receptor.[9] Previous research has shown that menthol in low concentrations is effective with no irritant effect.[10] The long-term use of menthol for chronic itch has not been studied.[6] In a letter to the editor of *The Lancet* in 1870, Dr A. Wright said that he had witnessed peppermint oil being used to treat “facial neuralgia” in the People’s Republic of China and that he had been able to repeat this success in his own practice.[6]

Only four patients who applied the oil in flexures (groin and axillae) complained of a burning sensation; otherwise, there were no reported side effects. Peppermint oil is generally recognized as safe according to the US Food and Drug Administration.[11] However, the higher doses of peppermint oil used for medicinal purposes have not been extensively regulated, as peppermint oil is sold as a dietary supplement.

The efficacy of peppermint oil in combination with sesame oil was only studied once in female patients with pruritus gravidarum and has shown a consistent statistical significance in comparison to placebo.12 The patients used peppermint oil 0.5% in sesame oil and applied twice daily for 14 days. The severity of the itch was assessed and compared before and after the study by the visual analog system. The severity of the itch in the treated group with peppermint oil in comparison with the placebo group showed a significant statistical difference.10

In this study, the use of peppermint oil for pruritus of hepatic, renal, and diabetic origin showed a significant improvement regarding all studied individual parameters (5-D IS), including duration, degree, direction, disability, and distribution domains (*P*-value <0.05).

conclusion

The topical treatment of chronic pruritus with peppermint is effective, easy to use, safe, cheap, has favorable odor, and is more acceptable for whom topical and systemic treatments tend to be irritating, contraindicated, or less well tolerated. This therapeutic option for chronic pruritus has excellent results and is free from toxic side effects.

Footnotes

Disclosure

The authors report no conflicts of interest in this work.

References

1. Reamy BV, Christopher W, Fletcher S. A diagnostic approach to pruritus. Am Fam Physician. 2011;**84**(2):195–202. [PubMed] [Google Scholar]
2. Ständer S, Weisshaar E, Mettang T, et al. Clinical classification of itch: a position paper of the International Forum for the Study of Itch. Acta Derm Venereol. 2007;**87**(4):291–294. [PubMed] [Google Scholar]
3. Hair B. Final report on the safety assessment of *Mentha piperita* (peppermint) oil, *Mentha piperita* (peppermint) leaf extract, *Mentha piperita* (peppermint) leaf, and *Mentha piperita* (peppermint) leaf water. Int J Toxicol. 2001;**20**(Suppl 3):61–73. [PubMed] [Google Scholar]
4. Herro E, Jacob SE. *Mentha piperita* (peppermint) Dermatitis. 2010;**21**(6):327–329. [PubMed] [Google Scholar]
5. Spirling LI, Daniels IR. Botanical perspectives on health peppermint: more than just an after-dinner mint. J R Soc Promot Health. 2001;**121**(1):62–63. [PubMed] [Google Scholar]
6. Wright A. Oil of peppermint as a local anaesthetic. Lancet. 1870;**2464**:726. [Google Scholar]
7. Elman S, Hynan LS, Gabriel V, Mayo MJ. The 5-D itch scale: a new measure of pruritus. Br J Dermatol. 2010;**162**(3):587–593. [PMC free article] [PubMed] [Google Scholar]
8. Weisshaar E, Szepietowski JC, Darsow U, et al. European guideline on chronic pruritus. Acta Derm Venereol. 2012;**92**(5):563–581. [PubMed] [Google Scholar]

4.6 Use of Thymol (Ajwain) in Psoriasis

INTRODUCTION

Herbal therapy for skin disorders has been used for thousands of years. Even our biologically close relatives, the great apes, use herbal self-medication (Huffman 2001). Specific herbs and their uses developed regionally, based on locally available plants and through trade in ethnobotanical remedies. Systems of herbal use developed regionally in Europe, the Middle East (Ghazanfar 1994), Africa, India (Behl and Srivastava 2002), China, Japan, Australia, and the Americas. Two well-known systems still in use are the Ayurvedic herbs in India (Kapoor 1990) and herb combinations developed as part of traditional Chinese medicine (TCM) in China (Xu 2004). In Europe and the United States, use of herbs declined as purified extracts and synthetic chemical drugs became available. In recent years, there has

been a resurgence of the use of herbs due to the following reasons: the side effects of chemical drugs became apparent, there was a call to return to nature, natural remedies became a part of the green revolution, and there was a return to organic produce. Herbal remedies, including those for skin disorders, are currently gaining popularity among patients and to a lesser degree among physicians. In Asia, especially in China and India, herbal treatments that have been used for centuries are now being studied scientifically. In Germany, the regulatory authority Commission E oversees herbal preparations and their recommended uses (Blumenthal et al. 1998). Currently, the United States does not regulate herbal products except as dietary supplements. There is no standardization of active ingredients, purity, or concentration. There are also no regulations governing which herbs can be marketed for specific indications.

Included in this review of herbal medications are those medications that show scientific evidence for clinical efficacy, as well as the more common herbs found to be useful in the treatment of dermatologic disorders. Information regarding the safety of each herb is also included in this chapter to better enable physicians to decide which herbal therapies they may want to use in practice. Common drug interactions and the side effects of herbal medicines that may be seen in the dermatologic setting are also included in this discussion.

BACKGROUND AND CONTEXT

In India, records of Ayurvedic medicine date back to about 3000 BC. The system of Ayurvedic medicine combines physiological and holistic principles. It is based on the concept that the human body consists of five energy elements that also make up the universe: (1) earth, (2) water, (3) fire, (4) air, and (5) space. The interactions of these five elements give rise to the three *doshas* (forces), seven *dhatus* (tissues), and three *malas* (waste products). All diseases are attributed to an imbalance among the three *doshas* (Bedi and Shenefelt 2002). Diagnosis is made by an elaborate system of examining the physical findings, pulse, and urine, as well as by an eightfold detailed examination to evaluate both the physical and mental aspects of the condition. The treatment is then tailored to suit an individual based on the findings (Routh and Bhowmik 1999).

Records of TCM date back to about 4000 years. Similar to Ayurvedic medicine, TCM also is aimed at treating the whole person. It is based on the complementary forces *yin* and *yang*. In healthy individuals, yin and yang are in balance, and illness occurs when there is inequality between the forces. The Chinese also recognize five elements: (1) earth, (2) water, (3) fire, (4) air, and (5) metal, each related to specific organs. In addition, they recognize a flow of energy, called *chi* or *qi*, through the body in 14 major meridians. The Chinese evaluate the exchange between the environment and the body, such as food, drink, and air into the body and waste leaving the body. Special attention is given to the physical examination of the tongue, iris, and pulses of the individual to determine the cause of the imbalance and then to determine the appropriate individual treatment. Treatment is usually a mixture of herbs, massage, and acupuncture (Latchman et al. 1994). An entire textbook on dermatology in TCM is available (Xu 2004).

In Western medicine, herbal therapy began as folk medicine. In the United States, it began in the colonial days, when homemade botanicals were used by women at home (Winslow and Kroll 1998). Native American use of botanical treatments also greatly influenced the use of herbal therapy in the United States. Iroquois medical botanicals in the northeastern United States became well known to the colonists (Herrick 1995). In the nineteenth century, these Old World European and Native American traditions were expanded and used by a group of physicians known as the “eclectics.” As herbal medicine continued to develop in the United States, it was further influenced by European and Chinese practices (Winston and Dattner 1999).

Herbal therapy has increased in popularity in the past two decades among patients seeking alternative treatments to conventional Western allopathic medicine. The number of visits to alternative medicine

practitioners in the United States has grown rapidly and in 1997 it was estimated to be 629 million, surpassing the number of visits to all primary care physicians (Neldner 2000). Approximately US$27 billion was spent on these alternative therapies in 1997, of which US$3.24 billion was spent on herbal therapy (Klepser and Klepser 1999). It has been estimated that about 50% of the population uses some form of alternative medicine. Many patients choose not to tell this information to their physicians. The group most likely to use unconventional treatment modalities according to a previous survey consisted of nonblack, college-educated individuals between the ages of 25 and 49 years, having an annual income greater than US$35,000 (Eisenburg et al. 1993). Most patients seek alternatives because conventional therapy has failed to help them sufficiently or because they feel there are fewer side effects with the natural products. The recent increase in the use of alternative medicine has led to more research regarding alternatives and requires education of physicians on the subject to enable them to better inform and care for their patients. In the United States, herbal remedies continue to be sold as dietary supplements, with no standards of potency and efficacy required currently. The Dietary Supplement Health and Education Act of 1994 did set purity standards for some commonly used herbs. In Germany, a regulatory authority known as Commission E extensively reviewed common European botanicals. In all, Commission E evaluated the quality of evidence for the clinical efficacy, safety, and uses of 300 herbal preparations (Blumenthal et al. 1998; Bisset and Wichtl 2001). In Germany, this information has led to standardization of herbal treatments. A number of herbal therapies have stood the test of time for their efficacy in treating dermatologic conditions, with a few having significant scientific evidence of usefulness.

With alternative herbal therapies, an individual patient often treats himself or herself, many times without high-quality professional advice. Patients are advised to ensure the safe use of herbal therapies by deciding on health goals; informing themselves on efficacy, safety, interactions, and usage of the medicine; selecting therapies that are likely to achieve their goals; having a correct diagnosis before using the therapy; consulting reputable practitioners; informing the practitioners about all the remedies they are using; monitoring the effects of the remedies, both positive and negative; waiting patiently for effects to become noticeable; and adjusting doses as needed to accommodate surgery, illness, or changes in conventional therapy (Dunning 2003). Product-labeling information that the patient should look for includes the name and composition of the product, including the parts of the plant and quantity of raw material used, daily dosage and timing of dosages, allergy and other warning statements, quality and safety testing, expiration date, manufacturer, country of manufacture, claims and indications for use, and details on how to store the product (Kron 2002). The *Botanical Safety Handbook* (McGuffin et al. 1997) places herbs in different classes of safety, with Class 1 herbs being safe to consume appropriately, Class 2 safe to consume with restrictions (2a for external use only, 2b not for use in pregnancy, 2c not for use while nursing, and 2d indicating other specific restrictions), Class 3 herbs restricted to use only when supervised by an expert, and Class 4 herbs have insufficient data for classification of safety.

HERBAL TREATMENTS FOR DERMATOLOGIC DISORDERS

Most common dermatologic disorders have beneficial herbal treatments available. The disorders are listed in alphabetical order below.

ACNE

Fruit acids, such as citric, gluconic, gluconolactone, glycolic, malic, and tartaric acids, used topically have demonstrated some effectiveness in treating acne because of their exfoliative properties. In one study, gluconolactone was found to be as effective in clearing inflamed and noninflamed acne lesions as 5% benzoyl peroxide and more effective than placebo (Hunt et al. 1992). Irritation is the main adverse effect of fruit acids, especially in higher concentrations. When contained in the fruit, they are Class 1.

Tannins have natural astringent properties and are used topically to treat acne. Witch hazel (*Hamamelis virginiana*) bark extract is commonly used as a household remedy by making a decoction from 5 to 10 g of herb in 1 cup (0.24 L) of water. Witch hazel is considered very safe to use topically and is Class 1 (McGuffin et al. 1997; Peirce, Fargis, and Scordato 1999). Similar astringents can be made from white oak tree bark or the English walnut tree bark. These preparations should be strained before use and can be used two or three times a day. Commercially available preparations are not astringent, as the tannins are lost in the distillation process (Buchness 1998).

Tea tree oil is an essential oil extracted from the leaves of *Melaleuca alternifolia*, a small tree indigenous to Australia. It contains approximately 100 compounds, mainly plant terpenes and their corresponding alcohols (Swords and Hunter 1978). A study of 124 patients compared 5% tea tree oil in a water-based gel with 5% benzoyl peroxide. Although the tea tree oil did not act as rapidly as benzoyl peroxide, it did show statistical improvement in the number of acne lesions at the end of 3 months, and there was a significantly lower incidence of adverse effects such as dryness, irritation, itching, and burning with tea tree oil (44%) than with benzoyl peroxide (79%; Peirce, Fargis, and Scordato 1999). There have been occasional reports of allergic contact dermatitis (de Groot and Weyland 1993; Knight and Hansen 1994; Selvaag, Eriksen, and Thure 1994) and of poisoning if taken internally (Elliot 1993; Moss 1994).
However, it is the degradation products of monoterpenes in the tea tree oil that actually appear to be the sensitizing agents (Hausen, Reichling, and Harkenthal 1999). Hence, topical treatment is considered very safe.

Oral administration of vitex (*Vitex agnus-castus*) is effective in treating premenstrual acne. The whole-fruit extract has an amphoteric hormone-regulating effect that is thought to act on follicle-stimulating hormone and luteinizing hormone levels in the pituitary to increase progesterone levels and reduce estrogen levels. It is included in Classes 2b, 2c, and 2d, and may counteract the effectiveness of oral contraceptives. The German Commission E monographs recommend a dose of 40 mg/day. The main adverse effects reported are gastrointestinal tract distress and occurrence of rashes. It should not be taken by pregnant or nursing women (Fleming 2000).

Bitter herbs that stimulate digestive function, including acid secretion, may improve acne (Yarnell and Abascal 2006). Commission E also approved topical bittersweet nightshade (*Solanum dulcamara*; Fleming 2000) and orally administered brewer's yeast (*Saccharomyces cerevisiae*; Fleming 2000, 118) for the treatment of acne because of their antimicrobial effects. Topical duckweed (*Lemna minor*) is used in China to treat acne (Fleming 2000). Herbal mixtures are also used in China both internally and externally to treat acne (Xu 2004).

ALOPECIA

Essential oils have been studied in a randomized, controlled, double-blind study of 86 patients with alopecia areata (Hey, Jamieson, and Ormerod 1998). A mixture of essential oils including thyme, rosemary, lavender, and cedarwood in carrier oils with grape seed 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 six-point scale and a computerized analysis of areas of alopecia. The treatment group had a statistically significant improvement over the control group (44% vs. 15%). There were no reported adverse effects.

A double-blind study that lasted 6 months and in which 396 patients participated evaluated the topical use of a Chinese herbal formula, Dabao (manufactured by Engelbert & Vialle, Venlo, Netherlands), for the treatment of androgenic alopecia (Kessels et al. 1991). The ingredients of Dabao include 50% ethanol, 42% water, and 8% Chinese herbal extracts, including saffron flowers, mulberry leaves, stemona root, fruits of the pepper plant, sesame leaves, skin of the Szechuan pepper fruit, ginger root, Chinese angelica root, bark of the pseudolarix, and fruit of the hawthorn plant. The ingredients of the placebo

included 50% ethanol, 48% water, and 2% odorizing and coloring agents consisting of cherry laurel water, cinnamon water, licorice syrup, sugar syrup, and a solution of burned sugar. In both groups, there was an increase in nonvellus hairs. Although the Dabao group was statistically superior to the placebo group in number of nonvellus hairs, the cosmetic improvement in both groups was minimal. There were no reported adverse effects. Other TCM herbal mixtures have also been used for alopecia areata (Xu 2004).

BACTERIAL AND FUNGAL INFECTIONS OF SKIN

Garlic (*Allium sativum*) contains ajoene, which has been demonstrated to exhibit antifungal activity. In a study of 34 patients treated topically with 0.4% ajoene cream once a day for tinea pedis, 79% noted clearing within 7 days and the remainder reported clearing within 14 days. In a 3-month follow-up, all participants remained free of fungus (Ledezma, De Sousa, and Jorquera 1996). Contact dermatitis has occasionally been reported with frequent topical exposure (Fleming 2000). Oral administration should be avoided while breast-feeding as this is regarded as a Class 2c herb (McGuffin et al. 1997). Prolonged bleeding may occur when garlic is taken orally (Fleming 2000).

Tea tree oil (see Section 18.3.1 for a description of tea tree oil) is applied topically for treatment of bacterial and fungal infections. Tea tree oil has shown in vitro activity against a wide variety of microorganisms, including *Propionibacterium acnes, Staphylococcus aureus, Escherichia coli, Candida albicans, Trichophyton mentagrophytes*, and *Trichophyton rubrum* (Beylier 1979; Williams, Home, and Zang 1988). Tea tree oil 10% cream was compared in a randomized, double-blind trial of 104 patients with 1% tolnaftate cream and placebo cream. Although symptomatic relief was comparable in tea tree oil and tolnaftate groups, there was significantly greater mycologic cure in the tolnaftate group (85%) than the tea tree oil group (30%). Cure rates between the tea tree oil and placebo groups were not statistically different (Tong, Altman, and Barnetson 1992). Another randomized, double-blind study of 117 patients compared a solution of 100% tea tree oil with 1% clotrimazole solution in the treatment of onychomycosis. The two groups showed comparable results after 6 months of treatment in terms of mycologic cure (11% for clotrimazole and 18% for tea tree oil), clinical assessment, and subjective rating of appearance and symptoms (61% for clotrimazole and 60% for tea tree oil; Buck, Nidorf, and Addini 1994). Tea tree oil may thus have a role in at least the symptomatic treatment of tinea pedis, onychomycosis, and other superficial wounds. However, it should not be used on burns because of its cytolytic effect on epithelial cells and fibroblasts (Faoagali, George, and Leditschke 1997).

Thyme oil from thyme (*Thymus vulgaris*) has been used topically as an antibacterial and an anticandidal agent (van Wyk et al. 2004), and is Class 1 (McGuffin et al. 1997). The traditional Korean antifungal herb *Galla rhois* was found to have a methanol extract active against *Candida albicans* (Seong 2007). The TCM herbal mixtures for treating bacterial and fungal infections of the skin are extensively discussed by Xu (2004).

CHRONIC VENOUS INSUFFICIENCY

Chronic venous insufficiency (CVI) and varicosities occur in at least 10–15% of men and 20–25% of women (Callam 1994) and results in and morbidity. Compliance with current treatments such as compression stockings is poor, leading to the search for alternative therapies (Abascal and Yarnell 2007).

The German Commission E approves the oral administration of butcher's broom (*Ruscus acuteatus*) and sweet clover (*Melilotus officinalis*) for relief from symptoms such as pain, heaviness, pruritus, and swelling associated with venous insufficiency. In animal studies, butcher's broom was demonstrated to increase venous tone and to also exhibit diuretic properties, whereas sweet clover was found to increase venous reflux, better termed "venous return" (Fleming 2000). Both butcher's broom, which is Class 1, and sweet clover appear to be safe when used as recommended (McGuffin et al. 1997; Fleming 2000).

Ginkgo (*Ginkgo biloba*) has been used orally in China for centuries and has come to use more recently in Europe and the United States for treating numerous conditions, including heart disease, asthma, vertigo, tinnitus, impotence, cerebral and vascular insufficiency, peripheral vascular disorders, dementia, and

other conditions. Research indicates that ginkgo promotes vasodilation, thereby improving many of these conditions. Most research on ginkgo focuses on cerebral insufficiency and claudication. Studies suggest ginkgo may be more useful for these vascular disorders than for CVI (Hadley and Petry 1999; Peirce, Fargis, and Scordato 1999). Caution should be used when ginkgo is taken orally, as there have been reports of subarachnoid and intracerebral hemorrhage, as well as increased bleeding time (Fleming 2000), although it is Class 1 (McGuffin et al. 1997).

Several double-blind trials conducted in France studied the effects of grape seed (*Virus vinifera*) extract on CVI. Grape seed extract contains oligomeric proanthocyanidins, which are bioflavonoids demonstrated to be beneficial by strengthening capillaries. Dosages in the studies varied from 50 mg orally once a day to 100 mg thrice a day. No serious adverse effects were reported (Fleming 2000).

Horse chestnut seed extract (HCSE) is one of the most researched herbal alternatives. Horse chestnut (*Aesculus hippocastanum*) contains the plant compounds known as "terpenes," with the most active component being aescin (Peirce, Fargis, and Scordato 1999). The mechanism of action appears to be related to the inhibition of leukocyte activation, an important pathophysiological mechanism contributing to CVI. Aescin is also thought to decrease vascular leakage by inhibiting elastase and hyaluronase, which are involved in proteoglycan degradation at the capillary endothelium (Pittler and Ernst 1998). Many double-blind, randomized trials of orally administered HCSE have been conducted on patients with CVI. It was demonstrated that HCSE decreases lower-leg volume as well as calf and ankle circumference. Patients also showed decreased symptoms such as fatigue, tenderness, and pruritus. One study showed the relative equivalency of using HCSE compared with grade II compression stockings for treatment of CVI (Diehm 1996). Most of the studies achieved statistically significant results for treatment of CVI with doses of HCSE containing 100–150 mg of aescin per day, most often taken as 50 mg twice a day. Adverse effects reported were minimal and included gastrointestinal tract discomfort, dizziness, headache, and pruritus. Rates of reported adverse effects were from 0.9% to 3.0% and in several studies were not statistically different from rates of adverse effects observed with placebo. Although there are no long-term studies of orally administered HCSE in treating CVI and its sequelae, these results seem promising and offer patients a safe alternative to compression stockings. In Europe, HCSE has also been used in the form of a topical gel, lotion, or ointment to reduce inflammation and discomfort associated with varicose veins, phlebitis, and hemorrhoids (Peirce, Fargis, and Scordato 1999).

It must be noted that the seeds of horse chestnut tree are poisonous and must be specially prepared by a reputable manufacturer to remove all toxins. Once the toxins have been removed, it is considered relatively safe when taken orally. There has been one case report of drug-induced lupus attributed to Venocuran (manufactured by Knoll AG, Ludwigshafen, Germany), a drug for venous insufficiency containing HCSE (Peirce, Fargis, and Scordato 1999). Contact dermatitis has occasionally been reported when HSCE was used topically (Bisset and Wichtl 2001).

Witch hazel (*H. virginiana*) contains considerable amounts of tannin (see the details of preparation in Section 18.3.1), making it a useful astringent. It has been used topically to soothe inflammation of the skin and mucous membranes in disorders such as varicose veins and hemorrhoids. Animal research suggests that witch hazel extract has local styptic and vasoconstrictive effects. The alcohol fluid extract has also been found to cause venous constriction in rabbits. It is often used orally for CVI in Europe. Although it appears safe when taken orally and is included in Class 1, the efficacy of such treatment has not been studied well in humans (McGuffin et al. 1997; Blumenthal et al. 1998). Various TCM herbal mixes for treating stasis dermatitis are listed by Xu (2004).

DERMATITIS

Arnica is derived from the dried flowers of *Arnica montana* or other arnica species. Although oral administration can cause severe health hazards even in small amounts, preparations for external use are very safe and effective. Arnica has been used for centuries as an anti-inflammatory drug to rub into sore muscles and joints, bruises, insect bites, boils, inflamed gums, acne eruptions, and hemorrhoids. It is also an ingredient found in many seborrheic dermatitis and psoriasis preparations. It is approved by Commission E for topical treatment of skin inflammation (Blumenthal et al. 1998). When used as a compress, 1 tablespoon (tbsp; 15 mL) of tincture is mixed with 0.5 L of water; if used as an infusion, 2 g of dried arnica is mixed with 100 mL of water. Cream or ointment preparations should contain a maximum of 15% arnica oil or 20–25% tincture (Bisset and Wichtl 2001; Peirce, Fargis, and Scordato 1999). The active ingredients of arnica are the sesquiterpene lactones such as helanalin, 11α,13-dihydrohelenalin, chamissonolid, and their ester derivatives. These components reduce inflammation by inhibiting the transcription factor nuclear factor κB (NF-κB). The factor NF-κB controls the transcription of many genes, including cytokines such as interleukin (IL)-1, IL-2, IL-6, IL-8, and tumor necrosis factor α, as well as adhesion molecules such as intercellular adhesion molecule 1, vascular cellular adhesion molecule 1, and endothelial leukocyte adhesion molecule 1. It also inhibits many genes responsible for antigen presentation and activation of cyclooxygenase 2 (Lyss et al. 1997). There are reports of contact dermatitis caused by arnica. There are also several reports of irritation when arnica is used at stronger concentrations or for longer periods than are recommended. It is not recommended for use on open wounds or broken skin, and is included in Class 2d (McGuffin et al. 1997). It is important to buy arnica from a reputable source, because it is a protected species in some countries and other plants are substituted fraudulently.

German chamomile (*Matricaria recutita*), a member of the daisy family, has been used for centuries, both internally and externally, for treating many conditions, especially gastrointestinal tract symptoms, oral or skin inflammation, as well as dermatitis. A tea is made by using 2–3 teaspoons (tsp; 10–15 mL) of dried flowers per cup of water and is taken internally or used as a compress. Topical preparations with cream or ointment bases are also used and researched in Germany (Bisset and Wichtl 2001). Studies have demonstrated that topical chamomile is comparable with 0.25% hydrocortisone and shows improvement in sodium lauryl sulfate–induced contact dermatitis (Brown and Dattner 1998). A small double-blind trial found that chamomile significantly decreased the surface area of wounds and, in animal studies, healing time was found to be reduced with chamomile. Chamomile also shows in vitro antimicrobial activities (Peirce, Fargis, and Scordato 1999). The main adverse effect reported is allergic contact dermatitis. Chamomile is considered safe to use topically and orally, and is included in Class 1 (McGuffin et al. 1997). The anti-inflammatory, wound-healing, and antimicrobial effects of German chamomile are attributed to an essential blue oil that contains sesquiterpene alcohol, α-bisabolol, chamazulene, and flavinoids. These substances showed anti-inflammatory and antispasmodic properties in animal studies, due in part to the inhibition of cyclooxygenase and lipoxygenase in vitro. The flavinoids also act by inhibiting histamine release from antigen-stimulated human basophilic polymorphonuclear leukocytes (Brown and Dattner 1998). The substance α-isabolol also demonstrated promotion of granulation tissue in wound healing (Peirce, Fargis, and Scordato 1999). Bittersweet nightshade (*S. dulcamara*) and brewer's yeast (*S. cerevisiae*) are thought to have similar anti-inflammatory and antibacterial effects.

Herbal medicine derived from TCM for the treatment of atopic dermatitis has been reported effective by British studies. In TCM, the body is treated as a whole and the aim of therapy is to restore harmony to the functions of the body (Atherton et al. 1992). A mixture of various herbs is individually formulated for a patient (Sheehan et al. 1992), making it difficult to undertake randomized, controlled trials. Two randomized, placebo-controlled crossover trials were performed in England to study the effects of standardized oral herbal TCM in the treatment of atopic dermatitis cases for which traditional Western

therapy had failed (Sheehan et al. 1992; Sheehan and Atherton 1992; Armstrong and Ernest 1999). The investigators were aided by a Chinese physician who created a standardized mixture of 10 herbs useful for treating atopic dermatitis characterized by erythema, lichenification, and plaques of dermatitis in the absence of active exudation or clinical infection. The 10 herbs used were *Potentilla Chinensis*, Class 1; *Tribulus terrestris; Rehmannia glutinosa*, Class 2d; *Lophatherum gracile; Clematis armandii*, Class 1; *Ledebouriella saseloides*, Class 1; *Dictamnus dasycarpus; Paeonia lactiflora*, Class 1; *Schizonepeta tenuifolia;* and *Glycyrrhizia glabra*, Class 1 (Sheehan and Atherton 1992; McGuffin et al. 1997). These herbs were placed in sachets and boiled to make a decoction that was orally administered daily as a tea. The placebo consisted of a decoction made from several herbs with similar smells and tastes that have no known efficacy in the treatment of atopic dermatitis. The first study with 37 children demonstrated a median decrease in erythema score of 51.0% in the treatment group compared with only a 6.1% improvement in the placebo group. The percentage surface involvement also decreased by 63.1% and 6.2% for the herb-treated and placebo groups, respectively. In this initial study, no serious adverse effects were found. These 37 children were offered continued treatment with the TCM herbal mixture and were then followed up for 1 year (Sheehan and Atherton 1994). Eighteen children completed the year of treatment and showed 90% reduction in eczema activity scores. The children who withdrew from the study did so because of lack of further response to treatment, unpalatability of the tea, or difficulty in preparation of the treatment. By the end of 1 year, seven patients were able to discontinue therapy without relapse. Asymptomatic elevation of aspartate aminotransferase level was noted in two patients, the levels returning to normal after discontinuing treatment. No serious adverse effects were observed. The design was similar in the other study that involved 31 adult patients with atopic dermatitis (Sheehan et al. 1992). The decrease in erythema and surface damage was statistically superior in the herb-treated group compared with the placebo group. There was also subjective improvement in itching and sleep. These patients also were followed up for 1 year, with reports of continued improvement and no serious adverse effects, although the patients who discontinued treatment noted a relapse in their condition (Sheehan and Atherton 1994). Although the sample sizes were limited, initial results were promising for patients for whom standard therapy had failed. The main limiting issue seemed to be the taste and the preparation of the decoction. It should be emphasized that although no serious adverse effects were noted in this study, careful monitoring of complete blood cell count and liver function is recommended, as liver failure and even death have been reported with these TCM herbs when baseline laboratory values were not followed (Graham-Brown 1992; Mostefa-Kara et al. 1992; Koo and Arain 1998). It is known that the specific herbs used in these studies have anti-inflammatory, antibacterial, antifungal, antihistaminic, immunosuppressant, and corticosteroid-like effects. A few of the ingredients are also smooth muscle relaxants, and inhibit the platelet-activating factor. Several studies have attempted to elucidate the mechanism of action of this group of 10 herbs (Zemophyte, manufactured by Phytotech Limited, Godmanchester, England) in treating atopic dermatitis. Patients with atopic dermatitis are known to have elevated levels of the low-affinity IgE receptor CD23 expressed on circulating monocytes. In studies of IL-4-induced CD23 expression on monocytes, there appeared to be a reduction in CD23 expression when the cells were exposed to the aqueous herb extracts (Latchman et al. 1994, 1996). Another study examined immunologic markers for T cells, macrophages, Langerhans cells, and low- affinity and high-affinity IgE receptors in biopsy specimens of lesional skin treated with Zemophyte compared with biopsy specimens of nonlesional skin (Xu et al. 1997). The investigators found clinical improvement similar to that seen in the aforementioned Sheehan studies, and also found that the improvement was associated with a statistically significant reduction in CD23 antigen-presenting cells. However, an attempt to replicate the Zemophyte double-blind randomized placebo-controlled study in Hong Kong failed to achieve a statistically significant effect of Zemophyte over placebo (Fung et al. 1999). A different TCM herbal mixture called PentaHerbs formula, with *Paeonia suffruticosa* root bark, Class 1; *Phellodentron chinensis* bark, Class 2b; *Lonicera japonica* flower, Class 1; *Mentha haplocalux* aerial part, Class 1; and *Atractylodes lancea* rhizome Class 1 in a ratio of 2:2:2:1:2, known clinically to be useful

in the management of atopic dermatitis, was tested on rat peritoneal mast cells and found to suppress histamine release and prostaglandin D2 synthesis (Chan et al. 2008). The bark of the birch tree (*Betula platyphylla* var. *japonica*), which is used to treat atopic dermatitis, was studied in NC/Nga mice. It decreased scratching and skin inflammation, as well as decreasing IgE and IL-4 messenger ribonucleic acid (mRNA) levels, suggesting that it suppresses the T-helper 2 cellular response (Kim et al. 2008). Other TCM herbal mixes for dermatitis are listed by Xu (2004).

Jewelweed (*Impatiens biflora*) is alleged to be useful topically for treating poison ivy contact dermatitis, but research results are conflicting. In one study, treatment with jewelweed was found to be comparable with standard treatment for poison ivy contact dermatitis, and in 108 of 115 patients studied, the symptoms cleared within 2–3 days (Lipton 1958). However, in another study, jewelweed extract failed to decrease symptoms of poison ivy dermatitis (Guin and Reynolds 1980). In yet another study, no prophylactic effect of jewelweed in treating poison ivy dermatitis was reported (Long, Ballentine, and Marks 1997). Jewelweed has been said to be most effective if applied to the area where the poison ivy touched as soon as possible after contact, but this aspect was not addressed by the aforementioned studies. There have been no reports of topical jewelweed causing adverse effects (Peirce, Fargis, and Scordato 1999, 365).

Several herbs contain a substance called "mucilage," which is useful topically to soothe and act as an emollient on skin. Heartseases (*Viola tricolor*), Class 1; marshmallow (*Althea officinalis*); English plantain (*Plantago lanceolata*), Class 1; fenugreek (*Trigonella foenum-gaecum*), Class 2b; mullein (*Verbascum thapsus*), Class 1; slippery elm (*Ulmus fulva*), Class 1; and flax (*Linum usitatissimum*) contain mucilages, which act as emollients on and soothe the skin. Mucilage quickly swells into a gooey mass when exposed to water, thereby ameliorating dry or mildly inflamed skin. Mucilage also dries as a mild adhesive and can be used as an herbal bandage for minor wounds (McGuffin et al. 1997; Peirce, Fargis, and Scordato 1999; Fleming 2000).

Oats (*Avena sativa*) have been used topically in baths for hundreds of years for their soothing and antipruritic properties, and they are approved for this use by the German regulatory authority Commission E and are listed as Class 1 (McGuffin et al. 1997; Fleming 2000; Bisset and Wichtl 2001). Colloidal oatmeal turns to a gooey sticky mass when mixed with liquid which can be used to coat the skin and sealing in moisture. This soothing and moisturizing property is attributed to the gluten content of the plant. This can be useful in treating atopic dermatitis as well as idiopathic pruritus of the elderly.

Pansy flower (*V. tricolor* hybrids) infusion is recommended as a nontoxic treatment for seborrheic dermatitis, especially in infants. The infusion is made by mixing 1–2 tsp of flowers per cup of water and is used as a wet dressing. Salicylic acid in concentrations of about 0.3% appears to be the active ingredient. It also contains saponins and mucilage, which have softening and soothing effects. No adverse effects have been reported with topical use, and pansy is included in Class 1 (McGuffin et al. 1997; Peirce, Fargis, and Scordato 1999).

In treating dermatitis, tannins used topically act by coagulating the surface proteins of cells and exudates, thereby reducing permeability and secretion. The precipitated proteins also form a protective layer on the skin (Brown and Dattner 1998). Tannins may also have antimicrobial properties. Tannins found in agrimony (*Agrimonia eupatoria*), Class 1; jambolan bark (*Syzygium cumini*), Class 1; oak bark (*Quercus robur*), Class 2d; English walnut leaf (*Juglans regia*), Class 2d; Labrador tea (*Ledum groenlandicum*); goldenrod (*Solidago* spp.), Class 2d; lady's mantle (*Alchemilla* spp.), Class 1; lavender (*Lavandula angustifolia*), Class 1; mullein (*Verbascum thapsus*), Class 1; rhatany (*Krameria* spp.), Class 1;
Chinese rhubarb (*Rheum officinale*), Class 2b, 2c, 2d; yellow dock (*Rumex crispus*), Class 2d; witch hazel bark (*H. virginiana*), Class 1; and St. John's wort (*Hypericum montana*), Class 2d, act as astringents. Oat straw (*A. sativa*) included in Class 1 is also approved for its soothing and antipruritic qualities (McGuffin et al. 1997; Blumenthal et al. 1998; Peirce, Fargis, and Scordato 1999; Fleming 2000; Bisset and Wichtl

2001). One study showed that a witch hazel extract in a phosphatidyl choline base was less effective in reducing erythema from ultraviolet (UV) radiation and cellophane tape stripping in 24 healthy patients than 1% hydrocortisone (Korting et al. 1993). In another clinical trial, one group with atopic dermatitis (*n* = 36) and another group with contact dermatitis (*n* = 80) compared witch hazel extract with control. In the atopic group, the witch hazel was slightly superior in reducing inflammation and itching. There are also anecdotal reports of witch hazel's usefulness in treating atopic dermatitis (Brown and Dattner 1998).

HERPES SIMPLEX

Lemon balm (*Melissa officinalis*) is a lemon-scented member of the mint family. An essential oil can be steam-distilled from the cut leaves. Topical uses include treatment of herpes simplex and minor wounds. In a randomized, double-blind trial of 116 patients with herpes simplex lesions, 96% reported complete clearing of lesions at day 8 after using 1% balm extract cream five times a day (Wobling and Leonhardt 1994). In another trial where balm extract was placed on lesions within 72 hours of the onset of symptoms, the size of the lesions and healing time were found to be statistically better in the group treated with balm (Brown and Dattner 1998). Tannin and polyphenols appear to be responsible for the antiviral effect of the balm (Peirce, Fargis, and Scordato 1999). Balm is included in Class 1, and is very safe to use both topically and orally (McGuffin et al. 1997; Peirce, Fargis, and Scordato 1999).

Other herbal preparations that have reported in-vitro activity against herpes simplex include *Echinacea* spp., sweet marjoram, peppermint, and propolis, although clinical studies for the latter three have not yet been performed (Peirce, Fargis, and Scordato 1999). A small, randomized, placebo-controlled crossover clinical trial found no statistically significant differences between *Echinacea* extract of 800 mg twice per day for 6 months and placebo controls in treating recurrent genital herpes (Basch et al. 2005). The TCM herbal mixtures for treating herpes simplex are listed by Xu (2004).

HERPES ZOSTER

Capsaicin, the main ingredient in cayenne pepper (*Capiscum frutescens*, Class 1 internally but Class 2d externally; McGuffin et al. 1997) is available as a cream for the treatment of postherpetic neuralgia. It is applied four or five times a day and initially causes a burning sensation. With continued use, it depletes substance P in the regional peripheral nerves, reducing pain. In China, herpes zoster is commonly treated topically with hibiscus (*Hibiscus sabdariffa;* Fleming 2000). Hibiscus has been proved to be a very safe Class 1 herb, both topically and orally (McGuffin et al. 1997). The TCM herbal mixtures for herpes zoster are listed by Xu (2004).

Herpes zoster and postherpetic neuralgia have been treated with a topical licorice (*Glycyrrhiza glabra, G. uralensis*) Class 1 gel preparation (Lininger 2000). Glycyrrhizen, one of the active components of licorice, has been demonstrated to inhibit the replication of varicella zoster in vitro (Baba and Shigeta 1987). There are so far no clinical studies to support this. Topical use is reported to be very safe, but care should be taken when it is taken orally as it is included in both Classes 2b and 2d (McGuffin et al. 1997).

HYPERHIDROSIS

By precipitating surface proteins, topical tannins can reduce the openings of sweat ducts and thus reduce sweating locally. Tannins also have antimicrobial properties that help to reduce odorous bacterial by-products (van Wyk and Wink 2004). See Section 18.3.5 for information about specific sources of tannins. Black tea also contains tannins.

PRURITUS

Camphor is derived from the camphor tree (*Cinnamomum camphora*) Classes 2b and 2d distillate of the wood (McGuffin et al. 1997, 30). It is toxic in large doses. As an antipruritic, it can be added to lotions or creams at one-half percent. Menthol is derived from Japanese mint (*M. arvensis*), which is included in

Class 1 (McGuffin et al. 1997). It has a cooling, antipruritic, and antibacterial effect. Lotions and creams typically contain 1–5% essential oil. As noted in Section 18.3.5, oats also have a soothing, antipruritic effect.

Tars derived from birch (*Betula* spp.), beech (*Fagus* spp.), or juniper (*Juniperus* spp.) trees (van Wyk and Wink 2004) are antipruritic and antiproliferative. They are used in a 5–10% concentration in creams, gels, and soaps. They are photosensitizing compounds, and judicious exposure to sunlight can be beneficial.

PSORIASIS

Aloe vera (*Aloe vera*), which is Class 1 internally and Class 2d externally (McGuffin et al. 1997), has been used for centuries in wound healing and was recently found to be a potential treatment for psoriasis. In a double-blind placebo-controlled study, 60 patients with slight to moderate plaque psoriasis were treated topically with either 0.5% hydrophilic aloe cream or placebo. The aloetreated group showed statistically significant improvement (83.3%) compared with the placebo group (6.6%). There were no adverse effects reported in the treatment group (Syed et al. 1996).

Capsaicin is the main ingredient in cayenne pepper (*C. frutescens*), which is Class 1 internally but Class 2d externally (McGuffin et al. 1997); it has also been studied for the treatment of psoriasis. In vitro, capsaicin was found to inhibit phorbol ester-induced activation of transcription factors NF-κB and AP-1 (Surh et al. 2000). Two trials showed that 0.025% cream used topically is effective in treating psoriasis. The first study showed a significant decrease in scaling and erythema during a 6-week period in 44 patients with moderate and severe psoriasis (Bernstein et al. 1986). The second was a double-blind study of 197 patients in whom psoriasis was treated with the capsaicin cream four times daily for 6 weeks, with a significant decrease in scaling, thickness, erythema, and pruritus (Ellis et al. 1993). The main adverse effect reported was a brief burning sensation at the application site. Capsaicin is contraindicated on injured skin or near the eyes, and the German authority Commission E suggests it should not be used for more than 2 consecutive days, with a 14-day lapse between applications.

A survey of patients with psoriasis at a large university dermatology practice revealed that 51% of patients used one or more alternative therapeutic modalities (Fleischer et al. 1996). This is consistent with previous Norwegian surveys of patients with psoriasis (Jensen 1990). Herbal therapy is one of the most frequently chosen alternative therapies. Psoriasis has been treated for centuries with herbal preparations, both topical and oral. There are many herbal preparations composed of furocoumarins, which act as psoralens when combined with ultraviolet A (UV-A, 320–400 nm). Furocoumarins derived from *Ammi majus* and related plants that produce 8-methoxy-psoralen when applied topically or taken orally intercalate with DNA. Further, when coupled with exposure to UV-A from the sun or a an ultraviolet light-box, the photoactivation causes cross-linkages with the thymine in the DNA, inducing cell death (van Wyk and Wink 2004). This, in turn, inhibits hyperproliferation in psoriatic lesions.

One commonly used TCM, Radix *Angelicae dahurica*, included in Class 1 (McGuffin et al. 1997), contains the furocoumarins imperatorin, isoimperatorin, and alloimperatorin. In a study involving 300 patients with psoriasis, this TCM, taken orally, was combined with UV-A therapy and was compared with the standard treatment of psoralen—UV-A with methoxsalen. The efficacy of the two treatments was equivalent; however, there were fewer adverse effects such as nausea and dizziness in the group treated with TCM and UV-A (Koo and Arain 1998). In addition, there are topical preparations made from herbs that show systemic efficacy against psoriasis, but are too toxic when given systemically (Ng 1998). Topical TCM of the plant *Camptotheca acuminata* in an open trial including 92 patients with psoriasis found that this TCM was statistically more effective than 1% hydrocortisone. A disadvantage was that allergic contact dermatitis was seen in 9–15% of the patients in the TCM group. Comparison of TCM mixtures in clinical trials is difficult, because the mixture of herbs prescribed varies individually depending on the subtype of psoriasis (“blood-heat” type, “blood deficiency dryness” type, and “blood

stasis" type), which is determined in TCM by many findings, including lesions of psoriasis, the pulse, and the condition of the tongue (Koo and Arain 1998). Some types of TCM may act in part on the microcirculation of the psoriatic lesion (Zhang and Gu 2007). Additional TCM herbal mixtures for psoriasis are listed by Xu (2004).

About 5% curcumin is present in turmeric (*Curcuma longa*), which is included in Classes 2b and 2d (McGuffin et al. 1997; see also Chapter 13 on turmeric). Turmeric has been used for centuries in India to provide glow and luster to the skin. It has antimicrobial, antioxidant, astringent, and other useful effects that help to heal wounds and reduce scarring (Chaturvedi 2009). In vitro, the purified turmeric extract curcumin has been found to inhibit phorbol ester-induced activation of transcription factors NF-κB and AP-1 (Surh et al. 2000). The resulting suppression of phosphorylase kinase activity correlates with the resolution of psoriasis when curcumin is applied topically to the lesions (Heng et al. 2000). Microencapsulation of curcumin reduces the yellow staining produced by application of topical curcumin on the skin, while prolonging the bioavailability of curcumin (Aziz, Peh, and Tan 2007).

Tars have been used for centuries to treat psoriasis. Tars derived from birch (*Betula* spp.), beech (*Fagus* spp.), or juniper (*Juniperus* spp.) trees (van Wyk and Wink 2004) are antipruritic and antiproliferative. They are used in a 5–10% concentration in creams, gels, and soaps. They are photosensitizing compounds, so judicious exposure to sunlight can be beneficial, or they can be used in conjunction with ultraviolet B (UV-B; 250–320 nm) or narrowband UV-B (311 nm).

PSYCHOSOMATIC

Depression and anxiety can cause skin problems. Kava kava (*Piper methysticum*) has moderate anxiolytic effects, but its use is not recommended due to its potential hepatotoxicity. It is included in Classes 2b, 2c, and 2d (McGuffin et al. 1997). Lavender oil aromatherapy (*Lavendula* spp.) has been demonstrated to produce significant reduction in anxiety. This may in part be a conditioned response, and it is important that the first exposure to lavender oil is a pleasant and relaxing one. It is Class 1 (McGuffin et al. 1997). Lemon balm (*M. officinalis*) is approved by the German authority Commission E for treating nervousness and insomnia. It is also Class 1 (McGuffin et al. 1997.) Magnolia bark (*Magnolia obovata*) has moderate anxiolytic effects. It contains honokiol and magnolol, which have antioxidant and anti- inflammatory (Kuribara, Stavinoha, and Maruyama effects. It is Class 2b (McGuffin et al. 1997). Passion flower (*Passiflora incarnata*) is approved by Commission E for treating nervousness and insomnia. It is Class 1 (McGuffin et al. 1997). St. John's wort (*H. perforatum*) is approved by Commission E for treating depression. It is helpful for treating mild to moderate depression but not for severe depression (Linde et al. 1996). It has significant interactions with the metabolism of a number of other drugs by inducing cytochrome P450 isoform 3A4, and is Class 2d (McGuffin et al. 1997). Valerian (*Valariana* spp.) is approved by Commission E for treating insomnia caused by nervousness. It is Class 1 (McGuffin et al. 1997).

SCABIES

Anise (*Pimpinella anisum*) seeds are a source of an essential oil that displays antibacterial and insecticidal activity in vitro and is used topically to treat scabies and head lice. It should not be used in pregnancy and is Class 2b (McGuffin et al. 1997). Neem (*Azadirachta indica*) is indigenous to India, and every part of the plant is used medicinally. In a study of more than 800 villagers in India, a paste of neem and turmeric applied topically was reported to treat chronic ulcers and scabies (Peirce, Fargis, and Scordato 1999). It seems to be safe for use in adults, but can be poisonous to children (Peirce, Fargis, and Scordato 1999). Numerous other herbs have been used for centuries in India and China to treat scabies (Fleming 2000).

Red ginseng (*Panax ginseng*) is a classic TCM. In a recent study, red ginseng extracts used topically were found to inhibit chemically induced skin tumors in mice. This is thought to be due to the immuno-modulating properties of red ginseng (Cheng, Lin and Lei et al. 1998). It is Class 2d (McGuffin et al. 1997). Propolis is a resinous material gathered by honeybees from the buds and bark of certain plants and trees.

Propolis has been used for centuries for its antimicrobial, anti-inflammatory, analgesic, and antitumor effects, which are thought to result from the flavinoid and related phenolic acids components. A tumoricidal component, clerodane diterpenoid, has also been isolated. This compound was studied regarding its topical effects on skin tumorigenesis in mice. Clerodane diterpenoid appeared to reduce the incidence of chemically induced dysplastic papillomas by inhibiting the synthesis of DNA in a de novo pathway and by suppressing the growth of tumors by decreasing DNA synthesis in a salvage pathway (Mitamura et al. 1996).

Rosemary (*Rosmarinus officinalis*) extract is reputed to have antioxidant activity. A methanol extract of the leaves was evaluated for its effects on skin tumors in mice. It was found that topically applied rosemary inhibited induction and promotion of skin tumors in mice treated with known chemical carcinogens. Although the exact mechanism of action is still under study, it appears that several components of the extract are important in this process. This finding suggests that it was not the antioxidant properties alone that were beneficial in the prevention of skin tumors (Huang et al. 1994). Rosemary should not be used in pregnancy as it is a Class 2b herb (McGuffin et al. 1997).

Silymarin is a flavinoid isolated from milk thistle (*Silybum marianum*), and is approved by the German Commission E for treating liver disease because of its antioxidant properties. An experiment was performed to assess whether this antioxidant effect would protect against tumor promotion. Topically applied silymarin was found to possess highly protective effects against chemically induced skin tumor promotion in mice. This may involve inhibition of promoter-induced edema, hyperplasia, and proliferation, as well as the oxidant state (Lahiri-Chatterjee et al. 1999). These results are promising, yet more research involving human models is needed. Silymarin is safe to use topically and orally when used appropriately, and is Class 1 (McGuffin et al. 1997).

Tea is manufactured from the leaf and bud of *Camellia sinensis* (see also Chapter 12 on tea). The majority of tea consumed worldwide is in the form of black tea, which is Class 2d (McGuffin et al. 1997). Green tea has been found in several mouse models to have anti-inflammatory and antitumorigenic properties. The polyphenolic constituent (–)-epigallocatechin-3-gallate is thought to be the active ingredient. Numerous studies of green tea and skin cancer were reviewed (Katiyar, Ahmad, and Mukhtar 2000). It was found that topical application or oral consumption of green tea protects against inflammation, chemical carcinogenesis, and photocarcinogenesis. Green tea demonstrated the blocking of many mediators in the inflammatory process important in the early steps of skin tumor promotion. It also appears that there is inhibition of biochemical markers of chemical carcinogenesis, inhibition of UV-induced oxidative stress, and prevention of UV-induced immunosuppression (Katiyar, Ahmad, and Mukhtar 2000) as a result of action of green tea. Green tea also protects against psoralen UV-A-induced photochemical damage to the skin (Zhao Jin and Yaping et al. 1999). Many cosmetics and skin care products have been recently supplemented with green tea, but more research in humans is needed to understand the true benefits. Black tea may also play a role in the prevention of skin tumors. It appears that theaflavins are the components active in chemoprevention (Nomura et al. 2000). Several studies provide evidence that topical application of the constituents of black tea can decrease UV-B-induced erythema, inhibit tumor initiation, and act as an antitumor promoter (Javed, Mehrotra, and Shukla 1998; Zhao Zhang and Jin et al. 1999). Oral administration of black tea was also found to inhibit tumor proliferation and promote tumor apoptosis in nonmalignant and malignant skin tumors (Lu et al. 1997). A survey of older patients compared tea consumption and history of squamous cell carcinoma. There

was a lower risk of squamous cell carcinoma in patients who regularly consumed hot black tea than in nonconsumers (Hakim, Harris, and Weisgerber 2000). Different studies comparing the effectiveness of black and green teas in protecting against UV-induced skin tumors give conflicting findings as to which is more beneficial (Wang et al. 1994; Huang et al. 1997; Record and Dreosti 1998; Lou et al. 1999). Caffeinated teas seem to be more protective than decaffeinated teas, and caffeine by itself has some inhibitory effects on UV-B-induced carcinogenesis (Wang et al. 1994; Huang et al. 1997; Lou et al. 1999).

VERRUCA VULGARIS AND CONDYLOMA ACCUMINATA

Podophyllin, used to treat condyloma acuminata, is extracted from the root of the American mayapple (*Podophyllum peltatum;* Fleming 2000). It should not be used during pregnancy and is Class 2b externally and toxic internally (McGuffin et al. 1997). Commission E approves bittersweet nightshade (*S. dulcamara*), Classes 2b and 2c, and oat straw (*A. sativa*), Class 1, for the treatment of common warts (McGuffin et al. 1997; Fleming 2000). Calotropis (*Calotropis procera*) is used in India, and greater celandine (*Chelidonium majus*), Classes 2b, 2c, and 2d (McGuffin et al. 1997, 28), is used in China for the treatment of warts (Fleming 2000). Bittersweet nightshade and celandine should also be avoided in pregnancy and while breast-feeding (Fleming 2000).

VITILIGO

Ginkgo (*G. biloba*) was found to be effective in a small study for treating limited, slowly spreading vitiligo (Parsad, Pandhi, and Juneja 2003). Caution should be used when ginkgo is taken orally, as there have been reports of subarachnoid and intracerebral hemorrhage, as well as increased bleeding time (Fleming 2000); but the herb is included in Class 1 (McGuffin et al. 1997).

Psoralens, such as the furanocoumarins derived from *A. majus* and related plants that produce 8-methoxy-psoralen, when applied topically or taken orally, intercalate with DNA. As noted in Section 18.3.10, with photoactivation they can induce cell death (van Wyk and Wink 2004). By thus reducing inflammatory cells while stimulating melanogenesis, the treatment often induces repigmentation of vitiliginous skin.

WOUNDS AND BURNS

Aloe vera (*A. vera*) leaves produce a gel and a juice or latex. The gel is obtained from the central core of the leaf and has been used topically for centuries for the treatment of wounds and burns. The juice or latex is a bitter yellow fluid extracted from the inner leaf skin and is generally sold dried as a powder that has very potent laxative effects (Peirce, Fargis, and Scordato 1999). Several case reports and animal studies demonstrate that aloe vera decreases burning, itching, and scarring associated with radiation dermatitis (Klein and Penneys 1988). Aloe vera was also found to accelerate healing of chronic leg ulcers, surgically induced wounds, and frostbite. The mechanism of action has been studied in vivo in animal studies. Aloe vera decreases thromboxane A2, thromboxane B2, and prostaglandin 2α, which cause vasoconstriction and platelet aggregation. By increasing dermal perfusion, tissue loss from ischemia is reduced (Klein and Penneys 1988). In vitro studies have also demonstrated a carboxypeptidase that inactivates bradykinin, decreasing pain at the treatment site (Fujita and Shosike 1976). Salicylic acid present in aloe vera acts as an analgesic and anti-inflammatory agent by inhibiting prostaglandin production (Robinson, Heggers, and Hagstrom 1982). Magnesium lactate is also present in aloe vera and is thought to be antipruritic by inhibiting histidine decarboxylase, which controls the conversion of histidine to histamine in mast cells (Klein and Penneys 1988). Reduction in inflammation is also thought to result from the immunomodulatory properties of the gel polysaccharides present, especially the

orally, aloe vera is considered very safe when used properly. It is Class 1 internally and Class 2d externally (McGuffin et al. 1997).

Asiaticoside in low concentrations has been found to enhance the healing of burn wounds, with evidence suggesting that enhanced angiogenesis may occur as a result of stimulation of vascular endothelial growth factor production (Kimura et al. 2008).

Honey has been used topically for centuries to assist healing of wounds, including burns, decubitus ulcers, and infected wounds (Greenwood 1993). It has been found in vitro to have antibacterial and antifungal activity against organisms that commonly infect surgical wounds (Efam and Udoh 1992). A study was performed on nine infants with large, open, culture-positive postoperative wound infections for whom standard treatment consisting of appropriate intravenous antibiotics and cleansing with chlorhexidine for more than 14 days had failed. The wounds were then treated with 5–10 mL of fresh, unprocessed honey twice a day. There was marked clinical improvement by day 5, and by day 21, the wounds were all closed, clean, and sterile (Vardi et al. 1998). In a randomized controlled trial, honey-impregnated gauze was compared with a polyurethane film (OpSite, manufactured by Smith & Nephew, North Humberside, England) for partial-thickness burns. The honey-treated wounds healed statistically earlier, with a mean of 10.8 days versus 15.3 days for film-treated wounds and with equal numbers of complications such as infection, excessive granulation, and contracture compared with the polyurethane-film-treated wounds (Subrahmanyam 1993). The wound-healing properties of honey are believed to result from the debriding properties of the enzyme catalase, absorption of edema due to honey's hygroscopic properties, its ability to promote granulation and reepithelialization from the wound edges, and its antimicrobial properties (Efam 1988). There have been no reports of significant adverse effects, although there are reports of contact dermatitis to honey (Efam 1988).

Marigold (*Calendula officinalis*) has been used topically since ancient times and is approved by the German regulatory authority Commission E as an antiseptic and for wound healing (Bisset and Wichtl 2001). A topical preparation of marigold continues to be recommended for the treatment of wounds, ulcers, burns, boils, rashes, chapped hands, herpes zoster, and varicose veins. Marigold gargles are used for mouth and throat inflammation (Peirce 1999). Marigold is also widely used as a topical treatment for diaper dermatitis and other mild skin inflammations (Brown and Dattner 1998). The treatment consists of an application several times a day of an ointment or a cream made by mixing 2–5 g of the flower heads with 100 g of ointment. A gargle or lotion is made by mixing 1–2 tsp (5–10 mL) of tincture with 0.25–0.5 L of water (Peirce 1999). The main adverse event is allergic contact dermatitis. No serious adverse effects have been reported, and it is considered safe to use both topically and orally. It is Class 1 (McGuffin et al. 1997). The anti-inflammatory effects of marigold are ascribed to the presence of triterpenoids. In animal studies, *Calendula* was suggested to stimulate granulation and increase glycoproteins and collagen at wound sites (Brown and Dattner 1998). Marigold also shows in vitro antimicrobial and immune-modulating properties (Peirce 1999).

There are many herbs containing tannins that act as astringents, helping to dry oozing and bleeding wounds. Some of the more commonly reported tannin-containing herbs that may be helpful for the topical treatment of wounds include English walnut leaf, goldenrod, Labrador tea, lavender, mullein, oak bark, rhatany, Chinese rhubarb, St. John's wort, and yellow dock (see Section 18.3.5 for a list of scientific plant names and ratings of toxicity; Peirce 1999).

ADVERSE EFFECTS OF HERBAL THERAPY

Herbal therapies vary greatly in their safety class ratings. For example, some are consumed as foods and have high safety ratings, whereas others are highly biologically active and toxic and must be used very carefully. The safety classes of the herbs mentioned in this chapter are addressed in each section, and further discussion of interactions of herbal therapies that may be encountered in dermatology is detailed in the remaining sections of the chapter. Many cutaneous reactions to herbal preparations have been

reported, with the most common cutaneous adverse event being allergic contact dermatitis. More serious cutaneous reactions have been reported. Two patients developed erythroderma after using topical herbal treatments for psoriasis and atopic dermatitis, and one patient developed Stevens-Johnson syndrome after taking "golden health blood-purifying tablets," which contained multiple herbs, including red clover, burdock, queen's delight, poke root, prickly ash, sassafras bark, and *Passiflora* (Monk 1986). Bullous and nodular lichen planus were reported to be induced by ingestion of native African herbal medicines (Soyinka 1973). A young woman was also described with leukemia- related Sweet syndrome elicited by a pathergic response to topical arnica cream (Delmonte et al. 1998).

Serious systemic adverse effects have been reported with the use of TCM herbal mixtures for the treatment of dermatologic disorders. The most common are hepatotoxic effects. Although most patients recover without serious consequences as long as the medication is stopped, there have been reports of patients with acute liver failure leading even to death. There are also reports of renal failure and agranulocytosis (Graham-Brown 1992; Mostefa-Kara et al. 1992; Koo and Arain 1998). One patient was described with adult respiratory distress syndrome after administration of a TCM, kamisyoyo-san, for seborrheic dermatitis (Shota et al. 1961). A patient was reported with reversible dilated cardiomyopathy after receiving treatment for her atopic dermatitis with a Chinese herbal tea (Ferguson, Chalmers, and Rowlands 1997). There are also reports of Chinese and Indian herbal medicines containing as contaminants heavy metals, such as lead, arsenic, and mercury. Prescription medications have also been found in over-the-counter herbal formulations from other countries. Some herbs are mislabeled or misidentified.

There are many possible drug interactions with herbs and prescription medications. It is crucial for patients to share information about what herbs, supplements, and other over-the-counter remedies they are taking or applying to their skin with their physicians. The most important drug interactions in the dermatologic setting are the immune-upmodulating effects of *Echinacea, Astragalus*, licorice, alfalfa sprouts, and vitamin E, and zinc may decrease the efficacy of corticosteroids and immunosuppressants (Miller 1998). Some herbs are reported to cause hepatic damage, and they should not be used in combination with medications such as methotrexate. These include many of the ingredients in TCM preparations, as well as *Echinacea*, chaparral, germander, ragwort, and life root (Ferguson, Chalmers, and Rowlands 1997; Borins 1998). Herbs containing y-linolenic acid, such as evening primrose oil, which has been used for treating dermatitis, psoriasis, and xerosis, lower the seizure threshold; thus, dosages of anticonvulsants may need to be increased (Ferguson, Chalmers, and Rowlands 1997). Rue (*Ruta graveolens*) and other herbs containing psoralens can cause phototoxic reactions externally on the skin (Eickhorst, Deleo, and Csaposs 2007). In addition to making them aware of the adverse effects already discussed, patients should be counseled on the relative lack of regulation for herbal medicines. There are minimal quality-control requirements currently in place in the United States to ensure the purity, concentration, or safety of herbal supplements. Although herb manufacturers are restricted from making efficacy statements, there are no regulations on claims for what symptoms these herbs can alleviate. In the United States, there are also minimal regulations on which herbs can be restricted in formulations (Shaw 1998).

CAVEATS CONCERNING HERBAL THERAPY AND DERMATOLOGIC SURGERY

Herbs may affect blood coagulation. A number of medicinal herbs contain coumarin, salicylate, or other platelet-inhibiting substances that can increase the risk of interoperative and postoperative bleeding. Some coumarin-containing herbs include danshen (*Salvia miltiorrhiza*), dong quai (*Angelica sinensis*), horse chestnut bark (*Aesculius hippocastanum*), sweet clover (*M. officinalis*), sweet vernal (*Anthoxanthum odoratum*), sweet-scented bedstraw (*Galium triflorum*), tonka beans (*Dipteryx odorata*), vanilla leaf (*Trilisa odoratissima*), and woodruff (*Asperula odorata*). Salicylate-containing herbs include black cohosh (*Cimifuga racemosa*), meadowsweet (*Spirea ulmaria*), poplar bark (*Populus* spp.), sweet birch bark (*Betula* spp.), willow bark (*Salix* spp.), and wintergreen (*Gaultheria procumbens*). Other

platelet function inhibitors include bromelain (*Ananas comosus*), cayenne (*C. frutescens*), Chinese skullcap (*Scutullaria baicalensis*), feverfew (*Tanacetum parthenium*), garlic (*A. sativum*), ginger (*Zingiber officinale*), ginkgo (*G. biloba*), ginseng (*Panex ginseng*), onion (*A. cepa*), papain (*Carica papaya*), reishi fruit (*Ganoderma lucidum*), and turmeric (*C. longa;* Pribitkin 2005).

Herbs may also affect blood pressure. Potentially hypertensive plants include black cohosh, ephedra or ma huang (*Ephedra* spp.), licorice (*G. glabra*), and yohimbe (*Pausinystalia yohimbe*). Potentially hypotensive plants include garlic (Pribitkin 2005).

RESEARCH NEEDS

Further research into the efficacy, safety, optimal uses, and standardization of herbal remedies is clearly needed. Inhibiting factors in the United States include the nonpatentability of herbal materials in a system in which the typical costs of double-blind testing for Food and Drug Administration (FDA) approval of drugs range in the millions of dollars, requiring patentability for private enterprises to attain a profit. Since herbal remedies currently remain in the category of dietary supplements, a different mechanism of funding for research is needed. The funding for complementary and alternative medicines research provided through the National Institutes of Health is meager compared with private and public funding of research for conventional drugs.

18.7. CONCLUSIONS

Many herbal therapies have been used for centuries, which show good anecdotal results. A few randomized, controlled trials have also demonstrated significant results in the use of herbal therapies for the treatment of dermatologic disorders. Some countries, such as Germany, now require standardization of herbal preparations and specific recommendations as to the use and efficacy of herbs in the treatment of disease. It is important to know what common herbal alternatives exist and which potential adverse effects or interactions can occur to permit more effective counseling of patients.

REFERENCES

Abascal K, Yarnell E. Botanicals for chronic venous insufficiency. Altern Complement Ther. 2007;13(6):304–11.
Armstrong N.C, Ernst E. The treatment of eczema with Chinese herbs: A systematic review of randomized clinical trials. Br J Clin Pharmacol. 1999;48:262–4. [PMC free article] [PubMed]
Atherton D.J, Sheehan M.P, Rustin M. H. A, Whittle B, Guy G. Treatment of atopic eczema with traditional Chinese medicinal plants. Pediatr Dermatol. 1992;9:373–5. [PubMed]
Aziz H.A, Peh K.K, Tan Y.T. Solubility of core materials in aqueous polymeric solution effect on microencapsulation of curcumin. Drug Dev Ind Pharm. 2007;33(11):1263–72. [PubMed]
Baba M, Shigeta S. Antiviral activity of glycyrrhizen against Varicella zoster virus in vitro. Antiviral Res. 1987;7:99–107. [PubMed]
Basch E, Ulbricht C, Basch S, et al., editors. An evidence-based systemic review of Echinacea (E. angustifolia DC, E. pallida, E. purpurea) by the natural standard research collaboration. J Herb Pharmacother. 2005;5(2):57–88. [PubMed]
Bedi M.K, Shenefelt P.D. Herbal therapy in dermatology. Arch Dermatol. 2002;138:232–42. [PubMed]
Behl P.N, Srivastava G. 2002Herbs Useful in Dermatological Therapy. 2nd ed. New Delhi, India: CBS Publishers.
Bernstein J.E, Parish L.C, Rapaport M, et al., editors. Effects of topically applied capsaicin on moderate and severe psoriasis vulgaris. J Am Acad Dermatol. 1986;14:504–7. [PubMed]
Beylier M.F. Bacteriostatic activity of some Australian essential oils. Perfum Flavourist. 1979;4(2):23–5.
Bisset N.G, Wichtl M. Herbal Drugs and Phytopharmaceuticals. 2nd ed. Boca Raton, FL: CRC Press; 2001.
Blumenthal M, Gruenwald J, Hall T, Rister R.S. The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicine. Boston, MA: Integrative Medicine Communications; 1998.
Borins M. The dangers of using herbs: What your patients need to know. Postgrad Med. 1998;104:91–100. [PubMed]
Brown D.J, Dattner A.M. Phytotherapeutic approaches to common dermatological conditions. Arch Dermatol. 1998;1:15–7. [PubMed]
Buchness M.R. Alternative medicine and dermatology. Semin Cutan Med Surg. 1998;17:284–90. [PubMed]
Buck D.S, Nidorf D.M, Addini J.G. Comparison of two topical preparations for the treatment of onychomycosis: Melaleuca alternifolia (tea tree) oil and clotrimazole. J Fam Pract. 1994;38:601–5. [PubMed]

Callam M.J. Epidemiology of varicose veins. Br J Surg. 1994;81:167–73. [PubMed]
Chan B.C, Hon K.L, Leung P.C, et al., editors. Traditional Chinese medicine for atopic eczema:PentaHerbs formula suppresses inflammatory mediators release from mast cells. J Ethnopharmacol. 2008;120(1):85–91. [PubMed]
Chaturvedi T.P. Uses of turmeric in dentistry: An update. Indian J Dent Res. 2009;20(1):107–9. [PubMed]
Cheng X, Liu H, Lei X, et al., editors. Cancer chemopreventive and therapeutic activities of red ginseng. J Ethnopharmacol. 1998;60:71–8. [PubMed]
De Groot A.C, Weyland J.W. Contact allergy to tea tree oil. Contact Dermatitis. 1993;28:309. [PubMed]
Delmonte S, Brusati C, Parodi A, Rebora A. Leukemia-related Sweet's syndrome elicited by pathergy to arnica. Dermatology. 1998;197:195–7. [PubMed]
Diehm C. Comparison of leg compression stocking and oral horse-chestnut seed extract therapy in patients with chronic venous insufficiency. Lancet. 1996;347:292–4. [PubMed]
Dunning T. Complementary therapies and diabetes. Complement Ther Nurs Midwifery. 2003;9:74–80. [PubMed]
Efam S.E. Clinical observations on the wound healing properties of honey. Br J Surg. 1988;75:679–81. [PubMed]
Efam S.E, Udoh K.T. The antimicrobial spectrum of honey and its clinical significance. Infection. 1992;29:527–9.
Eickhorst K, Deleo V, Csaposs J. Rue the herb: Ruta graveolens-associated phytotoxicity. Dermatitis. 2007;18(1):52–5. [PubMed]
Eisenburg D.M, Kessler R.C, Foster C, et al., editors. Unconventional medicine in the United States: Prevalence, costs and pattern uses. N Engl J Med. 1993;328:246–52. [PubMed]
Elliot C. Tea tree oil poisoning. Med J Aust. 1993;159:830–1. [PubMed]
Ellis C.N, Berberian B, Sulica V.I, et al., editors. A double-blind evaluation of topical capsaicin in pruritic psoriasis. J Am Acad Dermatol. 1993;29:438–42. [PubMed]
Faoagali J, George N, Leditschke J.F. Does tea tree oil have a place in the topical treatment of burns? Burns. 1997;23:349–51. [PubMed]
Ferguson J.E, Chalmers R. J. G, Rowlands D.J. Reversible dilated cardiomyopathy following treatment of atopic eczema with Chinese herbal medicine. Br J Dermatol. 1997;136:592–3. [PubMed]
Fleischer A.B, Feldman S.R, Rapp S.R, Reboussun D.M, Exum M.L, Clark A.R. Alternative therapies commonly used within a population of patients with psoriasis. Cutis. 1996;58:216–20. [PubMed]
Fleming T. Medical Economics Co.; PDR for Herbal Medicines. (2nd ed. Montvale, NJ) 2000
Fujita K, Shosike I. Bradykinase activity of aloe extract. Biochem Pharmacol. 1976;25:205. [PubMed]
Fung A.Y, Look P.C, Chong L.Y, But P.P, Wong E. A controlled trial of traditional Chinese herbal medicine in Chinese patients with recalcitrant atopic dermatitis. Int J Dermatol. 1999;38(5):387–92. [PubMed]
Ghazanfar S.A. 1994*Handbook of Arabian Medicinal Plants*. Boca Raton, FL: CRC Press.
Graham-Brown R. Toxicity of Chinese herbal remedies [letter] Lancet. 1992;340:673. [PubMed]
Greenwood D. Honey for superficial wounds and ulcers. Lancet. 1993;341:90–1. [PubMed]
Guin J.D, Reynolds R. Jewelweed treatment of poison ivy dermatitis. Contact Dermatitis. 1980;6:287–8. [PubMed]
Hadley S.K, Petry J.J. Medicinal herbs: A primer for primary care. Hosp Pract. 1999;34(6):105–23. [PubMed] H
I.A, Harris R.B, Weisgerber U.M. Tea intake and squamous cell carcinoma of the skin: Influences of type of tea beverages. Cancer Epidemiol Biomarkers Prev. 2000;9:727–31. [PubMed]
Hausen B.M, Reichling J, Harkenthal M. Degradation products of monoterpenes aresensitizing agents in tea tree oil. Am J Contact Dermat. 1999;10(2):68–77. [PubMed]
Heng M.C, Song M.K, Harker J, Heng M.K. Drug-induces suppression of phosphorylase kinase activity correlates with resolution of psoriasis as assessed by clinical, histological and immuno- histochemical parameters. Br J Dermatol. 2000;143(5):937–49. [PubMed]
Herrick J.W. 1995*Iroquois Medical Botany*. Syracuse, NY: Syracuse University Press.
Hey I.C, Jamieson M, Ormerod A.D. Randomized trial of aromatherapy. Arch Dermatol. 1998;134:1349–52. [PubMed]
Huang M.T, Ho C.T, Wang Z.Y, et al., editors. Inhibition of skin tumorigenesis by rosemary and its constituents carnosol and ursolic acid. Cancer Res. 1994;54:701–8. [PubMed]
Huang M.T, Xie J.G, Wang Z.Y, et al., editors. Effects of tea, decaffeinated tea, and caffeine on UVB light-induced complete carcinogenesis in SKH-1 mice: Demonstration of caffeine as a biologically important constituent of tea. Cancer Res. 1997;57:2623–9. [PubMed]

Huffman M.A. Self-medicative behaviorin the African great apes: An evolutionary perspective into the origins of human traditional medicine. Bioscience. 2001;51(8):651–61.
Hunt M.J, Barnston R.S. A comparative study of gluconolactone versus benzoyl peroxide in the treatment of acne. Australas J Dermatol. 1992;33:131–4. [PubMed]
Javed S, Mehrotra N.K, Shukla Y. Chemopreventive effects of black tea polyphenols in mouse skin model of carcinogenesis. Biomed Environ Sci. 1998;11:307–13. [PubMed]
Jensen P. Use of alternative medicine by patients with atopic dermatitis and psoriasis. Acta Derm Venereol. 1990;70:421–4. [PubMed]
Kapoor L.D. 1990*CRC Handbook of Ayurvedic Medicinal Plants*. Boca Raton, FL: CRC Press.
Katiyar S.K, Ahmad N, Mukhtar H. Green tea and skin. Arch Dermatol. 2000;136:989–94. [PubMed]
Kessels A.G.H, Cardynaals R.L.L.M, Borger R.L.L, editors. The effectiveness of the hair restorer "Dabao" in males with alopecia androgenetica: A clinical experiment. J Clin Epidemiol. 1991;44:439–47. [PubMed]
Kim E.C, Lee H.S, Kim S.K, et al., editors. The bark of Betula platyphylla var. japonica inhibits the developmentof atopic dermatitis-like skin lesions in NC/Nga mice. J Ethnopharmacol. 2008;116:270–8. [PubMed]
Kimura Y, Sumiyoshi M, Samukawa K, Satake N, Sakanaka M. Facilitating action of asiaticoside at low doses on burn wound repair and its mechanism. Eur J Pharmacol. 2008;584(2-3):415–23. [PubMed]
Klein A.D, Penneys N.S. Aloe vera. J Am Acad Dermatol. 1988;18:714–20. [PubMed]
Klepser T.B, Klepser M.E. Unsafe and potentially safe herbal therapies. Am J Health Syst Pharm. 1999;56:125–38. [PubMed]
Knight T.E, Hansen B.M. Melaleuca oil (tea tree oil) dermatitis. J Am Acad Dermatol. 1994;30:423–7. [PubMed]
Koo J, Arain S. Traditional Chinese medicine for the treatment of dermatologic disorders. Arch Dermatol. 1998;134:1388–93. [PubMed]
Korting H.C, Schafer-Korting M, Hart H, Laux P, Schmid M. Anti-inflammatory activity of hamamelis distillate applied topically to the skin. Br J Clin Pharmacol. 1993;44:315–8. [PubMed]
Kron J. Herbalism. Complement Med. 2002;1(2):27–31.
Kuribara H, Stavinoha W.B, Maruyama Y. Behavioral characteristics of honkiol, an anxiolytic agent present in extracts of magnolia bark, evaluated by an elevated plus-maze test in mice. J Pharm Pharmacol. 1998;50:819–26. [PubMed]
Lahiri-Chatterjee M, Katiyar S.K, Mohan R.R, Agarwal R. A flavinoid antioxidant, silymarin, affords exceptionally high protection against tumor promotion in the SENCAR mouse skin tumorigenesis model. Cancer Res. 1999;59:6232. [PubMed]
Latchman Y, Banerjee P, Poulter L.W, Rustin M, Brustoff J. Association of immunological changes with clinical efficacy in atopic eczema patients treated with traditional Chinese herbal therapy (Zemaphyte®). Int Arch Allergy Immunol. 1996;109:243–9. [PubMed]
Latchman Y, Whittle B, Rustin M, Atherton D.J, Brostoff J. The efficacy of traditional Chinese herbal therapy in atopic eczema. Int Arch Allergy Immunol. 1994;104:222–6. [PubMed]
Ledezma E, De Sousa L, Jorquera A. Efficacy of ajoene, an organosulphur derived from garlic, in the short-term therapy of tinea pedis. Mycoses. 1996;39:393–5. [PubMed]
Linde K, Ramirez G, Mulrow C, et al., editors. St Johns wort for depression: An overview and meta-analysis of randomized clinical trials. Br Med J. 1996;313:253–8. [PMC free article] [PubMed]
Lininger S.W. The Natural Pharmacy. 2nd ed. Montvale, NJ: Medical Economics Co.; 2000.
Lipton R.A. Comparison of jewelweed and steroid in the treatment of poison ivy contact dermatitis. Ann Allergy. 1958;16:526–67. [PubMed]
Long D, Ballentine N.H, Marks J.G Jr. Treatment of poison ivy/oak allergic contact dermatitis with an extract of jewelweed. Am J Contact Dermat. 1997;8:150–3. [PubMed]
Lou Y.R, Lu Y.P, Xie J.G, Huang M.T, Conney A.H. Effects of oral administration of tea, decaffeinated tea, and caffeine on the formation and growth of tumors in the high-risk SKH-1 mice previously treated with ultraviolet B light. Cancer. 1999;33:146–53. [PubMed]
Lu Y.P, Lou Y.R, Xie J.G, Yen P, Huang M.T, Conney A.H. Inhibitory effect of black tea on the growth of established skin tumors in mice: Effects on tumor size, apoptosis, mitosis, and bromode- oxyuridine incorporation into DNA. Carcinogenesis. 1997;18:2163–9. [PubMed]

Lyss G, Schmidt T.J, Merfort I, Pahl H.L. Helenalin, an anti-inflammatory sesquiterpene lactone from arnica, selectively inhibits transcription factor NF-κB. Biol Chem. 1997;378:951–61. [PubMed]
McGuffin M, Hobbs C, Upton R, Goldberg A, editors. Botanical Safety Handbook. Boca Raton, FL: CRC Press; 1997.
Miller L.G. Herbal medicinals. Arch Intern Med. 1998;158:2200–8. [PubMed]
Mitamura T, Matsuno T, Sakamoto S, Maemura M, Kudo H, Satoe S. Effects of a new clerodane diterpenoid isolated from propolis on chemically induced skin tumors in mice. Anticancer Res. 1996;16:2669–72. [PubMed]
Monk B. Severe cutaneous reactions to alternative remedies. BMJ. 1986;293:665–6. [PMC free article] [PubMed]
Moss A. Tea tree oil poisoning [letter] Med J Aust. 1994;160:236. [PubMed]
Mostefa-Kara N, Pauels A, Pines E, Biour M, Levy V.G. Fatal hepatitis after herbal tea. Lancet. 1992;340:674. [PubMed]
Neldner K.H. Complementary and alternative medicine. Dermatol Clin. 2000;18:189–93. [PubMed]
Ng S.K. Topical traditional Chinese medicine. Arch Dermatol. 1998;134:1395–6. [PubMed]
Nomura M, Ma W.Y, Huang C, et al., editors. Inhibition of ultraviolet B–induced AP-1 activation by theaflavins from black tea. Mol Carcinog. 2000;28:148–55. [PubMed]
Parsad D, Pandhi R, Juneja A. Effectiveness of oral *Ginkgo biloba* in treating limited, slowly spreading vitiligo. Clin Exp Dermatol. 2003;28(3):285–7. [PubMed]
Peirce A, Fargis P, Scordato E, editors. The American Pharmaceutical Association Practical Guide to Natural Medicines. New York: Stonesong Press Inc.; 1999.
Pittler M.H, Ernst E. Horse-chestnut seed extract for chronic venous insufficiency. Arch Dermatol. 1998;143:1356–60. [PubMed]
Pribitkin E.D. Herbal medicine and surgery. Semin Integr Med. 2005;3:17–23.
Record I.R, Dreosti I.E. Protection by black tea and green tea against UVB and UVA+B induced skin cancer in hairless mice. Mutat Res. 1998;422:191–9. [PubMed]
Reynolds T, Dweck A.C. Aloe vera leaf gel: A review update. J Ethnopharmacol. 1999;68:3–37. [PubMed]
Robinson M.C, Heggers J.P, Hagstrom W.J. Myth, magic, witchcraft, or fact? Aloe vera revisited. J Burn Care Rehabil. 1982;3:157–62.
Routh H.B, Bhowmik K.R. Traditional Indian medicine in dermatology. Clin Dermatol. 1999;17:41–7. [PubMed]
Selvaag E, Eriksen B, Thure P. Contact allergy due to tea tree oil and cross-sensitization to colo-phony. Contact Dermatitis. 1994;31:124–5. [PubMed]
Seong I. Antifungal activity of the extracts from *Galla rhois* against *Candida albicans*. Korean J Med Mycol. 2007;12(4):175–9.
Shaw D. Risks or remedies? Safety aspectsof herbal remedies in the UK. J R Soc Med. 1998;91:294–6. [PMC free article] [PubMed]
Sheehan M.P, Atherton D.J. A controlled trial of traditional Chinese medicinal plants in widespread non-exudative atopic eczema. Br J Dermatol. 1992;126:179–84. [PubMed]
Sheehan M.P, Atherton D.J. One-year follow-up of children treated with Chinese medicinal herbs for atopic eczema. Br J Dermatol. 1994;130:488–93. [PubMed]
Sheehan M.P, Rustin M.H.A, Atherton D.J, et al., editors. Efficacy of traditional Chinese herbal therapy in adult atopic dermatitis. Lancet. 1992;340:13–7. [PubMed]
Shota Y, Wilson J.G, Matsumoto H, et al., editors. Adult respiratory distress syndrome induced by a Chinese medicine, kamisyoyo-san. Intern Med. 1961;65:494–6. [PubMed]
Soyinka F. Atypical lichen planus induced by native medicine. Br J Dermatol. 1973;88:341–5. [PubMed]
Subrahmanyam M. Honey impregnated gauze versus polyurethane film (Op-Site®) in the treatment of burns: A prospective randomised study. Br J Plast Surg. 1993;46:322–3. [PubMed]
Surh Y.J, Seoung S.H, Keum Y.S, Seo H.J, Sang S.L. Inhibitory effects of curcumin and capsaicin on phorbol ester-induced activation of eukaryotic transcription factors, NF-κB and AP-1. Biofactors. 2000;12:107–12. [PubMed]
Swords G, Hunter G.L.K. Composition of Australian tea tree oil. J Agric Food Chem. 1978;26:734–7.
Syed T.A, Ahmad S.A, Holt A.H, Ahmad S.A, Ahmad S.H, Afzal M. Management of psoriais with aloe vera extract in a hydrophilic cream: A placebo-controlled, double-blind study. Trop Med Int Health. 1996;1:505–9. [PubMed]

Tong M.M, Altman P.M, Barnetson R. Tea tree oil in the treatment of tinea pedis. Australas J Dermatol. 1992;33:145–9. [PubMed]
van Wyk B, Wink M. Medicinal Plants of the World. Portland, OR: Timber Press; 2004.
Vardi A, Barzilay Z, Linder N, Cohen H.A, Paret G, Barzilai A. Local application of honey for the treatment of neonatal postoperative wound infections. Acta Paediatr. 1998;87:429–32. [PubMed]
Wang Z.Y, Huang M.T, Lou Y.R, Xie J.G, Reuhl K.R, Newmark H.L. Inhibitory effects of black tea, green tea, decaffeinated black tea, and decaffeinated green tea on ultraviolet B light-induced skin carcinogenesis in 7,12-dimethybez[a]anthracene-initiated SKH-1 mice. Cancer Res. 1994;54:3428–35. [PubMed]
Williams L.R, Home V.N, Zang X. The composition and bactericidal activity of oil of *Melaleuca alternifolia*. Int J Aromather. 1988;1(3):15–7.
Winslow L.C, Kroll D.J. Herbs as medicine. Arch Intern Med. 1998;158:2192–9. [PubMed]
Winston D, Dattner A. The American system of medicine. Clin Dermatol. 1999;17:53–6. [PubMed]
Wobling R.H, Leonhardt K. Local therapy of herpes simplex with dried extract of *Melissa officinalis*. Phytomedicine. 1994;1:25–31. [PubMed]
Xu Y. Dermatology in Traditional Chinese Medicine. St. Albans, UK: Donica Publishing Ltd.; 2004.
Xu X.J, Banerjee P, Rustin M.H.A, Poulter L.W. Modulation by Chinese herbal therapy of immune mechanisms in the skin of patients with atopic eczema. Br J Dermatol. 1997;136:54–9. [PubMed]
Yarnell E, Abascal K. Herbal medicine for acne vulgaris. Altern Complement Ther. 2006;12(6):303–9.
Zhang H, Gu J. Progress of experimental study on treatment of psoriasis by Chinese medicinal monomer and single or compound recipe in Chinese material medica. Chin J IntegrMed. 2007;13(4):312–6. [PubMed]
Zhao J, Jin X, Yaping E, et al., editors. Photoprotective effect of black tea extracts against UVB-induced phototoxicity in skin. Photochem Photobiol. 1999;70:637–44. [PubMed]
Zhao J.F, Zhang Y.J, Jin X.H, editors. Green tea protects against psoralen plus ultravioletA-induced photochemical damage to skin. J Invest Dermatol. 1999;113:1070–5. [PubMed]

4.7 USE OF SULFUR (GANDHAK) IN PSORIASIS

Is an Age-Old Treatment for Acne, Psoriasis, Eczema, Rosacea, and More

Let's be honest, sulfur stinks. No, we mean it *literally* stinks. For that reason, you might've sk as an acne remedy (who wants to put something that smells like rotten eggs near their nose?), but once you learn more about the popular acne ingredient, you might want to reconsider—besides, the formulations smell much better these days (more on that below).

Although we typically hear about the ingredient regarding breakouts, as it turns out, sulfur can address a myriad of other skin concerns. Find out what the experts think you should know about the naturally occurring element, from the benefits of sulfur to how it works.

SULFUR

TYPE OF INGREDIENT: Exfoliant

MAIN BENEFITS: Kills bacteria, reduces sebum, and sloughs away dead skin.

WHO SHOULD USE IT: Sulfur can be used to treat those with mild-to-moderate acne, rosacea, seborrheic dermatitis, psoriasis, and eczema.

HOW OFTEN CAN YOU USE IT: According to Shah, it can be used on a daily basis, and some skin types can tolerate some formulations (such as a wash) even twice a day.

WORKS WELL WITH: Sodium sulfacetamide. "There are newer formulations of topical sulfur lotions that are combined with sodium sulfacetamide, creating a more gentle and less stinky product," Cheung says.

DON'T USE WITH: Cheung says to avoid combining sulfur with other topicals that dry out the skin or exfoliate (such as retinoids, benzoyl peroxide, and salicylic acid) to prevent the skin from becoming too dry or inflamed.

What Is Sulfur?

Simply put, sulfur is a natural element that is an essential component for all living cells. As Cheung explains it, sulfur is common in rocks and minerals and essential for plant growth, and it's also found throughout our body in amino acids, vitamins, and our skin and hair. It's known for its yellow color and its strong smell (but you already knew that). Sulfur has been used throughout history for medical purposes (fun fact: It's also used in wine-making), but when it comes to skincare, you'll commonly find it in acne spot treatments, masks, and soaps.

"Sulfur-based products tend to work best for mild-to-moderate acne, primarily whiteheads, blackheads, and papules," Shah says. "It typically isn't as effective for more moderate-to-severe acne, especially as monotherapy." While it does have similar effects to benzoyl peroxide and salicylic acid, Shah says that typically sulfur is better tolerated than those two treatments.

Benefits of Sulfur for Skin

Some of the characteristics of sulfur that make it great as an acne treatment (for instance, its anti-inflammatory and antibacterial properties1) are also helpful for treating an array of other skin concerns.

Dries out blemishes: According to Shah, sulfur reduces sebum (oil) on the skin. When applied to the blemish, sulfur
works to dry out the skin so it can then be sloughed away.

Promotes exfoliation: Sulfur works to exfoliate dead skin and remove impurities: Shah says that sulfur has a
keratolytic effect (meaning it works to soften and thin the epidermis), which helps remove dead skin cells and prevent clogged pores.

Fights bacteria: Sulfur has antibacterial properties, and, according to Cheung, sulfur is a dermatologist-favorite
because it kills bacteria, fungi, and various parasites.

Treats sensitive skin conditions: Cheung says because sulfur is anti-inflammatory and helps to soften and exfoliate
thick, dead skin, it's often used to treat acne, psoriasis, and seborrheic dermatitis or dandruff. Shah adds that it's also known to treat eczema and rosacea.

Side Effects of Sulfur

Sulfur may be drying and might irritate sensitive skin, so Shah suggests those people use caution when trying products containing sulfur. With that said, she adds that it tends to be gentler than some other acne medications, which usually makes it a good choice for people with sensitive skin (confusing, we know). For this reason, it's always smart to consult your dermatologist for guidance in selecting the best topical for you.

How to Use It

Cheung says because it can be drying and irritating for some, sulfur is commonly prescribed as a short-contact cleanser to be used once a day, usually at bedtime because of the strong scent. Avoid layering sulfur with your other acne topicals that may dry out the skin or exfoliate such as retinoids, benzoyl peroxide, and salicylic acid. Experimenting with multiple acne treatments together may be too much of a good thing and cause the skin to become too dry and inflamed.

Not only can you apply sulfur to the skin topically, but you can also consume it orally through your diet or via sulfur supplements to support normal functions of the body.2 However, for skin-specific results, Cheung suggests sticking with a topical. "There aren't many good studies for oral sulfur supplements for acne, and there is no current recommended dosage," Cheung explains. "A topical makes more sense because it will affect the skin more efficiently, rather than going through the digestive tract and bloodstream." You're better off taking supplements to decrease inflammation and promote gut health, such as pre- and probiotics and adaptogens, according to Cheung, but always consult your doctor before trying any new supplements or making any changes to your routine.

4.8 Effect of an ointment containing boric acid,on psoriasis (Suhaga)

Abstract

A randomized double-blind controlled trial was undertaken to study the efficacy of a cow udder ointment versus petroalatum alone. A total of 30 patients participated in the study. Sixteen patients completed the trial with 8 of 9 patients improving in the active group and 6 of 7 patients improving in the placebo group. This difference was not statistically significant. The use of a cow udder ointment for psoriasis cannot be supported, particularly with the potential for side effects.

4.9 A review of the use of beeswax in skincare

Abstract

Background: Beeswax is a naturally occurring product secreted from worker bees that has varied uses in modern day. In skincare, its function ranges from its role as an occlusive, helping to create a semi-occlusive skin barrier that minimizes transepidermal water loss; as a humectant, locking in hydration; and an emollient to soften and soothe the skin. As a natural substance, its use has been shown to help alleviate symptoms associated with common cutaneous conditions like dermatitis, psoriasis, and overgrowth of normal skin flora. Aims: In this narrative review, we aim to describe current uses of beeswax in skincare that has been published in the literature. Materials and methods: A review of beeswax related publications was performed by searching the PubMed database studies.

Results: A total of five clinical studies were included with three studies on animals and two studies in humans.

Discussion: Several studies show the benefits of topical beeswax in supporting the skin barrier.

Conclusion: Beeswax can be a low-cost, natural ingredient for use in products. Further studies with topical beeswax are warranted.

1 | INTRODUC TION

Beeswax is a naturally formed secretion from wax-producing glands in the abdomen of worker bees. Depending on the bee's geographical location, diet, seasonality, and environmental effects, the composition of beeswax can vary in factors such as color and additive components. Beeswax is more likely to be white in its natural state, and turns yellow after contact with honey and pollen.1 Additionally, beeswax can include components like pollen oils and propolis obtained exogenously or endogenously. Mainly used by bees to build honeycomb cells, beeswax has been adopted in ancient and modern times for many uses. The Egyptians, Greeks, Romans, and Chinese found potential in beeswax for candles, embalming practices, and even medicinal purposes. Today, commercially sourced beeswax is derived from bees of the genus Apis, specifically A. mellifera and A. cerana, and continues to be useful in the manufacture of various waxes, finishing products like varnishes and polishes, drug development, and cosmetics. The U.S. Food and Drug Administration has designated yellow and white beeswax as “Generally Recognized as Safe” as a food additive and in food packaging.

Processing of beeswax is commonly performed through gas chromatography and mass spectrometry techniques. Its dynamic chemical properties allow it to take form in a solid state at room temperature and a liquid form when heat is applied. Structurally, alkanes, alkenes, free fatty acids, monoesters, diesters, and hydroxy-monoesters make this hydrophobic compound useful as an occlusive, emollient, and humectant in skin care products. Commonly mixed in beeswax is a component called propolis. Propolis is made up of phenolic acids, esters, flavonoids, and aromatic compounds. Beeswax containing high levels of propolis helps to provide antioxidant,2,3 antimicrobial, 1,4 and anti-inflammatory5,6 properties. As the largest organ of the human body, the skin provides protection against a multitude of external environmental irritants. The outermost layer called the stratum corneum (SC) plays a vital role in skin barrier protection. Transepidermal water loss (TEWL) passively occurs through the SC and is an indicator of the skin barrier integrity. When the skin barrier is disrupted, various cutaneous disorders can be triggered, including atopic dermatitis (AD), xerosis cutis, and psoriasis.7 Occlusives like beeswax found in many skincare products can help to buffer excess TEWL. Other uses of beeswax in skincare that have been described in the literature include treatment of burns, ulcers, and wounds. This article aims to describe a collection of scientific articles characterizing uses of beeswax in skincare.

2. ME THODS

A PubMed search for articles with the following keywords was performed: “beeswax” AND “skin” OR “dermatology” OR “dermis” OR“dermal.” One-hundred and nine (109) articles resulted, and article titles and abstracts were reviewed. Those with relevant subject matter were retrieved for full-text review. In addition, their associated references were scanned for additional relevant reports.

3 | RESULTS

3.1 | Effects on the microbiome The antimicrobial properties of beeswax have been acknowledged since ancient times, depicted by its incorporation in ancient European and Asian traditional medicines.8 Although there are few studies directly analysing the antimicrobial efficacy of beeswax, two studies evaluated such activity against various bacterial strains. Utilizing measurements including the zone of inhibition and minimum inhibitory concentration, Ghanem (2011) analysed the effect of crude beeswax on both gram-positive and negative bacteria.9 Although bee propolis was shown to have greater antimicrobial effects, crude beeswax is easier to obtain and still depicted efficacy against studied

bacteria. The beeswax was particularly effective against the bacteria Staphylococcus aureus, Streptococcus epidermidis, S. pyogenes, Bacillus subtilis, Pseudomonas aeruginosa, and Escherichiacoli, as well as the yeast C. albicans. Beeswax was ineffective against Proteus mirabilis and Salmonella typhimurium.

In addition, Kacániová et al. assessed the efficacy of beeswax methanol and ethanol extracts on the zone of inhibition of a variety of bacterial strains.4 For unclear reasons, beeswax extracted with methanol and ethanol exhibited different antimicrobial actions. The most sensitive strains were S. enterica and C. tropicalis with 99.9% methanol extract; E. coli, C. albicans, C. tropicalis, and Aspergillus niger with 70% methanol extract; A. niger, C. albicans, and C. glabrata with 96% ethanol extract; and Listeria monocytogenes, E. coli, and C. glabrata with 70% ethanol extract. The greatest zone of inhibition achieved was 4.83 ± 1.26 mm, depicted by 70% ethanol extract with C. glabrata. The results of these two studies depict the antimicrobial effectiveness of crude beeswax, and beeswax methanol and ethanol extracts against a variety of microbes. In addition, studies have evaluated the antimicrobial properties of beeswax mixtures. Due to the potential synergistic effects of each ingredient, it is difficult to conclude the efficacy of beeswax alone in such studies. Al-Waili has extensively analyzed the effects of a honey, olive oil, and beeswax mixture on a variety of dermatologic conditions that are associated with microbiome dysbiosis. For example, one of the studied conditions, pityriasis versicolor, is a superficial skin infection caused by four species of Malassezia (Fratini 2016).1 The associated antimicrobial effects are implicated in the mixture's efficacy in managing pityriasis versicolor, tinea cruris, tinea corporis, and tinea faciei.10 Furthermore, in 2005, Al-Waili directly assessed the mixture's antimicrobial properties.11 The effects of the honey, olive oil, and beeswax mixture on the growth of S. aureus and C. albicans were investigated via zones of inhibition measurements. The mixture resulted in a 4 mm zone of inhibition on media seeded with C. albicans, and a 3.5 mm zone of inhibition on media seeded with S. aureus. However, assessment of growth with separate media of (1) honey, (2) olive oil, and (3) beeswax revealed that the beeswax media was the least efficacious in preventing the growth of both S. aureus and C. albicans. Whereas the honey media completely inhibited growth, the olive oil media exhibited mild growth, and the beeswax media exhibited moderate growth. Yet, the control media consisting solely of nutrient agar depicted heavy growth, suggesting that beeswax still has intrinsic antimicrobial properties, albeit to a lesser extent than the other two ingredients.

3.2 | Protecting the skin barrier One of the many functions of the skin is to provide protection from external environmental irritants, such as sun irradiation and bacterial infections. The stratum corneum (SC) plays a key role in this skin barrier function by preventing transepidermal water loss (TEWL) that can be caused by environmental irritants.7 Occlusives such as petrolatum and mineral oil coat the SC to inhibit TEWL. Because petroleum in the form of crude oil has much greater shelf life and more protective effects on water vapor loss as compared to olive oil, it has become the gold standard of occlusives. Although effective, petroleum products have a greasy texture that many people dislike. Several additional occlusives including waxes (i.e., lanolin, paraffin, squalene, dimethicone, and propylene glycol) and natural oils (i.e., soybean, grapeseed, sunflower seed, evening primrose, olive, and jojoba oils) are commonly used as cosmetic ingredients. Beeswax is similarly an effective occlusive, as it forms a film on the skin's surface and resultantly protects against many external irritants.

The literature search included two studies that evaluated the use of a beeswax-containing formulation on measures of skin barrier integrity. Healthy skin tends to have low TEWL and high stratum corneum water content (SCWC), whereas a damaged skin barrier is associated with increasing TEWL.

In 2003, Frosch et al. evaluated the efficacy of various barrier creams vs. skin care products in dental laboratory technicians.

Dental laboratory technicians commonly experience irritant contact dermatitis due to frequent contact with irritants, yet traditional barrier creams can reduce the required tight grip of tools and risk contamination. As such, the authors compared two commercial barrier creams with a moisturizer containing either urea or beeswax. Of those receiving the first commercial cream, 58% reported a “good” or “very good” response, compared to 67% with the second commercial cream. On the contrary, 77% with the urea-containing moisturizer and 98% with the beeswax-containing moisturizer reported a “good” or “very good” response. Furthermore, improvement of skin condition, including erythema, infiltration, vesicles, fissures, and scaling, was as follows: 35% (barrier cream 1), 44% (barrier cream 2), 55% (urea-containing moisturizer), and 98% (beeswax-containing moisturizer), depicting superior performance of beeswax-containing moisturizers in comparison with the commercial barrier creams. Lastly, there was a statistically significant reduction in TEWL in technicians using beeswax-containing moisturizer in comparison with barrier cream 1 ($p = 0.007$).

These results demonstrate the efficacy of beeswax-containing moisturizer in improving skin condition and maintaining skin barrier integrity, as depicted by TEWL data. Souza et al. published a randomized, single-blinded study depicting improvement in skin barrier function with a topical formulation containing beeswax-based nanoparticles.13 Sixteen healthy volunteers were included in the study, and three test areas were utilized on each volar forearm: one control

area, one area for the beeswax-based nanoparticle (BN)-loaded formulation, and one area for a non-loaded gel-cream formulation. TEWL and SCWC were measured 28 days after topical treatment. They found only the BN-loaded formulation to depict a significant decrease in TEWL values and increase in SCWC values compared to baseline values.

Furthermore, there were no reported side effects such as irritation, discomfort, and itch. The results of these two studies depict the clinical utility of beeswax-containing formulations in maintaining skin barrier integrity, both in the setting of irritant contact dermatitis and in healthy volunteers.

3.3 | Uses in dermatitis and psoriasis

A combination of skin barrier dysfunction and immune dysregulation has been elucidated in the pathogenesis of atopic dermatitis (AD). Therapies for AD have focused on restoring the skin barrier through increased skin moisture retention. A study by Park et al (2021) examined the effects of cera flava (CF), which is a natural extract from beehives that is modified through heath compression filtration and purification, on a mouse model of AD.15 Using house dust mite as an irritant, the authors found that use of CF attenuated symptoms of pruritus and increased skin moisture content; restored skin barrier proteins like filaggrin, claudin-1, and occludin; and downregulated immune signalling associated with an inflammatory response.

A study by Al-Waili (2003) evaluated the effects of a product containing beeswax for AD and psoriasis.16 Psoriasis is a chronic inflammatory state that triggers a rapid turnover of skin cells, leading to thickening of the outermost layer of the skin. The mixture included honey, olive oil, and beeswax in a 1:1:1 ratio, and was prepared in various proportions with a corticosteroid ointment (Mixture A was 1:1, Mixture B was 2:1, and Mixture C was 3:1). In those with AD, there was a significant improvement in signs and symptoms in 80% of patients who did not have prior treatment for the disease. Among those who were using a corticosteroid therapy at the time of inclusion, application with the mixture helped to reduce the dose of corticosteroid required to control AD. Similarly, in those with psoriasis, 50% of patients demonstrated marked improvement with the honey mixture and a reduction in corticosteroid usage if they were previously using this therapy. Although the treatment involved a mixture of other materials with beeswax, the findings from this clinical trial further suggests the importance of therapeutics of natural materials to remedy common skin conditions like AD and psoriasis.

Another study by Al-Waili (2005) tested a mixture containing honey (50%), olive oil (29%), and beeswax (21%) on infants with diaper dermatitis.17 In this pilot study, use of the mixture consistently reduced mean total rash score, from 2.91 ± 0.79 at baseline to 0.66 ± 0.98 at the end of the study. A majority of participants (10/12 patients) had mild to no diaper dermatitis at their final visit (Day 7). Symptomatic improvements were also noted, possibly owing to the anti-inflammatory properties of the mixture. Interestingly, C. albicans was eliminated in two of the four patients testing positive at baseline.

3.4 | Uses in burns

In addition to restoration and maintenance of the skin barrier, beeswax is thought to be particularly effective in the treatment of burns. Pharmaceutical use of beeswax to treat burns dates back to ancient Egypt, where beeswax was the primary ingredient in many ointments and creams. It has since been utilized extensively in ancient Rome and Ayurvedic medicine.1 The literature 14732165, 2023, 8, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jocd.15718, Wiley Online Library on [19/09/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

3.4 | Uses in burns

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The authors found that BOB treatment increased regeneration of the epidermis and dermis, increased keratinization and fibroblast activity, and exhibited greater wound contraction levels than the burn control group (no topical treatment). Furthermore, BOB treatment increased TGF-β1 and VEGF-α expressions compared to the control group ($p < 0.05$), suggesting a mechanism for which the BOB treatment encouraged skin renewal and tissue modulation.

The utility of beeswax-containing substances has additionally been demonstrated in human subjects. Gümüş and Özlü (2017) conducted an experimental study to assess the effect of a mixture containing beeswax, olive oil, and Alkanna tinctoria Taush on epithelization initiation time, pain scores, and hospitalization duration.21 31 second-degree burn victims received the treatment mixture, and 33 second-degree burn victims received the clinic's routine dressing (control). They found the treatment mixture to significantly reduce epithelization initiation time, mean pain scores, and hospitalization duration ($p < 0.05$). Furthermore, whereas infections occurred in 6.1% of control group wound cultures, no infections occurred in experimental group wound cultures, likely due to the antioxidant, antibacterial, and anti-inflammatory properties of A. tinctoria, beeswax, and olive oil.21 The authors attributed the significantly reduced pain scores to A. tinctoria and olive oil, although they suggested that the beeswax contributed to reduced epithelization initiation time and mean hospital duration.

The prior studies have depicted beeswax-containing products to be efficacious in wound healing following second-degree burns, both in animal models and in human subjects. In addition, Lewis et al. suggest an additional use for beeswax in burn victims: relief from postburn pruritus.22 Postburn pruritus (itch) greatly impacts the burn population and has been reported to affect up to 87% of burn victims. The authors sought to assess the efficacy of beeswax and herbal oil cream against standard treatment (aqueous cream) in relief from postburn symptoms of pruritus. The results depict that the beeswax and herbal cream reduces itch more frequently than aqueous cream ($p = 0.001$) and prolongs recurrence of itch ($p \leq 0.001$).

Taken together, the literature suggests that beeswax-containing mixtures can effectively contribute to greater wound contraction, neovascularization, keratinization, and fibroblast activity; reduced exudation and inflammation, epithelization initiation time, and mean pain scores; and provide relief from postburn pruritus. The results of each study are depicted in Table 1. Additional randomized, controlled trials are necessary to analyze the effects of beeswax alone so that efficacy measures are not confounded by other contained ingredients. steam-based extraction. The types of wax used for cosmetic production are yellow (Cera flava) or white (Cera alba). Once processed, it is used as the base for lipsticks, emollient skin creams, ointments, lotions, and other cosmetics formulations. Additionally, beeswax can be used to alter a cosmetic product's physical properties, such as to increase a lipstick's luster and hardness, enhance its color and sensory characteristics, and improve its application characteristics. For example, it is used as a stiffener to provide elasticity, plasticity, and increase skin adhesiveness.12 Beeswax has been shown to be non- irritating and generally has a low comedogenic potential,23 in addition to its previously noted antimicrobial, anti-inflammatory, and antioxidant properties.

3.6 | Allergies and noxious effects

Beeswax is not considered an irritant and does not have a high potential for causing blackheads through blockage of pores. Furthermore, the literature suggests that contact allergy to beeswax is greatly uncommon relative to the extent of its usage of the many products derived from bees, beeswax is the least allergenic. Reports of allergic reactions to beeswax-containing products appear to be attributable to contamination with other products such as propolis or resins. For example, a case of occupational dermatitis in a beekeeper was determined to result from poplar resins in the beeswax.25 F urthermore, B orlin (1947) discussed several cases of allergic contact dermatitis from beeswax that depicted positive reactions to unpurified beeswax but negative reactions to purified beeswax.26 Still, cases of occupational dermatitis27 and contact cheilitis have rarely been attributed to beeswax.

In 2009, Rajpara et al. conducted a multicenter survey in which 2828 subjects in the UK were patch tested with propolis and beeswax. Whereas 1.9% had positive reactions to propolis, 0.45% had positive reactions to beeswax; 10 subjects were allergic to yellow beeswax and three subjects were allergic to white beeswax. While the report highlighted the importance of propolis inclusion in patch testing, it also depicted the relative infrequency of beeswax allergies. In light of prior reports of cheilitis caused by beeswax, however, Nyman et al. conducted a patch testing study to assess the prevalence of contact allergy to beeswax and propolis among a distinct population of subjects.24 The study population included 95 individuals with cheilitis, eczema around the lips, or adverse reactions to products containing beeswax. Seventeen patients had positive reactions to beeswax, fourteen of which were tested with both yellow and white beeswax; eight had a positive reaction to both waxes, five had a positive reaction to the yellow wax, and only one had a positive reaction to the white wax. It is important to note that the prevalence of beeswax allergy in this study is likely higher than in the general population due to the selected patient cohort. However, the results do suggest that cheilitis patients should undergo beeswax and propolis patch testing, in addition to the baseline series and their own products. Furthermore, although beeswax allergies are rare, with a true prevalence likely less than reported in this study, the results depict that such allergies do exist.

4 | DISCUSSION A ND C ONCLUSION

Beeswax, whether crude or combined, has demonstrated benefits for protection of the skin barrier. Much of the scientific literature described here has shown that beeswax can be a more natural approach to helping maintain skin hydration, easing inflammatory symptoms associated with skin diseases like atopic dermatitis or contact irritant dermatitis, and alleviating side effects of burns. Its effects on the microbiome have been shown to reduce overgrowth of the skin's natural microbes, preventing the development of various tinea-associated conditions. Outside of its medicinal uses, beeswax remains a mainstay in cosmetics to help shape various products, add soothing properties, and enhance brilliance.

Functional uses aside, beeswax can be a low-cost, natural ingredientin skincare products that is more accessible in developing countries. In a study by Miyar et al (2014), beeswax was combined with two other natural ingredients, zinc oxide and almond oil, to create an affordable sunscreen for villagers in Yucatan, Mexico. The homemade sunscreen demonstrated similar narrowband UVB (NBUVA) minimal erythema dose (MED) to a commercially available sunscreen with sun protection factor (SPF) of 15. Although providing protection below the minimally recommended SPF level, the homemade sunscreen cost averaged US$1.07 per 85 g bottle. The important value of cost-effectiveness should be considered with use of beeswax as an ingredient in skincare products. Author (year) Population Treatments Study Measures Results Lewis et al. (2012)22 Humans (n = 52)

1. Beeswax and herbal oil cream
2. Frequency of itch reduction
3. The beeswax and herbal cream reduced itch more frequently than control (p = 0.001)
4. Control, aqueous cream 2. Itch symptom onset 2. The beeswax and herbal cream prolonged symptoms of itch compared to control (p ≤ 0.001)

4.10 Use of Coconut Oil in Psoriasis:

Can Essential Oils/Botanical Agents Smart-Nano formulations Be the Winning Cards against Psoriasis?

Abstract

Although psoriasis remains one of the most devastating inflammatory disorders due to its huge negative impact on patients' quality of life, new "green" treatment approaches still need to be fully explored. The purpose of this review article is to focus on the utilization of different essential oils and active constituents of herbal botanical origin for the treatment of psoriasis that proved efficacious via both in vitro and in vivo models. The applications of nanotechnology-based formulations which displayed great potential in augmenting the permeation and delivery of these agents is also addressed. Numerous studies have been found which assessed the potential activity of natural botanical agents to overcome psoriasis. Nano-architecture delivery is applied in order to maximize the benefits of their activity, improve properties, and increase patient compliance. This field of natural innovative formulations can be a promising tool to optimize remediation of psoriasis while minimizing adverse effects.

Keywords: psoriasis, essential natural oils, botanical remedies, nano-delivery systems, novel pharmaceutical formulations

1. Introduction

Psoriasis is a common, yet debilitating, immune-mediated inflammatory condition. It usually appears in the form of reddened, raised lesions or "plaques" on the skin, which may be covered with silver or white-coloured scales. Individuals at risk of developing psoriasis often have genetic polymorphisms affecting genes that are involved in the

adaptive and innate immune systems and/or skin barrier regulation. Both environmental and genetic factors result in chronic inflammation and growth of psoriatic plaques from hyper-proliferating skin cells [1].

Some medications such as lithium, beta-blockers and antimalarial treatments may trigger psoriasis, as they affect normal cell proliferation and differentiation [2]. Additionally, several environmental factors contribute to psoriasis initiation and exacerbation, including physical trauma and pharyngeal infections (streptococcal throat infections). Smoking, alcohol consumption and obesity have also been linked to the disease incidence and have been implicated in worsening of the patient's condition, but the basis of a clear relationship between them and psoriasis does not exist [3]. Ethnicity can also affect prevalence of psoriasis, such that around 1–3% of the European population suffer from psoriasis, with prevalence varying depending on the geographical area or ethnic group studied [4]. According to the Global Psoriasis Atlas, within Great Britain, prevalence of psoriasis appears to be on the rise, from 2.3% in 1999 to 2.8% in 2013 [5], while its incidence is lower in Western Europe (1.92%) and in North Africa and the Middle East (0.57% of the total population).

Psoriasis can occur in any stage of life. However, epidemiological evidence suggests that onset occurs at two peak ages.

In the UK, approximately 75% of patients have hereditary early onset psoriasis (EOP) before 16 years of age, triggered by HLA-Cw*0602 positive (Type I), which is a very aggressive type, while the remaining 25% have uninherited late onset psoriasis (LOP) after 16 years of age, which is triggered by HLA-Cw*0602 negative (type II) [6]. Psoriasis is considered a multi-factorial disease caused by hyperproliferation of keratinocytes, angiogenesis and abnormal imbalanced cells differentiation, and increased secretions of excessive pro-inflammatory mediators such as interleukins, endothelin and vascular endothelial growth factors [7]. Topical treatment of psoriasis represents the first-line treatment. However, long-term therapy induces several side effects, either local or systemic. Nanotechnology-based drug delivery systems offer a solution to overcome the limitations of conventional therapies. They have different physicochemical characters from their active constituents, such as smaller particle size or different nanoscale materials, enabling deeper penetration and localized accumulation in targeted skin layers in a controlled release manner. For example, some advanced formulations contain surfactants or permeation enhancer components so they have the ability to change the molecular structure and barrier functions of skin and make pores in tight junctions, allowing active constituents to reach deeper skin layers and improve the therapeutic outcome [8].

2. Pathogenesis of Psoriasis

Psoriasis is now known to be driven by a cluster of differentiation cells (CD 4+) and T lymphocyte helper 17 (CD4+ Th17) subset, as well as Th1 cells [9]. Th17 cells produce the cytokine interleukin 17 (IL-17) in response to the cytokine IL-23 [10]. CD8 releases several inflammatory cytokines in the skin, including IL-17, IFN-γ, IL-22 and IL-13; of these, IFN-γ is thought to promote hyperproliferation of keratinocytes in the epidermis, which results in skin thickening [11].

Meanwhile, IL-17 causes abnormal differentiation of keratinocytes and stimulates pro-inflammatory cytokines production such as IL-6 and IL-8. The increased level of vascular endothelial growth factor (VEGF) contributes to angiogenesis, dilatation, and formation of high endothelial venues, reflected as skin redness and erythema, a hallmark in psoriatic lesions. IL-1 mediates the production of IL-2 and IFN-γ by T-cells. It is also responsible for the activation of neutrophils, monocytes, eosinophils and basophils, and stimulates macrophages to synthesize tumor necrosis factor- α (TNF), IL-6 and IL-8. IL-2 triggers B cell differentiation as well as production and action of natural killer (NK) cells, monocytes and macrophages. IL-2 encourages synthesis of IFN-g, TNF, IL-6 and IL-2R, and participates in its self-production. Augmentation in blood vessels number is mediated by IL-8, which also stimulates chemotaxis and neutrophil activation. IL-15 regulates the activation, proliferation and endurance of NK cells. This interleukin also stimulates formation of new blood vessels and T cells expression of IL-17 [12].

To sum up, T cells have a potential role in the development of psoriasis and understanding their role helps to localize the pathogenesis of disease. Th1, Th17, Treg and Th22 cells, and newly identified 'professional' IL-17-producing dermal CD T cells, all have significant roles in psoriasis pathogenesis. Environmental factors and pathogens activate the dendritic cells (DCs) and macrophages to release IL-23, IL-1b and other pro-inflammatory cytokines, which in turn activate the innate immunity that manifests as dermal CD T cells that produce IL17, which consecutively stimulates conventional acquired immune responses. IL-17, IL-22 and TNF-α stimulate progressively the process of keratinocytes hyperproliferation and create the inflammatory environment of disease [13]. A diagrammatic representation of the pathogenesis of psoriasis is illustrated in Figure 1.

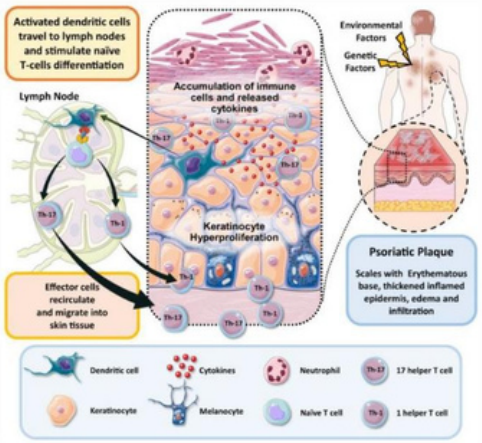

Figure 1

Schematic illustration of pathogenesis of psoriasis.

3. Phenotypes of Psoriasis

One of the main subtypes of psoriasis that accounts for 90% of all cases is Psoriasis Vulgaris (PV). It is chronic plaque psoriasis (CPP) [14], clinically represented as raised itchy or painful thick red patches on the skin which are clearly defined from the non-involved skin surrounding them. These hyperproliferating patches may be covered by silver-white scales, caused by a build-up of keratinocytes, with vascular alteration that participates in enlargement of these psoriatic plaques asymmetrically. Plaques in CPP commonly appear on the outer surfaces of the knees and elbows [15].

Nail psoriasis is also one of the most prevalent types [16]. It is most commonly manifested as nail pitting, which

appears

as small circular areas underneath the plate, red or white in color. Other symptoms include loosening of the nail from its bed (onycholysis), discoloration due to psoriatic lesions in the nail bed (oil drop lesions), raising of the nail bed (subungual hyperkeratosis), transverse ridges (Beau's lines), and longitudinal ridges with splitting (onychorrhexis) [17].

Another type is guttate psoriasis, an acute condition prevailing in the youth. Its name is derived from the Latin word "gutta" meaning "droplet", which refers to the small round pink papules that often appear on the face, ears, and scalp. It is often thought to be triggered by a prior pharyngeal infection or tonsillitis [18].

On the other hand, psoriatic arthritis (PsA) affects approximately 6% of psoriasis patients, with a prevalence of 0.06–0.25% in the United States, 0.21% in Sweden, 0.05% in Turkey and 0.07% in Asia [19]. PsA is similar to rheumatoid arthritis, gout and reactive arthritis since it often manifests as painful inflammation in the joints and tendons, which appears shortly after the development of cutaneous psoriasis. On a cellular level, PsA is thought to be due to accumulation of particular interleukins and other inflammatory mediators in the synovial fluid [20].

4. Therapeutic Approaches

Pertaining to the quality of life of psoriatic patients, researchers have shown that the disease impacts their social, physical, and psychological wellbeing, with 87.8% of the patients displaying a reduced compliance with life activities in comparison to controls [21].

Hence, the primary goal of treatment is to control the disease and its symptoms in order to enhance patients' wellbeing, but not necessarily achieve complete healing due to relapse waves. These therapies fall into four broad categories: topical treatments, ultraviolet (UV) light therapy, traditional systemic drugs, and biologics. The efficacy of therapies is commonly measured as a percentage of patients who improved in the Psoriasis Area and Severity Index (PASI) score—a tool to measure psoriasis severity by measuring skin thickness, scales and erythema. In past studies, the primary end target was to reach an improvement in PASI score by 75%; however, this has recently been updated to a target of 90% reduction (PASI 90) [22]. Different therapeutic approaches are illustrated in Figure 2.

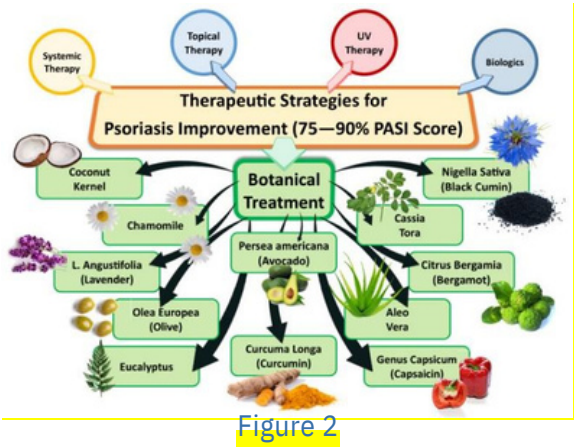

Figure 2

6.8. Coconut Oil

Virgin coconut oil (VCO) is a natural oil extracted from fully ripe *Arecaceae* coconut kernel [102]. VCO is composed mainly of fatty acids such as lauric, oleic, caprylic and capric acids. It has an emollient effect, which has a role in the improvement of psoriasis. In addition, it has an anti-inflammatory action, which is attributed to its hindering effect on the inflammatory mediators (cytokines) TNF-a, IFN-g, IL-6, IL-5, and IL-8, as well as an ROS scavenging property. A study conducted using a human monocyte (THP-1) model, in which cytokines production was induced by lipopolysaccharides, was used for the evaluation of VCO's regulation of cytokines. The results, which were semi-quantitative PCR, showed a significant reduction in the levels of TNF, INF, IL6 and IL8, and a reduction of their RNA expression and protein secretion compared with dexamethasone (positive control). A human keratinocyte HaCat cells model was also used to assess the role of VCO in maintaining the barrier skin function and enabling improvement in the symptoms of psoriasis. It was observed there was an increase in the content of both involucrin and filaggrin, which are usually disturbed in psoriasis patients, in addition to skin irritation studies which proved that no adverse effects or itching were observed upon using VCO [103].

A double-blind clinical study was carried out for the assessment of VCO efficacy against dermatological lesions. VCO was compared to mineral oil; both were applied to the affected area and the results showed a significant improvement with VCO application, as 93% of patients improved, compared to 53% of patients who applied mineral oil [104].

Verallo-Rowell et al. investigated the efficacy of coconut oil in comparison with olive oil, and the inflammation score decreased by 46.8% after coconut oil application, whereas the decline stopped at 30.6% after olive oil application [105].

7. Conclusions

A growing population of people and scientists are looking forward to finding the curative treatment for psoriasis, an incapacitating disease. However, controlling its manifestations and improving patients' quality of life requires the use of different essential oils and botanical herbal agents. They act via different mechanisms in order to terminate the pathogenesis of this inflammatory disease and minimize the burdens of psoriatic plaques. By developing innovative nano-based formulations of these agents such as turmeric oil, black cumin oil and avocado oil, we can enhance their penetration through skin, improve their efficacy and accumulation in targeted skin layers, and use them as adjuvants to other established guidelines of care, especially in cases which are resistant to conventional treatment or need long-term therapy. Thus, nano-based formulations may offer a solution to overcome the limitations of topical applications of herbal botanical agents and essential oils, and challenges related to drug delivery in dermatological skin conditions. Proper choice of the type of nano-system plays an important role in their interaction with the skin. It is evident that polymeric nanoparticles, especially those having a particle size less than 100 nm and carrying a charge, are an excellent choice for the treatment of inflammatory skin disorders due to the selective accumulation in the inflamed skin [136,137,138]. On the other side, lipidic systems such as lipid nanoemulsions and nanocapsules tend to enhance the transdermal permeation of the encapsulated drugs due to their greater ability to diffuse through the different skin layers [139,140]. Therefore, polymeric nanocapsules containing natural oils would offer an excellent candidate for topical therapy. SLNs and NLCs are also known for their ability to enhance skin deposition, due to the relatively solid nature of their matrices. Such carriers would also significantly improve the stability of the vulnerable volatile oils. Many clinical trials, studies and investigations, both in vivo and in vitro, have been undertaken to assess the therapeutic efficacy and monitor adverse reactions upon topical application of these formulations. Promising results related to NE were obtained in studies of black cumin oil, tea tree oil, turmeric oil and olive oil. Other curative formulations were obtained from NLC of olive oil and thymol oil incorporated into nanogel. The decreasing of PASI and improvement of

dermatological conditions were also observed through in vivo model studies of a nanosponge delivery system and ethosomal system for curcumin and thymoquinone, respectively. An albino rat model was used for the assessment of the curative efficacy of capsaicin-loaded vesicular systems, which showed promising results. However, further studies and trials are needed to thoroughly assess the potential activity and safety of these natural agents and new developments in their formulations, such as SLNs, NLCs, and nanoemulsions. Additionally, regulatory requirements and quality control guidelines are needed in order to establish a platform for standardizing herbal medicine and ensure its efficacy and safety on a large number of subjects, to achieve maximum benefit from such innovative nanotechnology delivery systems of essential oils and botanical agents against psoriasis.

Author Contributions

Conceptualization, M.M.A.A.-M., H.S.E.-S., G.M.E.Z. and M.A.; software, H.S.E.-S., supervision, M.M.A.A.-M., H.S.E.-S. and G.M.E.Z., visualization, M.M.A.A.-M., H.S.E.-S., G.M.E.Z. and M.A. writing—original draft preparation, M.A. and H.S.E.-S.; writing—review and editing, M.M.A.A.-M. and G.M.E.Z. All authors have read and agreed to the published version of the manuscript.

Footnotes

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References

1. Bergboer J.G.M., Zeeuwen P.L.J.M., Schalkwijk J. Genetics of Psoriasis: Evidence for Epistatic Interaction between Skin Barrier Abnormalities and Immune Deviation. *J. Investig. Dermatol.* 2012;132:2320–2331. doi: 10.1038/jid.2012.167. [PubMed] [CrossRef] [Google Scholar]
2. Milavec-Puretić V., Mance M., Ceović R., Lipozenčić J. Drug Induced Psoriasis. *Acta Dermatovenerol. Croat. ADC.* 2011;19:39–42. [PubMed] [Google Scholar]
3. De Oliveira M.F.S.P., de Rocha B.O., Duarte G.V. Psoriasis: Classical and Emerging Comorbidities. *An. Bras. Dermatol.* 2015;90:9–20. doi: 10.1590/abd1806-4841.20153038. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
4. Parisi R., Symmons D.P.M., Griffiths C.E.M., Ashcroft D.M. Global Epidemiology of Psoriasis: A Systematic Review of Incidence and Prevalence. *J. Investig. Dermatol.* 2013;133:377–385. doi: 10.1038/jid.2012.339. [PubMed] [CrossRef] [Google Scholar]
5. Springate D.A., Parisi R., Kontopantelis E., Reeves D., Griffiths C.E.M., Ashcroft D.M. Incidence, Prevalence and Mortality of Patients with Psoriasis: A U.K. Population-Based Cohort Study. *Br. J. Dermatol.* 2017;176:650–658. doi: 10.1111/bjd.15021. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
6. Bronckers I.M.G.J., Paller A.S., van Geel M.J., van de Kerkhof P.C.M., Seyger M.M.B. Psoriasis in Children and Adolescents: Diagnosis, Management and Comorbidities. *Paediatr. Drugs.* 2015;17:373–384. doi: 10.1007/s40272-015-0137-1. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
7. Fereig S., Mamdouh G., Arafa M., Abdel-Mottaleb M. Self-Assembled Tacrolimus-Loaded Lecithin-Chitosan Hybrid Nanoparticles for In Vivo Management of Psoriasis. *Int. J. Pharm.* 2021;608:121114. doi: 10.1016/j.ijpharm.2021.121114. [PubMed] [CrossRef] [Google Scholar]
8. Saleem S., Iqubal M.K., Garg S., Ali J., Baboota S. Trends in Nanotechnology-Based Delivery Systems for Dermal Targeting of Drugs: An Enticing Approach to Offset Psoriasis. *Expert Opin. Drug Deliv.* 2020;17:817–838. doi: 10.1080/17425247.2020.1758665. [PubMed] [CrossRef] [Google Scholar]
9. Lowes M., Krueger J., Lowes M.A., Bowcock A.M., Krueger J.G. Pathogenesis and Therapy of Psoriasis. *Nature.* 2007;445:866–873. doi: 10.1038/nature05663. [PubMed] [CrossRef] [Google Scholar]
10. Aggarwal S., Ghilardi N., Xie M.-H., de Sauvage F.J., Gurney A.L. Interleukin-23 Promotes a Distinct CD4 T Cell Activation State Characterized by the Production of Interleukin-17. *J. Biol. Chem.* 2003;278:1910–1914. doi: 10.1074/jbc.M207577200. [PubMed] [CrossRef] [Google Scholar]
11. Hijnen D., Knol E.F., Gent Y.Y., Giovannone B., Beijn S.J.P., Kupper T.S., Bruijnzeel-Koomen C.A.F.M., Clark R.A. CD8(+) T Cells in the Lesional Skin of Atopic Dermatitis and Psoriasis Patients Are an Important Source of IFN-γ, IL-13, IL-17, and IL-22. *J. Investig. Dermatol.* 2013;133:973–979. doi: 10.1038/jid.2012.456. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
12. Albanesi C., Scarponi C., Cavani A., Federici M., Nasorri F., Girolomoni G. Interleukin-17 Is Produced by Both Th1 and Th2 Lymphocytes, and Modulates Interferon-γ- and Interleukin-4-Induced Activation of Human Keratinocytes. *J. Investig. Dermatol.* 2000;115:81–87. doi: 10.1046/j.1523-1747.2000.00041.x. [PubMed] [CrossRef] [Google Scholar]

13. Cai Y., Fleming C., Yan J. New Insights of T Cells in the Pathogenesis of Psoriasis. *Cell. Mol. Immunol.* 2012;9:302–309. doi: 10.1038/cmi.2012.15. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
14. Griffiths C.E., Barker J.N. Pathogenesis and Clinical Features of Psoriasis. *Lancet Lond. Engl.* 2007;370:263–271. doi: 10.1016/S0140-6736(07)61128-3. [PubMed] [CrossRef] [Google Scholar]
15. Goodfield M., Hull S.M., Holland D., Roberts G., Wood E., Reid S., Cunliffe W. Investigations of the "active" Edge of Plaque Psoriasis: Vascular Proliferation Precedes Changes in Epidermal Keratin. *Br. J. Dermatol.* 1994;131:808–813. doi: 10.1111/j.1365-2133.1994.tb08582.x. [PubMed] [CrossRef] [Google Scholar]
16. Baran R. The Burden of Nail Psoriasis: An Introduction. *Dermatology.* 2010;221((Suppl. S1)):1–5. doi: 10.1159/000316169. [PubMed] [CrossRef] [Google Scholar]
17. Jiaravuthisan M.M., Sasseville D., Vender R.B., Murphy F., Muhn C.Y. Psoriasis of the Nail: Anatomy, Pathology, Clinical Presentation, and a Review of the Literature on Therapy. *J. Am. Acad. Dermatol.* 2007;57:1–27. doi: 10.1016/j.jaad.2005.07.073. [PubMed] [CrossRef] [Google Scholar]
18. Stern R.S. Psoriasis. *Lancet Lond. Engl.* 1997;350:349–353. doi: 10.1016/S0140-6736(97)05257-4. [PubMed] [CrossRef] [Google Scholar]
19. Ogdie A., Weiss P. The Epidemiology Psoriatic Arthritis. *Rheum. Dis. Clin. N. Am.* 2015;41:545–568. doi: 10.1016/j.rdc.2015.07.001. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
20. FitzGerald O., Haroon M., Giles J.T., Winchester R. Concepts of Pathogenesis in Psoriatic Arthritis: Genotype Determines Clinical Phenotype. *Arthritis Res. Ther.* 2015;17:115. doi: 10.1186/s13075-015-0640-3. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
21. Martínez-García E., Arias-Santiago S., Valenzuela-Salas I., Garrido-Colmenero C., García-Mellado V., Buendía-Eisman A. Quality of Life in Persons Living with Psoriasis Patients. *J. Am. Acad. Dermatol.* 2014;71:302–307. doi: 10.1016/j.jaad.2014.03.039. [PubMed] [CrossRef] [Google Scholar]
22. Hébert H.L., Ali F.R., Bowes J., Griffiths C.E.M., Barton A., Warren R.B. Genetic Susceptibility to Psoriasis and Psoriatic Arthritis: Implications for Therapy. *Br. J. Dermatol.* 2012;166:474–482. doi: 10.1111/j.1365-2133.2011.10712.x. [PubMed] [CrossRef] [Google Scholar]
23. Menter A., Griffiths C.E. Current and Future Management of Psoriasis. *Lancet Lond. Engl.* 2007;370:272–284. doi: 10.1016/S0140-6736(07)61129-5. [PubMed] [CrossRef] [Google Scholar]
24. Mason J., Mason A.R., Cork M.J. Topical Preparations for the Treatment of Psoriasis: A Systematic Review. *Br. J. Dermatol.* 2002;146:351–364. doi: 10.1046/j.1365-2133.2000.04713.x. [PubMed] [CrossRef] [Google Scholar]
25. Morita A. Current Developments in Phototherapy for Psoriasis. *J. Dermatol.* 2018;45:287–292. doi: 10.1111/1346-8138.14213. [PubMed] [CrossRef] [Google Scholar]
26. Wong T., Hsu L., Liao W. Phototherapy in Psoriasis: A Review of Mechanisms of Action. *J. Cutan. Med. Surg.* 2013;17:6–12. doi: 10.2310/7750.2012.11124. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
27. Zhang P., Wu M.X. A Clinical Review of Phototherapy for Psoriasis. *Lasers Med. Sci.* 2018;33:173–180. doi: 10.1007/s10103-017-2360-1. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
28. Valkova S. UVB Phototherapeutic Modalities. Comparison of Two Treatments for Chronic Plaque Psoriasis. *Acta Dermatovenerol. Alp. Pannonica Adriat.* 2007;16:26–30. [PubMed] [Google Scholar]
29. Bökkerink J.P., De Abreu R.A., Bakker M.A., Hulscher T.W., van Baal J.M., Schretlen E.D., De Bruijn C.H. Effects of Methotrexate on Purine and Pyrimidine Metabolism and Cell-Kinetic Parameters in Human Malignant Lymphoblasts of Different Lineages. *Biochem. Pharmacol.* 1988;37:2329–2338. doi: 10.1016/0006-2952(88)90359-0. [PubMed] [CrossRef] [Google Scholar]
30. Markham T., Watson A., Rogers S. Adverse Effects with Long-Term Cyclosporin for Severe Psoriasis. *Clin. Exp. Dermatol.* 2002;27:111–114. doi: 10.1046/j.1365-2230.2002.00998.x. [PubMed] [CrossRef] [Google Scholar]
31. Yamauchi P.S., Rizk D., Kormeili T., Patnaik R., Lowe N.J. Current Systemic Therapies for Psoriasis: Where Are We Now? *J. Am. Acad. Dermatol.* 2003;49:66–77. doi: 10.1016/mjd.2003.550. [PubMed] [CrossRef] [Google Scholar]
32. Hsu L., Armstrong A.W. Anti-Drug Antibodies in Psoriasis: A Critical Evaluation of Clinical Significance and Impact on Treatment Response. *Expert Rev. Clin. Immunol.* 2013;9:949–958. doi: 10.1586/1744666X.2013.836060. [PubMed] [CrossRef] [Google Scholar]
33. Alwawi E.A., Krulig E., Gordon K.B. Long-Term Efficacy of Biologics in the Treatment of Psoriasis: What Do We Really Know? *Dermatol. Ther.* 2009;22:431–440. doi: 10.1111/j.1529-8019.2009.01259.x. [PubMed] [CrossRef] [Google Scholar]
34. Lebwohl M.G., Bachelez H., Barker J., Girolomoni G., Kavanaugh A., Langley R.G., Paul C.F., Puig L., Reich K., van de Kerkhof P.C.M. Patient Perspectives in the Management of Psoriasis: Results from the Population-Based

Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. *J. Am. Acad. Dermatol.* 2014;70:871–881.e1-30. doi: 10.1016/j.jaad.2013.12.018. [PubMed] [CrossRef] [Google Scholar]
35. Farahnik B., Sharma D., Alban J., Sivamani R.K. Topical Botanical Agents for the Treatment of Psoriasis: A Systematic Review. *Am. J. Clin. Dermatol.* 2017;18:451–468. doi: 10.1007/s40257-017-0266-0. [PubMed] [CrossRef] [Google Scholar]
36. Gendrisch F., Haarhaus B., Krieger N., Quirin K.-W., Schempp C.M., Wölfle U. The Effect of Herbal Medicinal Products on Psoriasis-Like Keratinocytes. *Biomolecules.* 2021;11:371. doi: 10.3390/biom11030371. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
37. Nguyen L.T.H. Signaling Pathways and Targets of Natural Products in Psoriasis Treatment. *Explor. Med.* 2022;3:345–367. doi: 10.37349/emed.2022.00098. [CrossRef] [Google Scholar]
38. Herman A., Herman A.P. Topically Used Herbal Products for the Treatment of Psoriasis—Mechanism of Action, Drug Delivery, Clinical Studies. *Planta Med.* 2016;82:1447–1455. doi: 10.1055/s-0042-115177. [PubMed] [CrossRef] [Google Scholar]
39. Dabholkar N., Rapalli V.K., Singhvi G. Potential Herbal Constituents for Psoriasis Treatment as Protective and Effective Therapy. *Phytother. Res.* 2021;35:2429–2444. doi: 10.1002/ptr.6973. [PubMed] [CrossRef] [Google Scholar]
40. Abuelella K.E., Abd-Allah H., Soliman S.M., Abdel-Mottaleb M.M.A. Skin Targeting by Chitosan/Hyaluronate Hybrid Nanoparticles for the Management of Irritant Contact Dermatitis: In Vivo Therapeutic Efficiency in Mouse-Ear Dermatitis Model. *Int. J. Biol. Macromol.* 2023;232:123458. doi: 10.1016/j.ijbiomac.2023.123458. [PubMed] [CrossRef] [Google Scholar]
41. Abdel-Mottaleb M.M.A. Chapter 13—Nanoparticles for Treatment of Atopic Dermatitis. In: Hamblin M.R., Avci P., Prow T.W., editors. *Nanoscience in Dermatology.* Academic Press; Boston, MA, USA: 2016. pp. 167–175. [Google Scholar]
42. Ghasemiyeh P., Mohammadi-Samani S. Potential of Nanoparticles as Permeation Enhancers and Targeted Delivery Options for Skin: Advantages and Disadvantages. *Drug Des. Devel. Ther.* 2020;14:3271–3289. doi: 10.2147/DDDT.S264648. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
43. Qadir A., Aqil M., Ali A., Warsi M.H., Mujeeb M., Ahmad F.J., Ahmad S., Beg S. Nanostructured Lipidic Carriers for Dual Drug Delivery in the Management of Psoriasis: Systematic Optimization, Dermatokinetic and Preclinical Evaluation. *J. Drug Deliv. Sci. Technol.* 2020;57:101775. doi: 10.1016/j.jddst.2020.101775. [CrossRef] [Google Scholar]
44. Pradhan M., Singh D., Singh M.R. Novel Colloidal Carriers for Psoriasis: Current Issues, Mechanistic Insight and Novel Delivery Approaches. *J. Control Release Off. J. Control Release Soc.* 2013;170:380–395. doi: 10.1016/j.jconrel.2013.05.020. [PubMed] [CrossRef] [Google Scholar]
45. Gungor S., Rezigue M. Nanocarriers Mediated Topical Drug Delivery for Psoriasis Treatment. *Curr. Drug Metab.* 2017;18:454–468. doi: 10.2174/1389200218666170222145240. [PubMed] [CrossRef] [Google Scholar]
46. Ramanunny A.K., Wadhwa S., Singh S.K., Sharma D.S., Khursheed R., Awasthi A. Treatment Strategies Against Psoriasis: Principle, Perspectives and Practices. *Curr. Drug Deliv.* 2020;17:52–73. doi: 10.2174/1567201816666191120120551. [PubMed] [CrossRef] [Google Scholar]
47. El Zaafarany G.M., Awad G.A.S., Holayel S.M., Mortada N.D. Role of Edge Activators and Surface Charge in Developing Ultradeformable Vesicles with Enhanced Skin Delivery. *Int. J. Pharm.* 2010;397:164–172. doi: 10.1016/j.ijpharm.2010.06.034. [PubMed] [CrossRef] [Google Scholar]
48. Abdel-Mottaleb M., Try C., Pellequer Y., Lamprecht A. Nanomedicine Strategies for Targeting Skin Inflammation. *Nanomedicine.* 2014;9:1727–1743. doi: 10.2217/nnm.14.74. [PubMed] [CrossRef] [Google Scholar]
49. Abdel-Mottaleb M.M.A., Moulari B., Beduneau A., Pellequer Y., Lamprecht A. Nanoparticles Enhance Therapeutic Outcome in Inflamed Skin Therapy. *Eur. J. Pharm. Biopharm. Off. J. Arb. Pharm. Verfahr. EV.* 2012;82:151–157. doi: 10.1016/j.ejpb.2012.06.006. [PubMed] [CrossRef] [Google Scholar]
50. Yadav K., Soni A., Singh D., Singh M.R. Polymers in Topical Delivery of Anti-Psoriatic Medications and Other Topical Agents in Overcoming the Barriers of Conventional Treatment Strategies. *Prog. Biomater.* 2021;10:1–17. doi: 10.1007/s40204-021-00154-7. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
51. Svenson S. Dendrimers as Versatile Platform in Drug Delivery Applications. *Eur. J. Pharm. Biopharm. Off. J. Arb. Pharm. Verfahr. EV.* 2009;71:445–462. doi: 10.1016/j.ejpb.2008.09.023. [PubMed] [CrossRef] [Google Scholar]
52. Abdel-Mottaleb M.M.A., Lamprecht A. In Vivo Skin Penetration of Macromolecules in Irritant Contact Dermatitis. *Int. J. Pharm.* 2016;515:384–389. doi: 10.1016/j.ijpharm.2016.10.042. [PubMed] [CrossRef] [Google Scholar]

53. Martins A.M., Ascenso A., Ribeiro H.M., Marto J. Current and Future Therapies for Psoriasis with a Focus on Serotonergic Drugs. *Mol. Neurobiol.* 2020;57:2391–2419. doi: 10.1007/s12035-020-01889-3. [PubMed] [CrossRef] [Google Scholar]
54. Fereig S.A., El-Zaafarany G.M., Arafa M., Abdel-Mottaleb M.M.A. Tackling the Various Classes of Nano-Therapeutics Employed in Topical Therapy of Psoriasis. *Drug Deliv.* 2020;27:662–680. doi: 10.1080/10717544.2020.1754527. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
55. Damiani G., Pacifico A., Linder D.M., Pigatto P.D.M., Conic R., Grada A., Bragazzi N.L. Nanodermatology-Based Solutions for Psoriasis: State-of-the Art and Future Prospects. *Dermatol. Ther.* 2019;32:e13113. doi: 10.1111/dth.13113. [PubMed] [CrossRef] [Google Scholar]
56. Singhvi G., Hejmady S., Rapalli V.K., Dubey S.K., Dubey S. Chapter 4—Nanocarriers for Topical Delivery in Psoriasis. In: Shegokar R., editor. *Delivery of Drugs.* Elsevier; Amsterdam, The Netherlands: 2020. pp. 75–96. [Google Scholar]
57. Zhang M., Cheng J., Hu J., Luo J., Zhang Y., Lu F., Kong H., Qu H., Zhao Y. Green Phellodendri Chinensis Cortex- Based Carbon Dots for Ameliorating Imiquimod-Induced Psoriasis-like Inflammation in Mice. *J. Nanobiotechnol.* 2021;19:105. doi: 10.1186/s12951-021-00847-y. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
58. Ernst E. Adverse Effects of Herbal Drugs in Dermatology. *Br. J. Dermatol.* 2000;143:923–929. doi: 10.1046/j.1365-2133.2000.03822.x. [PubMed] [CrossRef] [Google Scholar]
59. Bassim Atta M. Some Characteristics of Nigella (*Nigella sativa* L.) Seed Cultivated in Egypt and Its Lipid Profile. *Food Chem.* 2003;83:63–68. doi: 10.1016/S0308-8146(03)00038-4. [CrossRef] [Google Scholar]
60. Babazadeh B., Sadeghnia H.R., Safarpour Kapurchal E., Parsaee H., Nasri S., Tayarani-Najaran Z. Protective Effect of *Nigella sativa* and Thymoquinone on Serum/Glucose Deprivation-Induced DNA Damage in PC12 Cells. *Avicenna J. Phytomed.* 2012;2:125–132. [PMC free article] [PubMed] [Google Scholar]
61. Sayeed S., Imam S.S., Najmi A.K., Aqil M., Akhtar M. Nonionic Surfactant Based Thymoquinone Loaded Nanoproniosomal Formulation: In Vitro Physicochemical Evaluation and in Vivo Hepatoprotective Efficacy. *Drug Dev. Ind. Pharm.* 2017;43:1413–1420. doi: 10.1080/03639045.2017.1318903. [PubMed] [CrossRef] [Google Scholar]
62. Yimer E.M., Tuem K.B., Karim A., Ur-Rehman N., Anwar F. *Nigella sativa* L. (Black Cumin): A Promising Natural Remedy for Wide Range of Illnesses. *Evid. Based Complement. Alternat. Med.* 2019;2019:e1528635. doi: 10.1155/2019/1528635. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
63. Akhtar M., Imam S.S., Afroz Ahmad M., Najmi A.K., Mujeeb M., Aqil M. Neuroprotective Study of *Nigella sativa*-Loaded Oral Provesicular Lipid Formulation: In Vitro and Ex Vivo Study. *Drug Deliv.* 2014;21:487–494. doi: 10.3109/10717544.2014.886640. [PubMed] [CrossRef] [Google Scholar]
64. Okasha E.F., Bayomy N.A., Abdelaziz E.Z. Effect of Topical Application of Black Seed Oil on Imiquimod-Induced Psoriasis-like Lesions in the Thin Skin of Adult Male Albino Rats. *Anat. Rec.* 2018;301:166–174. doi: 10.1002/ar.23690. [PubMed] [CrossRef] [Google Scholar]
65. Negi P., Sharma I., Hemrajani C., Rathore C., Bisht A., Raza K., Katare O.P. Thymoquinone-Loaded Lipid Vesicles: A Promising Nanomedicine for Psoriasis. *BMC Complement. Altern. Med.* 2019;19:334. doi: 10.1186/s12906-019-2675-5. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
66. Palaniswamy D., Nithyanantham M., Raghu P., Dwarampudi L. Antipsoriatic Activity and Cytotoxicity of Ethanolic Extract of *Nigella sativa* Seeds. *Pharmacogn. Mag.* 2012;8:268. doi: 10.4103/0973-1296.103650. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
67. Ahmed J.H., Ibraheem A.Y., Al-Hamdi K.I. Evaluation of Efficacy, Safety and Antioxidant Effect of *Nigella sativa* in Patients with Psoriasis: A Randomized Clinical Trial. *J. Clin. Exp. Investig.* 2014;5:186–193. doi: 10.5799/ahinjs.01.2014.02.0387. [CrossRef] [Google Scholar]
68. Khatoon K., Ali A., Ahmad F.J., Hafeez Z., Rizvi M.M.A., Akhter S., Beg S. Novel Nanoemulsion Gel Containing Triple Natural Bio-Actives Combination of Curcumin, Thymoquinone, and Resveratrol Improves Psoriasis Therapy: In Vitro and In Vivo Studies. *Drug Deliv. Transl. Res.* 2021;11:1245–1260. doi: 10.1007/s13346-020-00852-y. [PubMed] [CrossRef] [Google Scholar]
69. Sahu S., Katiyar S.S., Kushwah V., Jain S. Active Natural Oil-Based Nanoemulsion Containing Tacrolimus for Synergistic Antipsoriatic Efficacy. *Nanomedicine.* 2018;13:1985–1998. doi: 10.2217/nnm-2018-0135. [PubMed] [CrossRef] [Google Scholar]
70. Navarra M., Mannucci C., Delbò M., Calapai G. Citrus Bergamia Essential Oil: From Basic Research to Clinical Application. *Front. Pharmacol.* 2015;6:36. doi: 10.3389/fphar.2015.00036. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
71. Navarra M., Ferlazzo N., Cirmi S., Trapasso E., Bramanti P., Lombardo G.E., Minciullo P.L., Calapai G., Gangemi S. Effects of Bergamot Essential Oil and Its Extractive Fractions on SH-SY5Y Human Neuroblastoma Cell

Growth. *J. Pharm. Pharmacol.* 2015;67:1042–1053. doi: 10.1111/jphp.12403. [PubMed] [CrossRef] [Google Scholar]
72. Risitano R., Currò M., Cirmi S., Ferlazzo N., Campiglia P., Caccamo D., Ientile R., Navarra M. Flavonoid Fraction of Bergamot Juice Reduces LPS-Induced Inflammatory Response through SIRT1-Mediated NF-KB Inhibition in THP-1 Monocytes. *PLoS ONE.* 2014;9:e107431. doi: 10.1371/journal.pone.0107431. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
73. Impellizzeri D., Cordaro M., Campolo M., Gugliandolo E., Esposito E., Benedetto F., Cuzzocrea S., Navarra M. Anti-Inflammatory and Antioxidant Effects of Flavonoid-Rich Fraction of Bergamot Juice (BJe) in a Mouse Model of Intestinal Ischemia/Reperfusion Injury. *Front. Pharmacol.* 2016;7:203. doi: 10.3389/fphar.2016.00203. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
74. Costa R., Dugo P., Navarra M., Raymo V., Dugo G., Mondello L. Study on the Chemical Composition Variability of Some Processed Bergamot (*Citrus Bergamia*) Essential Oils. *Flavour Fragr. J.* 2010;25:4–12. doi: 10.1002/ffj.1949. [CrossRef] [Google Scholar]
75. Ferlazzo N., Cirmi S., Calapai G., Ventura-Spagnolo E., Gangemi S., Navarra M. Anti-Inflammatory Activity of Citrus Bergamia Derivatives: Where Do We Stand? *Molecules.* 2016;21:1273. doi: 10.3390/molecules21101273. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
76. Graziano A.C.E., Cardile V., Crascì L., Caggia S., Dugo P., Bonina F., Panico A. Protective Effects of an Extract from Citrus Bergamia against Inflammatory Injury in Interferon-γ and Histamine Exposed Human Keratinocytes. *Life Sci.* 2012;90:968–974. doi: 10.1016/j.lfs.2012.04.043. [PubMed] [CrossRef] [Google Scholar]
77. Xiao S., Yu H., Xie Y., Guo Y., Fan J., Yao W. The Anti-Inflammatory Potential of *Cinnamomum Camphora* (L.) J. Presl Essential Oil in Vitro and in Vivo. *J. Ethnopharmacol.* 2021;267:113516. doi: 10.1016/j.jep.2020.113516. [PubMed] [CrossRef] [Google Scholar]
78. Mannucci C., Navarra M., Calapai F., Squeri R., Gangemi S., Calapai G. Clinical Pharmacology of Citrus Bergamia: A Systematic Review. *Phytother. Res.* 2017;31:27–39. doi: 10.1002/ptr.5734. [PubMed] [CrossRef] [Google Scholar]
79. Wesołowska A., Jadczak D., Grzeszczuk M. Chemical Composition of the Pepper Fruit Extracts of Hot Cultivars *Capsicum Annuum* L. *Acta Sci. Pol. Hortorum Cultus.* 2011;10:171–184. [Google Scholar]
80. Jessell T.M., Iversen L.L., Cuello A.C. Capsaicin-Induced Depletion of Substance P from Primary Sensory Neurones. *Brain Res.* 1978;152:183–188. doi: 10.1016/0006-8993(78)90146-4. [PubMed] [CrossRef] [Google Scholar]
81. Farber E.M., Nickoloff B.J., Recht B., Fraki J.E. Stress, Symmetry, and Psoriasis: Possible Role of Neuropeptides. *J. Am. Acad. Dermatol.* 1986;14:305–311. doi: 10.1016/S0190-9622(86)70034-0. [PubMed] [CrossRef] [Google Scholar]
82. Yu C. Study on HIF-1α Gene Translation in Psoriatic Epidermis with the Topical Treatment of Capsaicin Ointment. *Int. Sch. Res. Not.* 2011;2011:821874. doi: 10.5402/2011/821874. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
83. Agrawal U., Gupta M., Vyas S.P. Capsaicin Delivery into the Skin with Lipidic Nanoparticles for the Treatment of Psoriasis. *Artif. Cells Nanomed. Biotechnol.* 2015;43:33–39. doi: 10.3109/21691401.2013.832683. [PubMed] [CrossRef] [Google Scholar]
84. Somagoni J., Boakye C.H.A., Godugu C., Patel A.R., Mendonca Faria H.A., Zucolotto V., Singh M. Nanomiemgel—A Novel Drug Delivery System for Topical Application—In Vitro and In Vivo Evaluation. *PLoS ONE.* 2014;9:e115952. doi: 10.1371/journal.pone.0115952. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
85. Desai P.R., Marepally S., Patel A.R., Voshavar C., Chaudhuri A., Singh M. Topical Delivery of Anti-TNFα SiRNA and Capsaicin via Novel Lipid-Polymer Hybrid Nanoparticles Efficiently Inhibits Skin Inflammation in Vivo. *J. Control Release Off. J. Control Release Soc.* 2013;170:51–63. doi: 10.1016/j.jconrel.2013.04.021. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
86. Gupta R., Gupta M., Mangal S., Agrawal U., Vyas S.P. Capsaicin-Loaded Vesicular Systems Designed for Enhancing Localized Delivery for Psoriasis Therapy. *Artif. Cells Nanomed. Biotechnol.* 2016;44:825–834. doi: 10.3109/21691401.2014.984301. [PubMed] [CrossRef] [Google Scholar]
87. Ramankutty C., Warrier P.K., Nambiar V.P.K. *Indian Medicinal Plants: A Compendium of 500 Species.* Orient Black Swan; Hyderabad, India: 1993. [Google Scholar]
88. Singhal M., Kansara N. Cassia Tora Linn Cream Inhibits Ultraviolet-B-Induced Psoriasis in Rats. *ISRN Dermatol.* 2012;2012:346510. doi: 10.5402/2012/346510. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
89. Ibezim A., Amara E.E. In-Silico Study of Flavonoids from Cassia Tora as Potential Anti-Psoriatic Agent. *J. Appl. Pharm. Sci.* 2019;9:82–87. doi: 10.7324/JAPS.2019.90410. [CrossRef] [Google Scholar]

90. Gaikwad R., Shinde A., Hajare A. Herbal Treatment for Management of Psoriasis: An Overview. *Res. J. Pharm. Technol.* 2022;15:1385–1392. doi: 10.52711/0974-360X.2022.00231. [CrossRef] [Google Scholar]
91. Shelton R.M. Aloe Vera. Its Chemical and Therapeutic Properties. *Int. J. Dermatol.* 1991;30:679–683. doi: 10.1111/j.1365-4362.1991.tb02607.x. [PubMed] [CrossRef] [Google Scholar]
92. Vazquez B., Avila G., Segura D., Escalante B. Antiinflammatory Activity of Extracts from Aloe Vera Gel. *J. Ethnopharmacol.* 1996;55:69–75. doi: 10.1016/S0378-8741(96)01476-6. [PubMed] [CrossRef] [Google Scholar]
93. Choonhakarn C., Busaracome P., Sripanidkulchai B., Sarakarn P. A Prospective, Randomized Clinical Trial Comparing Topical Aloe Vera with 0.1% Triamcinolone Acetonide in Mild to Moderate Plaque Psoriasis. *J. Eur. Acad. Dermatol. Venereol.* 2010;24:168–172. doi: 10.1111/j.1468-3083.2009.03377.x. [PubMed] [CrossRef] [Google Scholar]
94. El-Gammal A., Nardo V.D., Daaboul F., Tchernev G., Wollina U., Lotti J., Lotti T. Is There a Place for Local Natural Treatment of Psoriasis? *Open Access Maced. J. Med. Sci.* 2018;6:839–842. doi: 10.3889/oamjms.2018.106. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
95. Gupta S., Singhal P., Singh A., Chauhan R., Kumar B. Nutritional and pharmceutical benifits of avocado plant. *J. Adv. Res.* 2018;9:4–11. [Google Scholar]
96. Flores M., Saravia C., Vergara C.E., Avila F., Valdés H., Ortiz-Viedma J. Avocado Oil: Characteristics, Properties, and Applications. *Molecules.* 2019;24:2172. doi: 10.3390/molecules24112172. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
97. Stücker M., Memmel U., Hoffmann M., Hartung J., Altmeyer P. Vitamin B12 Cream Containing Avocado Oil in the Therapy of Plaque Psoriasis. *Dermatology.* 2001;203:141–147. doi: 10.1159/000051729. [PubMed] [CrossRef] [Google Scholar]
98. Srivastava J.K., Pandey M., Gupta S. Chamomile, a Novel and Selective COX-2 Inhibitor with Anti-Inflammatory Activity. *Life Sci.* 2009;85:663–669. doi: 10.1016/j.lfs.2009.09.007. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
99. Bhaskaran N., Shukla S., Srivastava J.K., Gupta S. Chamomile, an Anti-Inflammatory Agent Inhibits Inducible Nitric Oxide Synthase Expression by Blocking RelA/P65 Activity. *Int. J. Mol. Med.* 2010;26:935–940. [PMC free article] [PubMed] [Google Scholar]
100. Kolahdooz S., Karimi M., Esmaili N., Zargaran A., Kordafshari G., Mozafari N., Ayati M.H. Evaluation of the Efficacy of a Topical Chamomile-Pumpkin Oleogel for the Treatment of Plaque Psoriasis: An Intra-Patient, Double-Blind, Randomized Clinical Trial. *Biomed. Res. Ther.* 2018;5:2811–2819. doi: 10.15419/bmrat.v5i11.499. [CrossRef] [Google Scholar]
101. Aertgeerts P., Albring M., Klaschka F., Nasemann T., Patzelt-Wenczler R., Rauhut K., Weigl B. Comparative testing of Kamillosan cream and steroidal (0.25% hydrocortisone, 0.75% fluocortin butyl ester) and non-steroidal (5% bufexamac) dermatologic agents in maintenance therapy of eczematous diseases. *Z. Hautkr.* 1985;60:270–277. [PubMed] [Google Scholar]
102. Villarino B.J., Dy L.M., Lizada M.C.C. Descriptive Sensory Evaluation of Virgin Coconut Oil and Refined, Bleached and Deodorized Coconut Oil. *LWT—Food Sci. Technol.* 2007;40:193–199. doi: 10.1016/j.lwt.2005.11.007. [CrossRef] [Google Scholar]
103. Varma S.R., Sivaprakasam T.O., Arumugam I., Dilip N., Raghuraman M., Pavan K.B., Rafiq M., Paramesh R. In vitro anti-inflammatory and skin protective properties of Virgin coconut oil. *J. Tradit. Complement. Med.* 2019;9:5–14. doi: 10.1016/j.jtcme.2017.06.012. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
104. Evangelista M.T.P., Abad-Casintahan F., Lopez-Villafuerte L. The Effect of Topical Virgin Coconut Oil on SCORAD Index, Transepidermal Water Loss, and Skin Capacitance in Mild to Moderate Pediatric Atopic Dermatitis: A Randomized, Double-Blind, Clinical Trial. *Int. J. Dermatol.* 2014;53:100–108. doi: 10.1111/ijd.12339. [PubMed] [CrossRef] [Google Scholar]
105. Verallo-Rowell V.M., Dillague K.M., Syah-Tjundawan B.S. Novel Antibacterial and Emollient Effects of Coconut and Virgin Olive Oils in Adult Atopic Dermatitis. *Dermat. Contact Atopic Occup. Drug.* 2008;19:308–315. doi: 10.2310/6620.2008.08052. [PubMed] [CrossRef] [Google Scholar]
106. Chainani-Wu N. Safety and Anti-Inflammatory Activity of Curcumin: A Component of Tumeric (*Curcuma longa*) *J. Altern. Complement. Med. N. Y. N.* 2003;9:161–168. doi: 10.1089/107555303321223035. [PubMed] [CrossRef] [Google Scholar]
107. Sun J., Zhao Y., Hu J. Curcumin Inhibits Imiquimod-Induced Psoriasis-Like Inflammation by Inhibiting IL-1beta and IL-6 Production in Mice. *PLoS ONE.* 2013;8:e67078. doi: 10.1371/journal.pone.0067078. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
108. Ali M.S., Alam M., Imam F.I., Siddiqui M.R. Topical Nanoemulsion of Turmeric Oil for Psoriasis: Characterization, Ex Vivo and in Vivo Assessment. *Int. J. Drug Deliv.* 2012;4:184. doi: 10.5138/ijdd.v4i2.575. [CrossRef] [Google Scholar]

109. Varma S.R., Sivaprakasam T.O., Mishra A., Prabhu S., Rafiq M., Rangesh P. Imiquimod-Induced Psoriasis-like Inflammation in Differentiated Human Keratinocytes: Its Evaluation Using Curcumin. *Eur. J. Pharmacol.* 2017;813:33–41. doi: 10.1016/j.ejphar.2017.07.040. [PubMed] [CrossRef] [Google Scholar]
110. Algahtani M.S., Ahmad M.Z., Nourein I.H., Ahmad J. Co-Delivery of Imiquimod and Curcumin by Nanoemugel for Improved Topical Delivery and Reduced Psoriasis-Like Skin Lesions. *Biomolecules.* 2020;10:968. doi: 10.3390/biom10070968. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
111. Algahtani M.S., Ahmad M.Z., Ahmad J. Nanoemulsion Loaded Polymeric Hydrogel for Topical Delivery of Curcumin in Psoriasis. *J. Drug Deliv. Sci. Technol.* 2020;59:101847. doi: 10.1016/j.jddst.2020.101847. [CrossRef] [Google Scholar]
112. Mao K.-L., Fan Z.-L., Yuan J.-D., Chen P.-P., Yang J.-J., Xu J., ZhuGe D.-L., Jin B.-H., Zhu Q.-Y., Shen B.-X., et al.
Skin-Penetrating Polymeric Nanoparticles Incorporated in Silk Fibroin Hydrogel for Topical Delivery of Curcumin to Improve Its Therapeutic Effect on Psoriasis Mouse Model. *Colloids Surf. B Biointerfaces.* 2017;160:704–714. doi: 10.1016/j.colsurfb.2017.10.029. [PubMed] [CrossRef] [Google Scholar]
113. Iriventi P., Gupta N.V., Osmani R.A.M., Balamuralidhara V. Design & Development of Nanosponge Loaded Topical Gel of Curcumin and Caffeine Mixture for Augmented Treatment of Psoriasis. *Daru J. Fac. Pharm. Tehran Univ. Med. Sci.* 2020;28:489–506. doi: 10.1007/s40199-020-00352-x. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
114. Rahman M., Beg S., Ahmad M.Z., Kazmi I., Ahmed A., Rahman Z., Ahmad F.J., Akhter S. Omega-3 Fatty Acids as Pharmacotherapeutics in Psoriasis: Current Status and Scope of Nanomedicine in Its Effective Delivery. *Curr. Drug Targets.* 2013;14:708–722. doi: 10.2174/1389450111314060011. [PubMed] [CrossRef] [Google Scholar]
115. Schwab J.M., Chiang N., Arita M., Serhan C.N. Resolvin E1 and Protectin D1 Activate Inflammation-Resolution Programmes. *Nature.* 2007;447:869–874. doi: 10.1038/nature05877. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
116. Sharma S., Kumar A., Sahni J.K., Ali J., Baboota S. Nanoemulsion Based Hydrogel Containing Omega 3 Fatty Acids as a Surrogate of Betamethasone Dipropionate for Topical Delivery. *Adv. Sci. Lett.* 2012;6:221–231. doi: 10.1166/asl.2012.2097. [CrossRef] [Google Scholar]
117. Zulfakar M.H., Abdelouahab N., Heard C.M. Enhanced Topical Delivery and Ex Vivo Anti-Inflammatory Activity from a Betamethasone Dipropionate Formulation Containing Fish Oil. *Inflamm. Res.* 2010;59:23–30. doi: 10.1007/s00011-009-0065-z. [PubMed] [CrossRef] [Google Scholar]
118. Rehman K., Aluwi M.F.F.M., Rullah K., Wai L.K., Mohd Amin M.C.I., Zulfakar M.H. Probing the Effects of Fish Oil on the Delivery and Inflammation-Inducing Potential of Imiquimod. *Int. J. Pharm.* 2015;490:131–141. doi: 10.1016/j.ijpharm.2015.05.045. [PubMed] [CrossRef] [Google Scholar]
119. Huo M., Cui X., Xue J., Chi G., Gao R., Deng X., Guan S., Wei J., Soromou L.W., Feng H., et al. Anti-Inflammatory
Effects of Linalool in RAW 264.7 Macrophages and Lipopolysaccharide-Induced Lung Injury Model. *J. Surg. Res.* 2013;180:e47–e54. doi: 10.1016/j.jss.2012.10.050. [PubMed] [CrossRef] [Google Scholar]
120. Rai V.K., Sinha P., Yadav K.S., Shukla A., Saxena A., Bawankule D.U., Tandon S., Khan F., Chanotiya C.S., Yadav
N.P. Anti-Psoriatic Effect of Lavandula Angustifolia Essential Oil and Its Major Components Linalool and Linalyl Acetate. *J. Ethnopharmacol.* 2020;261:113127. doi: 10.1016/j.jep.2020.113127. [PubMed] [CrossRef] [Google Scholar]
121. Martín-Peláez S., Covas M.I., Fitó M., Kušar A., Pravst I. Health Effects of Olive Oil Polyphenols: Recent Advances and Possibilities for the Use of Health Claims. *Mol. Nutr. Food Res.* 2013;57:760–771. doi: 10.1002/mnfr.201200421. [PubMed] [CrossRef] [Google Scholar]
122. Palombo R., Savini I., Avigliano L., Madonna S., Cavani A., Albanesi C., Mauriello A., Melino G., Terrinoni A. Luteolin-7-Glucoside Inhibits IL-22/STAT3 Pathway, Reducing Proliferation, Acanthosis, and Inflammation in Keratinocytes and in Mouse Psoriatic Model. *Cell Death Dis.* 2016;7:e2344. doi: 10.1038/cddis.2016.201. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
123. Michalsen A., Eddin O., Salama A. A Case Series of the Effects of a Novel Composition of a Traditional Natural Preparation for the Treatment of Psoriasis. *J. Tradit. Complement. Med.* 2016;6:395–398. doi: 10.1016/j.jtcme.2015.08.006. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
124. Pradhan M., Alexander A., Singh M.R., Singh D., Saraf S., Saraf S., Yadav K. Ajazuddin Statistically Optimized Calcipotriol Fused Nanostructured Lipid Carriers for Effectual Topical Treatment of Psoriasis. *J. Drug Deliv. Sci. Technol.* 2021;61:102168. doi: 10.1016/j.jddst.2020.102168. [CrossRef] [Google Scholar]
125. Rashid S.A., Bashir S., Naseem F., Farid A., Rather I.A., Hakeem K.R. Olive Oil Based Methotrexate Loaded Topical Nanoemulsion Gel for the Treatment of Imiquimod Induced Psoriasis-like Skin Inflammation in an Animal Model. *Biology.* 2021;10:1121. doi: 10.3390/biology10111121. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

126Wechsler J.B., Hsu C.-L., Bryce P.J. IgE-Mediated Mast Cell Responses Are Inhibited by Thymol-Mediated, Activation-Induced Cell Death in Skin Inflammation. *J. Allergy Clin. Immunol.* 2014;133:1735–1743. doi: 10.1016/j.jaci.2013.12.024. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
127. Pivetta T.P., Simões S., Araújo M.M., Carvalho T., Arruda C., Marcato P.D. Development of Nanoparticles from Natural Lipids for Topical Delivery of Thymol: Investigation of Its Anti-Inflammatory Properties. *Colloids Surf. B Biointerfaces.* 2018;164:281–290. doi: 10.1016/j.colsurfb.2018.01.053. [PubMed] [CrossRef] [Google Scholar]
128. Hammer K.A., Carson C.F., Riley T.V., Nielsen J.B. A Review of the Toxicity of *Melaleuca alternifolia* (Tea Tree) Oil. *Food Chem. Toxicol. Int. J. Publ. Br. Ind. Biol. Res. Assoc.* 2006;44:616–625. doi: 10.1016/j.fct.2005.09.001. [PubMed] [CrossRef] [Google Scholar]
129. Finlay-Jones J., Hart P.H. Rural Industries Research and Development Corporation (Australia) In: Tea Tree Oil Research Program, editor. *Regulation of Immune Responses in Human Skin by Tea Tree Oil.* RIRDC; Barton, Australia: 2004. [Google Scholar]
130. Sonia K., Anupama D. Microemulsion Based Transdermal Drug Delivery of Tea Tree Oil. *Int. J. Drug Dev. Res.* 2011;3:191–198. [Google Scholar]
131. Alam M.S., Saraswat R., Sharma P., Ansari M.S. In-Vivo Assessment of Glucocorticoid Loaded Tea Tree Oil Nanoemulsion Gel. *J. Drug Deliv. Ther.* 2019;9:108–113. doi: 10.22270/jddt.v9i1.2178. [CrossRef] [Google Scholar]
132. Alam M.S., Ali M.D., Ansari M.S., Sharma P. Inhibitory effects on tumor necrosis factor alpha and interleukin 12 using clobetasol propionate loaded tea tree oil nanoemulsion gel on animal model. *Asian J. Pharm. Clin. Res.* 2018;11:182–185. doi: 10.22159/ajpcr.2018.v11i6.24888. [CrossRef] [Google Scholar]
133. Zrira S.S., Benjilali B.B. Seasonal Changes in the Volatile Oil and Cineole Contents of Five Eucalyptus Species Growing in Morocco. *J. Essent. Oil Res.* 1996;8:19–24. doi: 10.1080/10412905.1996.9700548. [CrossRef] [Google Scholar]
134. Nakamura T., Yoshida N., Yamanoi Y., Honryo A., Tomita H., Kuwabara H., Kojima Y. Eucalyptus Oil Reduces Allergic Reactions and Suppresses Mast Cell Degranulation by Downregulating IgE-FcεRI Signalling. *Sci. Rep.* 2020;10:20940. doi: 10.1038/s41598-020-77039-5. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
135. Hussein A., Abdel-Mottaleb M., El-assal M., Sammour O. Novel biocompatible essential oil-based lipid nanocapsules with antifungal properties. *Drug Del. Sci. Technol.* 2020;56:101605. doi: 10.1016/j.jddst.2020.101605. [CrossRef] [Google Scholar]
136. Abdel-Mottaleb M.M.A., Moulari B., Beduneau A., Pellequer Y., Lamprecht A. Surface-charge-dependent nanoparticles accumulation in inflamed skin. *J. Pharm. Sci.* 2012;101:4231–4239. doi: 10.1002/jps.23282. [PubMed] [CrossRef] [Google Scholar]
137. Fereig S., Mamdouh G., Arafa M., Abdel-Mottaleb M. Tacrolimus-loaded chitosan nanoparticles for enhanced skin deposition and management of plaque psoriasis. *Carbohydr. Polym.* 2021;268:118238. doi: 10.1016/j.carbpol.2021.118238. [PubMed] [CrossRef] [Google Scholar]
138. Fereig S., Mamdouh G., Arafa M., Abdel-Mottaleb M. Boosting the anti-inflammatory effect of self-assembled hybrid lecithin–chitosan nanoparticles via hybridization with gold nanoparticles for the treatment of psoriasis. *Drug Deliv.* 2022;29:1726–1742. doi: 10.1080/10717544.2022.2081383. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
139. Abdel-Mottaleb M.M.A., Neumann D., Lamprecht A. Lipid nanocapsules for dermal application: A comparative study of lipid-based versus polymer-based nanocarriers. *Eur. J. Pharm. Biophar.* 2011;79:36–42. doi: 10.1016/j.ejpb.2011.04.009. [PubMed] [CrossRef] [Google Scholar]
140. El-Tokhy F., Abdel-Mottaleb M.M.A., Abdel-Mageed S., Mahmoud A., El-ghany E., Geneidi A. Boosting the In Vivo Transdermal Bioavailability of Asenapine Maleate Using Novel Lavender Oil-Based Lipid Nanocapsules for Management of Schizophrenia. *Pharmaceutics.* 2023;15:490. doi: 10.3390/pharmaceutics15020490. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

INDICATION-DIRECTION TO USE- PRECAUTION

No Steroids Certificates

IDEAL ANALYTICAL AND RESEARCH INSTITUTION

Plot No.1 and 2 (PT),Brindhavanam Nagar,Pazhani samy Nagar, Villianur, Puducherry-605110

CERTIFICATE OF ANALYSIS

Report Date :	04.10.2023

1) Name of the manufacturer from whom sample received with manufacturing license number	XEMEX LIFE SCIENCES, XEMEX Towers, Plot no:34, Manikodi Srinivasan Nagar Main Road, Perungudi, Chennai-600 096					
2) Reference number & date of the sample forwarding letter	**3) Date of receipt of sample**	**4) Name of drug / cosmetics / raw material purporting to be contained/ final product in bulk / final product (in finished pack) as obtained from the manufacturer**				
29.09.2023	30.09.2023	XEMSIS OINTMENT				
5) Details of drug / cosmetics / raw material / final product in bulk / final product (in finished pack) as obtained from the manufacturer as follows						
a)Original manufacturer's name (in case of raw materials and drugs repacked)	**b)Batch No/ Control No.**	**c)Batch size as represented by sample**	**d)Date of manufacture, if any**	**e)Date of expiry, if any**	**f)Quantity submitted**	
-	-	-	-	-	2x10gms	

6) Results of test for analysis: *SAMPLE NOT DRAWN BY US*

PARAMETERS	SPECIFICATIONS	OBSERVATION
Description		Brown colour ointment.
Steroids: Betamethasone Dipropionate	-	Nil
Dexomethasone	-	Nil
Hydrocortisone acetate	-	Nil
Prednisolone	-	Nil

Opinion : For information.

Signature of Person-in-charge of testing

(K.Maruthappa Pandian)

Report(Report Editor)

==== Shimadzu LCsolution Analysis Report ====

@D:\HPLC\Data 2023\Project\steroids\OCT 2023\03.10.2023\BLANK.lcd

Acquired by	: guru
Sample Name	: Setride
Sample ID	: BLANK
Data File Name	: BLANK.lcd
Method File Name	: Project.lcm

Blank

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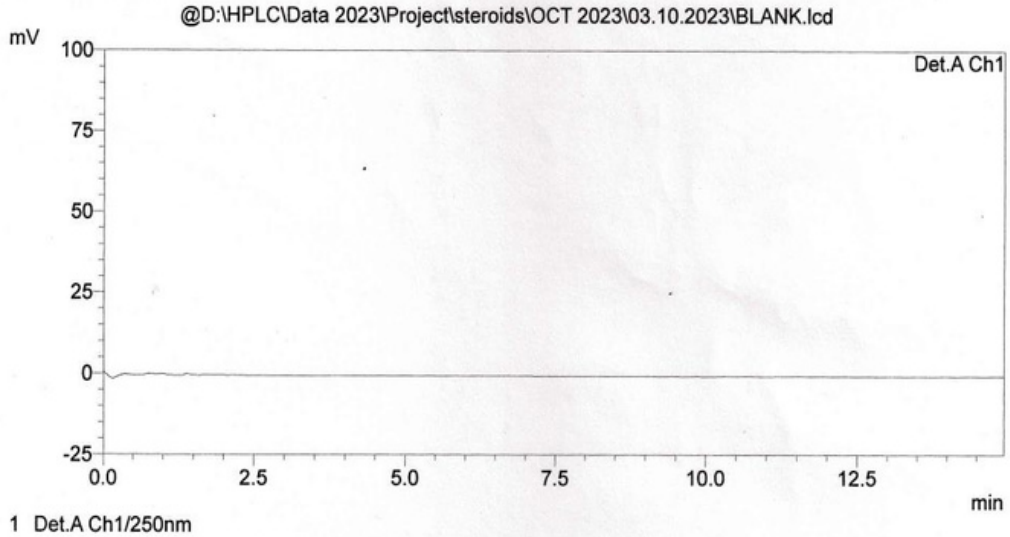

1 Det.A Ch1/250nm

PeakTable

Detector A Ch1 250nm

Report(Report Editor)

==== Shimadzu LCsolution Analysis Report ====

@D:\HPLC\Data 2023\Project\steroids\OCT 2023\03.10.2023\Trial.lcd

Acquired by : guru
Sample Name : Setride
Sample ID : 1
Data File Name : Trial.lcd
Method File Name : Project.lcm

Sample Solution

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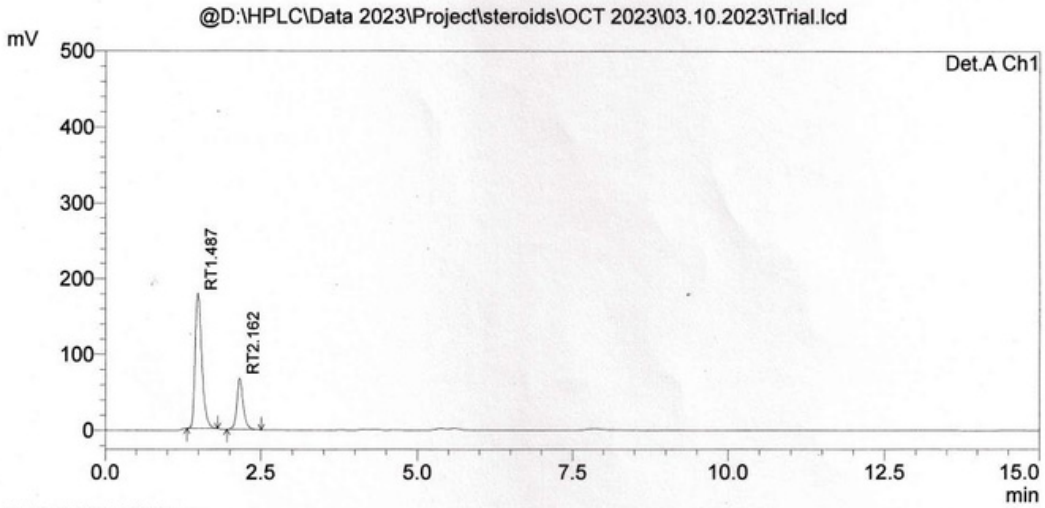

1 Det.A Ch1/250nm

PeakTable

Detector A Ch1 250nm

Name	Ret. Time	Area	Area %	Tailing Factor	Theoretical Plate#
RT1.487	1.49	1329012	73.86	1.54	865
RT2.162	2.16	470299	26.14	1.23	2096
		1799311	100.00		