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Evaluation of clinical trials of the plants, which have ethnobotanical uses for skin disorders in Turkey: a review

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Abstract

Background: Ethnobotanical studies investigating a large number of traditional herbs and uses have an important role in the discovery of new drugs. Nowadays, some of these traditional herbs are researched directly in the clinical trials. In this study, it is aimed to evaluate the 19 plant species that have been identified in the clinical trials among 300 plant species belonging to 79 families with traditional use for skin problems in Turkey.

Main body: Natural sources are very important to treat diseases for thousands of years. The ethnopharmacological research of natural products ranges from the collection of biogenic samples such as plants to preclinical and clinical studies with the aim of developing drug templates or new drugs. In the ethnopharmacological approach, it is aimed to reach the result based on the traditional and modern knowledge about natural resources. The biggest advantage of this approach is synthesizing new and old information. After the plant or natural compound is determined, other processes work similarly with conventional drugs.

Methods: Ethnobotanical papers, thesis and projects in Istanbul University Faculty of Pharmacy Department of Pharmaceutical Botany and databases (PubMed and Google Scholar) have been sought and results were synthesized.

Results: Most of the clinical uses of herbs have been seen similar to their traditional uses. On the other hand, there are some plants on which their clinical uses differ from the traditional uses such as *Borago officinalis, Calendula officinalis* or *Euphorbia peplus*. When the frequency of traditional uses of herbs are compared, *Plantago* species, *Plantago major* and *Plantago lanceolata* are the most used taxa in Turkey, secondly, *Hypericum perforatum* comes. However, *Plantago* species are not of much interest in clinical trials. It is seen that most of the plants in the clinical research are tried for wound healing occuring due to different origins such as cancer, surgery and injury.
Side effects were observed only during the application of *Allium cepa, Cydonia oblonga* and *H. perforatum*.

Conclusions: When clinical trials are evaluated in terms of efficacy and overall results, significant differences and effective results are seen in treatment groups given herbs in comparison with placebo or control groups.

Keywords: Ethnobotany, Skin diseases, Clinical trials, Medicinal plants

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Introduction

Numerous investigations depend on ethnopharmacological approaches have been carried out about medicinal plants and their bioactive compounds via using various different concepts and methods. These multidisciplinary researches concerned with the observation, description and experimental investigations are ranging from anthropology to various fields such as pharmaceutical botany, pharmacognosy, pharmacology, natural product chemistry, toxicology, pharmaceutics, clinical research, and molecular biology [1].

The best known modern drugs such as morphine, codeine, papaverine (*Papaver somniferum* L.), atropin (*Atropa belladonna* L.), quinine (*Cinchona succirubra* Pav), colchicine (*Colchicum autumnale* L.) and digitalis glycosides (*Digitalis purpurea* L.) were discovered at the end of these studies.

As an interesting example, it is also listed in our article, the species of *Euphorbia peplus* L (garden spurge or petty spurge) which is traditionally used for a number of skin problems like warts could be a novel anticancer agent for skin cancers in future [2].

The skin is the largest sensory and contact organ in the human body. It is composed of two layers: the epidermis and the dermis. The skin serves not only to protect the body from the external environment but also to prevent loss of water from the body. The outermost layer of the skin, the stratum corneum, acts as the primary permeability barrier [3].

There are many types of skin conditions that have a tremendous impact on human health and quality of life, including acne, psoriasis, dermatitis, chronic wounds, and infections. The majority of these skin diseases could be treated topically as shown in Table 1, thereby avoiding the potential for systemic side effects [4, 5].

In addition to the above mentioned first-line therapies, there has been a resurgence of the use of ethnobotanical remedies in recent years. Herbal therapies have been tried for the treatment of skin conditions for centuries in the world. Many plants and their extracts have been used traditionally for the management and treatment of various skin disorders. The aim of this paper is to compare the traditional uses of Turkey's wild plants which are used by local people for the treatment of skin disorders with their clinical trials.

Methods

The study consists of two stages, screening of ethnobotanical studies and determination of plants tried in clinical studies for skin problems. In the evaluation, firstly their suitability for traditional use was reviewed in detail. Then, clinical studies were evaluated according to the criteria of *Patient population, Design, and Intervention, Outcomes, Efficacy and Safety/ Tolerability.*

We assessed the significance of the results of clinical trials with p-value ($p < 0.05$ values are significant) and the healing percentage (complete healing is significant). The study includes randomized, non-randomized, double-blinded, single-blinded, non-blinded, and placebo-controlled clinical studies. However, non-randomized and non-blinded studies can give us limited results.

Table 1 Common skin disorders and existing topical treatment options

Skin Disease	Short Description	Topical Treatment
Atopic dermatitis	Atopic dermatitis is the most common type of eczema. It typically begins in childhood and it is a severe, chronic, and pruritic inflammatory skin disease.	Corticosteroids Calcineurin inhibitors Antimicrobials and antibiotics Antihistamines
Psoriasis	Chronic, immune-mediated skin disease that shows red and scaly patches on the skin that itch or burn.	Corticosteroids Retinoids Calcineurin inhibitors Vitamin D analogs
Acne vulgaris	Acne is caused by follicular epidermal hyperproliferation and abnormal sebum production within pilosebaceous units in the skin. The most important pathogens linked to acne-prone skin are *Propionibacterium acnes*, *Staphylococcus aureus* and *Staphylococcus epidermidis*	Antibiotics Benzoyl peroxide Retinoids
Acute and chronic wounds	Wound healing is a complex and dynamic process of replacing devitalized and missing cellular structures and tissue layers. Delayed acute wounds and chronic wounds frequently enter a state of pathologic inflammation due to a postponed, incomplete, or uncoordinated wound healing process.	Silver sulfadiazine Corticosteroids Antiseptics Analgesics Antimicrobials
Fungal infections	Fungal infections can be classified as superficial fungal infections that affect the skin, nails, hair or mucous membranes, and systemic infections affecting the whole body.	Polyenes Azoles Allylamines Benzylamines Morpholines

All documents have been sought on Pubmed and Google Scholar, thesis and projects in IU Faculty of Pharmacy Department of Pharmaceutical Botany.

Results and discussion

A total of 300 medicinal plants belonging to 79 families have been compiled from the research areas in Turkey as shown in Table 2. The family Asteraceae, in the first rank, is the largest family which includes the most species in the world and Turkey. Although the family Lamiaceae, in the second, is not the second largest family in Turkey, it has very important medicinal and aromatic plants in the Mediterranean phytogeographic area.

Considering the species, it could be to evaluate *Plantago* species, *P. major* and *P. lanceolata*, which are first in the most used taxa ranking, as the same plant. Because these species are used with a similar name and in a similar way without distinguishing. Then, *H. perforatum* comes as one of the most used species for skin problems in Turkey.

In the following table, 19 plant species on which their clinical studies are arranged alphabetically. The botanical names are followed by the family names, a Turkish name, traditional uses, and differentiations between clinical and traditional uses of 19 plants as shown in Table 3. In the last part, these clinical studies are summarized as shown in Table 4.

Table 2 Families and species of the plants are compiled from research areas

Total Family	79
Total Species	300
The most frequently families	**Number of species**
Asteraceae	40
Lamiaceae	25
Scrophulariaceae	17
Rosaceae	17
Boraginaceae	11
Euphorbiaceae	11
The most frequently taxa	**Number of studies**
Plantago major L. (Plantaginaceae)	15
Plantago lanceolata L. (Plantaginaceae)	14
Hypericum perforatum L. (Hypericaceae)	11
Malva sylvestris L. (Malvaceae)	9
Malva neglecta Wallr. (Malvaceae)	9
Allium cepa L. (Liliaceae)	7
Allium sativum L. (Liliaceae)	7
Rosa canina L. (Rosaceae)	7
Urtica dioica L. (Urticaceae)	6
Rubus sanctus Schreber (Rosaceae)	6

Especially, when we compare the healing efficacy of herbs or their mixtures considering complete healing response, *p* values, and methods, these could be more effective than others for their special clinical uses of skin disorders: Ankaferd Blood Stopper (*Vitis vinifera, Urtica dioica, Glycyrrhiza glabra, Alpinia officinarum, Thymus vulgaris*), *Calendula officinalis and H. perforatum.* Additionally, we have known that these herbs have been used by Turkish traditional medicine for many years. Unfortunately, all herbs we searched have very limited clinical trials and therefore it is hard to compare and understand their efficacy and side effects for longterm clinical uses [35, 36]. Hence, we propose to increase the number of clinical trials because of these reasons.

The clinical trials of the plants listed in Table 4 are different from each other, that's why the evaluation of these studies was done within some rules. The most important of these rules is the evidence hierarchy, when the data contradict each other. Therefore, the results of the meta-analysis are strongest evidence, when there is any contradiction. However, in some cases, the results of the retrospective studies could be also very important, even though they represent weak evidence [62]. Meta-analysis and randomized controlled trials are at the top of the evidence pyramid, while the case reports and expert opinions are at the bottom of the evidence pyramid. The best evidence is quality, while considering these studies. The quality of evidence increases as it goes from bottom to top [63]. Randomization provides epidemiologically the highest quality data. When randomization is not appropriate for various reasons, researchers may be required to rely on non-randomized studies. In randomized studies, performing blind study is to prevent taking sides. In the single-blind studies, only researchers or patients are not aware of the drug, while both patients and researchers do not know which drug is given to which group in the double-blind studies. These studies are among the valuable studies in the evidence pyramid.

As the technique and technology in the field of medicine advance, research on the use of herbs in diseases may differ over the centuries. For example, *Sambucus ebulus* L. has been used for different ailments including: joint pains, cold, wounds, and infections. Nevertheless, recent evidence has revealed its potential for making attempts at treating cancer and metabolic disorders [64]. This review aimed to provide a comprehensive information of herbs regarding their traditional uses and modern findings which may contribute to the development of novel natural-based therapeutic agents.

Conclusions

Most of the uses of herbs studied in the clinical trials appear to be similar to their traditional uses. Many products prepared from these plants are sold in the market.

Table 3 Traditional uses of the plants for skin problems in Turkey

Scientific name	Vernacular name	Used parts	Uses	Difference between traditional uses and clinical trials	References for traditional uses
Achillea millefolium L. (Asteraceae)	Civanperçemi	Whole plants and leaves	For wounds and inflamed sore	Same	[6]
Alkanna tinctoria L. Tausch (Boraginaceae)	Havacıva	Roots	Skin lesion	Same	[7, 8]
Allium cepa L. (Liliaceae)	Soğan	Bulb	For abscess, wound, panaris, burns and scabies	Same	[6, 9–11]
Allium sativum L. (Liliaceae)	Sarimsak, sarmisak	Bulb	For insect-bite, snake bite, sunstroke, ring-worm, scorpion poison, alopecia, bee sting.	Different (For treatment of venous ulcers in a clinical trial)	[11–14, 9]
Borago officinalis L. (Boraginaceae)	Hodan	Leaves	For wounds and burns	Different (For treatment of atopic dermatitis in clinical trials)	[6]
Calendula officinalis L. (Asteraceae)	Aynı safa	1. Whole plants 2. Aerial parts	For psoriasis For wounds and eczema	Different (For prevention and treatment of radiodermatitis in clinical trials)- -	[6, 15]
Cydonia oblonga (Mill.) (Rosaceae)	Ayva	1. Mature fruits 2. Leaves and seeds 3. Fruit	To treat lip cracks To cure eczema and bed wounds For swelling on women's breasts after nursing	- Same -	[16, 17]
Euphorbia peplus L. (Euphorbiaceae)	Sütleğen	Latex	To cure warts	Different (For treatment of nonmelanoma skin cancers in a clinical trial)	[18]
Ficus carica L. (Moraceae)	İncir ağacı, Yoz incir	1. Latex of fruits 2. Leaves	For warts For callosity, eczema, boils.	Different (For treatment of atopic dermatitis in a clinical trial) -	[19, 20]
Foeniculum vulgare Miller (Apiaceae)	Rezene, Mayasıl otu	1. Fruits 2. First leaves	Inflammation of skin disease For eczema	Different (For treatment of idiopathic hirsutism in clinical trials) -	[7, 21]
H. perforatum L. (Hypericaceae)	Sarı kantaron, kantaron	Whole plants, Aerial parts, Flowers, Leaves	For burns, wounds, ulcers, eczema, fungal infections	Same	[14, 22–25]
Lavandula stoechas L. (Lamiaceae)	Karabas otu, Karabas lavanta çiçeği	1.Flowers 2. Aerial parts	Antiseptic İnflamed wounds	- Same	[26, 27]
Melissa officinalis L. (Lamiaceae)	Oğul, Melisa, Kovan otu, Limon nanesi	1. Leaves 2. Aerial parts (young)	For eczema For acne	Different (For treatment of herpes labialis in a clinical trial) -	[15, 27]
Myrtus communis L. (Myrtaceae)	Mersin	1. Leaves 2. Dried leaves	For hair care For rash	Different (For treatment of acne in a clinical trial) -	[28, 29]
Olea europaea L. (Oleaceae)	Zeytin, Kara zeytin	1. Leaves (in oil) 2. Fruits' oil	For wounds For bruises	- Same	[29, 30]
Pistacia terebinthus (Anacardiaceae)	Menengiç, Çıtımık	1. Leaves 2. Roots 3. Fruits as soup	For antifungal effects For mouth sore Wound healing	- - Same	[12, 18, 31]
Rosmarinus officinalis L. (Lamiaceae)	Biberiye, Kuşdili, Mezar otu, Kirse	1. Seeds 2. Aerial parts	For oily hair For wounds	Different (For prevention of contact dermatitis in a clinical trial) -	[6, 22]
Urtica dioica L. (Urticaceae)	Isırgan, Dalağan, Deli ısırgan, Cızlağan, Gezgezok	1. Leaves 2. Roots 3. Aerial parts 4. Whole plants 5.. Young sprouts	For hair loss For eczema, itches For eczema For eczema, psoriasis, wounds, abscess, itches, dermatophytes For eczema	- Different (For using its hemostatic efficacy in clinical trials) - - -	[28, 14, 32]
Vitis vinifera L. (Vitaceae)	Üzüm, asma	1. Leaves 2. Fruits 3. Shoots	Hemostatic For bruises, sunstroke, abscess, boils For boils	Same - -	[33, 34, 11, 26]

However, there are some plants on which their clinical uses differ from the traditional uses. As shown in Table 3, these are: *A. sativum, Borago officinalis, Calendula officinalis, Euphorbia peplus, Ficus carica, Foeniculum vulgare, Melissa officinalis, Myrtus communis, Rosmarinus officinalis* and *Urtica dioica*.

As evident from Table 4, wound healing is the investigated mostly issue in clinical studies with traditional

Table 4 Clinical trials of the traditional plants used for skin problems in Turkey

Study	Patient population	Inclusion and Exclusion criterias	Design and intervention	Outcomes	Efficacy	Safety/ Tolerability	References
Alkanna tinctoria	$N = 60$	Inclusion: Wounds after removal of the skin graft. Exclusion: Hypersensiti- vity reaction to the topical formulation, diabetes, renal failure, liver failure, malnourish- ment, cancer and hypoalbumi- nemia (serum albumin < 4 g/dl), as well as elderly (age > 60 years) and pregnant patients	RCT, SB, PBO-controlled Groups: *A.tinctoria*: dressing with its root extract ointment 20% PBO: standard dressing (dressing with standart ointments) Follow-up at 4 weeks	Primary: Wound healing Secondary: The percentage change in wound surface area, complete healing, adverse effects	Wound scores (Bates- Jensen wound assessment tool): *A.tinctoria*: Day 0: 25.07 ± 7.24 (p = 0.08) Day 14: 9.97 ± 1.30 (p = 0.001) Day 28: 9.03 ± 0.18 ($p = 0.001$) PBO: Day 0: 25.17 ± 7.42 ($p = 0.08$) Day 14: 20.63 ± 6.64 ($p = 0.001$) Day 28: 11.83 ± 2.77 (p = 0.001) Complete wound healing (Patients with Wound score < 10, n (%)) *A.tinctoria*: Day 14: 15 (50%) (p = 0.001) Day 28: 29 (96.66%) (p = 0.001) PBO: Day 14: 0 (0%) Day 28: 7 (23.3%) (p = 0.001) Statistically significant difference was found between the wound scores of treatment and placebo groups.	No side-effects were noted during the study	[35]
Allium cepa	$N = 90$	Inclusion: Surgical wounds at least 2.5 cm, Asians over 18 years age Exclusion: Wound infections, taking agents that would affect wound healing, comorbidities such as diabetes, contractive skin disorders	RCT Groups: *A.cepa* extract 10% (Contractu-bex®)- 30 persons (twice daily) Silicone gel 10% (Kelo-cort®)- 30 persons (twice daily) No treatment group- 30 persons Follow-up at 12 weeks	Primary: Objective scar assessment Secondary: Subjective scar assessment, subject- reported compliance, adverse effects	A.cepa/ Silicone gel/ No treatment Objective scar assessment (results) Vancouver Scar Scale: 3.8 ± 1.4/ 3.9 ± 1.1/5.4 ± 1.1 (first and second group difference $p = 0.492$ Not significant) Image Panel Scale: 5.2 ± 1.7/ 5.4 ± 1.1/ 6.2 ± 1.3 (first and second group difference $p = 0.331$ Not significant) Subjective scar assessment Body Image Scale: 16.8 ± 3.8/ 16.3 ± 2.3/14.9 ± 1.9 (first and second group difference $p = 0.175$ Not significant) Cosmetic Scale: 15.9 ± 3.6/ 15.7 ± 4.2/13.7 ± 3.0 (first and second group	Patient compliance with the gel: A.cepa/ Silicone gel Excellent: 20(67%), 21(70%) Good: 8(27%),8(27%) Poor: 1(3%), 2(7%) Adverse events with the gel Irritation: 2(7%), 1 (3%) Itching: 1(3%), 0 Erythema and Burning sense: 0	[36]

Table 4 Clinical trials of the traditional plants used for skin problems in Turkey *(Continued)*

Study	Patient population	Inclusion and Exclusion criterias	Design and intervention	Outcomes	Efficacy	Safety/ Tolerability	References
					difference $p = 0.847$ Not significant) Vancouver Scar Scale ($p = 0.003$), Image Panel Scale ($p = 0.017$), Body Image Scale ($p = 0.004$), and Cosmetic Scala ($p = 0.035$) scores were significantly different between two groups and no treatment group. The method of the study is not blinded.		
Allium cepa	$N = 24$	Inclusion: New surgical wounds at least 4 cm Exclusion:-	RCT, DB, split-scar Each scar was divided into two equal portions, and each half was assigned treatment with either onion extract gel or petrolatum. Each product was applied three times daily Treatment up to 8 weeks and evaluation up to 12 weeks	Outcomes: Scar healing	A.cepa extract/ Petrolatum Week 2: Redness: 2.45 ± 0.50/ 2.50 ± 0.44 ($p = 0.9414$) Itchiness: 1.58 ± 0.53/ 1.09 ± 0.38 ($p = 0.2841$) Burning: 0.77 ± 0.34/ 0.85 ± 0.35 ($p = 0.8483$) Pain: 0.68 ± 0.29/ 0.68 ± 0.29 ($p = 4259$) Cosmetic appearance: Same changes 11(%46)- Better 5(21%)/ Better 8(33%)($p = 3654$) Week 12: Redness: 0.29 ± 0.11/ 0.29 ± 0.13 ($p = 0.9142$) Itchiness: 0.86 ± 0.047/0.57 ± 0.027 ($p = 0.4533$) Burning: 0.043 ± 0.02 0.043 ± 0.02 ($p = 1.0000$) Pain: 0.043 ± 0.02/ 0.043 ± 0.02 ($p = 1.0000$) Cosmetic appearance: Same changes 12(%86)- Better 1(7%)/ Better 1(7%) Not significant difference was seen in any value for 12 weeks	No side-effects were noted during the study	[37]
Allium sativum, H. perforatum, Calendula officinalis	$N = 25$	Inclusion: Venous ulcers Exclusion: Ulceration greater than 10 cm2, clinical signs of infection	Non-RCT, Pilot Treatment: Herbadermal® (Dry water extract of *Allii sativi bulbus* (2.7% allicin),	Outcomes: Venous ulcers healing	Ulcer area and healing parameters: Persons: 1–5 / 6–10 / 11–15 / 16–20 / 21–25 Before and after the	No side-effects were noted during the study	[38]

Table 4 Clinical trials of the traditional plants used for skin problems in Turkey *(Continued)*

Study	Patient population	Inclusion and Exclusion criterias	Design and intervention	Outcomes	Efficacy	Safety/ Tolerability	References
		thrombophlebitis; hyperglycemia; kidney disease, or malignancy.	Dry ethanol extract of *Hyperici herba (total flavonoid 3.1%,; hypericin 0.1%)*, Oil extract of Calendulae flos (1:5; total flavonoids 0.02%) and vaseline) Ointment was applied topically 5 times a day over a period of 7 weeks. Follow-up at 7 weeks		study: Pre-treatment: 4.23 / 7.54 / 7.22 / 6.32 / 6.98 Week 1: 3.80/ 7.45/ 7.0 / 6.14 /6.9 Week 3: 3.12/ 6.91/ 6.3/ 5.75/ 5.6 Week 5: 2.76/ 5.76/ 5.8/ 4.0/ 4.1 Week 7: 0.0(%100), 4.7(%37.66), 5.2(%31.03), 2.8(%62.86), 1.8(%76.12) Epithelialization: Average score/ İmprovement % Week 0: 7.43/– Week 1: 4.56/38.56 Week 3: 1.46/80.26 Week 5: 0.46/93.72 Week 7: 0.25/99.10 Ulcer surroundings: Week 0: 7.23/– Week 1: 5.10/ 29.49 Week 3: 3.33/ 53.91 Week 5: 2.93/ 59.44 Week 7: 2.13/ 70.50 Number of patients with isolated bacteria Week 0/1/3/5/7 S.aureus / *P. aeruginosa*: 5/–/5/ –/– S.aureus:15/10/10/ 20/15 P.aeruginosa: 5/15/ 10/5/10 Especially, epithelialization results are significant. But, the method of the study is limited.		
Borago officinalis	*N* = 32	Inclusion: Children with atopic dermatitis Exclusion: The patients with severe symptoms	RCT, DB, PBO-controlled Treatment: Undershirts coated with borage oil (including 498 mg of gamma linolenik asit per 100 g of cotton) PBO: Non-coated undershirts Follow-up at 2 weeks	Outcomes: Changes of clinical symptoms	Changes of scores of the clinical symptoms Treatment group: Week 0: Itch: 1.44 ± 0.51 Erythema: 0.81 ± 0.83 Transepidermal water loss: 10 Week 2: Itch: 0.94 ± 0.57 (p = 0.033) Erythema: 0.31 ± 0.48 (p = 0.033) Transepidermal water loss: 7–7.5 (p = 0.0480) While itching and erythema revealed	No side-effects were noted during the study	[39]

Table 4 Clinical trials of the traditional plants used for skin problems in Turkey *(Continued)*

Study	Patient population	Inclusion and Exclusion criterias	Design and intervention	Outcomes	Efficacy	Safety/ Tolerability	References
					statistically significant differences, papules, erosion, scaling and lichenification revealed in the treatment group. Transepidermal water loss from the back was decreased. PBO group: There were no statistically significant differences in the placebo group for all clinical symptoms. Overall assessments of response by children's parents Treatment group: Improved (75%) PBO: Improved (56.2%) Undershirts coated with borage oil showed better therapeutic response than the non-coated undershirt		
Calendula officinalis	*N* = 41	Inclusion: Patients with diabetic foot ulcers, adequate glycemic control, neuropathic ulcers(0.5–45 cm2), age 18–90 years Exclusion: Active Charcot foot, Cellulitis, osteomyelitis, gangrene, or deep tissue infection, pregnant women, allergy, receiving systemic corticosteroids	Prospective, descriptive Treatment: Hydroglyco-lic 4% flowers extract of *C.officinalis* for twice daily Follow-up at 30 weeks	Outcomes: Ulcers healing	Ulcer area reduction and healing rate: Ulcer area (cm^2): Baseline: 8.68 ± 8.55 Week 30: 0.57 ± 1.68 Healing rate (week 30): Complete healing: 32 (78%) The remaining 9 (22%) achieved an overall reduction in the wound area of 75%. Ulcer types: Baseline- Week 30 Wagner I: 34 (82.9%)- 9 (21.9%) Wagner II 7 (17.1%)- 0 (0.0%) Ulcer microbiology: Baseline- Week 30 Colonized diabetic foot ulcers: 26.8%- 14.6% Infected diabetic foot ulcers: 48.8% 2.4% Ulcer duration (weeks)- Median (range) Baseline: 65.0 Week 30: - Complete healing was seen for 78% of	No side-effects were noted during the study	[40]

Table 4 Clinical trials of the traditional plants used for skin problems in Turkey *(Continued)*

Study	Patient population	Inclusion and Exclusion criterias	Design and intervention	Outcomes	Efficacy	Safety/ Tolerability	References
					patients at the end of study and this rate is high. But, the method of the study is limited.		
Calendula officinalis	*N* = 51	Inclusion: Diagnosed with head and neck cancer and taken radiotherapy, aged over 18 years Exclusion: Tumor wounds in the head and neck, previous history of radiotherapy in the same treatment field, allergy	RCT, DB Treatment: 4% Calendula oil, 1% vitamin A and liquid vaseline. Control: Essential fatty acid - sunflower oil, 1% vitamin A, 0.2% vitamin E and 5% caprylic acid	Primary outcomes: Develop- ment of radioderma- titis, Radiation Therapy Oncology Group Acute Skin Toxicity Grades	Development of radiodermatitis 10th session of radiotherapy: Essential fatty acid(*n* = 27)-Calendula(*n* = 24) 10th session: Grade 0: 24(88.89%)-22(91.67%) Grade 1: 3(11.11%)-2(8.33%) 35th session: Grade 0: 0(0%)-2(22.22%) Grade 1: 4(57.14%)-5(55.56%) Grade 2: 1(14.29%)-0(0%) Grade 3: 2(28.57%)-2(22.22%) Last session: Grade 0: 1(7.69%)-3(21.43%) Grade 1: 6(46.15%)-8(57.14%) Grade 2: 3((23.08%)-1(7.14%) Grade 3: 3(23.08%)-2(14.29%) 30 days after the treatment period Grade 0: 9(90%)-11(91.67%) Grade 1: 0 (0%)-1(8.33%) Grade 2: 1(10%)-0(0%) Calendula showed better therapeutic response than the essential fatty acid, as the proportion of radiodermatitis Grade 2 in the essential fatty acid group is higher than Calendula group.	No side-effects were noted during the study	[41]
Calendula officinalis	*N* = 254	Inclusion: The women, 18 to 75 years of age, with a nonmetastatic breast adenocarcino-ma treated by either lumpectomy or mastectomy with or without adjuvant postoperative chemotherapy or hormonal treatment	Phase III, RCT Treatment: *C.officinalis*((Pommade au Calendula par Digestion) Control: Trolamine	Primary: Prevention of skin toxicity of Radiation Therapy Oncology Group grade 2 or higher Secondary: Assessment of pain, allergy, dermatitis, patient satisfaction, the quantity of the	Skin Toxicity in breast cancer patients treated with postoperative radiotherapy Skin toxicity (grade): Calendula/ Trolamine Breast 0–1: 78(79%)-75(71%) 2–3: 21(21%)-	No side-effects were noted during the study	[42]

Table 4 Clinical trials of the traditional plants used for skin problems in Turkey *(Continued)*

Study	Patient population	Inclusion and Exclusion criterias	Design and intervention	Outcomes	Efficacy	Safety/ Tolerability	References
		Exclusion: Women with bilateral or in situ breast cancer, allergy, pregnant women		agent used.	30(%29) ($p = 0.21$) Submammary fold 0–1: 65(66%)-52(50%) 2–3: 34(34%)-53(50%) ($p = 0.02$) Armpit and tangential area 0–1: 70(72%)-53(52%) 2–3: 27(28%)-48(48%) ($p = 0.004$) Chest wall 0–1:24(89%)-17(79%) 2–3: 3(11%)- 6(26%) ($p = 0.17$) Supraclavicular nodes 0–1: 55(72%)-29(37%) 2–3: 21(28%)-49(63%) ($p < 0.001$) Internal mammary nodes 0–1: 53(86%)-50(74%) 2–3: 9(14%)-18(26%) ($p = 0.09$) Overall 0–1: 74(59%)-47(37%) 2–3: 52(41%)-81(63%) ($p < 0.001$) Calendula is statistically effective for the prevention of acute dermatitis of grade 2 or higher.		
Cydonia oblonga (Quince)	$N = 50$	Inclusion: Skin ulcer caused by punch biopsy Exclusion: History of hypersensitivi-ty to phenytoin, immune suppression (cancer, HIV), autoimmune disorders, malig-nancy, pregnancy. Exclusion:-	RCT, DB Treatment: 5% Quince seed cream Control: 1% phenytoin cream All creams were used to twice a day for 2 weeks	Primary: Healing of ulcers Secondary: Adverse effects	The Mean of Ulcer Size Before and After the Treatments: Phenytoin/ C.oblonga Before: 0.525 ± 0.060/ 0.533 ± 0.090 ($p = 0.740$) Day 3: 0.306 ± 0.041/ 0.170 ± 0.109 ($p = 0.001$) Day 7: 0.161 ± 0.172/ 0.043 ± 0.029 ($p = 0.003$) Day 14: 0.033 ± 0.026/ 0.004 ± 0.005 ($p = 0.001$) Complete healing percentage: Day 3: 0/0 Day 7: 0/%13.6 Day 14: %21.7/ %86.4 Complete healing rate and changes of	Adverse effects Phenytoin/ *C.oblonga*: Burning: 26.1%/ 9.1% Pain: 13%/ 0% Itching: 8.7%/ 13.6% Contact dermatitis: 4.3%/ 0% No complica- ted: 39.1%/ 77.3%	[43]

Table 4 Clinical trials of the traditional plants used for skin problems in Turkey *(Continued)*

Study	Patient population	Inclusion and Exclusion criterias	Design and intervention	Outcomes	Efficacy	Safety/ Tolerability	References
					ulcer size in the treatment group was seen statistically superior to the control group.		
Euphorbia peplus	$N = 36$	Inclusion: Patients with basal cell carcinoma, intraepidermal carcinoma or squamous cell carcinomas	Phase I/II Treatment:100–300 uL of *E. peplus* sap once daily for 3 days	Outcomes: Treatment of Non- melanoma skin cancer	Number of lesions showing complete clinical response, partial clinical response and stable disease (S at 1 month Basal cell carcinoma (no:28): 23(%82)/ 5(18%)/0 İntraepidermal carcinoma(16): 15(94%)/0/1(6%) Squamous cell carcinomas(4): 3(75%)/0/1(25%) Complete response at last follow-up: Basal cell carcinoma: 16(57%) İntraepidermal carcinoma: 12(75%) Squamous cell carcinoma:2(50%) Biopsy histology (no.negative/no. tested) Basal cell carcinoma: 18/20 İntraepidermal carcinoma: 7/8 Squamous cell carcinoma:1/2 Complete healing was seen for the most of the patients	No side-effects were noted during the study	[2]
Ficus carica	$N = 59$	Inclusion: Children with atopic dermatitis Exclusion: Severe atopic dermatitis (Scoring atopic dermatitis index> 50), secondary skin infection, another skin disease, immünodefi- ciency disorder	RCT, DB, PBO Treatment: Fig fruit extract 8% (Melfi cream) Control: Hydrocortisone 1% Pbo: Base cream The patients were instructed to apply their allocated creams twice a day for two weeks.	Primary: Reduction of main symptoms (intensity and pruritus) Secondary: Complete healing, adverse effects	Scoring atopic dermatitis Before/ After Treatment: 33.84 ± 10.05/14.85 ± 8.83 ($p < 0.0001$) Control: 29.53 ± 13.58/ 16.73 ± 9.44 ($p < 0.001$) Pbo: 28.48 ± 10.34/ 34.30 ± 12.61 (Placebo results are failed) Intensity Treatment: 6.75 ± 2.81/ 3.06 ± 1.80 ($p < 0.0001$) Control: 6.28 ± 2.84/ 3.28 ± 1.77 ($p < 0.001$) Pbo: 5.60 ± 2.22/ 6.93 ± 2.89 (Placebo results are failed)	No side-effects were noted during the study	[44]

Table 4 Clinical trials of the traditional plants used for skin problems in Turkey *(Continued)*

Study	Patient population	Inclusion and Exclusion criterias	Design and intervention	Outcomes	Efficacy	Safety/ Tolerability	References
					Pruritus Treatment: 5.31 ± 2.70/1.93 ± 1.91 ($p < 0.0001$) Control:3.50 ± 2.76/ 2.35 ± 1.98 ($p < 0.004$) Pbo: 5.0 ± 2.80/ 5.66 ± 2.92 (Placebo results are failed) Treatment with fig extract had significant efficacy in terms of reducing the Scoring atopic dermatitis index, pruritus and intensity scores in comparison with Hydrocortisone 1.0% ($p < 0.05$).		
Foeniculum vulgare	$N = 38$	Inclusion: Female patients with idiopathic hirsutism localized to the face Exclusion:-	RCT, DB, PBO Treatment: *F. vulgare* (fennel) seed extract 1%, 2% PBO: Vehicle cream The creams were applied twice daily for 12 weeks	Outcomes: Reduction of hair diameters in patients	Baseline characteristics of three study groups Average hair diameter Fennel 1%: 67.5 Fennel 2%: 59.9 Pbo: 55.8 The mean value of reduction of hair diameter Fennel 1%: 7.8% (SD = 3.7) Fennel 2%: 18.3% (SD = 8.3) Pbo: − 0.5% (SD = 2.1) The efficacy of treatment with the fennel extracts is more potent in comparison with the placebo.	No side-effects were noted during the study	[45]
Foeniculum vulgare	$N = 22$	Inclusion: Patients with mild to moderate idiopathic hirsutism limited to face Exclusion: Severe hirsutism, increased serum androgen level.	RCT, DB, PBO Treatment: *F.vulgare* (Fennel) gel 3% PBO: Vehicle cream Follow-up at 24 weeks	Primary: Changes in hair thickness Secondary: Adverse effects	Degree of hirsutism Treatment/PBO Mild:2(9%)/8(40%) Moderate: 20(9%)/ 12(60%) Hair thickness Before/ After Treatment: 97.9 ± 31.5/ 75.6 ± 26.7 ($p < 0.001$) PBO: 92.1 ± 29.5/ 97.0 ± 29.6 (Not significant) The efficacy of treatment with the fennel extracts is more potent in comparison with the placebo.	No side-effects were noted during the study	[46]
Hypericum perforatum	$N = 21$	Inclusion: Patients with subacute atopic	RCT, DB, PBO Treatment: *H.*	Primary:The clinical intensity of	The half-side comparison of skin	In total, 4 adverse events were	[47]

Table 4 Clinical trials of the traditional plants used for skin problems in Turkey *(Continued)*

Study	Patient population	Inclusion and Exclusion criterias	Design and intervention	Outcomes	Efficacy	Safety/ Tolerability	References
		dermatitis (Scoring atopic dermatitis index< 80) Exclusion: İnfectious disease, Severe underlying clinical disease	*perforatum* extract cream (20–25:1; hyperforin content of 1.5%) PBO: Vehicle cream The patients were treated twice daily over a period of four weeks	the skin lesions Secondary: Bacterial colonisation of skin lesions, skin tolerance and cosmetic acceptability of the study medications	lesion intensities (Scoring atopic dermatitis index) Change from baseline: Mean ± SD/ Median [min.; max.]/ 95% CI/ *p*-value Day 7: Treatment: − 3.0 ± 3.1/ −3.0 [− 10.0; 5.0] / [− 5.0; − 2.0]/ ($p = 0.002$) Placebo: − 0.6 ± 1.2/ −0.5 [− 2.0; 2.0]/ [− 2.0; 0.0]/ ($p = 0.002$) Day 14: Treatment: − 4.7 ± 3.3/ −6.0 [− 10.0; 2.0] / [− 7.0; 3.0]/ ($p = 0.016$) Placebo: − 2.1 ± 3.0/ −2.0 [− 10.0; 4.0]/ [− 4.0; 0.0]/ ($p = 0.016$) Day 28: Treatment: − 5.4 ± 4.9/ −6.5 [− 12.0; 5.0] /[− 9.0; − 4.0]/ ($p = 0.022$) Placebo: − 2.3 ± 3.3/ −2.5 [− 8.0; 5.0]/ [− 4.0; − 1.0]/ ($p = 0.022$) Number of CFUs of bacteria in general and of *Staphylococcus aureus* in particular Day 0 Treatment/ PBO 0: 1(5.6%)/ 1(5.6%) 1–10: 4(22.2)/ 7(38.9) 11–20: 4(22.2%)/ 1(5.6%) > 20: 9(50%)/ 9(50%) Day 28: 0: 2(11.1%)/1(5.6%) 1–10: 8(44.4%)/ 5(27.8%) 11–20: 4(22.2%)/ 1(5.6%) > 20: 4(22.2%)/ 11(61.1%) The hypericum-cream was significantly superior to the vehicle according to the scoring atopic dermatitis index ($p < 0.05$).	recorded in 3 patients. None of the adverse events was classified as serious. In all cases, there was an acute episode of atopic dermatitis leading to withdrawal from the study. One patient additionally developed contact eczema; in this instance a relationship with the study medication (hypericum-free vehicle) was considered probable.	
Achillea millefolium, H. perforatum	*N* = 134	Inclusion: Primiparous women with episiotomy wounds, being nulliparous; gestational age of	RCT, PBO, DB Treatment groups: 1- *H. perforatum* ointment (Group 1) 2- *A. millefolium* ointment (Group 2)	Outcomes: Healing of wounds	Group 1(Min/Max/ Median/IQR)- Group 2 (Min/Max/Median/ IQR)- Placebo (Min/ Max/Median/ IQR)- No intervention	No side-effects were noted during the study	[48]

Table 4 Clinical trials of the traditional plants used for skin problems in Turkey *(Continued)*

Study	Patient population	Inclusion and Exclusion criterias	Design and intervention	Outcomes	Efficacy	Safety/ Tolerability	References
		37–42 weeks; having a single fetus; no use of particular medications Exclusion: mismatch between the fetus head and the mother's pelvis in pelvic examination; disorder in the labor progress; manual placenta removal; third and fourth degree perineal rupture	3- Placebo ointments (PBO) 4- Non-inter- vention (NI) The patients were treated twice a day for 10 days		(Min/Max/Median/ IQR) Pain level 2th Day Group 1: 3/ 10/9/2.5- Group 2: 6/10/9/ 2- PBO: 3/ 10/9/2.- NI: 6/10/9/2 ($p = 0.226$) 7th Day Group 1: 0/ 7/4/2.5- Group 2: 3/ 8/6/2- PBO: 1/9/6.5/ 3- NI: 4/9/7/1 ($p < 0.001$) 10th Day Group 1: 0/5/2/2.5- Group 2: 0/6/4/2 - PBO: 0/8/ 5.5/1.2- /NI: 2/8/6/2 ($p < 0.001$) 14th Day Group 1: 0/3/0/1- Group 2: 0/ 5/0/2- PBO: 0/7/3/ 4.25- NI: 0/7/4/3 ($p < 0.001$) Redness 7th Day Group 1: 0/ 8/3/5 Group 2: 0/15/ 5/6- PBO: 0/15/7/ 3.5- NI: 5/15/8/4 ($p < 0.001$) 10th Day Group 1: 0/5/0/0- Group 2: 0/ 8/0/2.5- PBO: 0/12/ 4/5- NI: 0/12/5/ 2 ($p < 0.001$) 14th Day Group 1: 0/0/0/0- Group 2: 0/ 5/0/0- PBO: 0/10/0/ 0.5 - NI: 0/10/04 ($p < 0.001$) Ecchymosis 7th Day Group 1: 0/ 3/0/0- Group 2: 0/3/ 0/0 - PBO: 0/6/0/5- NI: 0/7/0/5 ($p < 0.001$) 10th Day Group 1: 0/0/0/0- Group 2: 0/ 0/0/0- PBO: 0/4/0/0- NI: 0/4/0/0 ($p < 0.041$) Edema 7th Day Group 1: 0/ 5/0/4.5- Group 2: 0/ 10/0/5- PBO: 0/15/5/ 5.5- NI: 0/15/5/3 ($p < 0.001$) 10th Day Group 1: 0/0/0/0- Group 2: 0/ 5/0/0- PBO:0/8/0/1- NI: 0/10/0/5 ($p < 0.001$) 14th Day Group 1:0/ 0/0/0- Group 2: 0// 0/0- PBO: 0/4/0/0- NI: 0/5/0/0 ($p = 0.322$)		

Table 4 Clinical trials of the traditional plants used for skin problems in Turkey *(Continued)*

Study	Patient population	Inclusion and Exclusion criterias	Design and intervention	Outcomes	Efficacy	Safety/ Tolerability	References
					Frequency of wound dehiscence and wound discharge in patients in subject groups Dehiscence 7th Day Group 1: 5(31.3%)- Group 2: 3(18.8%)- PBO: 3(18.8%)- NI:5(31.3%) ($p = 0.807$) 10th Day Group 1: 2(50%)- Group 2: 0(0%)- PBO:0 (0%)- NI: 2(50%) ($p = 0.306$) Discharge 7th Day Group 1: 3(14.3%)- Group 2: 5(23.8%) PBO: 6(28.6%)- NI: 7(33.3%) ($p = 0.655$) 10th Day Group 1: 1(20%)- Group 2: 0(0%)- PBO: 2(40%)- NI: 2(40%) ($p = 0.755$) Almost all results of *H. perforatum* and *A. millefolium* showed significant difference in comparison with placebo and non-intervention except for discharge and dehiscence incidence.		
H. perforatum, Calendula arvensis	N = 24	Inclusion: Surgical wounds from childbirth with caesarean section Exclusion:-	Non-RCT Treatment: A mixture of oily extracts of *H.perfora- tum* 70% and *C. arvensis* 30% Control: Wheat germ oil (320:1000) The two groups were treated twice daily for 16 consecutive days	Outcomes: Healing of surgical wounds, Surface Perimeter Area assessment	Area of surgical wounds before and after treatment with the Hypericum–Calendula oily extract (treated group) Surface Perimeter Area (before-after)/ % wound reduction Mean: 13.58 ± 2.71–8.16 ± 1.40 (%37.6 ± 9.9) Extension of the wound before and after treatment with wheat germ oil (control group) Surface Perimeter Area (before-after)/ % wound reduction Mean: 15.75 ± 2.13 / 12.66 ± 2.49 (%15.83 ± 4.64) The *Hypericum–Calendula* mixture was found superior to the control	No side-effects were noted during the study	[49]

Table 4 Clinical trials of the traditional plants used for skin problems in Turkey *(Continued)*

Study	Patient population	Inclusion and Exclusion criterias	Design and intervention	Outcomes	Efficacy	Safety/ Tolerability	References
					treatment in terms of healing of surgical wounds.		
H. perforatum	$N = 10$	Inclusion: Symmetrical plaque-type psoriasis Exclusion:-	Single-blind, PBO, Pilot study Treatment: *H. perforatum* (5% wt/wt), vaseline (84% wt/wt), propylene glycol (10% wt/wt) and avicel (1% wt/wt) PBO: Vehicle cream -The hypericum ointment was applied to one side of each patient's body and the vehicle to the opposite side twice daily for 4 weeks	Outcomes: Healing of erythema	Mean erythema scores, scaling scores, and thickness scores Before/ After Treatment: Erythema: 2.6 (2.6 ± 0.5)/ 1.1 (1.1 ± 0.74)* Scaling: 2.5 (2.5 ± 0.85)/ 0.7 (0.7 ± 0.48)* Thickness: 2.4 (2.4 ± 0.52)/ 1.1 (1.1 ± 0.74)* PBO: Erythema: 2.6 (2.6 ± 0.7)/ 1.9 (1.9 ± 0.74)* Scaling: 2.4 (2.4 ± 0.52)/ 2.1 (2.1 ± 0.57)* Thickness: 2.1 (2.1 ± 7.4)/ 1.8 (1.8 ± 0.42)* *A statistically significant difference was found between the scores after treatment in placebo and formulated active ointment ($P = 0.01$, $P = 0.004$, $P = 0.04$). But the method of study is limited.	No side-effects were noted during the study	[50]
H. perforatum	$N = 125$	Inclusion: Women with first surgical childbirth, age range 17–35 years Exclusion: Scars from prior abdominal surgery, history of medical and obstetrical problems	RCT, DB Treatment: Oily extract of *H. perforatum* PBO: Vehicle ointment Control: No intervention The two groups were treated three times daily for 16 consecutive days	Outcomes: Healing of wounds	Assessment of the Wound Healing by the REEDA Scale on the 10th Day Postpartum Treatment ($n = 47$)/ Placebo ($n = 42$)/ Control ($n = 34$) Redness: 0.11(0.31)/ 0.36(0.49)/ 0.35(0.49) [$\chi^2 = 9.56$, $p < 0.008$] Edema: 0.06(0.25)/ 0.05(0.21)/ 0.21 (0.41) [$\chi^2 = 6.53$, $p < 0.04$] Ecchymosis: 0.02(0.14)/0.00 (0.00)/ 0.00 (0.00) [$\chi^2 = 1.66$, $p = 0.44$] Discharge: 0.00(0.00)/ 0.20(0.59)/ 0.21(0.54) [$\chi^2 = 7.22$, $p < 0.03$] Approximation: 0.00 (0.00)/ 0.16(0.37)/ 0.03(0.17) [$\chi^2 = 10.45$, $p < 0.005$] REEDA: 0.19(0.50)/ 0.75(1.08)/ 0.79(1.17)	No side-effects were noted during the study	[51]

Table 4 Clinical trials of the traditional plants used for skin problems in Turkey *(Continued)*

Study	Patient population	Inclusion and Exclusion criterias	Design and intervention	Outcomes	Efficacy	Safety/ Tolerability	References
					[$\chi^2 = 10.51$, $p < 0.005$] Assessment of the Hypertrophic Scar by the Vancouver scar scale on the 40th Day Postpartum Treatment ($n = 44$)/ Placebo ($n = 40$)/ Control ($n = 32$) Pigmentation: 1.91(1.05)/ 2.58(0.68)/ 2.62(0.71) [$\chi^2 = 15.72$, $p < 0.0001$] Height: 0.41(0.50)/ 0.73(0.55)/ 0.84(0.37) [$\chi^2 = 15.21$, $p < 0.0001$] Pliability: 0.98(0.63)/ 1.60(0.59)/ 1.84(0.63) [$\chi^2 = 30.03$, $p < 0.0001$] Vascularity: 0.02(0.15)/ 0.15(0.36) 0.16 (0.37) [$\chi^2 = 4.95$, $p = 0.08$] Vancouver: 3.32(1.54)/5.03(1.29)/ 5.50(0.92) [$\chi^2 = 43.23$, $p < 0.0001$] There were significant differences in wound healing and scar formation between treatment with placebo and control groups.		
Lavandula stoechas	$N = 120$	Inclusion: Primiparous women underwent episiotomy Exclusion: Allergy	RCT Treatment: Essential Lavender oil Control: Povidone-iodine The two groups were treated twice daily for 10 consecutive days.	Outcomes: Healing of episiotomy	Comparison of episiotomy healing evaluation in treatment and control groups Control/ Treatment Pain: No pain: 17(28.3%)/ 25(41.7%) Moderate: 25(41.7%)/ 27(45%) Severe: 18(30%)/ 8(13.3%) [$p = 0.063$] Edema: No edema: 36(60%)/ 30(50%) 1–2(cm): 19(15%)/ 16(26.7%) 2>: 7(1.7%)/ 0(0%) [$p = 0.320$] Leaved suture: No: 27(45%)/ 24(40%) 1–3:18(30%)/ 16(26.7%)	No side-effects were noted during the study	[52]

Table 4 Clinical trials of the traditional plants used for skin problems in Turkey *(Continued)*

Study	Patient population	Inclusion and Exclusion criterias	Design and intervention	Outcomes	Efficacy	Safety/ Tolerability	References
					4–6: 15(25%)/ 20(33.3%) [$p = 0.62$] Redness: No: 13(21.7%)/ 31(51.7%) 1–3: 8(13.3%)/ 6(10%) 4–7: 11(18.3%)/ (15 25%) 7>: 28(46.7%)/ 8(13.3%) [$p = 0.001$] Dehiscence: Yes: 26(43.3%)/ 19(31.7%) No: 34(56.7%)/ 41(68.3%) [$p = 0.129$] There was no significant difference between two groups in surgery site complications. However, redness in the lavender group was significantly less than controls ($p < 0.001$).		
Melissa officinalis	$N = 120$	Inclusion: History of recurrent herpes labialis (at least 4 episodes per year), experiences in noticing the typical prodromes (itching, tingling, burning, tautness) Exclusion: -	RCT, DB, PBO Treatment: 1% Lo-701 - dried extract from lemon balm leaves (70:1) PBO: Vehicle cream The two groups were treated four times daily for 5 days	Outcomes: Healing of Herpes labialis	Daily score of herpetic symptoms on day 2 of therapy Treatment: 4.03 ± 0.33 PBO: 4.94 ± 0.40 ($p = 0.042$) Total score of symptoms in both treatment groups over 5 days Treatment: 13.3 ± 0.96 PBO: 14.9 ± 1.24 ($p = 0.16$) Significant difference was seen on day 2 of therapy but the difference on day 5 wasn't statistically significant.	No side-effects were noted during the study	[53]
Myrtus communis (myrtle)	$N = 20$	Inclusion: Women with acne skin Exclusion: Atopy, chronic skin disease, having another acne treatment, taken a medicine which may affect the hormonal system	Non-ran- domized controlled Treatment: Foam cleanser, toner, emulsion, and cream pack including myrtle essential oil Control: Foam cleanser, toner, emulsion, and cream pack without myrtle The two groups were treated twice daily for 6 weeks	Outcomes: Healing of acne skin	The comparison of erythema in groups weekly Treatment/ Control Week 0: 392.5 ± 62.5/ 378.3 ± 47.9 Week 3: 379.5 ± 57.9/ 387.5 ± 68.3 Week 6: 365 ± 48.4/ 386 ± 68.2 ($p = 0.083$) The comparison of sebum in groups weekly Week 0: 7.6 ± 2.7/ 8.7 ± 5.4 Week 3: 6.7 ± 2.4/	No side-effects were noted during the study	[54]

Table 4 Clinical trials of the traditional plants used for skin problems in Turkey *(Continued)*

Study	Patient population	Inclusion and Exclusion criterias	Design and intervention	Outcomes	Efficacy	Safety/ Tolerability	References
					9.5 ± 5.4 Week 6: 5.2 ± 2.7/ 9.2 ± 4.3 ($p = 0.033$) The comparison of desquamation in groups weekly Week 0: 245.2 ± 95.2/ 232.5 ± 101.5 Week 3: 241.9 ± 97.8/ 252.4 ± 97.5 Week 6: 146.3 ± 75.4/ 268.1 ± 96.1 ($p = 0.000$) The comparison of skin microorganism in groups weekly Week 0: 8343.9 ± 3486.6/ 7883.3 ± 2192.8 Week 3: 6436.2 ± 2710.4/ 7555.7 ± 2252.9 Week 6: 5009.4 ± 1863.3/ 7548.1 ± 2426 ($p = 0.009$) The comparison in weekly average of outstanding pores, large pores, and blackheads Myrtle(weeks 0:3:6)/ Control (weeks 0, 3,6) Outstanding pores: 1271.9 ± 677.3: 1080.8 ± 586.7: 907.5 ± 484.6/ 1127.7 ± 905.9: 1132.5(± 799.9): 1146.9(± 853.8) ($p = 0.000$) Large pores: 38.8 ± 46.4: 35.1 ± 44.5: 34.5 ± 43.4 / 30.9 ± 54: 31.2 ± 53.5: 31.9 ± 54 ($p = 0.005$) Blackheads: 649.2 ± 468.2: 508.5 ± 342.4: 287.2 ± 229.8/ 569.5 ± 630.1: 569.5 ± 630.1: 619.1 ± 647.1 ($p = 0.000$) The comparison in the group Korean acne grading scale (0,1,2,3,4): (Mean ± SD) Treatment/ Control Week 0: 1.8 ± 1.0/ 1.6 ± 0.8 Week 6: 0.9 ± 0.9/ 1.5 ± 0.7 ($p = 0.006$) Statistically significant differences were		

Table 4 Clinical trials of the traditional plants used for skin problems in Turkey *(Continued)*

Study	Patient population	Inclusion and Exclusion criterias	Design and intervention	Outcomes	Efficacy	Safety/ Tolerability	References
					seen between the groups for almost all results. But, the method of study is limited.		
Olea europaea	$N = 34$	Inclusion: Patients with diabetic foot ulcer (grade1,2), age of 30–65 years, body mass index of 18 to 35 Exclusion: Foot gangrene, osteomyelit	RCT, DB Treatment: Olive oil Control: Routine care The two groups were treated once daily for 4 weeks	Outcomes: Healing of diabetic foot ulcer	Comparison of ulcer parameters and total ulcer status scores at the baseline and during follow up visits in each group Treatment/ Control Degree: Baseline: 69.0 ± 11.83/ 61.0 ± 17.54 ($p = 0.154$) After 1 week: 79.33 ± 10.15/ 69.33 ± 17.30 ($p = 0.064$) After 2 weeks: 87.33 ± 9.79/ 74.33 ± 17.20 ($p = 0.017$) After 3 weeks: 92.33 ± 9.79/ 80.0 ± 16.47 ($p = 0.019$) After 4 weeks: 96.66 ± 6.17/ 82.66 ± 15.56 ($p = 0.03$) Color: Baseline: 66.0 ± 9.10/ 65.33 ± 12.45 ($p = 0.868$) After 1 week: 84.0 ± 9.85 / 69.0 ± 11.68 ($p = 0.001$) After 2 weeks: 90.0 ± 10.1/ 78.66 ± 14.57 ($p = 0.019$) After 3 weeks 94.66 ± 6.39/ 86.0 ± 11.83 ($p = 0.019$) After 4 weeks 97.33 ± 4.57/ 86.66 ± 12.34 ($p = 0.04$) Surrounding tissues Baseline: 67.0 ± 15.32/ 69.0 ± 11.68 ($p = 0.691$) After 1 week: 81.33 ± 12.31/ 73.33 ± 8.16 ($p = 0.045$) After 2 weeks: 90.33 ± 9.72/ 79.33 ± 12.22 ($p = 0.011$) After 3 weeks: 94.66 ± 6.11/ 83.00 ± 13.33 ($p = 0.005$) After 4 weeks:	No side-effects were noted during the study	[55]

Table 4 Clinical trials of the traditional plants used for skin problems in Turkey *(Continued)*

Study	Patient population	Inclusion and Exclusion criterias	Design and intervention	Outcomes	Efficacy	Safety/ Tolerability	References
					97.33 ± 4.57/ 83.0 ± 13.33 ($p < 0.001$) Drainages Baseline: 86.0 ± 14.54/ 84.0 ± 16.81 ($p = 0.730$) After 1 week: 93.33 ± 9.75/ 87.33 ± 15.33 ($p = 0.212$) After 2 weeks: 97.33 ± 7.03/ 92.66 ± 13.34 ($p = 0.241$) After 3 weeks: 98.86 ± 5.16/ 94.00 ± 10.55 ($p = 0.135$) After 4 weeks 100 ± 00.00/ 96.00 ± 8.28 ($p = 0.072$) Total ulcer status Baseline: 288.00 ± 40.52/ 277.33 ± 35.55 ($p = 0.450$) After 1 week: 342.00 ± 33.63/ 301.67 ± 35.89 ($p = 0.004$) After 2 weeks: 365.00 ± 29.82/ 325.00 ± 43.91 ($p = 0.007$) After 3 weeks: 373.67 ± 37.48 / 43.00 ± 26.20 ($p = 0.056$) After 4 weeks: 391.33 ± 15.05/ 348.00 ± 43.08 ($p = 0.001$) At the end of the study: Complete healing: 73.33%/ 13.3% ($p = 0.003$) Partial healing: 26.7%/ 73.3% Lack of healing: 0%/ 13.3% Statistically significant differences were seen between the groups for the rate of complete ulcer healing at the end of study. Only, in terms of the results of ulcer drainages were not seen differences between the groups.		
Olea europaea, Helianthus	$N = 19$	Inclusion: Volunteers with and without a history of atopic	RCT, SB, Forearm-controlled, cohort study	Outcomes: Effect of Olive and Sunflower Seed	Cohort 1(7 volunteers with a self- reported	Olive oil applied twice daily for 4 weeks (less than a	[56]

Table 4 Clinical trials of the traditional plants used for skin problems in Turkey *(Continued)*

Study	Patient population	Inclusion and Exclusion criterias	Design and intervention	Outcomes	Efficacy	Safety/ Tolerability	References
annuus (Sunflower)		dermatitis Exclusion: Volunteers who were pregnant, breast- feeding, or using prescription immunomodulatory medication in the last 6 months	Group 1: Olive oil (olive oil to the designated one forearm and opposite forearm acted as an untreated control) Group 2: Sunflower seed oil and olive oil (olive oil to one forearm and Sunflower seed oil to the other forearm) The two groups were treated twice daily for 5 weeks	Oil on the Adult Skin Barrier	previous history of atopic dermatitis (no symptoms for 6 months)) Cohort 2 (12 volunteers, 6 with no history of skin disease and 6 with a self-reported previous history of atopic dermatitis (no symptoms for 6 months) Biophysical properties of test sites before and after 4 weeks of treatment Sunflower seed oil (grouped/healthy/ atopic dermatitis): Olive oil (grouped/ healthy/atopic dermatitis) Hydration (capacitance): Difference(%): Sunflower: 115 ± 5.8 ($p = 0.04$) / 112 ± 9.7 ($p = 0.39$)/ 118 ± 7.1 ($p = 0.045$): Olive: 110 ± 4.7($p = 0.07$)/ 112 ± 6.1($p = 0.15$)/ 109 ± 7.8($p = 0.33$) Skin surface-pH Difference(%): Sunflower: 0.01 ± 0.09($p = 0.89$)/ 0.26 ± 0.08($p = 0.02$)/ -0.23 ± 0.09($p =$ 0.06)/ Olive:-0.01 ± 0.09 ($p = 0.88$)/ 0.06 ± 0.13($p = 0.66$)/ − 0.09 ± 0.12($p =$ 0.51) Erythema Difference(%): Sunflower: 100 ± 6.2($p = 0.76$)/ 98 ± 10.7($p = 0.67$)/103 ± 7.3($p = 0.70$)/ Olive: 114 ± 8.1($p = 0.08$)/ 116 ± 10.5($p = 0.17$)/ 112 ± 13.3($p = 0.38$) In contrast to sunflower seed oil, topical treatment with olive oil can damage the skin barrier for patients with atopic dermatitis. Sunflower seed oil, when used in the same way, preserved stratum corneum integrity,	tablespoon- ful) caused a significant reduction in stratum corneum integrity and thickness, failed to impart a significant effect on stratum corneum hydration, and induced mild erythema in volunteers with and without a history of atopic dermatitis.	

Table 4 Clinical trials of the traditional plants used for skin problems in Turkey *(Continued)*

Study	Patient population	Inclusion and Exclusion criterias	Design and intervention	Outcomes	Efficacy	Safety/ Tolerability	References
					did not cause erythema, and improved skin hydration by 12% to 18% in the same volunteers.		
Pistacia terebinthus	*N* = 15	Inclusion: Metastatic colorectal patients who developed skin toxicity while receiving first-line cetuximab in combination with chemotherapy Exclusion:-	Non-ran- domized Treatment:*P. terebinthus* soap The group was treated twice daily for 1 week	Outcomes: Healing of skin toxicity	The features of patients, skin toxicity and response to soap treatment after the 1st week Skin toxicity grades (before-after) Numbers (15 persons): 1: Grade 3 to Grade 1 2: Grade 3 to Grade 1 3: Grade 2 to complete response (CR) 4: Grade 2 to CR 5: Grade 3 to Grade 1 6: Grade 3 to CR 7: Grade 2 to CR 8: Grade 3 to Grade 1 9:Grade 2 to CR 10: Grade 3 to CR 11: Grade 3 to Grade 1 12: Grade 3 to CR 13: Grade 3 to Grade 1 14: Grade 2 to CR 15: Grade 2 to CR Complete response rates in patients with Grade 2 and Grade 3 skin toxicities were 100 and 33%, respectively. In the remaining patients with Grade 3 toxicity the skin toxicity regressed to Grade 1. Significant difference was seen for patients with Grade 2 skin toxicities.	No side-effects were noted during the study	[57]
Rosmarinus officinalis, Calendula officinalis	*N* = 20	Inclusion: Volunteers with healthy skin Exclusion: Severe internal diseases, pregnancy, lactation, and uncertain contraception, dermatological diseases, immunosuppressive therapy	RCT, PBO, SB Treatment groups: 1-Rosemary extract dyed 5% 2-Rosemary extract undyed 5% 3-Marigold extract dyed 5% 4-Marigold extract undyed 5% 5-Faradiol myristic acid	Outcomes: Protective effects in healthy volunteers with experimen- tally induced Sodium-Lauryl-Sulfate Irritant contact dermatitis	Values of the visual score at days 1, 2, 3 and 5 Rosemary-undyed: 0/0.25/0.56/0.69 *** Cortisone: 0/0.44/0.69/0.69 *** Rosemary-dyed: 0/0.38/0.7/ 0.81 *** Marigold-dyed: 0/0.38/0.75/0.81 ***	No side-effects were noted during the study	[58]

Table 4 Clinical trials of the traditional plants used for skin problems in Turkey *(Continued)*

Study	Patient population	Inclusion and Exclusion criterias	Design and intervention	Outcomes	Efficacy	Safety/ Tolerability	References
			ester 5% 6-Faradiol palmitic acid ester 5% 7-Faradiol ester -enriched fraction 5% 8-Hydrocor-tisone 0.25% 9-Base cream DAC ((Deutscher Arzneimittel- Codex) - Ten minutes after application of the irritant, 9 test areas received treatment (parallel treatment).		Marigold-undyed: 0/ 0.38/0.75/0.88 ** FDE-enriched: 0/ 0.44/0.56/0.88 ** FD palmitic acid: 0/0.5/ 0.75/0.94 ** FD myristic acid: 0/ 0.5/ 0.81/1.31 * DAC (vehicle): 0/0.56/0.69/ 1.06 ** Control (untreated): 0/0.88/1.44/ 1.75 Values of the Chromametry at days 2, 3 and 5 Marigold-undyed: 3.07/5.9971.19 ** FDE-enriched: 4.07/ 6.73/1.23 *** Cortisone: 3.79/ 6.17/1.73 *** Rosemary-dyed: 4.40/7.63/2.01 *** Marigold-dyed: 4.14/ 5.90/2.11 *** FD palmitic acid: 4.30/6.34/ 2.17 ** FD myristic acid: 3.88/6.61/2.31 ** Rosemary-undyed: 4.61/6.22/ 2.43 *** DAC (vehicle): 3.44/ 6.34/2.58 *** Control (untreated): 5.07/ 7.30/3.37 Values of the Tewametry at days 2, 3 and 5 Rosemary-dyed: 7.48/11.68/17.13 *** Rosemary-undyed: 6.05/10.76/17.54 ** Marigold-dyed: 7.29/ 12.53/18.55 ** Cortisone: 7.33/12.44/ 19.42 * FDE-enriched: 6.40/ 11.53/19.58 ** FD palmitic acid: 6.94/ 11.99/21.18 * Marigold-undyed: 7.79/14.49/22.02 * FD myristic acid: 7.68/14.72/22.60 * DAC (vehicle): 6.33/ 14.11/20.60 * Control (untreated): 10.86/20.89/31.58 (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ Statistically significant difference was seen between the scores treatment and placebo groups for these results)		
Vitis vinifera, $N = 49$	Inclusion: Patients	RCT, Nonblinded	Outcomes:	Success rate of	No side-effects were	[59]	

Table 4 Clinical trials of the traditional plants used for skin problems in Turkey *(Continued)*

Study	Patient population	Inclusion and Exclusion criterias	Design and intervention	Outcomes	Efficacy	Safety/ Tolerability	References
Urtica dioica, Glycyrrhiza glabra, Alpinia officinarum, Thymus vulgaris		with anterior epistaxis Exclusion: Pregnant, epistaxis after the nasal operation, systemic disease, posterior epistaxis	Treatment: Ankaferd Blood stopper®[*V.vinifera*(0.08 mg/ml), *U.dioica*(0.06 mg/ml), *G.glabra*(0.07 mg/ml), *A.officinarum*(0. 07 mg/ml), *T.vulgaris*(0.05 mg/ml)] Control: Phenylephrine Ankaferd blood stopper and Phenylephrine tampons were applied when bleeding times.	Hemostatic efficacy	ankaferd blood stopper and phenylephrine applications (Number of applications and success rates): 1: Treatment: 15(62.5%), Control: 7(28%) 2: Treatment: 4(16.7%), Control: 9(36.0%) No: Treatment: 5(20.8), Control: 9(36.0) ($p < 0.05$) Success rate of ankaferd blood stopper and phenylephrine compared against bleeding intensity (Bleeding intensity(1,2,3): group (application numbers) and success rates): 1: Treatment (1): 5(100%), Treatment (2): 0(0%), Treatment (unsu): 0(0%), Control(1): 6(85.7%), Control(2): 1(14.3%), Control (unsu): 0(0%) 2: Treatment(1): 5(100%), Treatment(2): 0(0%), Treatment (unsu): 0(0%), Control(1): 1(12.5%), Control(2): 6(75%), Control (unsu): 1(12.5%) 3: Treatment(1): 5(35.7%), Treatment(2): 4(28.6%), Treatment (No): 5(35.7%), Control(1): (0%), Control(2): 2(20%), Control (unsu): 8(80%) Treatment (unsu) and Control (unsu) values indicated unsuccessful rates. Ankaferd blood stopper was seen more effective than phenylephrine at control of anterior epistaxis (79.2 vs. 64%, $p < 0.05$).	noted during the study	
Vitis vinifera, Urtica	$N = 47$	Inclusion: Pediatric patients undergoing	Nonrando- mized, Nonblinded	Outcomes: Blood loss, surgical time	Assessment of hemostasis time,	No side-effects were noted during the	[60]

Table 4 Clinical trials of the traditional plants used for skin problems in Turkey *(Continued)*

Study	Patient population	Inclusion and Exclusion criterias	Design and intervention	Outcomes	Efficacy	Safety/ Tolerability	References
dioica, Glycyrrhiza glabra, Alpinia officinarum, Thymus vulgaris		tonsillectomy Exclusion: Patients with bleeding disorders	Treatment: Ankaferd Blood stopper® Control: Knot-tie technique	and complications	blood loss and number of knot-tie Right tonsil (Treatment)/Left tonsil (Knot-Tie): Operation time (min): 3.19 0.74 / 7.29 2.33 Blood loss (ml): 1.57 2.26/ 14.04 7.23 Knot tie number: 0.006 0.32/ 1.97 1.22 ($p = 0.001$) Statistically significant difference was seen for all results.	study No complica- tions were seen after the study	
Vitis vinifera, Urtica dioica, Glycyrrhiza glabra, Alpinia officinarum, Thymus vulgaris	$N = 630$	Inclusion: Patients undergoing transradial catheterization Exclusion: Sheath diameter different form 6F, age < 18 years, abnormal Barbeau's test before puncture.	RCT, PBO Groups: 1-Ankaferd Blood stopper® 2-Conven- tional Sterile Gauze 3- TR band	Primary: Hemostatic efficacy Secondary: Radial artery occlusion	Treatment/ Conventional sterile gauze/ TR band Radial artery occlusion at the end of hemostasis: 0(0)/ 1(0.49)/ 1(048) ($p = 0.36$) Radial artery occlusion at 24 h follow-up 0(0)/ 1(0.49)/ 1(0.48) ($p = 0.63$) Radial artery occlusion at 30-day follow-up: 0(0)/ 0(0)/ 0(0) ($p = 1.00$) Hematoma: 4(1.98)/ 3(1.47)/ 2(0.97) ($p = 0.70$) Bleeding after device removal: 19(9.40) / 55(26.96)/ 56(27.31) ($p < 0.001$) Statistically significant difference was found for the bleeding results.	No side-effects were noted during the study	[61]

herbs. Because, skin wounds, either acute or chronic, might affect the quality of patients' life significantly. Especially, chronic wounds might be progressive and resistant to treatments. These wounds become chronic because of a number of underlying conditions such as diabetes, vascular disease, and neuropathy [65–67]. Herbs studied clinically for general wound healing are: *Alkanna tinctoria, Allium cepa, H. perforatum, Achillea millefolium/H. perforatum* and *H. perforatum/Calendula arvensis*. Some studies have been also made in specific areas, these are: for episiotomy or caesarean section wounds with *Lavandula stoechas, Achillea millefolium/ H. perforatum* and *H. perforatum/Calendula arvensis* combinations; for undergoing transradial catheterization and tonsillectomy with *Vitis vinifera/Urtica dioica/Glycyrrhiza glabra/Alpinia officinarum/Thymus vulgaris*; for skin ulcer caused by punch biopsy with *Cydonia oblonga*.

Oncology is another important area where clinical studies with herbs have been carried out frequently. Although there is not much direct use of herbs in cancer treatment, they have been generally tried for the side effects of cancer treatment. However, an example of a clinical study can be given as follows, even if it is not used for this purpose in Turkey: *Euphorbia peplus* was tried directly for basal cell carcinoma, intraepidermal carcinoma or squamous cell carcinoma in Phase I/II clinical study [2]. Some herbs, such as the use of

Calendula officinalis for radiotherapy or lumpectomy or mastectomy wounds, have also been tried to prevent skin problems that may develop due to cancer treatment [41, 42]. Another example, *Pistacia terebinthus* was tried in metastatic colorectal patients who developed skin toxicity while receiving first-line cetuximab in combination with chemotherapy [57].

Other skin diseases and plants that have been studied clinically are as follows: for atopic dermatitis: *Borago officinalis, Ficus carica* and *H. perforatum*, for diabetic foot ulcers adequate glycemic control, neuropathic ulcers: *Calendula officinalis* and *Olea europaea;* for epithelialization in venous ulcers: *A. sativum/H. perforatum/ Calendula officinalis* combinations, for protective effects: *Rosmarinus officinalis, Calendula officinalis* or protection mild erythema *Olea europaea/Helianthus annuus,* for anterior epistaxis: *Vitis vinifera/Urtica dioica/Glycyrrhiza glabra/Alpinia officinarum/ Thymus vulgaris*, for idiopathic hirsutism localized to the face: *Foeniculum vulgare*, for symmetrical plaque-type psoriasis: *H. perforatum*, for acne: *M. communis*, for recurrent herpes labialis: *M. officinalis*. In addition, most of these herbs have been found to be statistically effective in their studies as shown in Table 4.

As a result, ethnobotanical studies could have an important role in the discovery of new drugs. Turkish traditional herbs learned from these studies have been used for various diseases locally, but more preclinical and clinical studies are needed to prove the clinical efficacy of these herbs and their compounds.

Abbreviations

DB: Double blind; NI: Non-intervention; PBO: Placebo; RCT: Randomized controlled trial; SB: Single blind

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