Research Journal of Pharmacognosy (RJP) 9(1), 2022: 89–101
Received: 22 July 2021
Accepted: 22 Nov 2021
Published online: 27 Nov 2021
DOI: 10.22127/RJP.2021.291844.1720

Original article

Efficacy of a Topical Herbal Cream Containing Frankincense Oil, Pumpkin Oil and Licorice Aqueous Extract in Patients with Mild-to-Moderate Plaque Psoriasis: a Randomized Clinical Trial

Fatemeh Fadaei[1], Mohammad Hossein Ayati[1], Alireza Firooz[2], Shima Younespour[3], Morteza Abouali[4], Malihe Tabarrai[1], Laila Shirbeigi[1*]

[1]Department of Traditional Medicine, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran.
[2]Center for Research and Training in Skin Diseases and Leprosy, Tehran University of Medical Sciences, Tehran, Iran.
[3]Dentistry Research Institute, Tehran University of Medical Sciences, Tehran, Iran.
[4]Department of Pharmacognosy, Faculty of Pharmacy, Tehran University of Medical Science, Tehran, Iran.

Abstract

Background and objectives: Psoriasis is a prevalent, chronic, and inflammatory disorder with good response rates using novel treatment strategies. However, side effects are a limiting factor in long-time treatment. Recent studies have demonstrated that many natural remedies have fewer side effects and are thus safer options. The aim of this study was to evaluate the efficacy of a novel topical herbal preparation in patients with plaque psoriasis. **Methods:** This randomized, triple-blind, vehicle-controlled, two-arm parallel trial was conducted in patients with mild-to-moderate plaque psoriasis (psoriasis area & severity index= PASI score< 12). We randomized 108 patients in 1:1 ratio to receive *Boswellia*-based cream (containing *Boswellia spp.* ethanolic extract, *Boswellia spp.* oil, *Glycyrrhiza glabra* extract, *Cucurbita pepo* pulp oil) or vehicle cream, both applied as a thin layer on skin lesions twice daily for four weeks. **Results:** Compared with vehicle, the *Boswellia*-based cream group showed greater reduction in mean PASI score from baseline to week two and from week two to week four (both $p<0.001$). After two weeks of therapy, Dermatology Life Quality Index decreased in both groups, but to a greater extent in the intervention group compared with vehicle ($p=0.004$). From week two to week four, this item showed an additional decrease in *Boswellia*-based group compared to vehicle ($p=0.001$). After four weeks of therapy, patients in the *Boswellia*-based group were more satisfied than patients in vehicle group (median score: 8 in *Boswellia*-based group and 5 in vehicle, $p<0.001$). **Conclusions:** The outcomes showed significant alleviation of psoriasis signs and symptoms with this herbal cream.

Keywords: clinical trial; medicinal plants; Persian medicine; psoriasis; topical cream

Citation: Fadaei F, Ayati MH, Firooz A, Younespour S, Abouali M, Tabarrai M, Shirbeigi L. Efficacy of a topical herbal cream containing frankincense oil, pumpkin oil and licorice aqueous extract in patients with mild-to-moderate plaque psoriasis: a randomized clinical trial. Res J Pharmacogn. 2022; 9(1): 89–101.

Introduction

Psoriasis is a prevalent, chronic, recurrent, immune-mediated, noncontagious, and inflammatory dermatological disorder with equal gender distribution [1]. According to the world health organization (WHO) reports, the current worldwide prevalence of psoriasis is estimated to be approximately 125 million cases [2]. This condition is associated with significant psycho-

*Corresponding author: L-shirbeigi@sina.tums.ac.ir

social burden including sunbathing, depression, social embarrassment, and negative effect on quality of life [3]. Plaque psoriasis is the most common form (approximately 90% of all cases), manifesting as round to oval, erythematous occasionally itchy patches, with white-silver scales and periods of relapse, and remission [4]. Bacterial infections, climate, autoimmune dysfunction, and stress, as well as genetics are considered as exacerbating factors, although the underlying immune mechanism is still unclear [5]. Primary treatment strategies include topical corticosteroids, topical immunomodulatory calcineurin inhibitors, vitamin D analogues, tazarotene, coal tar, and photochemotherapy. In severe cases, immunomodulatory drugs and biological agents are used. These systemic therapies have undesirable side effects in long-term [6], limiting their use due to increased predisposition to life-threatening infections [7], and abnormalities in laboratory parameters including increased triglyceride levels and liver enzymes [8].

A cross-sectional study reported a wide range of traditional and complementary medicines used by 94% of psoriatic patients in semi-urban areas due to their availability, affordability, efficacy, and safety [9] while there is a growing trend in using complementary and alternative medicine by psoriatic patients all over the globe [10].

Persian Medicine (PM) is an ancient traditional medicine with a history that dates back to two thousand years ago [11]. "Ghooba", the most similar term for psoriasis in PM literature, is characterized by roughness, desquamation, and redness of the skin with or without itching [12]. According to ancient Persian texts, topical herbal preparations such as Frankincense (*Boswellia* spp.) oil, pumpkin (*Cucurbita pepo* L.) oil and licorice (*Glycyrrhiza glabra* L.) aqueous extract are recommended for management of skin conditions such as psoriasis [13]. Medical use of frankincense has a long history. The anti-inflammatory and anti-psoriatic potential of its compounds has been demonstrated by computational analysis in silico [7]. Several scientific studies have revealed anti-inflammatory potency for topical pumpkin oil on dermatitis and eczema [14]. Bioactive flavonoids isolated from the licorice root have anti-inflammatory, antioxidant, and anti-proliferation activities [15]. We hypothetically supposed that the mentioned herbal combinations can improve plaque psoriasis. This study evaluated the safety and efficacy of a topical *Boswellia*-based cream containing frankincense ethanolic extract, frankincense oil, licorice root extract and pumpkin oil in the treatment of plaque psoriasis.

Material and Methods

Ethical considerations

This clinical trial was registered at the Iranian Registry of Clinical Trials website at 31 December 2018 (IRCT20180804040694N1), followed the principles of the Declaration of Helsinki of 1975, as revised in 1983. The Research Ethics Committee of Tehran University of Medical Sciences (TUMS) reviewed and approved the study protocol (registration ID: IR.TUMS.VCR.REC.1397.523). All of the participants dated and signed a written informed consent form prior to enrollment in the clinical study.

Plant material

The resin of *Boswellia* spp., "Kundur" in Persian language, pulp of *Cucurbita pepo* L., "Kadoo" in Persian, and roots of *Glycyrrhiza glabra*, "Shirin bayan" in Persian, were purchased from a local market of Tehran in December 2018. The plants were identified and registered at the Herbarium of Faculty of Pharmacy, Tehran university of Medical Sciences, with voucher number of: PMP-884, PMP-2629, and PMP-1200, respectively.

Preparation of *Boswellia*-based cream

Boswellia ethanolic extract was prepared by adding 1000 ml ethanol 70% to 100 g powdered *Boswellia* resin. The liquid extract was separated after 48 hours. Extraction was performed three times. The extract was then concentrated under vacuum by rotary evaporator. To prepare frankincense oil, 100 g of the powdered *Boswellia* resin was boiled with 500 mL water and stirred occasionally for 3 hours. After filtering, 250 mL of sesame oil was added, and heating continued until the water evaporated and the oil remained. To prepare pumpkin oil, 500 g of chopped fresh pumpkin was boiled with 3 liters of water. After filtering and adding 1 liter of sesame oil, it was boiled again until the water evaporated, and the pumpkin oil remained. To prepare licorice extract, 100 g of powdered licorice root was boiled with 300 mL of water for 15 min. The obtained extract was then passed

through a filter paper and concentrated by a rotary evaporator. It was then dried at room temperature.

Semisolid formulation (oil in water emulsion cream) was prepared by initially melting span 60 at 50-60 °C, followed by the addition of Tween 80, butylated hydroxy toluene (BHT), pumpkin oil, *Boswellia spp.* ethanolic extract and *Boswellia spp.* Oil.

The aqueous phase along with glycerin, *Glycyrrhiza glabra* extract, ethanol and water were heated at the same temperature as the oil phase. Both phases were mixed slowly with continuous stirring to form a homogenous mixture. Preservatives (including methyl paraben, and propyl paraben) were added in the water phase before mixing.

The vehicle cream was prepared via the same process, without the active ingredients including *Cucurbita pepo* L. pulp oil, *Boswellia spp.* ethanolic extract, *Boswellia spp.* oil and *Glycyrrhiza glabra* aqueous extract.

Quality control tests

Organoleptic characteristics

Observing the smell, color, texture, and homogeneity of cream was performed.

Determination of pH

The cream was diluted with distilled water in the proportions of 1:10 and pH was determined at 25 °C using digital pH meter.

Mechanical stability

To evaluate mechanical stability, 5 gr of the sample was centrifuged at 4800 rpm for 30 min using a centrifuge machine and its stability was evaluated based on "Cosmetics Europe Guidelines on Stability Testing of Cosmetic Products 2004" [16].

Temperature cycle test

A heating/cooling cycle test was performed and the cream was stored in a fridge/oven and temperature was changed, respectively, between 4 and 40 °C every 24 h. Stability tests were carried out as many as 6 cycles. The cream was then observed for phase separation or crystal formation.

Determination of viscosity

The viscosity of the cream was measured by rotational viscometer DV2RV model (Brookfield, USA) room temperature.

Microbial tests

Microbial tests including total aerobic microbial count (TAMC), total yeast and mold count (TYMC) and tests for specific species (*Staphylococcus aureus, Pseudomonas aeruginosa*, total aerobic microbial count, were performed based on United States Pharmacopoeia guideline [17].

Total phenolics content

The total phenolics content was determined according to the method described by Merouane et al. with some modification using Folin-Ciocalteu reagent and gallic acid as the standard [18]. Ten mL methanol 80% was added to 1 g of cream and stirred for 5 minutes. Then the solution was centrifuged and the supernatant was separated. About 100 µL of the supernatant was mixed with 0.75 mL of the Folin–Ciocalteu reagent (diluted 10-fold with deionized water previously) in the test tube. The liquid mixture was allowed to stand for 5 minutes at room temperature. Then 0.75 mL of sodium carbonate (Na_2CO_3) was added and the test tube was shaken gently. After 90 minutes, the absorbance of the mixture was measured using the UV-Vis spectrophotometer at 725 nm. A calibration curve of standard was plotted using gallic acid (range of concentration from 0.01 to 0.05 mg/mL) as the standard references. Total phenolics content was measured as gallic acid equivalents in milligrams per 1g of the cream.

Study design

A randomized, triple-blind, vehicle -controlled, parallel-group study was conducted at the clinic of Center for Research and Training in Skin Diseases and Leprosy (CRTSDL) in Tehran, Iran from January 2019 to May 2020. One hundred and eight participants were randomly [19] assigned in 1:1 ratio to receive *Boswellia*-based cream or vehicle cream twice daily, in the morning and evening, for four weeks. All participants were instructed to use 1 g equal to two Fingertip Units (FTU) of topical cream on affected areas. Also, all patients were evaluated at baseline, week 2 and week 4. Photos of skin lesions were captured with a Nikon COLPIXs 630 camera (Japan) and a sensor accuracy of 12 megapixels during each visit. Compliance was evaluated via text message, email or phone call.

Patient demographics and clinical data including age, sex, occupation, height, weight, body mass index (BMI), disease duration, family history of psoriasis, presence of nail psoriasis, and lesion location were recorded in the case report forms (CRFs). The Psoriasis Area and Severity Index (PASI) score, Physician's Global Assessment (PGA) score, Body Surface Area (BSA) score, Dermatology Life Quality Index (DLQI), pruritus severity scale, and patient satisfaction were assessed both before and 2 weeks after treatment.

Eligibility criteria

Participants were screened for eligibility by a dermatologist.

Inclusion criteria

- Mild-to-moderate psoriasis (PASI score< 12)
- Age range of 18-70
- Involvement of body surface area < 10%

Exclusion criteria

- History of pregnancy and lactation
- Known allergic reaction to components of the study medication
- Guttate, pustular, erythrodermic, or palmoplantar psoriasis or patients with face involvement only
- Patients on medications that aggravate psoriasis such as beta-blockers, anti-malaria drugs, terbinafine, calcium channel blockers, interleukins, and lithium
- Treatment with biologic or immunosuppressive drug, systemic corticosteroids, or phototherapy within the previous four weeks
- Previous treatment with topical corticosteroids within the previous two weeks
- Treatment with herbal drug (oral and topical) within the previous two weeks
- Infectious or malignant lesions in the treatment area

Outcome measurements

Primary outcome measures

The primary outcomes were PASI and DLQI. PASI was rated as follows: "complete response" when the PASI score was 0 at week 4; PASI 75, or a reduction of ≥ 75% in PASI score, PASI 50, or a reduction of ≥ 50% in PASI score, "slight response" when PASI decreased <50% from the baseline visit. If the lesions showed no change at the end of study, "no response" was considered. PASI was used to measure disease severity. More than 50% improvement in the baseline PASI score is currently considered clinically significant [20]. Quality of life of participants was measured using DLQI questionnaire (validated Persian version) before and after intervention [21].

Secondary outcome measures

Body Surface Area (BSA), Physician's Global Assessment (PGA), pruritus severity index, and patient satisfaction were considered as secondary outcomes. BSA was measured with the patient's flat palm and fingers considered approximately equivalent to 1% of the BSA and reported as percentage [22]. PGA score was used to assess disease severity based on erythema, induration, and desquamation ranging from 0 (no evidence) to 5 (severe disease) points [23]. Patient satisfaction after intervention was assessed using Visual Analogue Scale (VAS) ranging from 0 (completely unsatisfied) to 10 (completely satisfied) at 2nd and 4th weeks. Pruritus severity was also evaluated using VAS ranging from 0 (no pruritus) to 10 (very severe pruritus) at baseline, weeks 2 and 4.

Clinical safety was monitored by a clinician via the Common Terminology Criteria for Adverse Event (CTCAE) V5.0 at every therapeutic visit [24]. Participants were asked to report skin reactions following application of cream.

Sample size calculation

A sample size of 45 individuals in each group achieved 80% power in detecting a difference between the group proportions of 0.3. The proportion of patients with PASI improvement (at least 50%) in the *Boswellia* -based cream group was assumed to be 0.2 under the null hypothesis and 0.5 under the alternative hypothesis. The proportion in the vehicle group was 0.2. The significant level of the test is 0.05. Considering a probable 15% dropout rate, 54 patients were required for each group.

Randomization and blinding

In this study, randomly permuted blocks of size 6 were used to assign participants into two study groups (*Boswellia*-based cream and vehicle groups). There were 108 participants in this study and thus, 18 blocks of size 6 were determined [18]. The patients, treating physicians, assessors

and biostatistician were blind to allocation of the participations. The vehicle cream was similar to *Boswellia*-based cream in appearance, consistency, smell, weight and color, and was packed in the same blind tubes. One of the investigators prepared sequentially numbered, sealed, opaque envelopes for allocation of treatment. The physicians, outcome assessors and patients remained unaware of treatment allocation. The codes of *Boswellia*-based cream, and vehicle groups were only revealed after the end of the trial.

Statistical analysis

Data analyses were conducted using the statistical software JMP, Version 7 (SAS Institute Inc., Cary, NC, 1989-2007, USA). All tests were two-sided and $p<.05$ was considered statistically significant. The Kolmogorov–Smirnov was used to examine the normality assumption of continuous variables. Categorical data were summarized as numbers (percentages). Continuous variables were reported as mean±SD or medians with interquartile ranges (25^{th}, 75^{th} percentiles). Independent-t test, Mann-Whitney U-test, Chi-square or Fisher's exact tests were applied to compare study variables between the two groups. Generalized Estimating Equation (GEE) models were applied to examine the association between the type of treatment and changes in PASI, BSA, pruritus score, PGA and DLQI over time. GEE models included two main effects (group and time) and the interaction of these effects. Time points in the analyses included baseline and visits at the end of weeks 2 and 4.

Results and Discussion

The topical herbal cream was formulated for the treatment of plaque psoriasis (Table 1). According to the results, the total phenolic content of the cream was 23.16 mg GAE/g cream. This study recruited 108 eligible patients (54 in each group). Forty-eight patients in *Boswellia* cream and 44 in vehicle groups attended at least one of the therapy sessions after the baseline visit. The process of study enrolment and accomplishment is illustrated in Figure 1. Baseline demographics and clinical characteristics of the two groups are summarized in Table 2. No significant difference was found neither in the demographic factors nor in the clinical characteristics.

PASI: After 4 weeks of therapy, complete clearance of psoriasis was found in 4 patients (8.51%) in *Boswellia* cream group and none in vehicle group. Ten patients (21.28%) in *Boswellia* cream group and none in vehicle group achieved PASI 75 by the end of the study. Twenty-Five patients (53.19%) in *Boswellia* cream group and one (2.44%) in vehicle group achieved PASI 50 by week 4. Twenty-two patients (46.81%) in *Boswellia* cream group and 40 patients (97.56%) in vehicle group experienced slight improvement by the end of the study. No change was observed in lesions in one of the patients of *Boswellia* cream group at the end of intervention (Tables 3 and4).

DLQI: The mean DLQI score decreased significantly from baseline to week 2 in both groups (both $p<0.001$) and continued to decrease up to week 4 ($p<0.001$ in *Boswellia*-based cream group and $p<0.001$ in vehicle group (Table 3 and Figure 2).

BSA: In the *Boswellia*-based cream group, the mean BSA score decreased significantly from baseline to week 4 ($p<0.001$), while the change was not significant over this period for the vehicle group (Table 3).

Pruritus: The mean pruritus score (according to VAS) decreased significantly from baseline to week 2 in both groups ($p<0.001$ in *Boswellia*-based cream group and $p<0.001$ in vehicle group) and reduced further in week 4 ($p<0.001$ in *Boswellia*-based cream group and $p<0.001$ in vehicle group, Tables 3 and 4, Figure 2).

Patients' satisfaction: After two weeks of therapy, the median patient satisfaction score (according to VAS) was 4 (IQR: 4 to 5; range: 0 to 8) in *Boswellia*-based cream group and was 3 (IQR: 2 to 4; range: 1 to 6) in the vehicle group. After 4 weeks of therapy, the median patient satisfaction score was significantly higher in patients treated with *Boswellia*-based cream compared to those treated with vehicle cream (median score: 8 in *Boswellia*-based group and 5 in vehicle, $p<0.001$).

PGA: The mean PGA score reduced significantly from baseline to week 2 in both groups (both $p<0.001$) and reduced further up to week 4 ($p<0.001$ in boswellia group and $p<0.001$ in vehicle group, Tables 3 and 4). Photos of some lesions at baseline and at the end of study are shown in Figure 3.

Adverse events: During the study, skin reactions (rash and severe itching), occurred in two patients, 24 hours after exposure to *Boswellia*-based cream. They were controlled by oral anti-

histamines and temporary discontinuation of the drug. The participants were withdrawn from the study due to unwillingness to continue treatment.

Management of psoriasis is a major topic of investigation in dermatology [25]. A primary alternative to systematic therapies is topical anti-inflammatory agents that instantly alleviate dermal symptoms and are not associated with serious side effects in prolonged or continuous use [26]. The present study attempted to assess the clinical efficacy of a topical herbal formulation, *Boswellia*-based cream versus vehicle in patients with plaque psoriasis. This formula contained *Boswellia spp.* oil, pumpkin oil and licorice aqueous extract. A new proprietary combination, this pharmaceutical preparation was designed based on PM knowledge to improve psoriasis symptoms. Application of topical *Boswellia*-based cream, twice daily for four weeks, resulted in a PASI50 in 53.19% and PASI75 in 21.28% of patients.

Table 1. Composition of *Boswellia*-based cream

No	Ingredients	Quantity for 100 g (%)
	Oil Phase	
1	*Cucurbita pepo* oil	10.0 %
2	*Boswellia spp.* ethanolic extract	5.0 %
3	*Boswellia spp.* oil	10.0%
4	Tween 80	4.5 %
5	Span60	2.5 %
6	BHT	0.2 %
	Aqueous Phase	
7	*Glycyrrhiza glabra* aqueous extract	0.2 %
8	Glycerin	10.0 %
9	Ethanol	10.0 %
10	Methylparaben	0.18 %
11	Propylparaben	0.02%
12	Water	Up to 100%

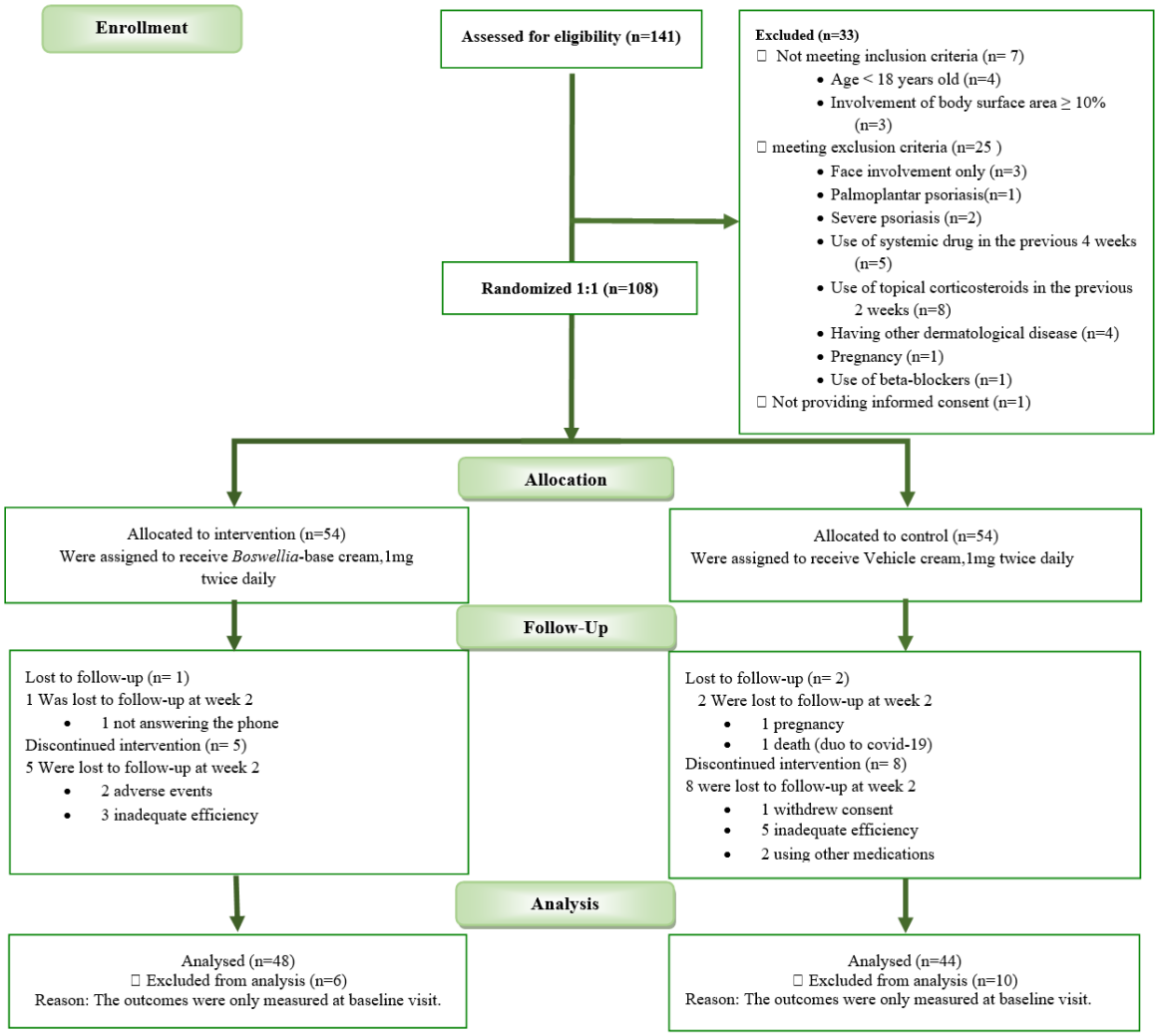

Figure 1. Consort diagram of clinical trial

Table 2. Baseline demographics and clinical characteristics of the two study groups

Characteristic	Vehicle cream (n=54)	*Boswellia* cream (n=54)	p-value
Gender			
Female	26 (48.1%)	28 (51.9%)	0.700 [c]
Male	28 (51.9%)	26 (48.1%)	
Age (mean±SD years)	40.04±11.63	42.28±11.36	0.313 [a]
BMI	26.28 (24.77 to 30.39)	24.94 (23.73 to 28.44)	0.108 [b]
Duration of disease (year)	4 (2 to 7)	5 (3 to 6)	0.681 [b]
Positive family history	4 (7.4%)	8 (14.8%)	0.221 [c]
Nail psoriasis	5 (9.3%)	3 (5.6%)	0.462 [d]
BSA at baseline	2 (2 to 3)	2 (2 to 3)	0.649 [b]
BSA categories[€] at baseline			
< 3%	28 (51.9%)	32 (59.3%)	0.600 [c]
3% to 10%	26 (48.1%)	22 (40.7%)	
> 10%	0 (0.0%)	0 (0.0%)	
PASI at baseline	3.6 (2.6 to 4.8)	3.6 (2.4 to 4.8)	0.663 [b]
PASI categories[£] at baseline			
<10	54 (100.0%)	54 (100.0%)	NA
≥10	0	0	
PGA at baseline	3 (2 to 3)	2.5 (2 to 3)	0.374 [b]
Pruritus at baseline	8 (5 to 10)	8 (5 to 9)	0.709 [b]
Pruritus* at baseline			
0	2 (3.7%)	0 (0.0%)	0.198 [c]
1 to 3	5 (9.3%)	8 (14.8%)	
4 to 6	16 (29.6%)	12 (22.2%)	
7 to 8	12 (22.2%)	20 (37.0%)	
9 to 10	19 (35.2%)	14 (25.9%)	
DLQI at baseline	11 (5 to 12)	11 (6 to 15)	0.376 [b]
DLQI categories[#] at baseline			
0 to 1	1 (1.9%)	1 (1.9%)	0.890 [c]
2 to 5	14 (25.9%)	10 (18.5%)	
6 to 10	11 (20.4%)	13 (24.1%)	
11 to 20	23 (42.6%)	26 (48.1%)	
21 to 30	5 (9.3%)	4 (7.4%)	

a: independent t-test; b: Mann-Whitney U test; c: Chi-Square; d: Fisher's Exact; Values are expressed as no. (%) or median (25^{th} percentile to 75^{th} percentile) (minimum to maximum) unless otherwise stated; BSA: body surface area; PASI: psoriasis area and severity index; PGA: physician global assessment; DLQI: dermatology life quality index; £, interpretation of the PASI: <10: mild and ≥10: moderate-to-severe; *: pruritus was measured according to Visual Analogue Scale (VAS), interpretation of the scores: 0: no pruritus; 1 to 3: mild; 4 to 6: moderate; 7 to 8: severe; 9 to 10: very severe; #, the higher the score, the more quality of life is impaired. interpretation of DLQI: 0 to 1: no effect at all; 2 to 5: small; 6 to 10: moderate; 11 to 20: very large; and 21 to 30: extremely large effect on patient's life

Table 3. PASI, BSA, Pruritus score, PGA and DLQI over time between two groups

Outcomes	Therapy visits			p-value*
	Baseline	Week 2	Week 4	
PASI				<0.001
Boswellia group[£#¥]	3.769±0.290	2.979±0.269	2.175±0.268	
Vehicle group[£#¥]	3.868±0.261	3.477±0.252	3.221±0.254	
BSA				<0.001
Boswellia group[¥]	2.958±0.304	-	2.265±0.295	
Vehicle group	2.841±0.261	-	2.818±0.263	
Pruritus				0.040
Boswellia group[£#¥]	6.875±0.372	4.958±0.333	2.914±0.350	
Vehicle group[£#¥]	7.000±0.435	5.546±0.342	4.201±0.359	
PGA				<0.001
Boswellia group[£#¥]	2.362±0.083	1.835±0.987	1.335±0.122	
Vehicle group[£#¥]	2.439±0.100	2.130±0.108	1.966±0.097	
DLQI				0.002
Boswellia group[£#¥]	11.208±0.833	8.750±0.718	5.846±0.650	
Vehicle group[£#¥]	10.591±0.854	9.250±0.790	7.576±0.770	

The values are expressed as estimated mean (SE); PASI: psoriasis area and severity index; PGA: physician global assessment; BSA: body surface area; DLQI: dermatology life quality index; Pruritus was measured according to Visual Analogue Scale (VAS); *: the p-value for group×time interaction (based on the results of GEE analysis); £: $p< 0.05$ for statistical difference from baseline to week 2 within the group; #: $p< 0.05$ for statistical difference from week 2 to week 4 within the group; ¥: $p< 0.05$ for statistical difference from baseline to week 4 within the group

Table 4. Bonferroni-corrected pairwise comparisons following GEE analysis

Outcome	*Boswellia* -based cream group		Vehicle group		Difference (*Boswellia* -based cream group minus vehicle group)	
	Mean (95% CI)	**P-value**	**Mean (95% CI)**	**P-value**	**Mean (95% CI)**	**p-value***
PASI						
Week 2 minus Week 0	-0.790 (-1.010 to -0.571)	<0.001	-0.391 (-0.487 to -0.295)	<0.001	-0.399 (-0.558 to -0.239)	<0.001
Week 4 minus Week 0	-1.594 (-2.015 to -1.173)	<0.001	-0.647 (-0.786 to -0.508)	<0.001	-0.947 (-1.243 to -0.651)	<0.001
Week 4 minus Week 2	-0.804 (-1.063 to -0.545)	<0.001	-0.256 (-0.374 to -0.138)	<0.001	-0.548 (-0.738 to -0.358)	<0.001
BSA						
Week 2 minusWeek 0	-	-	-	-	-	-
Week 4 minus Week 0	-0.694 (-0.943 to -0.444)	<0.001	-0.023 (-0.065 to -0.020)	0.94	-0.671 (-0.859 to -0.483)	<0.001
Week 4 minus Week 2	-	-	-	-	-	-
Pruritus						
Week 2 minus Week 0	-1.917 (-2.515 to -1.319)	<0.001	-1.454 (-2.084 to -0.826)	<0.001	-0.462 (-1.042 to -0.117)	0.120
Week 4 minus Week 0	-3.961 (-4.777 to -3.145)	<0.001	-2.800 (-3.940 to -1.658)	<0.001	-1.162 (-2.099 to -0.225)	0.020
Week 4 minus Week 2	-2.045 (-2.577 to -1.512)	<0.001	-1.345 (-2.000 to -0.690)	<0.001	-0.700 (-1.264 to -1.136)	0.020
PGA						
Week 2 minus Week 0	-0.527 (-0.671 to -0.384)	<0.001	-0.309 (-0.382 to -0.239)	<0.001	-0.218 (-0.326 to -0.110)	<0.001
Week 4 minus Week 0	-1.028 (-1.267 to -0.789)	<0.001	-0.472 (-0.563 to -0.382)	<0.001	-0.555 (-0.726 to -0.384)	<0.001
Week 4 minus Week 2	-0.500 (-0.639 to -0.362)	<0.001	-0.163 (-0.246 to -0.806)	<0.001	-0.337 (-0.445 to -0.229)	<0.001
DLQI						
Week 2 minus Week 0	-2.458 (-3.365 to -1.552)	<0.001	-1.341 (-2.080 to -0.674)	<0.001	-1.117 (-1.869 to -0.366)	0.004
Week 4 minus Week 0	-5.362 (-7.006 to -3.718)	<0.001	-3.015 (-4.050 to -1.979)	<0.001	-2.347 (-3.645 to -1.050)	<0.001
Week 4 minus Week 2	-2.904 (-3.872 to -1.936)	<0.001	-1.674 (-2.248 to -1.100)	<0.001	-1.230 (-1.981 to -0.479)	0.001

PASI: psoriasis area and severity index; PGA: physician global assessment; BSA: body surface area; DLQI: dermatology life quality index; GEE: generalized estimating equations; Pruritus was measured according to Visual Analogue Scale (VAS). *: P-values from contrasts of *Boswellia*-based cream group versus vehicle group in a generalized estimating equations model of outcome as a function of group, time and group×time

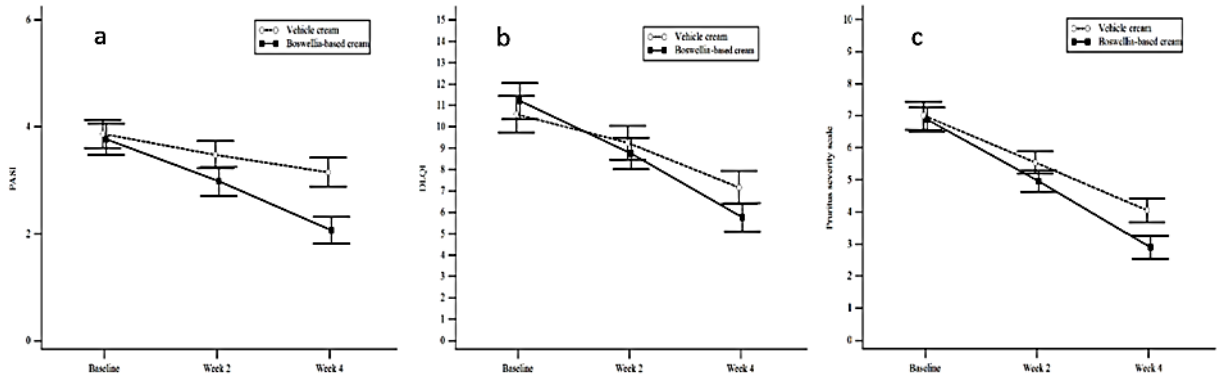

Figure 2. (a): Mean PASI, (b): DLQI, (c): Pruritus severity scale (with SE error bars) over time between *Boswellia*- based cream and vehicle cream

Herbal preparations have been used to manage psoriatic lesions. Fioranelli et al. studied the effects of an herbal complex on chronic plaque psoriasis in children and adults. In their trial, 16.6% in the treatment group achieved PASI 75, while PASI 50 was seen in 40% [27]. The disadvantages of the study by Fioranelli as compared to our study were the low number of participants and lack of a control group.

Psoriasis is a common immune-mediated disorder, with increased inflammatory mediators and epidermal hyperplasia in skin lesions [4]. Pathogenesis pathways of this disease are known to involve production of pro-inflammatory cytokines such as TNF-α, IL-17A, and IL-12/23 immune axis [28], Nuclear Factor-κB (NF-κB) and interleukin-1β (IL-1β) [29], activation of proliferation of keratinocytes, and also activation of T cells [30].

There are a few studies on the effects of the ingredients of our formulation on psoriasis patients; however, there is evidence in favor of their use. Regarding frankincense, mounting evidence have shown that in addition to downregulating inflammatory processes, it also plays an inhibitory role in cell proliferation [31]. A placebo-controlled, double-blind, randomized trial by Togni et al. demonstrated a *Boswellia serrata* based topical cream, used twice a day for 30 days in psoriatic patients, to be an efficient anti-inflammatory formula in improving scales and erythema [32].

Frankincense properties can be related to its active biological derivatives including boswellic acids, diterpenoids and triterpenoids [7] that are recently reported as excellent pharmacological agents against chronic and inflammatory diseases including psoriasis [31]. Molecular mechanisms of boswellic acid from gum resin of *Boswellia* include reduction in inflammatory mediators like leukotriene synthesis via 5-lipoxygenase (5-LO) [33], suppression of TNF-α [34], inhibition of IL-12, IL-23 [35], NF-κB and IL-1β secretion and expression, [29] reduction in T helper 17 cell (Th17) differentiation [36], inhibition of keratinocyte hyperproliferation [37], and also T-cell suppression [33].

Pharmacological studies have shown that pumpkin pulp contains high amounts of polysaccharides, proteins, vitamins (carotenoids, vit E) and minerals (like zinc, Fe, Cu, Ca). It has been used as an antiseptic, anti-eczematous, antidermatitic, antitoxic, and antipyretic agent [38]. Moreover, it has skin nourishing and hydrating properties, and can thus, promote skin barrier function, which is impaired in psoriatic patients [39]. Humectants decrease skin dryness and relieve itching in long-term [25], and this can be considered as a beneficial agent in *Boswellia* cream.

A double-blind clinical study was conducted to investigate the effect of a pumpkin ointment with topical almond and Eucerin, on eczema. This intervention showed good anti-inflammatory effects of pumpkin and significantly reduced hand eczema severity index scores without any side effects [14].

Moreover, in a 2020, randomized clinical trial, Kolahdooz et al. demonstrated topical chamomile-pumpkin oleogel to be safe and effective in treating mild-to-moderate plaque psoriasis [40].

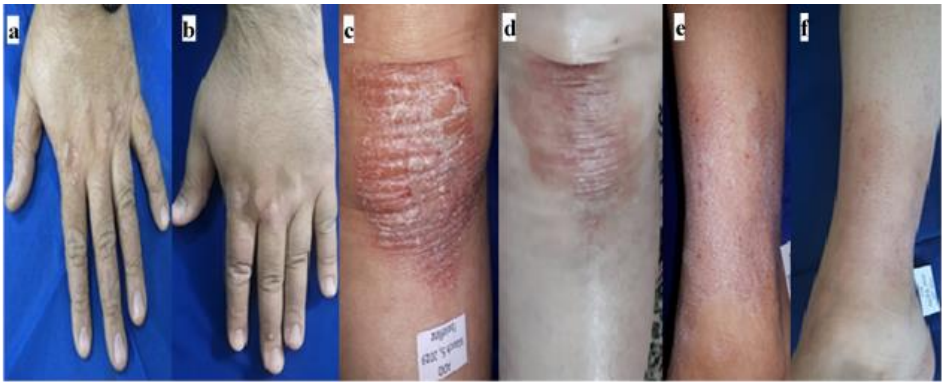

Figure 3. Digital photographs of two psoriasis patients before (a, c and e) and after 4 weeks of treatment with *Boswellia* cream (b, d and f); a and b: a 37-year-old male patient; c and d: a 58-year-old female patient; e and f: a 18-year-old female patient

Increasing evidence shows that *Glycyrrhiza glabra* exerts anti-inflammatory, antiviral, antioxidant, anticarcinogenic, antiulcer, and also immunomodulatory activities, due to the presence of bioactive derivatives such as glycyrrhetic acid, glycyrrhizin, saponins, triterpenes, and flavonoids compounds [41]. The anti-inflammatory effects of licorice were investigated in a double-blind clinical study by Saeedi et al. which demonstrated that topical licorice gels, applied three times a day for two weeks, significantly reduced atopic dermatitis [42].

Sesame oil (common vehicle in Persian Medicine formulas) has anti-inflammatory, anti-proliferative, and anti-oxidant activities [40]. It appears to improve the effects of frankincense.

Overall, experimental studies on the ingredients of our formulation, namely *Boswellia spp.*, *Cucurbita pepo L.*, and *Glycyrrhiza glabra* show that they possess anti-inflammatory, anti-proliferative, tissue-repairing, skin-moisturizing, and other properties of relevance in management of psoriasis.

In terms of side effects, *Boswellia spp.* is listed in substances generally recognized as safe (GRAS), and is approved by the Food and Drug Administration (FDA) as a food additive, although mild toxicity has been detected on human skin [43]. Licorice (or 'liquorice') root extract, pumpkin and their derivate are also listed as GRAS and are FDA-approved [44]. No side effects have been reported in topical use of licorice [5]. Moreover, the safety of sesame seed oil is specifically confirmed as a vehicle in cosmetic products [46].

The evidence discussed above suggests that our compound formulation can act as an anti-inflammatory, antiproliferative, and immunomodulatory agent and can thus be beneficent in management of psoriasis.

We acknowledge that the present research had some limitations including lack of comparing the intervention with a conventional topical anti-psoriatic treatment (e.g., corticosteroids) and not performing follow-up in long-term.

To summarize, four weeks of treatment with *Boswellia*-based cream significantly decreased psoriatic scales (vs. vehicle), and thus improved the quality of life in participants of this study. These results confirmed similar findings from other double-blind vehicle-controlled clinical studies, which reported a significant effect of topical therapy in plaque psoriasis.

Conclusion

According to the results of this study, topical herbal preparation containing *Boswellia spp.* oil, pumpkin oil and licorice aqueous extract can be beneficial in reducing PASI score and enhancing the quality of life in mild-to-moderate plaque psoriasis. The burden of this prevalent dermatologic disorder can be reduced by low-cost, convenient, and safe treatment methods with minimum side effects, including topical herbal treatments. The formula studied in this trial, was based on a PM approach to treat psoriasis. The authors suggest that future investigations be designed to study the effects of this cream or its ingredients in comparison with conventional therapies.

Acknowledgments

The authors thank the individuals who participated in this study. We are also grateful to the doctors who participated in this study. this assistance was funded by Tehran University of Medical Sciences in Iran.

Author contributions

Fatemeh Fadaei was involved in study design, data acquisition, and manuscript preparation; Laila Shirbeigi participated in study design, patient recruitment and selection, review and revision of the manuscript; Mohammad Hossein Ayati contributed in the study design, critical review and revision of the manuscript; Alireza Firooz was involved in patient recruitment and selection and data interpretation; Shima younespour participated in data analysis and data interpretation, review and revision of the manuscript; MaliheTabraei was involved in patient recruitment and selection; Morteza Abouali formulated the medication. All authors read the final version of the article and approved it.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

References

[1] Dinulos JG. Habif' clinical dermatology e-book, a color guide to diagnosis and therapy. 7th ed. Edinburgh: Elsevier Health Sciences, 2020.

[2] Yang CC, Yen YY, Hsu CK, Cheng NY, Tzeng SY, Chou SJ, Chang JM, Tseng SH. Investigation of water bonding status of normal and psoriatic skin in vivo using diffuse reflectance spectroscopy. *Sci Rep*. 2021; 11(1): 1–10.

[3] Lin W, Yu Q, Qin Y, Xiao J, Peng L, Zhang J, He J, Xiang H, Xiao M, Chen M. Safety and efficacy of Chinese herbal bath for psoriasis vulgaris: a protocol for systematic review and meta-analysis. *Medicine*. 2020; 99(21): Article ID 7249964.

[4] Kang S. Fitzpatrick's dermatology. 9th ed. New York: McGraw-Hill Education, 2019.

[5] Qiu J, Yuan Y, Li Y, Haley C, Mui UN, Swali R, Mohan C, Tianfu WU. Discovery of IgG4 anti-gliadin autoantibody as a potential biomarker of psoriasis using an autoantigen array. *Proteomics Clin Appl.* 2020; Article ID 31671471.

[6] Ramanunny AK, Wadhwa S, Singh SK, Sharma DS, Khursheed R, Awasthi A. Treatment strategies against psoriasis. principle, perspectives and practices. *Curr Drug Deliv*. 2020; 17(1): 52–73.

[7] Halim SA, Khan A, Csuk R, Al-Rawahi A, Al-Harrasi A. Diterpenoids and triterpenoids from frankincense are excellent anti-psoriatic agents. an in silico approach. *Front Chem.* 2020; Article ID 32671018.

[8] Hoffmann JH, Knoop C, Enk AH, Hadaschik EN. Routine laboratory parameter dynamics and laboratory adverse events in psoriasis patients on long-term treatment with adalimumab, etanercept, and ustekinumab. *Acta Derm Venereol*. 2017; 97(6): 705–710.

[9] Aina O, Gautam L, Simkhada P, Hall S. Prevalence, determinants and knowledge about herbal medicine and non-hospital utilisation in southwest Nigeria. a cross-sectional study. *BMJ Open*. 2020; Article ID 8662215406.

[10] Wang D, Lu C, Yu J, Zhang M, Zhu W, Gu J. Chinese medicine for psoriasis vulgaris based on syndrome pattern: a network pharmacological study. *Evidence-Based Complement Altern Med*. 2020; Article ID 5239854

[11] Rezaeizadeh H, Alizadeh M, Naseri M, Shams AM. The traditional Iranian medicine point of view on health and disease. *Iran J Public Health*: 2009; 38(S1):169–172.

[12] Atyabi A, Shirbeigi L, Eghbalian F. Psoriasis and topical Iranian traditional medicine. *Iranian J Med Sci*. 2016; Article ID 27840520.

[13] Aghili Shirazi MH. Moalejat-e Aghili. Tehran: Institute of Medical History, Islamic Medicine and Complementary Medicine, 2008.

[14] Khademi A, Mansuri P, Pahlevan D, Bozorgi M, Nasiri M, Hejazi S, Azizian Z, Shirbeigi L . Efficacy of pumpkin ointment in treatment of chronic hand eczema. a randomized, active-controlled, double blind clinical trial. *Iran J Public Health*. 2020; 49(7): 1339–1347.

[15] Hsu YW, Chen HY, Chiang YF, Chang LC, Lin PH, Hsia SM. The effects of isoliquiritigenin on endometriosis in vivo and in vitro study. *Phytomedicine*. 2020; Article ID 153214.

[16] Cosmetics Europe, the personal care association, the cosmetic, toiletry, fragrance association. Guidelines on stability testing of cosmetic products, 2004. Brussels: COLIPA Guidelines, 2004.

[17] United States Pharmacopeial Convention. United States Pharmacopeia. Microbiological examination of nonsterile products: microbial enumeration tests. Rockville: United States Pharmacopeia, 2019.

[18] Merouane A, Noui A, Medjahed H, Nedjari Benhadj Ali K, Saadi A. Antioxidant activity of the phenolic compounds of olive oil extracted by traditional methods. *Int J Biol Chem Sci*. 2014; 8(4): 1865–1870.

[19] Fleiss JL. Design and analysis of clinical experiments. New York: John Wiley & Sons, 2011.

[20] Carlin CS, Feldman SR, Krueger JG, Menter A, Krueger GG. A 50% reduction in the psoriasis area and severity index (PASI 50) is a clinically significant endpoint in the assessment of psoriasis. *J Am Acad Dermatol.* 2004; 50(6): 859–866.

[21] Finally AY. Quality-of-life issues and economic burden of psoriasis and atopic dermatitis. *Clin Drug Investig.* 1995; 10(1): 1–6.

[22] Imafuku S, Zheng M, Tada Y, Zhang X, Theng C, Thevarajah S, Zhao Y, Song H. Asian consensus on assessment and management of mild to moderate plaque psoriasis with topical therapy. *J Dermatol.* 2018; 45(7): 805–811.

[23] Shikiar R, Bresnahan BW, Stone SP, Thompson C, Koo J, Revicki DA. Validity and reliability of patient reported outcomes used in psoriasis: results from two randomized clinical trials. *Health Qual Life Outcomes*. 2003; 1(1): 1–9.

[24] National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). [Accessed 2019]. Available from https://ctep.cancer.gov/protocoldevelopment/ electronic.

[25] Song B, Song R, Cheng M, Chu H, Yan F, Wang Y. Preparation of calcipotriol emulsion using bacterial exopolysaccharides as emulsifier for percutaneous treatment of psoriasis vulgaris. *Int J Mol Sci*. 2020; Article ID 31861934.

[26] Samarasekera EJ, Sawyer L, Wonderling D, Tucker R, Smith CH. Topical therapies for the treatment of plaque psoriasis: systematic review and network meta-analyses. *Br J Dermatol*. 2013; 168(5): 954–967.

[27] Fioranelli M, Hercogová J, Gianfaldoni S, Chokoeva AA, Tchernev G, Wollina U, Tirant M, Roccia MG, Franca K, Lotti T. Clinical evaluation of the effectiveness of Dr Michaels® (also branded as Soratinex®) products in the topical treatment of patients with plaque psoriasis. *J Biol Regul Homeost Agents*. 2016; 30(3): 29–34.

[28] Mease PJ, Rahman P, Gottlieb AB, Kollmeier AP, Hsia EC, Xu XL, Xu XL, Sheng Sh, Agarwal P, Zhou B, Mclnnes LB. Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2). a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet*. 2020; Article ID 41553.

[29] Goldminz A, Au S, Kim N, Gottlieb A, Lizzul P. NF-κB: an essential transcription factor in psoriasis. *J Dermatol Sci*. 2013; 69(2): 89–94.

[30] Zimmermann-Klemd AM, Reinhardt JK, Nilsu T, Morath A, Falanga CM, Schamel WW, Huber R, Hamburger M, Grundemann C. *Boswellia carteri* extract and 3-O-acetyl-alpha-boswellic acid suppress T cell function. *Fitoterapia*. 2020; Article ID 32712132.

[31] Efferth T, Oesch F. Anti-inflammatory and anti-cancer activities of frankincense. Targets, treatments and toxicities. *Sem Cancer Biol.* In press.

[32] Togni S, Maramaldi G, Di Pierro F, Biondi M. A cosmeceutical formulation based on boswellic acids for the treatment of erythematous eczema and psoriasis. *Clin Cosmet Investig Dermatol.* 2014; Article ID 25419153

[33] Siddiqui M. *Boswellia serrata*, a potential antiinflammatory agent: an overview. *Indian J Pharm Sci.* 2011; 73(3): 255–261.

[34] Al-Harrasi A, Hussain H, Csuk R, Khan HY. Chemistry and bioactivity of boswellic acids and other terpenoids of the genus *Boswelli*a. Amsterdam: Elsevier, 2018.

[35] Wang MX, Zhao JX, Meng YJ, Di TT, Xu XL, Xie XJ, Lin Y, Zhang L, Wang N, Wang Y. Acetyl-11-keto-β-boswellic acid inhibits the secretion of cytokines by dendritic cells via the TLR7/8 pathway in an imiquimod-induced psoriasis mouse model and in vitro. *Life Sci*. 2018; 207: 90–104.

[36] Stürner KH, Verse N, Yousef S, Martin R, Sospedra M. Boswellic acids reduce T h17 differentiation via blockade of IL-1β-mediated IRAK 1 signaling. *Eur J Immunol.* 2014; 44(4): 1200–1212.

[37] Bai J, Gao Y, Chen L, Yin Q, Lou F, Wang Z, Xu Z, Zhou H, Niu L, Lu Sh, Wang H. Identification of a natural inhibitor of methionine adenosyltransferase 2A regulating one-carbon metabolism in keratinocytes. *EBioMedicine*. 2019; 39: 575–590.

[38] Salehi B, Capanoglu E, Adrar N, Catalkaya G, Shaheen S, Jaffer M, Giri L, Suyal R, Jugran AK, Calina D, Capasso R. Cucurbits plants: a key emphasis to its pharmacological potential. *Molecules*. 2019; Article ID 31091784.

[39] Adnan M, Gul S, Batool S, Fatima B, Rehman A, Yaqoob S, Shabir H, Mussarat H, Nawab A, Aziz M. A review on the ethnobotany, phytochemistry, pharmacology and nutritional composition of *Cucurbita pepo* L. *J Phytopharm*. 2017; 6(2): 133–139.

[40] Kolahdooz S, Karimi M, Esmaili N, Zargaran A, Kordafshari G, Mozafari N, Ayati MH. 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(11): 2811–2819.

[41] Sharma V, Katiyar A, Agrawal R. *Glycyrrhiza glabra*: chemistry and pharmacological activity. *Sweeteners*. 2018; Article ID 7124151.

[42] Saeedi M, Morteza-Semnani K, Ghoreishi MR. The treatment of atopic dermatitis with licorice gel. *J Dermatol Treat*. 2003; 14(3): 153–157.

[43] Raja AF, Ali F, Khan IA, Shawl S, Arora DS, Shah BA, Taneja CS. Antistaphylococcal and biofilm inhibitory activities of acetyl-11-keto-β-boswellic acid from *Boswellia serrata*. *BMC Microbiol*. 2011; Article ID 21406118.

[44] Quirós-Sauceda A, Ovando-Martínez M, Velderrain-Rodríguez G, González-Aguilar G, Ayala-Zavala J. Licorice (*Glycyrrhiza glabra* Linn.) oils. In: Preedy V, Ed. Essential oils in food preservation, flavor and safety. Amesterdam: Academic Press, 2016.

[45] Passali D, Ciprandi G, Damiani V, De Marco AM, Cianfrone F, Passali FM. Glycyrrhizin for topical use and prophylaxis of COVID-19: an interesting pharmacological perspective. *J Biol Regul Homeost Agents*. 2021; 35(S2): 15–19.

[46] Johnson W, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler DC, Liebler DC, Marks JG, Shank RC, Andersen FA. Amended safety assessment of *Sesamum indicum* (sesame) seed oil, hydrogenated sesame seed oil, *Sesamum indicum* (sesame) oil unsaponifiables, and sodium sesameseedate. *Int J Toxicol*. 2011; 30(3 Suppl): 40–53.

Abbreviations

PM: Persian medicine; PASI: psoriasis area and severity index; PGA: physician's global assessment; VAS: visual analog scale; DLQI: dermatology life and quality index; BSA: body surface area; BMI: body mass index; GRAS: generally recognized as safe; FDA: Food and Drug Administration; CRFs: case report forms; BHT: butylated hydroxy toluene; CTCAE: common terminology criteria for adverse event