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Boswellia carterii Birdwood Topical Microemulsion for the Treatment of Inflammatory Dermatological Conditions; a Prospective Study

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ABSTRACT

Several dermatological conditions, such as acne, eczema and urticaria, underlie inflammation among its pathogenesis. *Boswellia carterii* Bird. oleo-gum-resin has been extensively used in Ayurveda, Egyptian and Chinese traditional medicine for its anti-inflammatory activity. The aim of this study is to investigate the therapeutic potential of a topical microemulsion of *B. carterii* oleo-gum-resin standardized bioactive fraction on patients with acne, eczema and urticaria. This prospective study included 47 patients; 34 males and 13 females; 8 of which were suffering from acne, 29 from eczema and 10 from urticaria, receiving a topical dose twice daily from the standardized bioactive fraction of *B. carterii* oleo-gum-resin in the form of topical microemulsion. The number of acne lesions was significantly decreased in all study groups from basal to week 2 and from week 2 to week 4 of the study. Patients' satisfaction was high in all the groups which further ascertained the improvement detected by the doctors' visual inspection. In conclusion, topical microemulsion of *B. carterii* oleo-gum-resin standardized bioactive fraction is effective in the treatment of patients with acne, eczema and urticaria.

Keywords: Traditional medicine, *Boswellia carterii* Bird. Oleo-gum-resin, Topical Microemulsion, Acne.

Introduction

Skin inflammatory diseases arise generally from chemical, physical or microbial insults.[1]Acne is a disease that affects the pilosebaceous follicles which consist of the sebaceous glands connected functionally and anatomically to the hair follicles. It does not affect the sebaceous gland only but rather extend to the entire pilosebaceous unit. The face, back and chest are the body areas most commonly affected followed by the upper arms, back and hips. Acne results from the combination of different factors; excessive production of sebum as a result of stimulation of the sebaceous glands by endogenous androgens; obstruction of the exit of the sebaceous follicles due to excess keratinocytes production; hyperactivity of *Propionibacterium acnes* which is normal flora living in the pilosebaceous unit; and inflammation triggered by sebum released into the surrounding areas of the skin.[2]

The early stage of acne is a non-inflammatory process. It involves a number of open and closed comedones. However, the epithelium of the sebaceous follicle is often destructed due to the continuous dilation of the pilosebaceous follicle causing the release of sebum, keratinocytes and hair debris into the adjacent skin areas. Upon contact with such irritants, an inflammatory cascade is triggered resulting in the development of the erythematous lesions, pimples, pustules and bumps. *Propionibacterium acnes*, living in the follicle, dies on follicular disruption releasing toxins into the dermis which further aggravate inflammation. With the aggravation of inflammation, papules become enlarged and pustules are formed.[2]

Eczema and urticaria are forms of dermatitis, or inflammation of the epidermis, chronically relapsing, non-contagious and extremely pruritic skin ailment. Eczema by definition is generally used to describe a range of chronic skin inflammatory cases. It occurs with a frequency of 2-5% of a population and reaches up to 10% in children and young adults. The specific etiology of eczema is not well defined. Nevertheless, a number of parameters can be involved; the sensitivity of the skin, altered immunity, exposure to irritants, dryness of the skin, in addition to genetic factors. The clinical investigation of inflamed dry skin with eczematous lesions suggests impairment in skin barrier function. Stratum corneum maintains skin barrier function as it constitutes a constant layer of alternating squamous cells; protein-enriched corneocytes embedded in an intercellular matrix.[3] Molecular genetics underlined the important role of skin barrier function in the protection against developing immunological counteractions in response to the abnormal presentation of allergens. Hence, the primary shortcoming in eczema is the deficiency of skin barrier function as manifested by abnormal presentation of skin irritants that trigger the immune system. Moreover, patients suffering from eczema start to contact several infectious diseases due to fungal, viral or bacterial infection.

Oleo-gum-resin of *Boswellia carterii* Birdwood family Burseraceae (incense) is an ancient remedy used by Ancient Egyptians in several medicinal uses as well as in mummification balms and religious rituals.[4] The oleo-gum-resin of Boswellia species has also been used in Ayurvedic medicine in India for the treatment of inflammatory conditions such as Crohn's disease and arthritis. Previous pharmacological, phytochemical and toxicological studies revealed the safety and efficacy of the isolated bioactive fraction which showed a significant anti-inflammatory activity using carragennan-induced oedema in rats.[5-7] The active principles of the bioactive fraction are the

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boswellic acids; where acetyl-11-keto-β-boswellic acid (AKBA) has been reported to be the most potent.[8]

Microemulsions (MEs) are modern pharmaceutical dosage forms where dispersions of oil in water, are stabilized by an intermediate layer of surfactants producing transparent colloid with low viscosity, optically isotropic and thermodynamically stable.[9,10] Microemulsions present promising vehicles for dispensing drugs in the form of dermal and topical delivery systems.[11] They also markedly improve penetration of hydrophilic, lipophilic and amphiphilic drugs throughout the dermis. In the course of our trials for the application of the biologically active fraction of *Boswellia carterii* Bird., various pharmaceutical dosage forms were formulated.[12,13] The formulation of the bio-efficient fraction of the oleo-gum-resin of *Boswellia carterii* Bird. was performed in a topical pharmaceutical dosage form; microemulsion in order to achieve an advanced anti-inflammatory effect. The formulation as such produced higher anti-inflammatory activity as compared with the standard topical piroxicam formulation.

Materials and Methods

General experimental procedures

Chromatographic elution was monitored by spotting the successive fractions on silica gel TLC plates eluted with several mobile phases constituting of hexane, ethyl acetate, chloroform and methanol in various proportions. The spots were visualized by spraying with vanillin sulfuric acid spray reagent followed by heating in an oven at 110°C for 10 minutes. ^{1}H-NMR and ^{13}C-NMR of the active compound were done using NMR (JEOL-JNM-ECX-400 NMR Spectrometer, Tokyo, Japan). Mass spectrometry was done using ESI/MS (Electron spray ionization / mass spectrometer (Agilent LC-MSD Trap Mass Spectrometer, Bruker Daltronics, Bremen, Germany) and the UV was run on a UV–visible spectrophotometer (Shimadzu UV 240 (PIN 204-5800, North America).

Plant material

Samples of the dried oleo-gum-resin of *Boswellia carteri* were purchased from Haraz Egyptian herbal store, Cairo, Egypt. A voucher specimen was authenticated by Dr. Trease Labib, Herbarium of Orman Botanical garden and the specimen was deposited in the Herbarium of the National Research Centre (no. 2004/119).

Preparation of the bioactive fraction

The powdered oleo-gum-resin of *Boswellia carteri* Bird. (3000 g) was extracted in a continuous extraction apparatus (Soxhlet apparatus, Fischer-scientific, USA) until exhaustion with petroleum ether (40-60°C) followed by diethyl ether; the solvent was stripped off by distillation under reduced pressure at a temperature below 40°C and dried to constant weight in a vacuum desiccator over anhydrous calcium chloride (1892 g). The extract (500 g) was applied on the top of a glass column dry-packed with silica gel and eluted with hexane with increasing proportions of ethyl acetate and the collected fractions (250 mL) were pooled and spotted against boswellic acids previously isolated and identified as described by Ammar *et al*.[7] Fractions from 6 to 15 containing the boswellic acids were combined and dried under reduced pressure at a temperature below 40°C and are further used as the bioactive fraction. The process is repeated till fractionating all of the crude extract.

Isolation, purification and identification of AKBA

The bioactive fraction (50 g) was applied on the top of a glass column dry-packed with silica gel and eluted with hexane with increasing proportions of ethyl acetate for further separation of boswellic acids. Fractions (100 mL each) were collected and pooled and screened for AKBA through its characteristic peeks in ^{1}H-NMR analysis. Fractions 9-21 were combined and loaded on top of a silica sub-column. Elution was done with chloroform 100% then adding methanol gradient wise starting with 0.1% up to 5% where AKBA was isolated in fractions 3-7.

Standardization of B. carteri L. bioactive fraction

The bioactive fraction of *B. carterii* was analysed for AKBA content by HPLC by dissolving 100 mg in 10 mL methanol (HPLC grade). The mixture was shaken on an isothermal water bath shaker (GFL mbH 3032 Burgwedel, Germany) at 25°C and 100 rpm, for 72 h. The supernatant was filtered through a membrane filter (Nylon Acrodisc, 0.45 µm, Gelman Sciences Inc., USA; which is an efficient filtration tool providing adequate removal of any undissolved matter thus enhancing analytical procedures) and analysed for AKBA content. The experiment was conducted in triplicate. HPLC analysis method for AKBA was previously reported by Singh *et al*.[14] Isocratic separation was done at 25°C using reversed phase Zorbax-C18 column (5 µm; 250 mm x 4.6 mm) on an Agilent 1200 series instrument equipped with an online diode-array detector. Detection was done at 210 nm. The mobile phase consisted of acetonitrile/water/acetic acid (99:1:0.01 v/v/v). The flow rate was adjusted to 0.5 mL/min for 10 min and injection volume 20 µL. The concentration of AKBA was determined using external standard method where the isolated AKBA was used as the external standard.

Preparation of MEs and determination of active constituent

The selection of the ME for the preparation of the standardized bioactive fraction of *B. carteri* was done in accordance to our previous study.[12] Briefly, MEs were formulated by drop wise addition of distilled water to the oil/Smix mixture. The bioactive fraction of *B. carteri* was added as 2%. The components were mixed by gentle stirring. Smix was used at 70% and the ratios of oil to Smix used in microemulsions were selected to be 10:90 and 20:80.

Clinical study

Before commencement of clinical trial, all procedures were approved by the Medicinal Research Ethics Committee of the National Research Centre under the number 19040/2017. Patients were recruited from the outpatient clinic of the Dermatology and Venerology Department, National Research Centre, and private clinics. Case discrimination was randomly selected by the case monitoring physician. A full history was taken from each patient regarding age, gender and duration of the disease. Toxicity studies demonstrated safety of the drug.

This study included 47 patients diagnosed as follows; 8 acne, 29 eczema and 10 urticaria, (34 male and 13 female) who gave informed consents for the trial without any application of outsource treatment all through the study; method of application was twice daily for 2 weeks duration, triple blinding technique was followed (patient, clinical evaluator and statistician don't know the applied treatment) if patient notice improvement he will continue for two more weeks, and if not he was given the right to take alternative treatments available. One out of every nine patients counseled gave their consent for the trials; without any conflict of interest, medications were given without any financial obligations to the patients, they were given the right to retreat at any time they wish.

Clinical data outcome was measured according to the following criteria; patient report of degree of improvement in the form of mild, moderate, satisfactory improvement and no improvement; on the other hand, a single physician who encountered the case primarily will report the degree of improvement the same way aided with the degree of itching, erythema, number of papules, pustules, open and closed heads.

Regarding acne patients, the severity of lesion was based on the total number of lesions, mild if less than 10, moderate from 10 – 20 and severe if more than 20 papule and pustule. The primary outcome was defined as the change in the mean total lesion count at the end of the study, the primary total number was considered 100% at the beginning of the study and any decrease was calculated accordingly.

Statistical analysis

Data was analyzed using two tests: Independent t-test as well as Fisher Exact test using Graphpad prism version 8.0. The statistical significance of each test was calculated and illustrated as P value.

Results and Discussion

Inflammation is considered a hallmark of the pathogenesis of acne.[16] A scientific discussion broke out lately as to whether to consider the hyperkeratinisation that occurs to the pilosebaceous follicle opening causes the breakthrough of inflammatory reaction or the converse. Alestas *et al*. showed that both COX-1 and COX-2 were expressed in human sebocyte cell lines. They also reported that the expression of COX-2 was particularly higher in affected pilosebaceous glands *in vivo*. Several studies also reported the activation of NF-κB, a transcription factor essential for the expression of proinflammatory cytokine genes in acne lesions,[17] where the levels of TNFα, IL-1*β*, IL-8 and IL-10 were shown to be significantly higher in skin involved in acne lesions compared to uninvolved skin. It was also reported that the up regulation of IL-1 activity relapses prior to the excessive proliferation in the skin around uninvolved follicles leading to keratinocytes activation.[18] Accordingly, cutaneous inflammation occurs resulting in hyperproliferation of keratinocytes leading to the development of acne lesions.

When the pilosebaceous follicle gets obstructed, a micro-comedon is developed which is considered the ancestor of various acne lesions. Following obstruction of the follicle, the lower part becomes inflated and swollen filled with sebum and keratinocytes. The follicle eventually enlarges and the opening is stretched causing the trapped matter to be exposed to air. This causes its oxidation which results in the distinctive dark color of open comedones also known as blackheads. Open comedones appear as plane or somewhat raised black papules that are three to five mm wide. In early stages, acne appears as comedones (blackheads and whiteheads), pustules, papules and red, scaly skin while in severe cases, inflammatory manifestations appear in the form of nodules, cysts or scars. Further itching and scratching causes skin injury and excessive release of allergens causing severe inflammation and increased risk of microbial infection. Additional inflammation will worsen the case because it causes the relapse of acne lesions in the surrounding unaffected skin.[16]

Atopic dermatitis, commonly described as eczema, is a common, chronic, skin condition which is underlined by immunoglobulin E–mediated sensitization following the exposure to endogenous or exogenous allergens. Among the factors that would trigger this reaction is food, drugs, or cosmetics. Eczema is characterized by pruritis and severe itching.[19] Eczema is conventionally classified according to the patient's age into adult and infantile eczema. The symptoms vary widely from a minor pruritic erythematous skin area, in the hand for example, to major lichenified papules sometimes accompanied with serous exudates. Urticaria (hives), on the other hand, is generally caused by cutaneous mast cell degranulation and is attributed to immunological, nonimmunological and idiopathic causes. It appears and peaks in minutes to hours and is accompanied by pruritus that worsens during the night.[20]

Conventional treatment of acne, eczema and urticaria would depend on two prospective; protective approach including the avoidance of exposure to possible irritants and the conservation of sufficient moisture content in the skin and a therapeutic approach using anti-inflammatory agents and in some cases immunomodulatory drugs. Other treatments include sun-protective agents, antibiotics and antihistamines.[19]

The oleo-gum-resin of *B. carterii* has proved potent anti-inflammatory activity in carragennan-induced edema in rats. Bioassay-guided fractionation resulted in the identification of boswellic acids as the active constituents responsible for pharmacological activity.[7] *Boswellia* oleo-gum-resin inhibited leukotriene biosynthesis through the down regulation of the activity of 5-lipoxygenase and caused a dose-related decline in LTB_4 levels of peritoneal neutrophils in rats.[6, 21]

Among all boswellic acids, 3-acetyl-11-keto-*β*-boswellic acid (AKBA) was found to be the most effective compound with IC_{50} = 1.5 μM and consequently it was isolated and used for the standardization of the bioactive fraction.

Repeated column chromatography of the bioactive fraction of *B. caterii* led to the isolation of AKBA which was identified by spectral analysis using ^{1}H-NMR, ^{13}C-NMR and EI/MS.

ESI/MS analysis showed [M^+] peak at *m/z* 512, suggesting the molecular formula; $C_{32}H_{48}O_5$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 0.82 (d, *J* = 5.98 Hz, 3H, H30) 0.85 (s, 3H, H27) 0.89 (d, *J* = 5.93 Hz, 3H, H29) 0.90 (m, 1H, H20) 0.94 (m, 2H, H21) 1.10 (m, 2H, H15) 1.10 (s, 3H, H26) 1.13 (s, 3H, H25) 1.20 (s, 3H, H28) 1.20 (m, 1H, H19) 1.26 (m, 1H, H18) 1.31 (m, 1H, H16) 1.59 (m, 2H, H22) 1.63 (m, 2H, H2) 1.64 (s, 3H, H23) 1.68 (m, 1H, H5) 1.94 (m, 2H, H7) 2.10 (d, *J* = 11.15 Hz, 2H, H1) 2.08 (m, 1H, H6) 2.09 (s, 3H, CH3*CO) 2.49 (s, 1H, H9) 5.32 (dd, *J* = 10.53, 5.53 Hz, 1H, H3) 5.66 (s, 1H, H12). ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm 13.34 (C25) 17.40 (C29) 17.46 (C26) 19.78 (C6) 21.32 (C27) 21.38 (*CH_3CO) 22.68 (C28) 23.68 (C2) 24.95 (C23) 25.67 (C16) 27.20 (C21) 29.35 (C30) 31.91 (C7) 33.80 (C15) 34.11 (C17) 37.13 (C1) 37.40 (C10) 39.40 (C20) 39.60 (C19) 40.03 (C22) 42.26 (C8) 46.61 (C14) 47.27 (C4) 51.43 (C5) 59.20 (C18) 60.5 (C9) 73.40 (C3) 130.00 (C12) 167.18 (C13) 170.31 (CH_3*CO) 181.74 (C24) 213.5 (C11).

Spectral data were compared with the previous reported spectral data of AKBA.[15] Apart from AKBA, the previous phytochemical study of the biologically active fraction using column chromatography, preparative TLC and HPLC led to the isolation of 3-acetyl-*β*-boswellic acid, *β*-boswellic acid and *α*-boswellic acid as shown in Figure 1.

The bioactive fraction of *B. carterii* L. was standardized to contain not less than 5% AKBA. AKBA content of the bioactive fraction was 6.45%. On the basis of our previous study, an optimized topical microemulsion containing the standardized bioactive fraction of *Boswellia carterii* Bird. oleo-gum-resin showing high encapsulation efficiency > 80% was considered for clinical studies addressing treatment of various inflammatory skin conditions; acne, eczema and urticaria to confirm the promising results obtained in the conducted pre-clinical study.[13]

This study is a prospective one that included 47 patients (34 males and 13 females) to study the therapeutic effect of topical microemulsion of *B. carterii* oleo-gum-resin standardized bioactive fraction on acne (8), eczema (29) and urticaria (10) patients. The mean age was 27.6, 28.4 and 17.6 years in acne, eczema and urticarial, respectively, with no significant difference between study groups. The study included 5, 21, 8 males and 3, 8, 2 females in acne, eczema and urticarial, respectively, with no significant difference between study groups as shown in Table 1.

The degree of improvement of the patients was recorded in the form of mild, moderate, satisfactory improvement and no improvement after two and four weeks as shown in Table 2. The degree of improvement of the cases was estimated by a single physician who encountered the cases primarily in accordance to the degree of itching, erythema, number of papules, pustules, open and closed heads after two and four weeks as shown in Table 3.

Seven out of eight acne patients, all 29 eczema patients and all 10 urticaria patients (87.5%, 100% and 100% of acne, eczema and urticaria, respectively) reported satisfactory improvement after 2- and 4-weeks treatment with *Boswellia* microemulsion as inspected visually by the dermatologist as well as through recording patients' satisfaction. Patient satisfaction was non-significantly higher in the case of urticaria and eczema groups, and lesser in the acne group. The numbers of acne lesions were recorded before and after the treatment with *Boswellia* topical formulation as shown in Table 4. The number of acne lesions was significantly decreased from basal to week 2 and from week 2 to week 4 of *Boswellia* microemulsion treatment.

According to the present study, *Boswellia* topical microemulsion exerted a significant anti-inflammatory activity resulting in a marked decrease in the number of acne lesions in all study groups from basal to week 2 and from week 2 to week 4 of the study. Eczema and urticaria patients were highly relieved showing satisfying improvement after 2- and 4-weeks treatment. Patients' satisfaction was higher; yet not significantly, in urticaria and eczema groups than in acne group.

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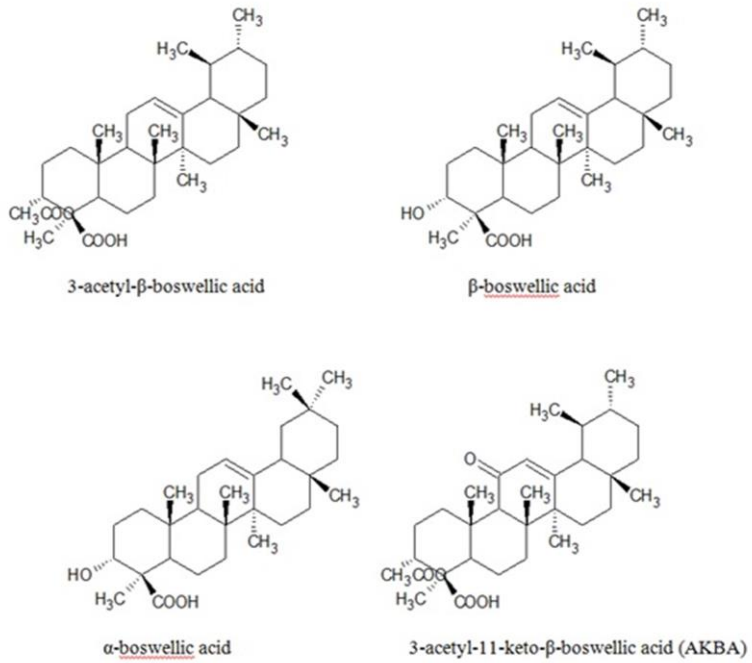

Figure 1: Chemical structures of compounds isolated from *Boswellia carteri* oleo-gum-resin

Table 1: Age and sex distribution among different diagnoses groups; Acne (**A**), Eczema (**E**) and Urticaria (**U**)

Variable	Measure	Acne (N = 8)	Eczema (N = 29)	Urticaria (N = 10)	P A/E	P A/U	P E/U
Age (years)	Mean ± SD	27.6 ± 8.4	28.4 ± 12.0	17.6 ± 11.5	#0.869	#0.996	#0.779
	Range	17.0 - 46.0	9.0 - 55.0	19.0 - 55.0			
Sex (n, %)	Male	5 (62.5%)	21 (72.4%)	8 (80.0%)	^0.672	^0.608	^1.000
	Female	3 (37.5%)	8 (27.6%)	2 (20.0%)			

Statistical significance of the two variables; age and sex among study population was calculated as P values (# indicated P value calculated by Independent t-test and ^ indicates P value calculated by Fisher Exact test)

Table 2: Patient satisfaction among different diagnoses groups; Acne (**A**), Eczema (**E**) and Urticaria (**U**)

Time	Improvement	Acne (N = 8)	Eczema (N = 29)	Urticaria (N = 10)	P A/E	P A/U	P E/U
2 weeks	Improved patients	7 (87.5%)	29 (100.0%)	10 (100.0%)	#0.216	#0.444	--
	Non-improved patients	1 (12.5%)	0 (0.0%)	0 (0.0%)			
4 weeks	Improved patients	7 (87.5%)	29 (100.0%)	10 (100.0%)	#0.216	#0.444	--
	Non-improved patients	1 (12.5%)	0 (0.0%)	0 (0.0%)			
^P		1.000	--	--			

Statistical significance was calculated as P values (# indicated P value calculated by Fisher Exact test and ^ indicates P value calculated by ^McNemar)

Table 3: Doctor Satisfaction among different diagnoses groups; Acne (**A**), Eczema (**E**) and Urticaria (**U**)

Time	Improvement	Acne (N = 8)	Eczema (N = 29)	Urticaria (N = 10)	P A/E	P A/U	P E/U
2 weeks	Improved patients	7 (87.5%)	29 (100.0%)	10 (100.0%)	#0.216	#0.444	--
	Non-improved patients	1 (12.5%)	0 (0.0%)	0 (0.0%)			
4 weeks	Improved patients	7 (87.5%)	29 (100.0%)	10 (100.0%)	#0.216	#0.444	--
	Non-improved patients	1 (12.5%)	0 (0.0%)	0 (0.0%)			
^P		1.000	--	--	--		

Statistical significance was calculated as P values (# indicated P value calculated by Fisher Exact test and ^ indicates P value calculated by ^McNemar)

Table 4: Number of acne lesions before and after treatment with topical *Boswellia* microemulsion (N = 8)

	Time	Degree	Number of acne lesions
Patients receiving no treatment	Basal	Med (IQR)	16.0 (10.8 - 17.8)
		Range	8.0 - 30.0
	2 weeks	Med (IQR)	11.5 (7.8 - 13.5)
		Range	6.0 - 27.0
	4 weeks	Med (IQR)	7.0 (4.0 - 8.8)
		Range	3.0 - 26.0
Patients receiving Boswellia microemulsion	Improvement at week-2 compared to basal	Med (IQR)	-3.5 (-4.8 - 3.0)
		Range	-5.0 - 2.0
		^P	0.011*
	Improvement at week-4 compared to week-2	Med (IQR)	-4.0 (-4.8 - 3.0)
		Range	-5.0 - 1.0
		^P	0.011*
	Improvement at week-4 compared to basal	Med (IQR)	-7.5 (-9.0 - 5.3)
		Range	-10.0 - 4.0
		^P	0.012*

Med (IQR): Median (1^{st} – 3^{rd} inter-quartile range), and Negative values indicate reduction
#Mann Whitney test, ^Wilcoxon signed rank test, *Significant

Conclusion

The use of topical formulation of *B. carterii* oleo-gum-resin standardized bioactive fraction presents a potent remedy suitable for controlling the underlining inflammatory complications associated with eczema, urticaria and acne providing a safe substituent for corticosteroidal treatment**.**

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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