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Topical Boswellic acids for treatment of photoaged skin

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ABSTRACT: Boswellic acids (BAs) are pentacyclic triterpenes extracted from the gum resins of the tropical tree *Boswellia serrata*. They are orally administered in traditional Indian medicine for the treatment of several inflammatory disease and cancer because of their anti-inflammatory and immunomodulatory activities as well as stimulatory effects on fibroblasts.

The present authors have investigated efficacy, tolerability, and safety of a base cream containing 0.5% BAs in the treatment of clinical manifestations of photoaging of facial skin with a randomized, double-blind, placebo-controlled, split-face study.

Fifteen female volunteers applied the creams with or without BAs on the half sides of the face once daily for 30 days. Significant improvements of the Dover's global score for photoaging, tactile roughness, and fine lines, as well as, with noninvasive diagnostic techniques, an increase of elasticity, a decrease of sebum excretion, and a change of echographic parameters were observed with topical BAs in comparison with placebo. The treatment was always well tolerated without adverse effects. The present findings seem to indicate that topical application of BAs may represent a suitable treatment option for selected features of skin photoaging.

KEYWORDS: 20-MHz B-mode echography, *Boswellia serrata*, Boswellic acids, skin photo and chronoaging

Introduction

Chronic excessive sun exposures cause a heterogeneous group of skin lesions, known as photoaging, that are characterized histologically by skin atrophy, pigmentary changes and chronic dermal inflammation. It is a health problem of growing relevance in the Western world and the search for new treatment options is continuous.

Boswellia serrata (Burseracee) is a large, branching, deciduous tree that grows in the dry areas of subtropical Asia and Africa. Its fragrant gum is orally administered in Indian ayurvedic medicine for the treatment of various inflammatory disorders and tumors. The active components of the gum are the Boswellic acids (BAs). They are pentacyclic triterpenes, with methyl- groups in alpha or beta position, a carboxyl group, and at least another functional (hydroxyl-, acetyl-, or keto-) group.

In in-vitro and in-vivo studies, BAs have shown various inhibitory effects on pro-inflammatory molecular pathways and a stimulatory activity on the metabolism of collagen and elastin (1–4).

In the present randomized, double-blind, split-face, placebo-controlled comparative study, the present authors evaluated clinically and with noninvasive diagnostic techniques the efficacy and tolerability of a cream containing BAs in the treatment of photoaged skin of the face.

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Materials and methods

Patients

Fifteen women, mean age 44.4 years (range 31–68 years), with photodamaged skin of the face, were enrolled in the study. The study was approved by the local ethics committee and all patients gave their written informed consent.

Exclusion criteria were pregnancy and lactation, inflammatory or neoplastic skin diseases of the treated area, subjects who had undergone physical treatments or any other cosmetic treatment for photoaging, as well as subjects who had used any systemic drug (including oral contraceptives) in the past 3 months.

Treatment protocol

The face of each patient was split into two parts along the vertical axis. One side was randomly assigned to the treatment with a base cream containing 0.5% BAs that are obtained from a *Boswellia serrata* gum resin extract (collected in India by Laila Impex Research Center, Vijayawada, Andhra Pradesh, India). The other half side was treated with an identical cream without BAs and served as control. Both preparations were provided by Scharper Healthcare Srl (Milan, Italy) in identical tubes identified by blinded coding. The density, color, and smell of the two creams were indistinguishable.

After randomizing the side of application, the two tubes were given to the patient. Neither the patient nor the physician knew to which side of the face the cream containing BAs was applied.

Application was repeated once a day for 30 days. The severity of the clinical manifestations of photoaging, i.e., fine surface lines, mottled pigmentation, sallowness, tactile roughness, coarse wrinkling, facial erythema, teleangiectasia, and sebaceous gland hypertrophy, were scored independently by two blinded investigators according to the 0–10 visual analog scale of the modified Dover photodamage classification system (5).

For the purposes of the present investigation, unlike the original scoring system, the scores of each side of the face were summed separately, and the score of the dorsa of the hands, which were not treated, was ignored.

Biophysical measurements and echographic investigations

At T0, T1, and T2, trans epidermal water loss (TEWL) was measured with the Tewameter TM 210, the water content of the horny layer with the Corneometer CM 820 and the skin surface lipids with the Sebumeter SM 810 PC (all from Courage and Khazaka GmbH, Koln, Germany). Skin distensibility was measured with the MicroCAMERA, (Dermotricos s.r.l, Brescia, Italy).

High-frequency echography (Dermascan C, Cortex Technology, Hadsund, Denmark) was used at T0, T1, and T2 to obtain quantitative data of four parameters: (i) skin thickness (mm), (ii) number of pixels (their number increases in photodamaged dermis), (iii) area in which the echoes' amplitude is included within the values of the selected band (201–255), and (iv) the thickness of the subepidermal low-echogenic band (SLEB; the increase of its thickness in photodamaged areas has been attributed to the accumulation of elastotic material).

Statistical Analysis

Data are given as mean ± standard deviation (m ± SD).

Clinical scores and instrumental measurements were compared with a parametric test, the paired Student's *t*-test. Significance was defined as $p < 0.05$.

Results

All patients completed the study; the treatment was well tolerated without adverse effects.

In the half side treated with the daily application of the cream containing BAs, the mean total score for photoaging showed significant differences after the therapy and after follow-up 2 months later (T2) in comparison to baseline scores (Table 1). In the same half side of the face, statistically significant reductions of tactile roughness and fine surface lines were also observed after 30 days (T1), and these scores remained statistically unchanged at follow-up. Other clinical features of photoaging did not show any significant change (Table 1).

Skin sebum and distensibility decreased significantly and remained statistically significant at follow-up in comparison to baseline (Table 2). There were no statistical differences of TEWL or corneometry after the therapy (Table 2).

Echographic measurements (Table 3) showed a statistical increase of skin thickness as well as the pixel count. These values remained statistically significant at T2 in comparison with baseline. Measurements of area and SLEB remained unchanged at T1 and T2 (Table 3).

The side of the face treated with emollient cream without BAs did not show any appreciable change in echographic or biophysical values.

Table 1. Variation of parameters (mean ± SD) of the Dover score at baseline (T0), after 4 weeks (T1), and after 3 months (T2)

	Half-side treated with the cream containing Boswellic acids			Control half-side treated with the cream without Boswellic acids		
	T0	T1	T2	T0	T1	T2
Fine surface lines	2.23 ± 0.83	1.69 ± 0.18*	1.77 ± 0.60*	2.23 ± 0.83	2.23 ± 0.83	2.17 ± 0.80
Mottled pigmentation	0.92 ± 0.86	0.92 ± 0.86	0.85 ± 0.9	0.69 ± 0.85	0.92 ± 0.86	1.07 ± 0.64
Sallowness	0.69 ± 0.85	0.69 ± 0.85	0.61 ± 0.76	0.69 ± 0.85	0.69 ± 0.85	0.77 ± 0.72
Tactile roughness	1.46 ± 1.2	1.08 ± 0.95*	1.08 ± 0.95*	1.46 ± 1.2	1.15 ± 1.06	1.30 ± 1.11
Coarse wrinkling	1.92 ± 0.76	1.77 ± 0.83	1.69 ± 0.94	1.92 ± 0.76	1.85 ± 0.8	1.92 ± 0.64
Facial erythema	0.46 ± 0.52	0.38 ± 0.51	0.54 ± 0.66	0.46 ± 0.52	0.38 ± 0.51	0.52 ± 0.52
Teleangiectasia	0.46 ± 0.52	0.38 ± 0.51	0.30 ± 0.48	0.46 ± 0.52	0.54 ± 0.52	0.38 ± 0.5
Sebaceous gland hypertrophy	0.54 ± 0.66	0.54 ± 0.66	0.38 ± 0.65	0.54 ± 0.66	0.54 ± 0.66	0.69 ± 0.63
Total score	8.69 ± 5.15	7.45 ± 4.31*	7.23 ± 3.8*	8.46 ± 4.99	8.30 ± 5.05	8.85 ± 3.67

*$p < 0.05$ in comparison with baseline.

Table 2. Measures of biophysical parameters (mean ± SD) at baseline (T0), after 4 weeks (T1), and after 3 months (T2)

	Half-side treated with the cream containing Boswellic acids			Control half-side treated with the cream without Boswellic acids		
	T0	T1	T2	T0	T1	T2
Sebum (μg/cm^2)	63.77 ± 33.69	45 ± 24.2*	40.38 ± 23.68*	64 ± 32.06	57 ± 23.42	58.46 ± 20.51
Corneometry (corn-units)	67.92 ± 15.82	70.92 ± 10.34	70.84 ± 10.00	67.85 ± 15.17	71.69 ± 5.57	71.92 ± 4.85
TEWL (g/m^2·h)	19.38 ± 6.26	19.38 ± 5.23	20.02 ± 5.01	19.17 ± 6.29	19.16 ± 5.22	18.75 ± 5.01
Uf (mm)	2.21 ± 0.46	1.87 ± 0,47*	1.89 ± 0.40*	2.18 ± 0,45	1.99 ± 0,58	2.05 ± 0.39

*$p < 0.05$ in comparison to baseline.
TEWL, trans epidermal water loss; Uf, measurement (in mm) of skin distensibility.

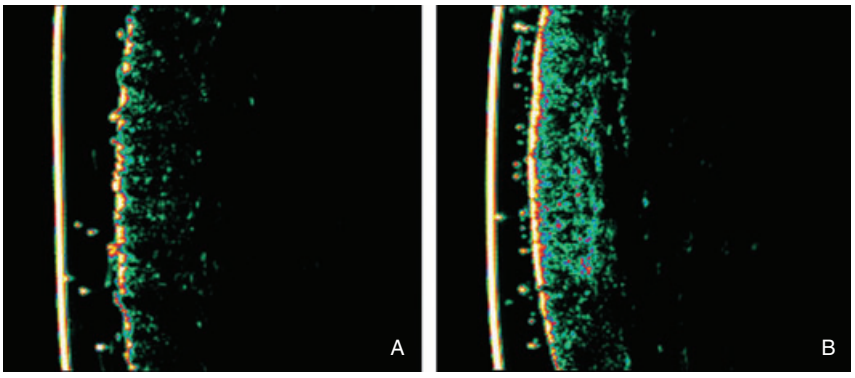

FIG. 1. A. Ultrasound (US) at the baseline (T0). B. US after the treatment (T1); there was an improvement of echogenicity of the dermis (increase of the skin thickness and pixel count).

Discussion

In the present investigation, a cream containing a low (0.5%) concentration of BAs was found well tolerated and effective with a significant persistent improvement of the Dover's global score for photoaging and scores of selected features of photodamaged skin, i.e., fine lines and tactile roughness.

Echography showed an increase of the number of pixels and skin thickness suggesting a reshaping and a new deposition of collagen and elastic fibers (FIG. 1). The increase of skin distensibility

Table 3. Echographic measures (mean ± SD) at baseline (T0), after 4 weeks (T1), and after 3 months (T2)

	Half-side treated with the cream containing Boswellic acid			Half-side treated with the cream without Boswellic acid		
	T0	T1	T2	T0	T1	T2
Thickness (mm)	1.36 ± 0,12	1.58 ± 0.25*	1.60 ± 0.23*	1.36 ± 0.12	1.37 ± 0.12	1.39 ± 0.12
Number of pixels	49441.23 ± 7375.68	54504.38 ± 9622.6*	54854.77 ± 9364.17*	49346.62 ± 7362.03	50800 ± 8525.28	50654.31 ± 8832.93
Area (mm^2)	20.37 ± 2.54	20.88 ± 3.08	21.18 ± 3.24	20.38 ± 2.55	20.56 ± 2.48	20.81 ± 2.58
SLEB (mm)	0.52 ± 0.17	0.42 ± 0.14	0.44 ± 0.16	0.46 ± 0.14	0.41 ± 0.14	0.47 ± 0.14

*$p < 0.05$ in comparison to baseline.
SLEB, subepidermal low-echogenic band.

suggests an increase of functional elastic fibers as well.

These effects of BAs can be related to both their anti-inflammatory activities and the stimulatory activity on the metabolism of collagen and elastic fibers.

BAs have a strong anti-inflammatory effect via a selective nonredox and noncompetitive inhibition of 5-lipoxygenase (1,6–9), and the inhibition of transforming growth factor beta activated kinase (TAK)/transforming growth factor beta activated binding protein (TAB)-mediated Ikappa kinase phoshorylation with consequent inhibition of activation and translocation of nuclear factor (NF)-kappa B to the nucleus (2).

BAs enhance the metabolism of fibroblasts with inhibition of the transcription of matrix metalloproteinase protein-1 (MMP-1), an enzyme that plays a pivotal role in the cleavage of dermal fibrillar collagen with dermal damage (1–3).

At the same time, BAs inhibit human leukocyte elastase (10) and hyaluronidase (3) as well as tumor necrosis factor (TNF)-α-induced transcription, expression and activity of MMP-1, MMP-3, MMP-10, and MMP-12 in human microvascular endothelial cells (4). All these enzymes have a key importance in the degradation of the extracellular matrix, collagen, and elastic fibers.

The improvement of tactile roughness suggests that an improved and more even keratinization of the epidermis with the disappearance of hyperkeratotic skin areas took place; this effect could be related to the antiproliferative and prodifferentiative effects of BAs that have been demonstrated in several normal and tumoral human cell lines (11–12).

The decrease in sebum excretion suggests an inhibitory effect on the activity of the sebaceous glands and may be related to the above-mentioned antiproliferative and prodifferentiative activities of BAs. Deep wrinkles, mottled pigmentation, sallowness, facial erythema, and teleangiectasias showed no improvement. Further studies with a longer treatment period will clarify whether BAs lack is simply not effective or whether the period of application was too short to produce positive results.

In experimental models, BAs proved effective in the treatment not only of inflammatory disorders, but also of cancer including brain tumor (13–14), gastrointestinal neoplasm (15), and leukemia (16). These antitumoral effects of BAs can be theoretically useful in the prevention or treatment of skin cancers that, like photoaging, are most often caused by chronic UV exposure.

In conclusion, the present investigation demonstrates that a cream containing a low concentration of BAs is an effective and well-tolerated treatment option against skin manifestations of photoaging, i.e., fine wrinkling and tactile roughness, and provides a sustained improvement after 2 months at follow-up.

Disclosure

The authors have declared no conflicts of interest.

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