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Bacillus velezensis Endophyte Extract: A Multi-functional Ingredient for Adult Acne and Skin Well-Aging

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1. Introduction

Endophytes are symbiotic microorganisms that live inside plants, promoting beneficial effects on their growth and development. This plant microbiota synthesizes bioactive phytochemicals, offering an alternative source of raw material for developing cosmetic actives. Bioactive compounds from medicinal plants are often produced in very low quantities, while the demand is high. This leads to plant overexploitation, which in turn reduces plant natural populations or increases the use of natural resources and the amount of waste derived from plant cultivation [1]. In order to fulfil a sustainable large-scale production of bioactive compounds, alternative biotechnological approaches such as the use of plant endophytes, among others, are adopted [2].

Endophytes present in plants are considered a treasure house of different bioactive compounds which are known to have different biological properties [3]. In this context, we have isolated a collection of endophytic strains and started a screening of bioactivities to select the best candidates for subsequent active ingredients developments. In this work, we present BFE, a biotechnologically obtained cosmetic active ingredient. BFE is a ferment extract from the bacterial endophyte *Bacillus velezensis* isolated from *Hyssopus officinalis*—a plant with antioxidant, anti-inflammatory, and antimicrobial properties [4]—. Some *Bacillus velezensis* strains have been described to produce bioactive peptides and lipopeptides [5] .

Although acne is traditionally recognized as an adolescent skin disorder, its prevalence among adults is increasing, creating a need for multifunctional cosmetic ingredients targeting both acne and skin aging. In this work, we show the anti-acne, anti-aging ant anti-inflammatory activities of BFE in sebocytes and HDFs *in vitro* and in human volunteers *in vivo*. The final goal of this study was to assess whether BFE had the ability to improve blemished and acne-prone skin in adult women, while ameliorating signs of aging skin.

2. Materials and Methods

2.1 *In vitro* study material and methods

2.1.1 Evaluated active

Bacillus velezensis ferment was used in the *in vitro* assays, diluted in the corresponding cell culture medium to obtain concentrations ranging from 0.00175% to 0.056%.

2.1.2 Sebocyte culture and treatment

After thawing and expanding for 5 days primary human sebocytes —isolated from a 50-year-old Caucasian woman—, cells were cultured in fibronectin-coated plates with Seb4Gln medium. Two days after seeding, treatments with Pureblome™ at 0.028% and 0.056% were applied on days 0, 2, and 3. Samples were harvested on day 4. Additionally, linoleic acid (0.1mM), known to promote sebaceous lipid accumulation [6], was tested both alone and in combination with BFE.

2.1.3 Sebocyte lipid production analysis

By the end of the experiment, sebocytes were fixed with 4% formaldehyde (Sigma-Aldrich) and stained with Hoechst (50 µg/mL) and Nile Red (7 µg/mL). Fluorescence intensity (FI) was measured using a TECAN SPARK® fluorometer at excitation/emission wavelengths for nuclei (356 nm/465 nm), neutral lipids (475 nm/530 nm), and total lipids (520 nm/625 nm). All assays were conducted in triplicate, with at least three readings per well. Microscopy images were obtained using an Eclipse Ti fluorescence microscope (Nikon) under standard settings for DAPI (blue, nuclei), FITC (green, neutral lipids), and TRITC (red, total lipids). Merged images showed colocalization of FITC and TRITC in yellow.

2.1.4 IL-6 and IL-8 levels in sebocyte's supernatants

Levels of both cytokines IL-6 and IL-8 were measured with the ELISA kits DuoSet for Human IL-6 and IL-8 (R&D Systems), respectively, in the supernatants that were harvested at day 4 of the above-mentioned protocol, following manufacturer's instructions. All conditions were assayed in triplicate.

2.1.5 Collagen Type I and Elastin content in NHDF

NHDFs were cultured in 6-well plates and stimulated with BFE at 0.007% and 0.014% for 24 hours. Collagen Type I levels were measured in the supernatants by using the Human Pro-Collagen I alpha 1 DuoSet ELISA (R&D Systems), while Elastin content in cells was assessed using the Fastin kit (Biocolor Ltd). Both collagen and elastin measurements were normalized to protein content determined with the Pierce™ BCA Protein Assay Kit (Thermo Fisher Scientific). All conditions were performed in triplicate.

2.1.6 Migration test of HDF (exclusion zone assay)

Cell migration was assessed using the Oris™ Cell Migration Assay (Platypus Technologies), which measures migration into an exclusion zone without causing cell injury, ensuring improved reproducibility. Cells were grown to confluency within 24 hours in a 96-well plate with Oris™ stoppers. Stoppers were removed to create a 2 mm detection zone, and cells were incubated with Pureblome™ (0.014%) or control for 48 hours at 37°C with 5% CO_2. Migration into the detection zone was imaged using a DMi1 microscope (Leica Microsystems) and analyzed with ImageJ based on confluency. Results were quantified as a percentage of control.

2.1.7 Advanced Glycation End (AGE) products assay.

A solution of BSA 1 mg/ml with 200 mM fructose in DPBS was incubated for 7 days at 37ºC in the presence of BFE at 0.00175% and 0.0035%. After incubation, all treatments were transferred to opaque 96-well plate with clear bottom to quantitatively assess the formation of fluorescent AGEs using a SpectraMax M2 Microplate Reader (Molecular Devices, Sunnyvale) at excitation and emission wavelengths of 355 nm and 460 nm, respectively. % inhibition was calculated as follows:

% inhibition = [1 − (F test) / (F control)] × 100; where "F test" stands for fluorescence of the active at a given concentration, and "F control" for fluorescence without BFE.

2.1.8 Statistical analysis

Statistical differences were determined by using Graphpad Prism® v10 software (Graphpad Software) on a PC. The alpha nominal level is set at 0.05 in all cases. A P value of < 0.05 was considered significant where * P <0.05, **P<0.01, ***P<0.001, ****P<0.0001 vs non-stimulated control or stimulated control. One-way ANOVA was used for experiments comparing three or more groups, while unpaired t test was used for tests comparing two groups.

2.2 *In vivo* study material and methods

2.2.1 Study protocol

A double-blind study was performed using placebo as control, alongside untreated areas for additional controls in some tests (e.g., skin renewal SCTT). Products were applied twice daily (morning and evening) on the whole face for 56 days.

76 Caucasian female subjects, aged between 30-50 years with:

- Different levels of wrinkles/fine lines in the crow's feet area.
- Dilated pores.
- Acne severity of 1-2 (IGA scale).

The whole-face study was conducted with 2% of the active versus placebo formulations and foresaw both short- and long-term tests, as measurements were made after 14, 28, and 56 days of treatment.

The placebo formula contains the same components as the active formula, with the exception of the active ingredient.

2.2.2 Instrumental measurements

2.2.2.1 Skin elasticity

Skin elasticity and firmness evaluation were performed using a Cutometer® dual MPA 580 (Courage & Khazaka, Germany. In this study, the following parameters were analyzed: R0 (skin distensibility or firmness), R2 (gross-elasticity), and R9 (tiring effects of the skin). The measurement area was on the cheek of each subject.

2.2.2.2 Skin profilometry

Skin surface is quantitatively assessed by PrimosCR SF (Canfield Scientific Europe, BV, Utrecht, Netherlands). In this study the following parameters were evaluated in the crow’s feet area: Sv (wrinkle depth), Ra (skin smoothness) RZ (roughness) and pore size.

2.2.2.3 Skin complexion evenness

The skin complexion evenness is measured by a colorimetric image analysis technique (Visia®-CR, Canfield Scientific). The measured parameter is the variance of color distribution of the cross-filter images.

2.2.2.4 Skin sebum content

The sebum measurement is based on the Sebumeter® method (Sebumeter 815, Courage+Khazaka GmbH).

2.2.2.5 Acne imperfections count

Before the study starts and after 14, 28 and 56 days of product use, the expert assesses the number of inflammatory and non-inflammatory lesions.

2.2.2.6 Stratum corneum turnover rate assessment (SCTT)

A 10% aqueous dihydroxyacetone (DHA) solution was applied to the volar forearm surface for 2 hours under occlusive conditions using a 12 mm Finn Chamber® to induce a brown skin tint. Each subject received four DHA patch tests, and skin color was assessed visually and instrumentally before DHA application, 24 hours post-removal, and at subsequent checkpoints using a CM-700D spectrophotometer (Konica Minolta) to track fading due to cell turnover. The staining process was monitored until complete disappearance within 28 days. Skin color evaluation included the calculation of the individual typology angle (ITA°).

2.2.3 Clinical Evaluation

This evaluation combined direct visual grading by a dermatological expert, photographic analysis, and dermatological scales to ensure accurate assessment of the following parameters: Acne spots visibility, Mattified appearance, Protoporphyrin-IX distribution — evaluated by Visia®-CR pictures (Canfield Scientific) after single product use, compared to baseline—. The Protoporphyrin-IX distribution correlates with bacterial population. Finally, skin tone uniformity was also assessed.

All these results were based on a defined score of improvement by the expert. The positive effect of the product on the measured parameter is confirmed when more than 50% of the subjects register an improvement.

2.2.4 Statistical data treatment

For each parameter and time point of analysis, the absolute values obtained during the study for each volunteer were used to calculate the variation vs D0 and the % of variation vs D0 (% var vs D0). The means and standard deviations of the % var values were then calculated. Normal distribution of data was evaluated using the Shapiro–Wilk W-test. Differences between results obtained by groups applying BFE and placebo, and between the beginning, the middle and the end of the study were analyzed by the t-student test for normal distributions, and by Wilcoxon Signed Rank test or Mann-Whitney test for non-normal distributions.

All the calculations were performed using GraphPad Prism® v8 software. A 95% level of significance was adopted.

3. Results

3.1 *In vitro* results

3.1.1 BFE reduces total and neutral lipids in Human Sebocytes

We evaluated the impact of BFE in the content of total and neutral lipids in primary sebocytes isolated and cultured in 2D monolayer. We first sought to understand whether at the doses of 0.0035%, 0.007%, 0.014%, 0.028% and 0,056% BFE showed any effect on cell viability. Of note, since linoleic acid (LA) is used in experiments to induce sebum production, LA was added alone and together with BFE when studying viability in sebocytes. Results showed there was no cytotoxicity effect found at any of the concentrations in sebocytes (data not shown).

Since acne results from a combination of several factors and involves the overproduction of sebum, we sought to analyze BFE's action on the production of sebum by sebocytes. In Figure 1, it is shown that LA elicits a strong increase in both total and neutral lipids. Interestingly, this increase is reduced by BFE following a dose-response up to BFE 0.056 %, which significantly reduced the production of total and neutral lipids by 27 % and 21 %, respectively.

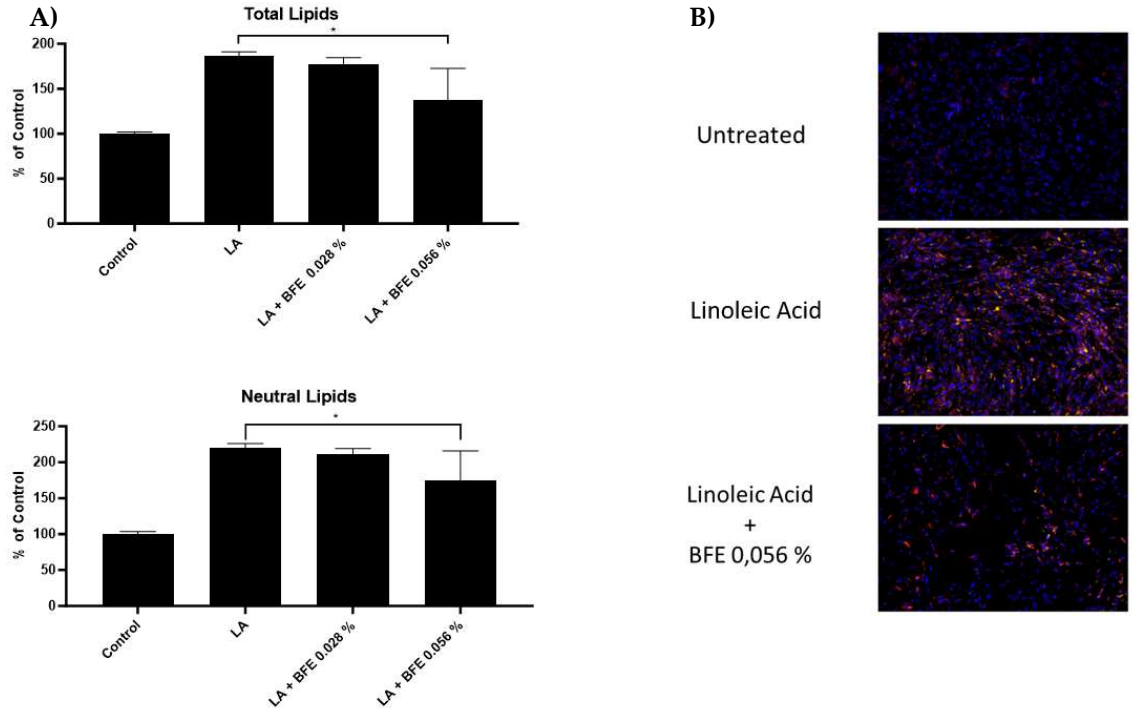

Figure 1. Total and Neutral lipids production by human Sebocytes. As described in the *In vitro* Methods section, human sebocytes were stimulated and treated with Linoleic Acid (LA) and BFE at 0.028% and 0.056 %. **A)** Total and Neutral lipids were quantified and **B)** fluorescent images were captured. Data represents mean ± SD. Statistics was performed by the one-way ANOVA followed by Dunnett's posttest, where *P<0.05 vs. LA.

As explained in the *In vitro* methods section, since neutral lipids always colocalize with total lipids, the yellow color above represents this overlap (total lipids in red, neutral lipids in green). These results let us conclude that BFE reduces the sebum production by sebocytes, thus helping to reduce the appearance of acne.

3.1.2 BFE inhibits the production of cytokines IL-6 and IL-8 in Human Sebocytes

We also sought to analyze whether BFE had an action in the inhibition of pro-inflammatory cytokines IL-6 and IL-8, the most well-studied cytokines in acne research, measured in the sebocyte's supernatants, as described in the In vitro Methods section. BFE at concentration of 0.056% significantly reduced the production of both cytokines Il-6 and IL-8 by 33.5%* and 41.36%** respectively vs control (*p<0.05, **p<0.01), which were increased by LA induction thus helping to mitigate the inflammatory response involved in the acne condition.

3.1.3 BFE increased Collagen Type I and Elastin in HDF

Next, we studied BFE's effect on Collagen Type I and Elastin production in fibroblasts, finding that BFE significantly increased collagen I (up to 14%*) and elastin (up to 25%****) levels vs control (*p<0.05, ****p<0.0001), at doses previously found not to be toxic in NHDF (data not shown).

3.1.4 BFE improves fibroblast migration

To further analyze the potential anti-aging effect of BFE, we performed a migration test on HDF treated with the active at 0.014% and the results showed that, after 48 h, in HDF the addition of BFE significantly increased cell migration to 77% of control (Figure 2).

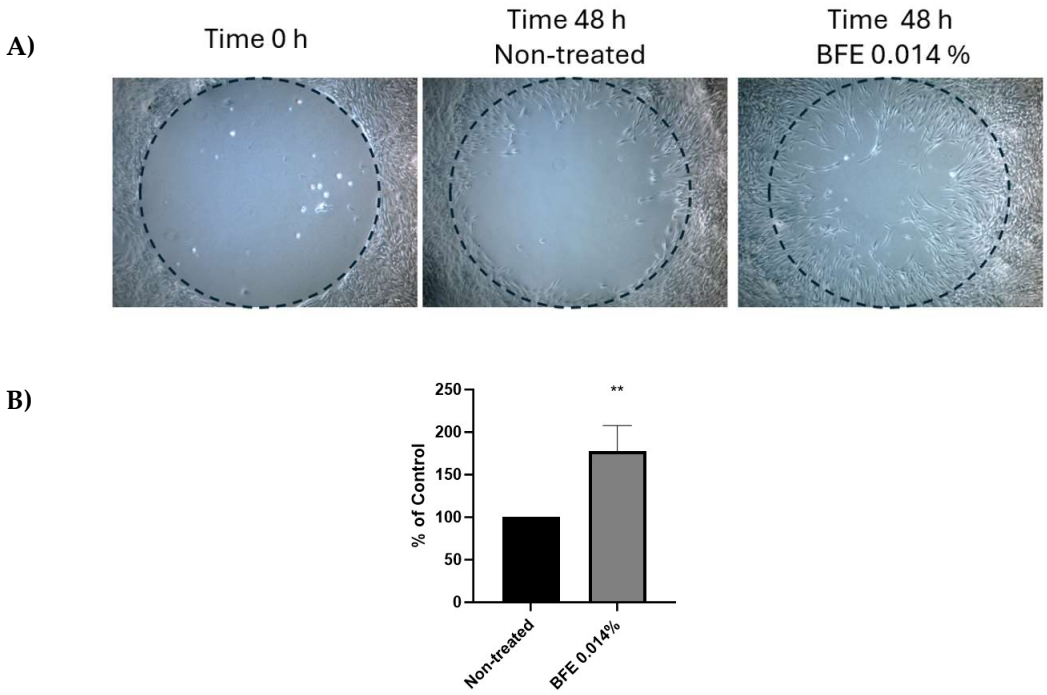

Figure 2. Dermal Fibroblasts Migration. As described in the In vitro Methods section, **A)** Human Dermal Fibroblasts (HDF) were stimulated with BFE 0.014 % for 24 and **B)** cellular migration was quantified. Data represents mean ± SD. Statistic was performed Unpaired t test, where **P<0.01 vs. Control.

These results show a consistent effect on wound healing properties in the migration test, thus revealing that BFE is a potential active ingredient for the rejuvenation of the skin.

3.1.5 BFE reduces AGEs content

The ability to suppress AGEs formation is directly related to the anti-glycation activity. In this respect AGE's were reduced in a dose-response manner by BFE by 37%* and 22% vs. control (*p<0.05) at concentration of 0.0035% and 0.00175%, respectively, being statistically significant only at higher concentration. This reduction in the production of AGEs could contribute to delaying the progress of skin aging and promoting the health of cells and tissues.

3.2 *In vivo* results

3.2.1 Instrumental parameters

The results obtained suggest that BFE treatment has the capacity to induce a visible anti-aging effect improving the skin elasticity and firmness(R0,R2 and R9 parameters), the skin smoothness and wrinkles depth (Ra, Rz and Sv parameters) and the skin tone (evenness parameter). Regarding antiacne-related parameters, BFE is effective in reducing pore size, decreasing the skin sebum and reducing the acne lesions number (see Table 1). Finally, the stratum corneum turnover (SCTT) was 1.7 days faster thanks to the application of BFE.

	% change BFE vs placebo		
Parameters	**D14**	**D28**	**D56**
R0	-1.8%**	-3.4%****	-4.1%****
R2	+2%***	+4.1%****	+5.3%****
R9	-0.05%	-3.5%*	-6.5%***
Ra	-3.23%	-7.6%***	-6.8%***
Rz	-3.9%	-8.2%***	-8%***
Sv	-7.9%***	-10.8%****	-12.4%***
Pore size	-5.2%****	-7.2%****	-10.1%****
Sebum content	-3.75%	-11.4***	-16.5%****
Evenness	-5.4%*	-6.9%**	-9.3%***
Blemish n.	-7.8%*	-10.6%**	-10.7%**

Table 1. Results of the instrumental analysis of elasticity, firmness, profilometry, pore size, sebum, evenness and blemishes number at days 14, 28 and 56. Mean values of all the subjects (BFE and placebo). The statistical comparison between both treatments is also shown (*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001).

3.2.2 Clinical study

Moreover, BFE demonstrated at a clinical level an improvement in several parametres: skin evenness, mattifying effect, reduction of Protoporphyirins-IX and reduction of acne spots visibility (Figure 3).

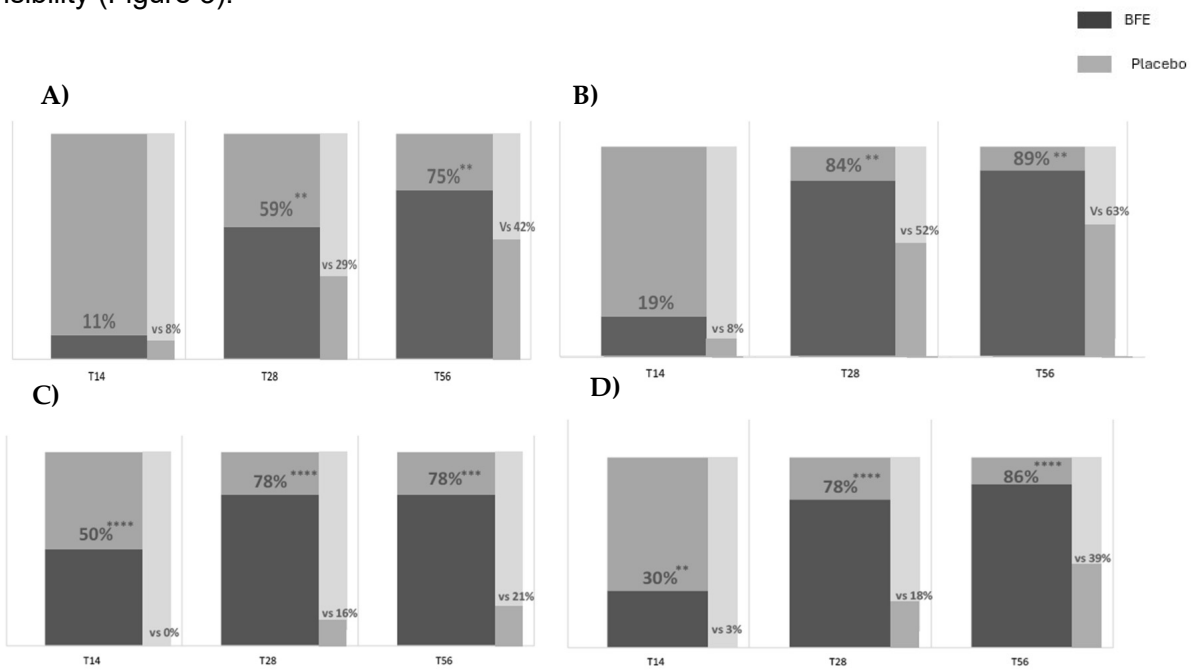

Figure 3. The graphs report the % of subjects related to the effect. **A)** Matt effect, **B)** Porphyrins-IX, **C)** acne spots, **D)** evenness. The positive effect of the product on the measured parameter is confirmed if more than 50% of the subjects register an improvement. Results are statistically superior compared to those obtained with the use of placebo at each experimental time (**p<0.01; ****p<0.0001).

4. Discussion

Sebum is produced by the sebaceous glands which are holocrine glands composed of specific cells called sebocytes. Undifferentiated sebocytes, located at the periphery of the gland, proliferate and some of them regularly begin to differentiate and to produce lipid droplets, while migrating towards the center of the gland. The ultimate final stage of sebocyte differentiation is their death, which allows the release of the cellular content in the duct of the hair follicle to which the gland is generally connected. This constitutes sebum, composed of the following total lipids: triacyl glycerides, wax esters, cholesterol, cholesterol esters, squalene and free fatty acids, from which neutral lipids (triacylglycerol and cholesterol esters) form its main proportion [7]. This production depends on both sebocyte proliferation and lipid metabolism.

The pathogenesis of acne is complex, with the sebaceous gland playing a prominent role. In adulthood the etiopathogenesis of acne vulgaris involves a complex interaction between the main factors such as: genetic predisposition; androgenic hormone stimulation leading to an increase in sebaceous secretion; alteration of the lipid composition; follicular hyper keratinization; bacterial colonization mainly by *Cutibacterium acnes* (*C. acnes*) and peri glandular dermal inflammation [8]. This activity results in the formation of sebum plugs, which, combined with other factors, results in the characteristic open (blackheads) and closed (whiteheads) comedones of acne.

On the other hand, cytokines are key regulators produced by host cells in response to infections and immune responses. Particularly IL-6 and IL-8, play critical roles in acne-associated inflammation. IL-6 and IL-8 are secreted by sebocytes [9] when stimulated by *C. acnes* or substance P. IL-6 functions as a proinflammatory cytokine and induces pilosebaceous duct hyperkeratosis [10], while IL-8 is crucial for attracting neutrophils to the site of inflammation in acne vulgaris, the pilosebaceous unit [11].

Skin aging adds complexity to these inflammatory processes by altering the extracellular matrix (ECM), which includes collagen, elastin, and glycosaminoglycans [12,13]. Inflammaging reduces collagen production, elasticity, and wound healing efficiency [14]. This process is further impacted by Advanced Glycation End Products (AGEs), formed via glycation reactions between reducing sugars and proteins, nucleic acids, or lipids [15]. AGEs degrade collagen's elasticity and rigidity, contributing to wrinkles, sagging, and skin aging [16-18]. Additionally, AGEs trigger inflammatory responses, exacerbating dryness and discomfort.

Amid these challenges, *Bacillus velezensis*, isolated from *Hyssopus officinalis* leaves, offers a novel solution. This endophytic bacterium produces peptides and lipopeptides (surfactin, fengycin, iturin), shown to disrupt *C. acnes* cell walls, reduce inflammation, stimulate collagen production, promote wrinkles reduction and accelerate wound healing [19-21]. Metabolomic analysis of its ferment (data not shown), has revealed not only peptides and lipopeptides but also a range of bioactive compounds, including sesquiterpene lactones tipycally produced by plants with antimicrobial and anti-inflammatory properties [22], and pyrrolidine derivatives that could mitigate glycation and prevent AGEs formation [23]. Leveraging this metabolic power and in view of the *in vitro* and *in vivo* results obtained, BFE could offer a bioactive ingredient for addressing acne, inflammation, and aging.

5. Conclusion

We have provided evidence about the positive *in vitro* anti-acne activities of BFE by means of sebum reduction effect and anti-inflammatory action by reducing levels of both IL-6 and IL-8 in sebocytes, and anti-aging activity by increasing Collagen Type I and Elastin, improving fibroblast migration and reducing the AGE's. In addition, our results show that BFE produces a clear rejuvenating effect *in vivo*, significantly improving aspects related to firmness and elasticity of the skin, the skin relief and evenness. Regarding anti-acne-related parameters, BFE is effective in reducing pore size, decreasing skin sebum and minimizing acne lesions. Moreover, BFE demonstrated at a clinical level an improvement in skin evenness, in the mattifying effect, in the reduction of protoporphyirins-IX and in the reduction of acne spots visibility. Finally, the stratum corneum turnover was accelerated thanks to the application of BFE showing its regenerative potential. In conclusion, these results demonstrate that BFE, obtained through a biotechnology platform for the isolation and culture of plant endophytes, is a multi-functional cosmetic active ingredient for managing adult acne while delivering anti-aging and skin-regenerating benefits.

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