

Article

Sebum Regulating, Anti-Inflammatory, and Lipid Restoring Efficacy of Isorhamnetin Extracted from *Opuntia ficus-indica*: Results from a Randomized Double-Blind Clinical Trial

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Abstract

Oily skin is a prevalent dermatological condition characterized by excessive sebum production, due to hyperactivity of the sebaceous glands. In this study, a randomized split-face clinical trial was conducted on 22 subjects with combination to oily skin to evaluate the efficacy of a cosmetic cream containing a standardized amount of isorhamnetin extract from prickly pear (*Opuntia ficus-indica*), applied twice daily over a 28-day period. Efficacy assessments included instrumental measurements of skin sebum content, Sebum Excretion Rate (SER), pore size, tumor necrosis factor-alpha (TNF- α) levels, skin microbiome composition, and lipid profile. Additionally, the study included an assessment of participants' subjective perception. After 14 and 28 days of product use, respectively, a significant reduction in skin sebum content was observed, with decreases of 13.1% and 21.1% on the forehead, and 10.4% and 15.8% in the alar groove. This reduction in sebum levels was associated with a mattifying effect lasting up to 7.1 h, a 37.2% decrease in the sebum excretion rate (SER), and a 9.6% reduction in pore size. The TNF- α levels decreased by 7.4%. The extract was well tolerated by the skin microbiome, which remained stable. Additionally, analysis of the skin lipid profile revealed an increase in both ceramide and triacylglycerol levels. Overall, our findings demonstrate the role of the extract in modulating sebaceous gland activity, improving skin appearance, reducing inflammation, and supporting barrier integrity and hydration in individuals with oily skin.

Keywords: *Opuntia ficus-indica*; isorhamnetin; oily skin; clinical trial; lipidomics



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1. Introduction

Sebaceous glands (SG), closely associated with hair follicles, play a pivotal role in maintaining skin homeostasis by regulating lipid production and contributing to the skin's barrier function. Under normal conditions, the SG activity consists of holocrine secretion of an oily secretion (sebum) that lubricates the hair and contributes to the lipid barrier of the skin [1–3]. Beyond its well-known function as a skin lubricant, sebum exhibits additional less-explored roles, including protection against UVB-induced apoptosis,

contribution to the skin's innate immune defense, and modulation of systemic energy metabolism [4–8]. Notably, SG activity dysregulation is a central factor in the pathogenesis of acne and contributes to the development of other debilitating dermatological conditions, including atopic dermatitis and psoriasis [1,9,10].

SG activity exhibits dynamic changes across the human lifespan, influenced by hormonal fluctuations and physiological maturation [11,12]. Under normal conditions the average sebum excretion rate (SER) every three hours in adults is $1.0 \text{ mg} \times 10 \text{ cm}^{-2}$, and it exceeds $1.5 \text{ mg} \times 10 \text{ cm}^{-2}$ every three hours in subjects with oily skin [11,13]. SER exhibits significant interindividual variability, and the underlying mechanisms governing this variation remain incompletely understood. The “risk factors” for the oily skin condition include the male sex, ovulation, spring or summer seasons, humid climate, African American ethnicity, and androgens [14].

An increase in the SG activity characterizes the oily skin condition, leading to excessive sebum accumulation on the skin surface. This increase in lipid content contributes to a persistently greasy appearance, visibly enlarged pores, and a dull or uneven complexion, among other commonly reported dermatological concerns [15,16]. Excess sebum not only compromises the aesthetic quality of the skin but also creates a favorable environment for the accumulation of impurities (i.e., porphyrins), lipid oxidation, and microorganisms' proliferation [17–20]. These alterations contribute to clogged pores, the formation of blackheads, and the development of acne and related dermatological issues [21–24]. Dysregulation of SG activity has also been implicated in the promotion of cutaneous inflammation, with evidence suggesting an active role in modulating inflammatory pathways [9]. Recent findings have clarified that the oily-skin condition is not only the consequence of increased sebum secretion but also the expression of a complex biological loop defined as the “oily-skin loop” in which oxidative stress, sebocyte overproliferation, inflammation, and microbial dysbiosis sustain and amplify each other (Figure 1) [9].

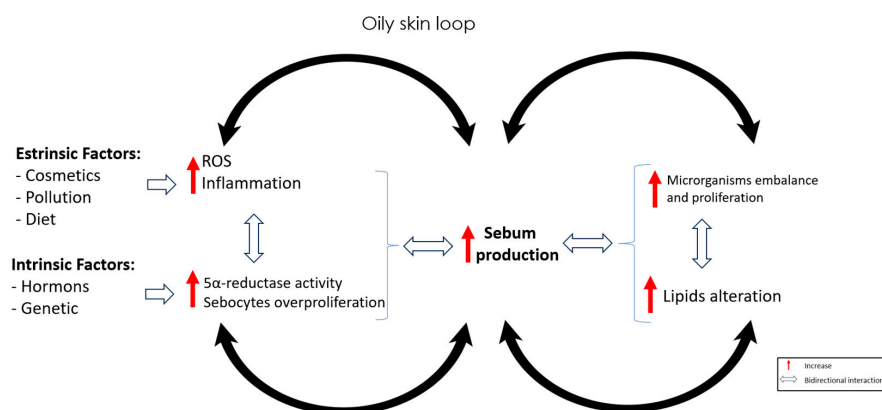


Figure 1. Schematic representation of the oily-skin loop and its modulation by PURYFLOWER™. Extrinsic factors (cosmetics, pollution, diet) and intrinsic factors (hormonal and genetic) converge to promote oxidative stress and inflammation (ROS, TNF- α), as well as increased 5 α -reductase activity and sebocyte overproliferation. These processes enhance sebum production, leading to lipid alteration and microbial imbalance, which in turn further amplify oxidative and inflammatory signaling, establishing a self-reinforcing “oily-skin loop”.

Extrinsic factors such as cosmetics, pollution, and diet contribute to reactive oxygen species (ROS) generation and inflammatory signaling, while intrinsic factors, including hormonal stimulation and genetic predisposition, enhance 5 α -reductase activity and sebocyte proliferation [25–28]. Together, these mechanisms lead to increased sebum production and altered lipid composition, creating a favorable microenvironment for microbial imbalance. The resulting dysbiosis, characterized by *Cutibacterium acnes* predominance and reduced

microbial diversity, triggers the release of lipases, porphyrins, and short-chain fatty acids that activate TLR2/NF- κ B and PPAR γ pathways in sebocytes, further promoting lipogenesis and cytokine production. This self-reinforcing cycle establishes a persistent condition of hyperseborrhea, inflammation, and altered barrier function.

Breaking this loop requires strategies capable of acting simultaneously on oxidative, inflammatory, and microbiome-related components of the sebaceous ecosystem, while supporting physiological SER regulation. Polyphenolic compounds, particularly isorhamnetin derivatives, have been reported to exert antioxidant, anti-inflammatory, and anti-lipogenic effects in sebocytes and keratinocytes [29]. Among botanical sources, the flowers of *Opuntia ficus-indica* are particularly rich in these bioactives, together with flavonols and polysaccharides conferring antioxidant and antimicrobial activity [30]. In vitro and ex vivo studies described in a patented formulation [31] demonstrated that *O. ficus-indica* flower extracts inhibit lipid peroxidation, reduce nitric oxide and TNF- α release, and modulate 5 α -reductase activity, supporting their potential relevance for conditions characterized by sebaceous hyperactivity.

Given its high prevalence, there is a growing demand for effective therapeutic strategies to manage oily skin, with particular interest in safe, non-invasive, and well-tolerated treatments derived from natural ingredients. In this context, cosmetic or dermocosmetics formulations represent an optimal approach, offering tangible benefits while minimizing the risk of adverse effects. Aligned with this objective, we investigated the safety and efficacy of a natural standardized commercially available cosmetic ingredient obtained from prickly pear cactus flowers, in having a part in the oily-skin loop. Specifically, we assessed the skin tolerability (epicutaneous patch test) of the ingredient, along with its efficacy in regulating sebum production, modulating cutaneous inflammation, and influencing the overall lipid profile of the skin (clinical trial). The tested ingredient was a powdered extract of *Opuntia ficus-indica* (OFI) flowers, supported on maltodextrin, and standardized to contain isorhamnetin at a concentration of $\geq 0.3\%$ (*w/w*). Extracts from OFI flowers have been traditionally used for their anti-inflammatory, antibacterial, and antioxidant properties [31–37]. In the cosmetic field, OFI extracts are currently used in cosmetics for their skin conditioning properties; however, a more comprehensive understanding and extensive research on their efficacy profile are needed [38–41].

2. Materials and Methods

2.1. Primary Skin Irritation

An epicutaneous patch test was conducted on 25 subjects with sensitive skin to assess the primary skin irritation. Participants were selected based on their medical history and their response to the lactic acid stinging test. In brief, a 10% aqueous lactic acid solution was applied to the alar groove, and the reaction was evaluated according to the perceived stinging intensity. Subjects who exhibited a positive stinging response were classified as having sensitive skin and subsequently included in the study.

The product was applied undiluted (previously imbibed with demineralized water) to the skin of the back using 8 mm Finn Chambers[®] on Scanpor[®] tape (SmartPractice, Rome, Italy) for 48 h. A negative control, consisting of a Finn Chamber containing a blotting paper disk soaked in demineralized water, was also included.

During the entire study period, subjects were required to refrain from exposure to both natural and artificial sunlight, as well as from physical exercise, water immersion, sauna, and steam baths. Mechanical stress or friction at the test site was also not permitted.

After the exposure period, the chambers were removed, and primary cutaneous reactions (erythema and edema) were evaluated 15 min, 1 h, and 24 h after removal. Reaction scoring was performed according to Draize scoring system (Table 1) [42]. A

mean irritation index (MII) was then calculated for each timepoint according to the following equation:

$$MII_{15\text{min}/1\text{h}/24\text{h}} = \frac{\sum_1^n \text{Erythema}_{\text{score}}}{n} + \frac{\sum_1^n \text{Oedema}_{\text{score}}}{n} \quad (1)$$

Table 1. Scoring of erythema and edema reactions.

Erythema		Edema	
No erythema	0	No edema	0
Light erythema (hardly visible)	1	Very Light edema (hardly visible)	1
Clearly visible erythema	2	Light edema	2
Moderate erythema	3	Moderate edema (about 1 mm raised skin)	3
Serious erythema (dark red with possible formation of light scars)	4	Strong edema (extended beyond the application area)	4

The irritancy of the product was classified according to the MII as follows: $MII < 0.5$ not irritating, $0.5 \leq MII < 2.0$ slightly irritating, $2.0 \leq MII < 5.0$ moderately irritating, $5.0 \leq MII < 8.0$ highly irritating.

All the study procedures were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964) and its subsequent amendments.

2.2. Clinical Study

2.2.1. Trial Design

This was a monocentric, randomized, split-face, double-blind, and placebo-controlled trial conducted in the Complife Italy facility in San Martino Siccomario (Pavia, Italy) between November 2024 and January 2025.

The trial comprised a screening visit (D-1), a baseline visit (D0), and two follow-up visits after 14 days (D14) and 28 days (D28) of product use. During the screening visit, subjects were informed of the study procedures, potential risks, and benefits, and were asked to sign the informed consent form either on the same day or within the following days, if additional time was needed to make an informed decision. At the baseline visit, the investigator verified the subject's compliance with the inclusion and exclusion criteria (listed in Section 2.2.2. Participants), collected the medical history, and recorded baseline values for all trial outcomes. The outcome measures were then evaluated at D14 and D28. These included the skin sebum content (measured on both the forehead and alar grooves), sebum excretion rate (SER), pore diameters, TNF- α levels, skin microbiome composition, and skin lipids profile. All outcome measures were assessed at D14 and D28, except for the TNF- α levels, skin microbiome, and skin lipid content, which were evaluated only at baseline (D0) and D28.

All trial procedures were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964) and its subsequent amendments.

Ethical review and approval were not required for this trial, as the tested products complied with EU Cosmetic Regulation No. 1223/2009. This regulation mandates that cosmetic products undergo a safety assessment to ensure they do not pose a risk to human health under normal or reasonably foreseeable conditions of use. Therefore, no additional ethical approval was necessary prior to testing on human subjects.

2.2.2. Participants

Eligible participants were healthy adult male (50%) and female (50%) subjects, aged 18 to 40 years, with mixed or oily skin types, enlarged pores, and excessive sebum production. Subjects were excluded from the trial if they were participating in or planning to participate in another clinical trial; planning a hospitalization during the study period; or had participated in a similar study without observing an appropriate washout period. Additional exclusion criteria included the presence of any acute, chronic, or progressive illness that could interfere with study data or was deemed by the investigator to pose a risk to the subject or to be incompatible with study requirements. Subjects were also excluded if they were undergoing pharmacological treatments or had skin conditions considered incompatible with the study, had a known allergy or sensitivity to cosmetic products, drugs, patches, or medical devices; were pregnant, breastfeeding, or unwilling to take appropriate contraceptive precautions (for women of childbearing potential); or had facial hair (beard) that could interfere with assessments.

2.2.3. Interventions and Randomization

The active and placebo products were randomly assigned to either the right or left side of each participant's face to ensure intra-individual comparison and minimize variability. Randomization was conducted using a restricted randomization list generated with the 'Efron's biased coin' algorithm, which balances treatment assignments while preserving randomness. This list was created using PASS 11 software (version 11.0.8; PASS, LLC, Kaysville, UT, USA) by an independent statistician who was not involved in the trial's conduct. The randomization process ensured allocation concealment and helped prevent selection bias. Investigators and participants were blinded to the side of application for each product to maintain the integrity of the study results.

The active product (PRF) was a cream formulation containing 1% PURYFLOWER™ (Bionap S.r.l., Piano Tavola Belpasso, CT, Italy). PURYFLOWER™ is a natural extract derived from the flowers of *Opuntia ficus-indica*, standardized to contain $\geq 0.3\%$ (*w/w*) isorhamnetin. The complete ingredient list of PRF was: AQUA/WATER, GLYCERIN, DIETHYLHEXYL CARBONATE, SODIUM ACRYLATE/SODIUM ACRYLOYLDIMETHYL TAURATE COPOLYMER, SQUALANE, OPUNTIA FICUS-INDICA FLOWER EXTRACT, MALTODEXTRIN, HYDROXYACETOPHENONE, PHENOXYETHANOL, ETHYLHEXYLGLYCERIN, POLYACRYLATE CROSSPOLYMER-6, SODIUM POLYACRYLATE, SODIUM PHYTATE, ALCOHOL, CITRIC ACID. The placebo formulation (PLA) was identical to the PRF formulation, except it did not contain the active ingredient (OPUNTIA FICUS-INDICA FLOWER EXTRACT), which was replaced by MALTODEXTRIN. Both the PRF and PLA formulations were applied twice daily (morning and evening) to the cleansed face. Each application was followed by gentle massage to promote product absorption.

2.2.4. Outcomes

Skin Sebum Content and Sebum Excretion Rate (SER)

The skin sebum content was measured using the grease spot photometry method with a Sebumeter® SM 815 (Courage + Khazaka Electronic, Cologne, Germany). The skin sebum content was measured at two facial sites: the alar grooves and the forehead.

The SER was measured as previously described by Liu et al., with minor modifications [43]. Briefly, subjects were instructed to cleanse their face at least 4 h prior to the visit, and the skin sebum content was measured as follows:

- Four hours after the last washing at home (T0);
- After complete removal of surface sebum (delipidization) using cotton pads soaked in a 30% aqueous ethanol solution (Tdpl);

- After 0.5, 2, and 4 h (T0.5, T2, and T4, respectively) after the removal of surface sebum and the application of the PLA and PRF products.

Pore Diameters

The pore diameters were measured using the PRIMOS^{CR} Small Field device (Canfield Scientific Europe, BV, Utrecht, The Netherlands). After the images' alignment and the application of the "robust high pass filter", a line was drawn through the pore within the region (alar area) of interest (ROI), and the pore diameter was measured using PRIMOS^{CR} software (version 5.8). The results are reported as the mean value of five pore diameter measurements taken within the region of interest (ROI).

Tumor Necrosis Factor-Alpha (TNF- α) Dosage

Tumor necrosis factor-alpha (TNF- α) levels were measured on the skin of the cheeks, following the protocol previously described by Roveda et al. [43]. Briefly, samples were collected using non-invasive tape stripping (Corneofix[®] foils, Courage + Khazaka Electronic, Köln, Germany) and stored at -80°C until analysis. When all the samples were collected, TNF- α was then extracted and quantified using a commercially available ELISA kit (Catalog No. E-EL-H0109, Elabscience, Houston, TX, USA), in accordance with the manufacturer's instructions.

Skin Microbiome

Sterile moistened swabs (FLOQSwab[®], Copan Spa, Brescia, Italy) were rubbed 10 times horizontally and 10 times vertically over a 3.5×5.5 cm area on the cheek and immediately placed in 1 mL of preservation medium (eNat[®], Copan Spa, Brescia, Italy). All collected swabs were immediately stored at -20°C . Procedures for DNA extraction, library generation, and sequencing were performed as previously described [44]. Briefly, bacterial DNA was extracted using the QIAamp[®] DNA Microbiome Kit (Qiagen, Hilden, Germany); the yield and quality of the extraction procedure was assessed using the QubitTM 1X dsDNA HS Assay Kit (Invitrogen Co., Carlsbad, CA, USA) on a QubitTM Flex Fluorometer (Thermo Fisher Scientific, Waltham, MA, USA). V1–V3 hypervariable regions of the bacterial 16S rRNA gene were amplified by Polymerase chain reaction (PCR) using the Microbiota Solution A kit (Arrow Diagnostics, Genoa, Italy), and the resulting products were purified using Agencourt AMPure XP magnetic beads (Beckman Coulter Inc., Brea, CA, USA). The final amplicon libraries were sequenced in equimolar concentrations on a MiSeq Illumina[®] sequencing platform using a MiSeq Reagent Kit v2 cartridge for 2×250 paired-end sequencing (Illumina Inc., San Diego, CA, USA) after amplicon size and purity of the PCR products via electrophoresis on a 1.5% agarose gel in TAE buffer ($1\times$).

Skin Lipids Profile

Skin lipids were collected using non-invasive tape stripping (Corneofix[®] foils, Courage + Khazaka Electronic, Köln, Germany) and stored at -80°C . The lipidome was then identified and quantified by liquid chromatography coupled to mass spectrometry. High-purity LC-MS-grade solvents, including water, methanol, acetonitrile, and isopropanol, as well as methyl tert-butyl ether (MTBE) and mobile phase additives (formic acid and ammonium formate) were obtained from VWR International (Barcelona, Spain). The deuterated internal standard, SPLASH[®] LIPIDOMIX[®] Mass Spec standard, was obtained from Avanti Polar Lipids.

Lipids were extracted from Corneofix[®] foils by incubating the samples in 900 μL of ice-cold methanol (4°C) under constant agitation at 1400 rpm for 1 h. The extracted lipids were then evaporated to dryness, and the resulting residue was subsequently reconstituted in a

methanol:methyl tert-butyl ether (80 MeOH: 20MTBE, *v/v*) mixture and filtered through a Captiva 96-well filter plate with a 0.22 µm pore size (A5960045, Agilent Technologies, CA, USA). Lipids were then analyzed by UHPLC mass spectrometry using a 1290 Infinity II ultra-high performance liquid chromatograph (Agilent Technologies, CA, USA) coupled to a 6560 Ion Mobility Q-TOF mass spectrometer (Agilent Technologies, CA, USA). Lipids were separated on a Water Acquity UPLC CSH C18 column (130 Å, 1.7 µm, 2.1 mm × 100 mm) equipped with an additional Water Acquity VanGuard CSH C18 pre-column (130 Å, 1.7 µm, 2.1 mm × 5 mm) and maintained at 65 °C. The mobile phases consisted of (phase A) acetonitrile/H₂O (60:40 *v/v*, with 10 mM ammonium formate and 0.1% formic acid) and (phase B) isopropanol/acetonitrile (90:10 *v/v*, with 10 mM ammonium formate and 0.1% formic acid). The gradient was as follows: 0 min 15% (B); 0–2 min 30% (B); 2–2.5 min 48% (B); 2.5–11 min 82%; 11–11.5 min 99%; 11.5–12 min 99% (B); 12–12.1 min 15% (B); and 12.1–15 min 15% (B). The mobile phase flow rate was 0.6 mL/min, and the injection volume was 15 µL. At the end of the elution period, the MS detector was operated in electrospray ionization (ESI) with the following parameters: spray voltage 3.0 kV (ESI+) and −3 kV (ESI−); gas temperature 200 °C; sheath gas (nitrogen) flow rate 11 L/min and temperature 350 °C; drying gas (nitrogen) flow rate 14 L/min; nebulizer gas (nitrogen) pressure 35 psi; acquisition rate 2 spectra; MS/MS spectra collection at 20 eV collision energy with an acquisition rate of MS of 10 spectra/s (100 ms) and an acquisition rate for MS/MS of 13 spectra (77 ms) with 4 precursor ions per cycle [45,46].

Skin Tolerability

In case of the occurrence of local skin tolerance reactions, the dermatologist assessed their severity using a 5-point clinical scale, as follows: 0 = none, 1 = very mild, 2 = mild, 3 = moderate, and 4 = severe.

Self-Assessment Questionnaire

At the final visit, subjects were invited to provide their subjective evaluation regarding the self-perceived efficacy and duration of the mattifying effect.

2.2.5. Statistical Methods

Sample Size

The required sample size was estimated based on a two-sided significance level of 5% ($\alpha = 0.05$) and a statistical power of 80% ($1 - \beta = 0.80$). The calculation considered an expected 20% variability in the primary endpoints, accounting for both inter-individual differences and potential measurement errors. Sample size estimation was performed using PASS 11 statistical software (version 11.0.8; PASS, LLC, Kaysville, UT, USA), resulting in a minimum of 20 subjects per treatment group. Two additional subjects were included to account for an anticipated dropout rate of 10%.

Statistical Analysis of Instrumental Data

Data were analyzed using Student's *t*-test for paired samples. Intragroup comparisons (post-treatment vs. baseline) were conducted on raw data, whereas intergroup comparisons (PRF vs. PLA) were performed on percentage changes relative to the baseline values.

The area under the curve (AUC) was calculated according to Equation (2) (trapezoidal rule).

$$AUC = \frac{1}{2} \sum_{n=1}^{n-1} (T_{i+1} - T_i)(S_{i+1} + S_i - 2B) \quad (2)$$

where *n* is the number of time points, *T_i* is the *i*th time value, *S_i* is the *i*th sebum concentration value, and *B* is the baseline value.

All statistical analyses were carried out using NCSS 10 software (version 10.0.7 for Windows; NCSS, Kaysville, UT, USA).

Statistical Analysis of Microbiome Data

Raw sequencing data were processed using MicrobAT (Microbiota Analysis Tool) v.1.1.0 software (SmartSeq Srl, Novara, Italy), based on a comparison with the Ribosomal Database Project (RDP) database. Once filtered for read length (<200 nt) and quality (average Phred quality score < 25) [47], the resulting sequences were aligned with a similarity threshold of $\geq 97\%$ and assigned to taxonomic levels with a query coverage of 80% [48]. Features without taxa designation were ascribed to the corresponding unclassified group. A secondary analysis of the results was performed using MicrobiomeAnalyst Software [49,50], where features with low counts and variance were identified and removed, while the remainder were analyzed according to their median abundance levels (minimum count of 4) across samples.

Microbial diversity was assessed at both the alpha (within-group) and beta (between-group) levels. Alpha diversity was quantified using two complementary indices: the Shannon index, which accounts for both richness and evenness of taxa, with higher values indicating greater taxonomic diversity; and the Simpson index, which measures dominance and evenness, where values approaching 1 suggest dominance by a few taxa, while lower values indicate a more even distribution. Beta diversity was evaluated to compare the overall taxonomic composition across groups. A Bray–Curtis dissimilarity matrix was computed and visualized using Principal Coordinates Analysis (PCoA), wherein each point represents the microbial profile of an individual sample. Differences in microbial community structure between groups were tested for statistical significance using PERMANOVA (Permutational Multivariate Analysis of Variance). Linear Discriminant Analysis Effect Size (LEfSe) was employed to identify microbial taxa that were differentially abundant between groups. The magnitude of the effect size is reported by the Linear Discriminant Analysis (LDA) score.

Statistical Analysis of Lipidomic Analysis

Compound identification was performed using three-dimensional lipidomic data, integrating accurate mass, retention time, and mass spectral features. Method validation was carried out using a panel of 69 deuterated internal standards, representative of 14 lipid classes. These standards were further used to calibrate the signal intensity across the analytical run. Additionally, retention time locking was applied to ensure the consistency and reproducibility of chromatographic alignment.

3. Results

3.1. Primary Skin Irritation

The primary skin irritation was performed by epicutaneous patch testing on 25 subjects with sensitive skin. A slight (barely perceptible) erythema was observed in 24% of participants after 15 min, in 36% after 1 h, and in 4% after 24 h (Table 2).

Table 2. Mean irritation index. Continuous data are expressed as the mean value; categorical data are expressed as counts (number of subjects showing a skin reaction).

	15 min					1 h					24 h				
Score	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Erythema	19	6	0	0	0	16	9	0	0	0	24	1	0	0	0
Edema	25	0	0	0	0	25	0	0	0	0	25	0	0	0	0
MII	0.24 (<0.5)					0.36 (<0.5)					0.04 (<0.5)				

The mean irritation index at each timepoint was always below the 0.5 threshold value, indicating a non-irritating potential.

3.2. Trial Population and Skin Tolerability

A total of 28 subjects were screened for eligibility. Of these, six were excluded from the trial population for the following reasons: five failed to meet the inclusion criteria, and one declined to participate. As a result, 22 subjects were randomized to receive both the active and placebo formulations, each applied to one half of the face in a split-face design. The per protocol (PP) population consisted of 21 subjects since one subject dropped out at D14 for personal reasons (Figure 2). The study population consisted of 50% male and 50% female subjects, with a mean age of 26.2 ± 1.3 years (range: 20–39 years). Other demographics are reported in Table 3.

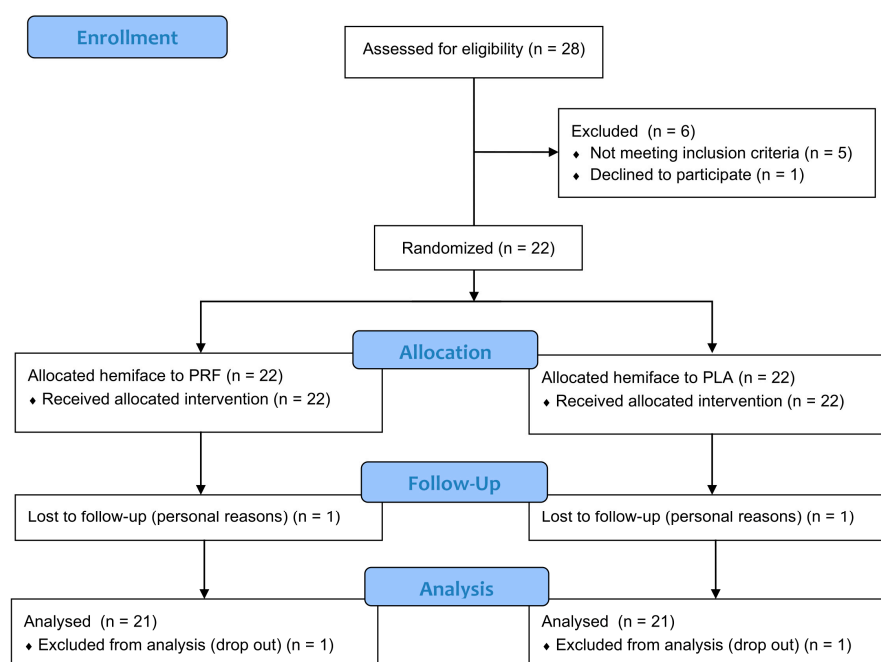


Figure 2. CONSORT flow diagram. The study was conducted using a split-face design, in which each participant simultaneously received the active formulation and the placebo.

Table 3. Baseline and demographic characteristics. Data are mean $\pm$ SEM.

	Active	Placebo	Units	<i>p</i> -Value ¹
Sex				
Male	50% (11)		% (no.)	n.a.
Female	50% (11)		% (no.)	n.a.
Age	26.2 $\pm$ 1.3		Years	n.a.
Skin sebum content				
Forehead	189.2 $\pm$ 4.5	186.6 $\pm$ 5.1	$\mu\text{g} \times \text{cm}^{-2}$	0.2212
Alar grooves	189.6 $\pm$ 6.0	190.3 $\pm$ 5.7	$\mu\text{g} \times \text{cm}^{-2}$	0.8608
Sebum Excretion Rate (SER)	37.5 $\pm$ 1.2	37.2 $\pm$ 1.0	$\mu\text{g} \times \text{cm}^{-2} \times \text{h}^{-1}$	0.6302
Pore diameter	871.3 $\pm$ 25.7	870.6 $\pm$ 27.1	μm	0.9622
TNF- α	11.1 $\pm$ 0.6	11.6 $\pm$ 0.6	pg/mL	0.4399

¹ Two-way Student's *t*-test for paired data.

Both the active and placebo formulations were well tolerated, with no clinically significant adverse reactions reported.

3.3. Skin Sebum Content

At baseline, the skin sebum content on the forehead was $189.2 \pm 4.5 \mu\text{g} \times \text{cm}^{-2}$ in the PRF-treated hemi-face and $186.6 \pm 5.1 \mu\text{g} \times \text{cm}^{-2}$ in the PBO-treated hemi-face. Following 14 days of product application, the sebum level in the PRF-treated hemi-face decreased by 13.1% ($p < 0.001$), with a further reduction of 21.1% ($p < 0.001$) observed at D28 (Figure 3a). In contrast, no statistically significant ($p > 0.05$) change was observed in the PBO-treated hemi-face throughout the study period.

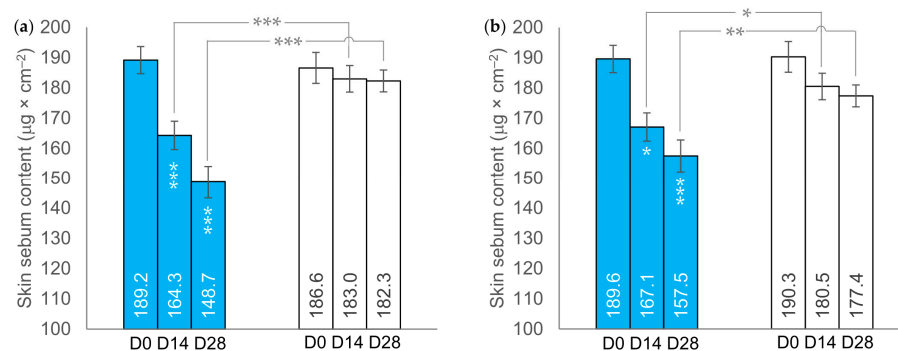


Figure 3. Skin sebum content. (a) Forehead. (b) Alar grooves. The intragroup (vs. D0) statistical analysis is reported inside the bars, while the intergroup (active vs. placebo) statistical analysis is reported above the bars. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. ■ PRF □ PBO.

The baseline skin sebum levels in the alar grooves were $189.6 \pm 6.0 \mu\text{g} \times \text{cm}^{-2}$ for the PRF-treated hemi-face and $190.3 \pm 5.7 \mu\text{g} \times \text{cm}^{-2}$ for the PBO-treated hemi-face, showing values comparable to those measured on the forehead. In the PRF-treated area, the sebum content significantly decreased by 10.4% ($p < 0.05$) at D14, with a further significant reduction of 15.8% ($p < 0.001$) observed at D28 (Figure 3b). In the PBO-treated hemi-face, a slight reduction (-4.2% at D14 and -5.7% at D28) in skin sebum content was observed; however, the change was not statistically significant ($p > 0.05$).

The differences observed between the PRF and PBO in the forehead and in the alar grooves were statistically significant (Figure 3).

3.4. Sebum Excretion Rate

The area under the curve (AUC, Table 4) of the post-delipidation sebum excretion kinetics was $340.4 \pm 14.4 \text{ mg} \times \text{cm}^{-2} \times \text{h}^{-1}$ in the PRF-treated hemiface and $330.2 \pm 15.2 \text{ mg} \times \text{cm}^{-2} \times \text{h}^{-1}$ in the PBO-treated hemiface. After 14 days, the AUC decreased by 27.9% in the PRF-treated hemiface ($244.7 \pm 15.7 \text{ mg} \times \text{cm}^{-2} \times \text{h}^{-1}$; $p < 0.001$) and by 5.6% in the PBO-treated hemiface ($306.3 \pm 16.3 \text{ mg} \times \text{cm}^{-2} \times \text{h}^{-1}$). At day 28, the AUC further decreased by 37.2% in the PRF-treated hemiface ($217.1 \pm 24.7 \text{ mg} \times \text{cm}^{-2} \times \text{h}^{-1}$; $p < 0.001$), whereas it increased by 4.3% in the PBO-treated hemiface ($336.2 \pm 17.5 \text{ mg} \times \text{cm}^{-2} \times \text{h}^{-1}$). Differences between the PRF and PBO were statistically significant at both D14 and D28 ($p < 0.001$).

In both the PRF-treated and PBO-treated hemi-faces, the post-delipidation sebum recovery followed a linear kinetic profile, with a coefficient of determination (R^2) higher than 0.8, an average slope of approximately 51, and an SER of approximately $37 \mu\text{g} \times \text{cm}^{-1} \times \text{h}^{-1}$ (Figure 4a,b and Table 4). In the PRF-treated hemi-face, the SER decreased by 25.9% ($p < 0.001$) and 38.1% ($p < 0.001$) at D14 and D28, respectively. In the PBO-treated hemiface, the SER was decreased (-11.6% , $p < 0.01$) only at D14, while it was unchanged (-4.0% , $p > 0.05$) at D28. The differences observed between PRF and PBO were statistically significant ($p < 0.001$). The rate of sebum production (slope of the regression

curve) in the PRF-treated hemi-face was reduced by 2.2-fold at D14 and by 10.1-fold at D28 compared to the PBO-treated hemi-face.

Table 4. Sebum excretion rate (SER). Data are mean $\pm$ SEM. Values in parentheses indicate the percentage change relative to baseline (D0). Intragroup comparisons (vs. D0) and intergroup comparisons (PRF vs. PBO) are indicated by asterisks (*) and hash symbols (#), respectively, with statistical significance denoted as follows: ** $p < 0.01$; ***/### $p < 0.001$.

		AUC	SER ($\mu\text{g} \times \text{cm}^{-2} \times \text{h}^{-1}$)	Slope	R ²
PRF	D0	340.4 $\pm$ 14.4	37.5 $\pm$ 1.2	0.9742	0.9742
	D14	244.7 $\pm$ 15.7 *** (−27.9%) ###	27.8 $\pm$ 2.0 *** (−25.9%) ###	0.9789	0.9789
	D28	217.1 $\pm$ 24.7 *** (−37.2%) ###	23.2 $\pm$ 2.1 *** (−38.1%) ###	0.9838	0.9838
PBO	D0	330.2 $\pm$ 15.2	37.2 $\pm$ 1.0	0.9705	0.9705
	D14	306.3 $\pm$ 16.3 (−5.6%)	32.9 $\pm$ 1.5 ** (−11.6%)	0.9890	0.9890
	D28	336.2 $\pm$ 17.5 (4.3%)	35.7 $\pm$ 1.0 (−4.0%)	0.9843	0.9843

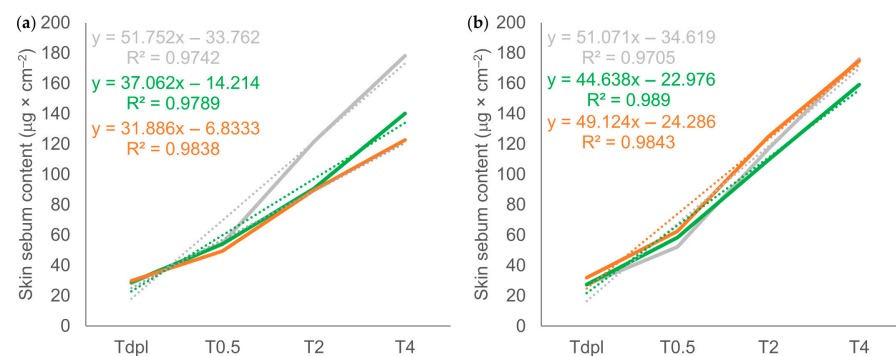


Figure 4. Sebum excretion rate. (a) PRF-treated hemi-face. (b) PBO-treated hemi-face. Tdpl after delipidization; T0.5, T2, T4 represent half-an-hour, 2, and 4 h after product application and delipidization. Solid lines represent the skin sebum content, while dot lines represent the regression curves. ■ D0 ■ D14 ■ D28.

3.5. Pore Diameters

At baseline, the participants exhibited enlarged pores with a mean diameter of $870.9 \pm 18.7 \mu\text{m}$. Application of the active product resulted in a statistically significant ($p < 0.001$) reduction in pore diameter by 5.4% (up to 17%) at D14 and 9.6% (up to 26%) at D28, compared to baseline (Table 5). In contrast, no significant change was observed in the placebo (PBO)-treated hemiface, with the pore diameter remaining statistically unchanged ($p > 0.05$).

Table 5. Pore diameters and TNF- α levels. Data are mean $\pm$ SEM. Values in parentheses indicate the percentage change relative to baseline (D0). Intragroup comparisons (vs. D0) and intergroup comparisons (PRF vs. PBO) are indicated by asterisks (*) and hash symbols (#), respectively, with statistical significance denoted as follows: * $p < 0.05$, ***/### $p < 0.001$. n.d. not determined.

		D0	D14	D28
Pore diameter (μm)	PRF	871.3 $\pm$ 25.7	822.0 $\pm$ 22.8 *** (−5.4%) ###	783.4 $\pm$ 18.7 *** (−9.6%) ###
	PBO	870.6 $\pm$ 27.1	865.7 $\pm$ 26.4 (−0.5%)	861.7 $\pm$ 26.3 (−1.0%)
TNF- α (pg/mL)	PRF	11.1 $\pm$ 0.6	n.d.	10.3 $\pm$ 0.7 * (−7.4%)
	PBO	11.6 $\pm$ 0.6	n.d.	11.3 $\pm$ 0.4 (−1.3%)

3.6. Tumor Necrosis Factor-Alpha (TNF- α)

At D28, the TNF- α levels were statistically significantly ($p < 0.05$) decreased by 7.4% (up to 34.7%) in the PRF-treated hemiface and unchanged in the PLA-treated hemiface (Table 5).

3.7. Skin Microbiome

At baseline, both alpha diversity (as measured by Shannon and Simpson indices) and beta diversity at the phylum and genus levels were comparable between the hemiface treated with PRF and that treated with PBO (Figures 5a,e and S1). A total of 156 genera were shared between PRF- and PBO-treated samples, with the 12 most abundant taxa summarized in Table 6. These findings suggest a similar microbial community structure and composition between the two treatment sites, indicating a comparable baseline microbial signature (Figure 6).

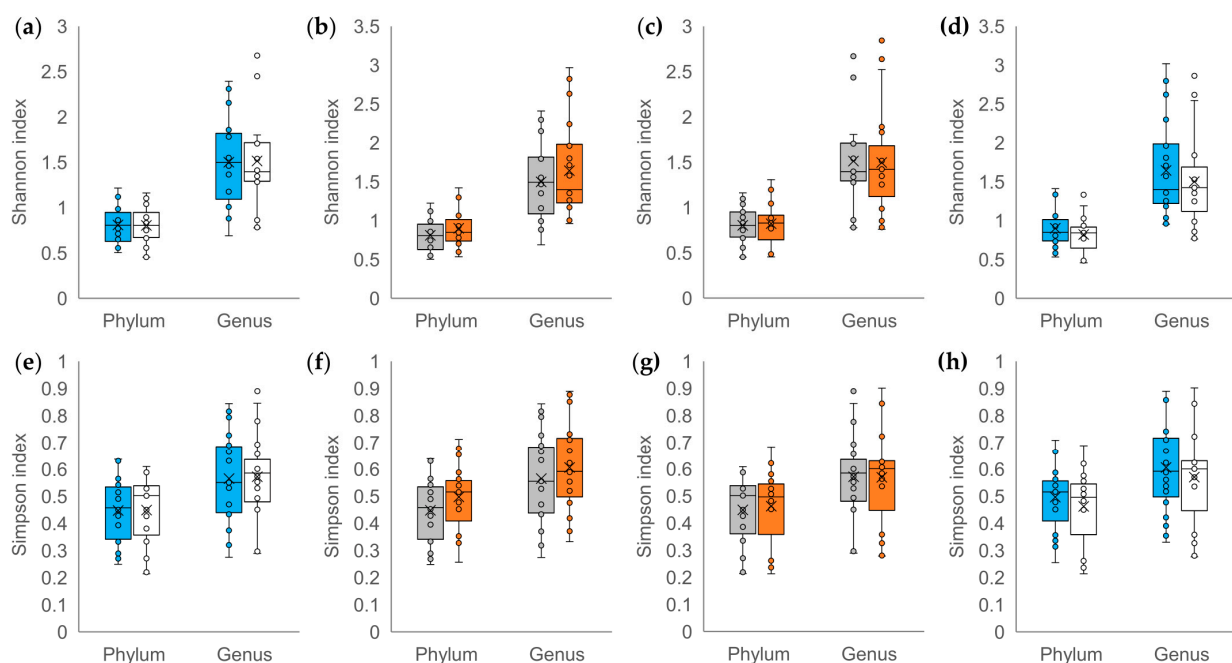


Figure 5. Shannon and Simpson index. (a) Shannon index at baseline, PRF vs. PBO. (b) Shannon index variation in the PRF-treated hemiface. (c) Shannon index variation in the PBO-treated hemiface. (d) Shannon index at D28, PRF vs. PBO. (e) Simpson index at baseline, PRF vs. PBO. (f) Simpson index variation in the PRF-treated hemiface. (g) Simpson index variation in the PBO-treated hemiface. (h) Simpson index at D28, PRF vs. PBO. ■ PRF □ PBO. ■ D0 ■ D28.

Table 6. Relative abundance at genus level and LEfSe analysis of the most abundant genera.

Genus	PRF (n = 21)				PBO (n = 21)			
	D0	D28	LEfSe	LDA Score	D0	D28	LEfSe	LDA Score
Cutibacterium	60.25%	55.96%	0.414	4.32	56.63%	54.63%	0.753	4.11
Corynebacterium	1.84%	1.54%	0.910	3.08	2.08%	1.47%	0.443	3.40
Kocuria	0.43%	0.20%	0.811	3.06	0.48%	0.13%	0.166	3.22
Micrococcus	0.34%	0.29%	0.660	2.31	0.26%	0.31%	0.870	−2.56
Uncl. Actinobacteria	1.64%	1.47%	0.753	2.91	1.71%	1.31%	0.320	3.22
Uncl. Neisseriaceae	0.68%	0.68%	0.594	−1.64	0.70%	0.58%	0.084	−1.89
Acinetobacter	0.03%	0.56%	0.060	−3.39	0.03%	0.02%	0.372	1.69
Staphylococcus	17.35%	18.78%	0.473	−3.99	19.83%	21.72%	0.589	−4.09

Table 6. Cont.

Genus	PRF (n = 21)				PBO (n = 21)			
	D0	D28	LEfSe	LDA Score	D0	D28	LEfSe	LDA Score
Gemella	0.93%	0.40%	0.606	3.43	0.86%	0.82%	0.660	2.59
Uncl. Caryophanales	1.38%	1.65%	0.333	−3.14	1.54%	1.72%	0.473	−3.08
Lactobacillus	1.07%	1.30%	0.950	−2.94	0.90%	1.96%	0.753	−3.70
Streptococcus	2.25%	2.77%	0.385	−3.39	2.30%	3.00%	0.428	−3.58
Finegoldia	0.63%	0.55%	0.308	2.68	0.62%	0.45%	0.950	2.73
Anaerococcus	0.74%	0.83%	0.624	−2.79	1.52%	0.80%	0.753	3.58
Peptoniphilus	0.33%	0.26%	0.428	2.42	0.32%	0.23%	0.860	2.66
Uncl. bacteria	4.70%	4.47%	0.870	3.51	4.32%	4.32%	0.521	2.70

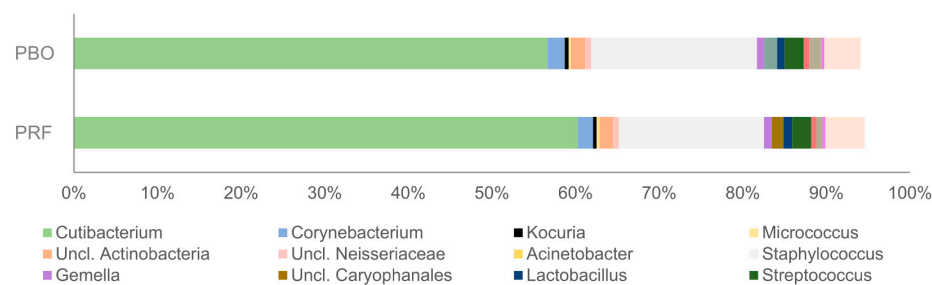


Figure 6. Microbial signature at genus level at baseline.

After 28 days of treatment, both the alpha and beta diversity indices remained unchanged ($p > 0.05$) in comparison to baseline values in the PRF- and PBO-treated hemiface (Figures 5b,c,f,g and S1). Furthermore, the relative abundance of the most predominant genera remained stable over time (Table 6). No statistically significant ($p > 0.05$) differences were observed between the PRF- and PBO-treated hemiface (Figures 5d,h and S1).

3.8. Skin Lipids Profile

A total of 1135 lipids were quantified and grouped in seven lipid categories, which were divided into 27 main lipid classes and 83 lipid subclasses (Figure S2). The most abundant lipid classes were as follows: 38.2% glycerolipids, 30.4% sphingolipids, 17.2% fatty acyls, 9.6% glycerophospholipids, 2.82% others, and 1.67 sterol lipids (Figure S3).

Among the lipids identified, the following major lipid classes exhibited statistically significant ($p < 0.05$) changes after treatment in both the PRF- and PBO-treated hemiface: triradylglycerols, ceramides [SP02], fatty amides [FA08], fatty esters [FA07], neutral glycosphingolipids, diradylglycerols [GL02], glycerophosphocolines [GP01], glycosyldiradylglycerols, other sterol lipids [ST00], glycerophosphoethanolamines [GP02], and other lipids (Table 7).

Among all lipid classes exhibiting statistically significant variation at day 28 ($p < 0.05$), ceramides and triradylglycerols demonstrated the most pronounced differences in trend between the PRF- and PBO-treated hemiface, suggesting a treatment-specific influence on skin lipid remodeling dynamics (Table 8). At D28, the level of Cer 26:0;03/17:0(2OH) was statistically significantly ($p < 0.05$) increased in the PRF-treated hemiface. In contrast several ceramides species, namely Cer 27:0;02/8:0, Cer 18:1;03/29:1(2OH), Cer 28:1;02/9:0, Cer 22:1;02/15:1;O, and Cer 32:0;4O; Cer 17:0;3O/15:0;(2OH) were decreased ($p < 0.05$) in the PBO-treated hemiface. The same trend was observed for the triradylglycerols lipid main class. At D28, TG60:11(3); TG 16:0_22:5_22:6, TG 11:0_11:0_17:2;O, TG 10:0_20:4_22:3;O(FA 20:4), TG 10:0_20:4_20:3;O(FA 20:4), and TG 58:9(3); TG 16:0_20:4_22:5 levels, in the PRF-treated hemiface, were statistically significantly ($p < 0.05$) increased compared to baseline. In contrast, TG 10:0_10:0_15:2, TG 5:0_14:1_16:1, TG O-46:1; TG O-16:0_12:0_18:1, TG 52:5;2O(2); TG 16:0_18:2_18:3;2O, TG 42:1; TG 8:0_16:0_18:1 levels were decreased ($p < 0.05$) in the PBO-treated hemiface.

Table 7. List of lipids grouped for main classes that were statistically significant between D0 and D28. FC 2-fold change.

Lipid Main Class	PRF (n = 21)				PBO (n = 21)			
	No.	log ₂ (FC)	FC Sum	p Value ¹	No.	log ₂ (FC)	FC Sum	p Value ¹
Triradylglycerols [GL03]	7	1.591	47.453	0.019	9	0.837	50.382	0.031
Ceramides [SP02]	2	0.351	3.218	0.028	6	−0.504	5.178	0.014
Fatty amides [FA08]	2	3.083	27.385	0.006	2	3.271	35.818	0.014
Fatty esters [FA07]	2	0.671	4.506	0.013	2	0.872	6.154	0.003
Neutral glycosphingolipids [SP05]	2	4.642	49.988	0.016	3	2.968	57.745	0.033
Diradylglycerols [GL02]	1	−0.996	0.501	0.015	1	−0.554	0.681	0.025
Glycerophosphocolines [GP01]	1	−0.595	0.662	0.016	2	0.627	3.094	0.020
Glycosyldiradylglycerols [GL05]	1	−1.504	0.353	0.014	1	0.630	1.548	0.019
Other sterol lipids [ST00]	1	−6.737	0.009	0.000	1	−5.996	0.016	0.000
Glycerophosphoethanolamines [GP02]	1	---	---	---	1	−1.178	0.442	0.030
Others	1	0.678	1.600	0.002	---	---	---	---

¹ Welch's *t*-test.**Table 8.** List of lipids showing a divergent trend between the PRF- and the PBO-treated hemiface. Data are reported in ng/cm².

	Lipid Main Class	Metabolite Name	D0	D28	FC	% var.	p Value ¹
PRF-treated hemiface (n = 21)	Neutral glycosphingolipids [SP05]	HexCer 17:2;02/32:0	0.001	0.017	23.883	2288.27%	0.014
		HexCer 18:0;02/34:1	0.001	0.036	26.105	2510.53%	0.018
	Ceramides [SP02]	Cer 26:0;03/17:0(2OH)	0.003	0.007	2.590	159.00%	0.025
		Cer 17:1;02/8:0;O	0.032	0.020	0.628	−37.16	0.031
	Triradylglycerols [GL03]	TG60:11 (3); TG 16:0_22:5_22:6	0.000	0.003	28.041	2704.08%	0.022
		TG 11:0_11:0_17:2;O	0.007	0.045	6.564	556.35%	0.014
		TG 10:0_20:4_22:3;O(FA 20:4)	0.001	0.004	5.794	479.44%	0.033
		TG 10:0_20:4_20:3;O(FA 20:4)	0.006	0.025	4.337	333.72%	0.030
		TG 58:9 (3); TG 16:0_20:4_22:5	0.001	0.001	1.607	60.68%	0.028
		TG 53:2; TG 16:0_18:1_19:1	0.162	0.102	0.632	−36.76%	0.007
		TG O-46:1; TG O-16:0_12:0_18:1	0.010	0.005	0.478	−52.17	0.003
PBO-treated hemiface (n = 21)	Neutral glycosphingolipids [SP05]	HexCer 18:0;02/34:1	0.001	0.043	29.442	2844.25%	0.033
		HexCer 17:2;02/35:0	0.001	0.021	27.715	2671.53%	0.036
		HexCer 47:0;4O	0.035	0.020	0.587	−41.32%	0.030
	Ceramides [SP02]	Cer 26:0;03/17:0(2OH)	0.002	0.006	2.314	131.38%	0.013
		Cer 27:0;02/8:0	0.116	0.080	0.691	−30.87%	0.002
		Cer 18:1;03/29:1(2OH)	0.028	0.019	0.680	−32.00%	0.021
		Cer 28:1;02/9:0	0.042	0.026	0.629	−37.11%	0.009
		Cer 22:1;02/15:1;O	0.049	0.025	0.516	−48.39%	0.002
		Cer 32:0;4O; Cer 17:0;3O/15:0;(2OH)	0.003	0.001	0.348	−65.17%	0.035
	Triradylglycerols [GL03]	TG60:11 (3); TG 16:0_22:5_22:6	0.000	0.003	29.617	2861.68%	0.046
		TG 11:0_11:0_17:2;O	0.007	0.059	8.932	793.21%	0.048
		TG 10:0_20:4_22:3;O(FA 20:4)	0.001	0.003	5.213	421.34%	0.042
		TG 10:0_20:4_20:3;O(FA 20:4)	0.005	0.020	4.011	301.14%	0.031
		TG 10:0_10:0_15:2	0.040	0.027	0.677	−32.27%	0.008
		TG 5:0_14:1_16:1	0.032	0.019	0.606	−39.42%	0.037
		TG O-46:1; TG O-16:0_12:0_18:1	0.008	0.004	0.509	−49.09%	0.033
		TG 52:5;2O (2); TG 16:0_18:2_18:3;2O	0.001	0.001	0.487	−51.34%	0.026
		TG 42:1; TG 8:0_16:0_18:1	0.009	0.003	0.330	−67.04%	0.014

¹ Welch's *t*-test.

3.9. Self-Assessment Questionnaire

Clinical assessment at D28 revealed that the PRF-treated hemiface demonstrated a larger improvement compared to the PBO-treated hemiface across all the evaluated parameters (Figure 7). Among the evaluated parameters, statistically significant improvements were observed in the PRF-treated hemiface compared to the PBO-treated side for the following items: shiny skin appearance ($p = 0.027$), rebound effect ($p = 0.036$), and skin blemishes, the latter showing a borderline significance ($p = 0.061$). The long-lasting mattifying effect in the PRF-treated hemiface (7.1 h) was two-fold higher ($p < 0.05$) compared to the PBO-treated hemiface (3.5 h).

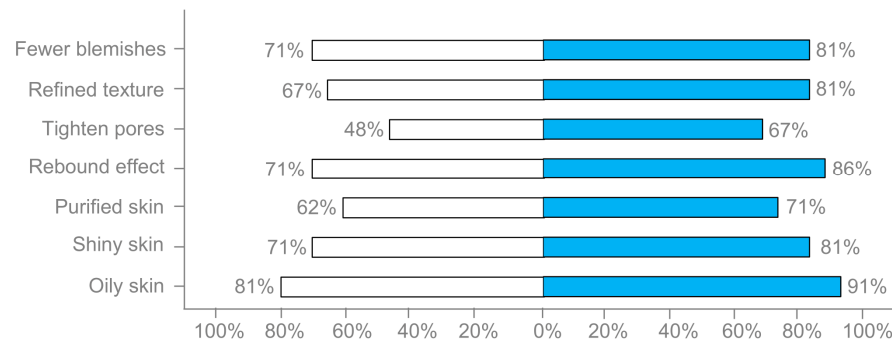


Figure 7. Self-assessment questionnaire. Data are reported as the percentage of positive answers (i.e., “Completely agree” and “Agree”). ■ PRF-treated hemiface, □ PBO-treated hemiface.

4. Discussion

Oily skin is one of the most prevalent dermatological concerns, commonly reported across diverse populations, including individuals without clinical manifestations of acne [14]. From an aesthetic standpoint, it is characterized by a shiny greasy appearance and prominently enlarged pores, which contribute to a less uniform, less refined, and often “dirty” appearance of the skin surface [51]. Additionally, oily skin is associated with poor makeup adherence, reduced cosmetic durability, and heightened consumer dissatisfaction with skin appearance. As a result, individuals with oily skin often report challenges such as foundation breakdown, unwanted shine throughout the day, and increased frequency of cleansing or blotting. All these aspects have contributed to a growing consumer demand for topical interventions aimed at normalizing sebum production and enhancing the skin’s overall aesthetic appearance [14]. In response to this need, this study was designed to evaluate the efficacy of a cosmetic formulation containing, as active ingredient, isorhamnetin from *Opuntia ficus-indica* flower extract in modulating sebum production and improving clinical and biochemical markers of oily skin.

The findings of this study demonstrate the efficacy of the tested active ingredient, *Opuntia ficus-indica* extract (PURYFLOWER™), in improving key clinical and biochemical features associated with oily skin. The significant reductions in both the skin sebum content and the SER observed in the PRF-treated hemiface are consistent with the sebum-regulating potential of polyphenols [52,53]. Notably, the decrease in SER at both D14 and D28 was more pronounced than in the placebo-treated hemiface, suggesting a direct effect of the active ingredient on sebaceous gland activity. This aligns with the reported anti-androgenic mechanisms attributed to plant flavonoids and to *Opuntia ficus-indica* [54–56]. In parallel, the observed reduction in pore diameter further supports the clinical relevance of sebum normalization, as enlarged pores are closely associated with sebaceous hyperactivity and follicular distension [51,57].

The significant reduction in TNF- α levels (−7.4%) in the PRF-treated hemiface supports the anti-inflammatory potential of the tested extract. This cytokine is a known pro-inflammatory marker elevated in acne and seborrheic conditions, and its downregulation suggests a role for isorhamnetin in modulating inflammatory pathways. These results corroborate earlier in vitro findings demonstrating the inhibitory activity of *Opuntia ficus-indica* extracts on inflammatory mediators such as TNF- α and IL-6 [58,59].

These clinical and biochemical outcomes can be mechanistically interpreted in light of the “oily-skin loop” model, a self-reinforcing biological circuit linking sebocyte hyperproliferation, inflammation, oxidative stress, and microbial dysbiosis [9]. In this loop, extrinsic factors such as pollution, cosmetics, and diet can induce ROS formation and cytokine activation, while intrinsic regulators including hormonal signaling and genetic predispositions enhance 5 α -reductase activity and sebocyte proliferation [25]. Sebum overproduction then

promotes lipid oxidation and microbiota imbalance, favoring the dominance of virulent *Cutibacterium acnes* strains and the release of lipases, porphyrins, and short-chain fatty acids that further stimulate sebocyte activity and inflammation, perpetuating the cycle [60,61]. Within this framework, PURYFLOWER™ acts as a multi-target modulator capable of interrupting several nodes of the oily-skin loop. The observed reduction in TNF- α and normalization of SER reflect its action on both the extrinsic (oxidative/inflammatory) and intrinsic (sebocyte/hormonal) axes. This interpretation aligns with preclinical evidence showing that *O. ficus-indica* flower extracts inhibit lipid peroxidation, nitric oxide release, and 5 α -reductase activity [62].

The microbiome profiling revealed no significant alterations in alpha or beta diversity or in the relative abundance of dominant genera over the 28-day period. This indicates that the PRF formulation preserves the skin's ecological balance. Genera such as *Cutibacterium*, *Staphylococcus*, and *Corynebacterium*, which dominate the facial microbiome, remained stable, underscoring the formulation's skin tolerance. This finding is particularly relevant in the context of the oily-skin loop, as dysbiosis is both a driver and a consequence of sebaceous hyperactivity. Preserving microbial homeostasis may prevent the reactivation of inflammatory pathways and the overproduction of lipid mediators, consolidating the extract's role as a holistic normalizer of the sebaceous ecosystem [9,63].

The lipidomic analysis demonstrated that PRF treatment induced distinct remodeling of the skin lipid profile. Among the lipid classes that significantly changed, ceramides and triradylglycerols exhibited divergent trends between the PRF- and PBO-treated hemiface. Specifically, ceramide Cer 26:0;O3/17:0(2OH) was significantly increased in the PRF-treated site, while multiple ceramide species were reduced in the PBO-treated hemiface. Given the central role of ceramides in maintaining skin barrier integrity and hydration, this observation suggests a barrier-repair effect linked to PRF application. Furthermore, the increase in specific triradylglycerol species in the PRF-treated side points to an active modulation of sebaceous lipid synthesis, with potential implications for skin homeostasis and protection against oxidative stress. These lipidomic shifts mirror the broader physiological remodeling induced by the active ingredient and suggest that isorhamnetin-containing formulations may exert dual effects: reducing excess sebaceous output while enhancing the skin's structural lipids, particularly ceramides and TGs relevant to barrier and emollient function.

The subjective perception data further support the instrumental results. Participants reported significantly higher improvement in the PRF-treated hemiface. Importantly, the mattifying effect lasted over 7 h post-application, twice as long as the placebo, highlighting the product's consumer-relevant benefit in managing oily skin.

While the results are promising, the study was limited by a relatively short treatment duration (28 days) and a modest sample size. Future studies with longer follow-up and broader demographic representation (e.g., various Fitzpatrick skin types, acne-prone individuals) are warranted to assess the long-term efficacy and preventive potential of this formulation. Additionally, mechanistic studies investigating the direct molecular targets of isorhamnetin in sebaceous gland regulation and ceramide metabolism would provide valuable insights.

5. Conclusions

This randomized, double-blind, split-face, and placebo-controlled clinical trial provides novel evidence supporting the efficacy of a cosmetic formulation containing *Opuntia ficus-indica* flower extract standardized to isorhamnetin (PURYFLOWER™) in the management of oily skin. Starting from 14 days of treatment, the active formulation significantly reduced the sebum content and sebum excretion rate, improved the pore size, and de-

creased the TNF- α levels, indicating not only seoregulating but also anti-inflammatory activity. These effects were supported by subjective evaluations, with participants reporting higher satisfaction on the PRF-treated hemiface. Importantly, lipidomic analysis revealed that the PRF-treated skin underwent significant remodeling of key lipid classes, notably ceramides and triradylglycerols, which are critical for maintaining barrier integrity and skin homeostasis. In parallel, microbiome analysis confirmed that the formulation preserved the cutaneous microbial diversity and stability, reinforcing its compatibility with skin health.

Together, these results highlight the multitarget role of *Opuntia ficus-indica* flower extract as a cosmetic active for oily skin, addressing key drivers of this condition such as oxidative and inflammatory stress, excess sebum, and barrier-microbiome imbalance, and supporting its inclusion in dermocosmetic formulations aimed at improving skin appearance, functionality, and consumer satisfaction in individuals with oily or combination skin types. Future research should explore its long-term preventive potential and elucidate the molecular targets involved in sebocyte and microbiome modulation, further validating its role as a natural bioactive for restoring balance in the sebaceous ecosystem.

To the best of our knowledge, this is the first human study to demonstrate the clinical efficacy of an OFI flower extract in improving sebum regulation and reducing skin inflammation.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/cosmetics13010037/s1>, Figure S1: Beta diversity index; Figure S2: Identified lipid categories; Figure S3: Most abundant lipid classes.

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Institutional Review Board Statement: All trial procedures were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964) and its subsequent amendments. Ethical review and approval were not required for this trial, as the tested products complied with EU Cosmetic Regulation No. 1223/2009. This regulation mandates that cosmetic products undergo a safety assessment to ensure they do not pose a risk to human health under normal or reasonably foreseeable conditions of use. Therefore, no additional ethical approval was necessary prior to testing on human subjects.

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Abbreviations

The following abbreviations are used in this manuscript:

AUC	Area Under the Curve
ESI	Electrospray Ionization
LC-MS	Liquid Chromatography Mass Spectrometry
LEfSe	Linear Discriminant Analysis Effect Size
MicrobAT	Microbiota Analysis Tool
PBO	Placebo
PERMANOVA	Permutational Multivariate Analysis Of Variance
PCR	Polymerase Chain Reaction
PRF	Puriflow
Q-TOF	Quadrupole Time-Of-Flight
RDP	Ribosomal Database Project
ROI	Region Of Interest
SER	Sebum Excretion Rate
SG	Sebaceous Gland
TNF- α	Tumor Necrosis Factor-Alpha
UHPLC	Ultra-High Performance Liquid Chromatography
UVB	Ultraviolet B

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