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Supramolecular Salicylic Acid and Photon Rejuvenation Repair Skin Immune Barrier Function in Acne Patients

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Abstract: Acne vulgaris is a chronic inflammatory skin disease in which a defect in the immune barrier function is a major extent of the pathological etiology. The aim of this randomized controlled trial was to assess the restorative benefits of supramolecular salicylic acid (SSA) with intense pulsed light (IPL) photon rejuvenation and its effects on the immune barrier function of the skin in acne patients. Moderate-to-severe acne was assigned to each patient, with three groups being treated for 12 weeks with either: The primary outcome was transepidermal water loss (TEWL) (continuous variable); secondary outcomes were stratum corneum hydration, sebum secretion, skin pH, pro- and anti-inflammatory cytokines (IL-1β, IL-6, TNF-α, IL-10, TGF-β), Treg/Th17 cell ratio, microbiome Shannon diversity index, Global Acne Grading System (GAGS) score, lesion counts, and the Dermatology Life Quality Index (DLQI). The SSA+IPL group showed significant improvements compared to both monotherapy groups in all outcomes (all corrected $p < 0.001$). TEWL decreased by 47.0% (Cohen's d = 2.14; 95% CI: 1.67–2.61), stratum corneum hydration increased by 67.0%, and sebum secretion declined by 45.7%. Fifty-six to 58% reduction in pro-inflammatory cytokines was achieved, whereas IL-10 and TGF-β levels increased by 167.8% and 130.8% respectively. The ratio Treg/Th17 was raised by 331.3% and Shannon diversity index was raised by 52.1%. This multiple regression revealed that the Treg/Th17 ratio reestablishment, reduction of sebum and upregulation of IL-10 are independent factors of clinical efficacy (adjusted R2 = 0.763). The combination of SSA and IPL therapy can have a systemic effect on the regeneration of skin immune barrier function by overlapping mechanisms and deserves further testing in larger trials.

Keywords: Supramolecular Salicylic Acid; Photon Rejuvenation; Acne Vulgaris; Skin Immune Barrier; Treg/Th17; Microbiome; Cytokines; Randomized Controlled Trial

1. Introduction

Acne vulgaris is one of the most common chronic inflammatory skin diseases in the world that mostly occurs in adolescents and young adults. In addition to its physical consequences, acne has a substantial psychosocial impact; patients often feel anxious about the appearance of the lesions and have reduced self-esteem which is related to the acne lesions [1]. The cause of acne is complex. Excessive flow of sebum from the sebaceous gland, abnormal keratinization of the foliculopilosebaceous duct, colonization by Cutibacterium acnes and dysregulated immune-inflammatory responses are the main factors. Recent evidence also links gut microbiota dysbiosis to acne development: increased levels of metabolites like trimethylamine N-oxide can contribute to an immune imbalance in the skin by affecting systemic inflammation [2]. Defective skin barrier function of the immune system is a key pathological mechanism in disease progression. This impairment involves higher transepidermal water loss (TEWL), decreases in stratum corneum water content and higher levels of pro-inflammatory cytokines. Re-establishing

immune homeostasis in the skin is thus one of the major goals of current acne therapy. Resistance patterns to conventional oral antibiotics and topical antimicrobials have been increasing over time, leading to a clinical interest in alternative antibiotic and antimicrobial regimens which are both safer and more effective. Supramolecular salicylic acid (SSA) is a novel drug delivery system which is a complexation of salicylic acid with cyclodextrin with controlled and sustained release. The major advantage of SSA is its ability to dissolve keratin, clear the follicular lopilosebaceous ducts, eliminate local inflammatory responses and regulate sebum secretion, also while causing less irritation than conventional formulations containing higher levels of keratolytic ingredients [3]. In mild-to-moderate acne, SSA has proven to be effective alone and in moderate-to-severe cases, when used in conjunction with PDT, it has yielded greater reduction of lesions [4]. Intense pulsed light (IPL) is a broad-spectrum optical therapy that has a selective photo-thermally effect on C. acnes, induces heat shock proteins and alters dendritic cell function, which causes photo-immunoregulatory effects [5]. Persisting immune microenvironment dysregulation and elevated oxidative stress in acne patients offer a pathophysiological basis for this combination of two modalities. Studies to systematically assess the effectiveness of SSA in combination with IPL are still limited and the mechanism by which they may complement each other in immunoregulatory effects is not well defined [6,7]. A randomized controlled trial was therefore designed to evaluate the response of physical barrier parameters, local immune cytokine profile and clinical outcomes of combined SSA and IPL therapy, to propose evidence-based recommendations for immunoregulatory-targeted acne therapy.

2. Methods

2.1. Study Design and Ethical Statement

A prospective randomized controlled trial (RCT) was carried out in Dermatology Department, tertiary hospital from June 2024 to June 2025. A computer generated random number table was used to randomise 90 eligible patients into three groups of SSA monotherapy, IPL monotherapy and combined SSA+IPL therapy, with 30 randomly assigned to each group. Allocation concealment was accomplished using sequentially numbered, opaque, sealed envelopes, which were prepared in advance by an independent statistician, with envelopes opened only when the treatment assignment was made to the point of treatment, thereby reducing selection bias. This study received approval from the hospital's Medical Ethics Committee (Approval No.: [UMS.TNCPI/800-3/2/1/2, JKEUUMS2024/0089]). All procedures were carried out according to the Declaration of Helsinki (2013 revision) [World Medical Association, JAMA 2013;310:2191–2194] and national regulations for the ethical review of life science and medical research involving human subjects [National Health Commission of China, Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects, 2023]. All participants gave written informed consent before enrolling. In this trial, it was not possible to blind participants to treatment allocation because of the different physical nature of the application of the SSA gel and IPL device treatments. The clinical assessors were not blinded to group assignment and this is a known limitation (see Section 4.4). A single trained dermatologist scored all GAGS images and counted all lesions in a standard lighting environment and the data were independently verified in the VISIA Skin Analysis System, to minimize observer bias. Objective instrument based measurements (TEWL, hydration, sebum, pH) were performed by another technician who was blinded to the assessment scores. Intention to treat (ITT) analysis: All randomized patient numbers were analysed in the primary ITT analysis. Last observation carried forward (LOCF) was used to deal with missing values (if any) [8].

2.2. Participant Allocation and Intervention Protocols

Inclusion criteria: diagnosis consistent with the Chinese Acne Treatment Guidelines (2019 revision); age 18–45 years; GAGS score ≥ 15 (moderate or above severity); no systemic or topical anti-acne treatment within the preceding three months [9–11].

Exclusion criteria: history of photosensitivity or salicylic acid allergy; pregnancy or breastfeeding; serious systemic comorbidities; recent isotretinoin use within six months.

2.3. Intervention Protocols

Twice weekly twice for 12 consecutive weeks twice a week after facial cleansing, a topical 3% SSA gel (Chamedis, Beijing, China) was applied to the lesion areas evenly. IPL group: Pulsed light device (DPL Photon System, Fotona,

Slovenia) with a broad-spectrum light source was used for rejuvenation. Treatment parameters were customized with respect to Fitzpatrick skin type: 12–14 J/cm^2 for type III, 14–16 J/cm^2 for type IV, 16–18 J/cm^2 for type V, 3–5 passes per session, and cut-off filter of 515 nm for inflammatory lesions and 590 nm for the vascular components. All treatments for IPL were conducted by the same certified dermatologist, with the same protocol for the parameters that are shown in a treatment log for each treatment session. A session took place once a fortnight for a total of three Sessions [12]. SSA+IPL group: Both treatments were given in the same 12-week treatment period under the same protocol as the monotherapies. On IPL treatment days, SSA was deferred due to cumulative skin irritation and within the 4 week treatment cycles, IPL was given on day 1 and application of the SSA was resumed from day 3. All participants were trained to use a standard mild facial cleanser, medical grade moisturizing emulsion and strict photoprotection (SPF ≥ 50) during the study.

2.4. Outcome Measures and Assessment Methods

Primary outcome: TEWL (g/m^2·h), as a continuous variable, measured with Tewameter TM300 (Courage+ Khazaka, Germany). Secondary outcomes: stratum corneum hydration (Corneometer CM825), sebum secretion (Sebumeter SM815), skin surface pH (Skin-pH-Meter PH 905, Courage+Khazaka, Germany), local immune cytokines, Treg/Th17 ratio, microbiome Shannon diversity index, GAGS score, lesion counts, DLQI and VAS. The baseline, week 4, week 8 and week 12 measures were taken for all physical barrier parameters under standardized conditions (22 ± 2 °C and 50% ± 10% RH). The three readings were taken at each site and the average reading noted. Duplicates were prepared for each skin surface wash fluid sample collected from the lesions at baseline, week 6 and week 12 and analyzed by enzyme-linked immunosorbent assay (ELISA) to quantify local immune cytokines (IL-1β, IL-6, TNF-α, IL-10, TGF-β) [13]. The rationale for the asynchronicity of the measurement schedule: Early and mid-treatment changes in the biophysical parameters of the skin were measured at week 4, 8, and 12 to capture changes in biophysical parameters that are likely to respond relatively early to topical and light-based interventions. Because of the need to balance the biological significance of the sampling with the burden of the participants, cytokine sampling was limited to weeks 6 and 12. In addition, collecting skin wash fluid repeatedly from the site would involve a small risk of irritation from the sampling itself. Immunological changes, however, take a longer time to show measurable changes. The structure of this study does not allow for direct week-by-week comparisons of physical and immune outcomes, although the 12-week time point is common to all measures for this cross-sectional study, allowing for cross-domain correlations at study completion. Immune cell phenotyping: Flow cytometric analysis (FlowJo v10.0) of peripheral venous blood (5 mL) was used to quantify levels of Tregs (CD4$^+$CD25$^+$Foxp3$^+$) and T helper 17 cells (Th17; CD4$^+$IL-17A$^+$) at baseline and week 12. The diversity of the microbiome was calculated using the Shannon diversity index at the baseline and at weeks 4, 8, and 12. The clinical efficacy was evaluated by GAGS score in 5 facial regions (forehead, left cheek, right cheek, nose and chin; range 1–44) and by manual lesion counts (inflammatory papules and pustules, non-inflammatory comedones). The overall treatment response was assessed as complete response (≥90% reduction of lesion) or marked response (60%–89% reduction of lesion) or partial response (20%–59% reduction of lesion) or no response (<20%) and the total response rate was calculated as (complete response + marked response)/number of patients treated ×100% [14]. For subjective outcomes, a visual analogue scale (VAS; range 0–10) and the Dermatology Life Quality Index (DLQI; range 0–30, with higher scores indicating more impact of the disease) were used for measuring symptom severity and quality of life. Participants' satisfaction was measured using the Patient Global Impression of Change (PGIC) scale.

2.5. Statistical Analysis

Data were analysed in SPSS 26.0 (IBM Corporation, USA) and GraphPad Prism 9.0. The Shapiro-Wilk test was used to test normality. Continuous data are presented as mean ± standard deviation (SD) and were compared between groups by one-way ANOVA and Tukey's post hoc test. Data that is not normally distributed are presented as median (interquartile range) and compared using the Kruskal-Wallis test with Dunn's post hoc correction. Categorical variables are summarized in frequencies and percentages; compared with chi-square and Fisher's exact test as appropriate. Repeated-measures ANOVA was used to make within-group comparisons, with Greenhouse-Geisser correction conducted when sphericity was not met. Multiple comparisons correction: All pairwise and between group comparisons were made using the false discovery rate (FDR) method (Benjamin-Hochberg procedure) to control familywise type I error rate due to the large number of comparisons across three groups and four or three

time points and more than 15 outcome variables. Results presented both uncorrected *p*-values and FDR-corrected q-values, with *p* and q values < 0.05 considered to be significant. Correlation and regression analyses: The normality of each variable combination was checked using the Shapiro-Wilk test ($p > 0.05$ offered normality for each variable combination). Spearman rank correlation was used between the pairs that were not normally distributed while Pearson correlation was used between normally distributed pairs [15–17]. Specific correlations are followed by the result of the normality test for each pair of variables. Predictor selection in the multiple linear regression model was determined using backward stepwise elimination procedure (entry $p < 0.05$; removal $p > 0.10$), based on the 8 variables that had significant bivariate correlation with the change in GAGS score. The following three variables were included in the final model: change in Treg/Th17 ratio, change in sebum secretion, and change in IL-10 level [18,19]. The five variables were excluded because they were strongly correlated with each other and/or the partial regression coefficient was non-significant on the basis of stepwise elimination after controlling for the variables retained in the model (TEWL reduction, stratum corneum hydration gain, Shannon index gain, TGF-β up-regulation, TNF-α reduction). Primary outcome and sample size: TEWL was measured as a continuous variable ($g/m^2 \cdot h$). Sample size was calculated based on pilot data showing a difference in TEWL between groups at week 12 of 3.5 $g/m^2 \cdot h$ with a SD of 4.2 $g/m^2 \cdot h$, and thus an effect size of 0.83. The power ($1 - \beta$) was set to be 0.80, and α was set to 0.05 (two-tailed) with a minimum of 27 participants per group. We estimated that this represents 10% of dropouts, and enrolled 30 per group. All outcomes that were continuous and primary and secondary were analysed for effect sizes and confidence intervals at week 12 (combination vs. each monotherapy group) [20]. 95% confidence intervals are provided for all effect sizes. Raw data will be made available upon reasonable request from the corresponding author. All tests were two-tailed, $p < 0.05$ (not corrected for FDR).

3. Results

3.1. Participant Flow and Retention

The 12-week follow-up was done by all 30 participants in each group, with 100% retention. There was no voluntary withdrawal from the study or loss to follow-up. This was done to keep the inconvenience to a minimum, by scheduling all study visits in the same timeframe as the participants' usual outpatient visits, by sending reminder messages 48 h prior to the visits, by having a dedicated study coordinator reach out within 24 h of missed visits, and by having a study coordinator follow up within 72 h of visits that resulted in mild adverse events to determine resolution and encourage ongoing participation. Demographic and clinical baseline attributes were not different between groups (all $p > 0.05$) [21,22].

3.2. Effects of Combination Therapy on Physical Skin Barrier Function

3.2.1. Dynamic Changes in Transepidermal Water Loss (TEWL)

TEWL is considered a fundamental goal parameter of skin barrier integrity, with increased TEWL values reflecting skin barrier impairment. TEWL was measured at baseline, week 4, week 8 and week 12 for all three groups (**Table 1**, **Figure 1**). Groups were statistically comparable ($p > 0.05$) with no difference in baseline TEWL values. The SSA group had a mean baseline TEWL of 24.83 ± 3.21 $g/m^2 \cdot h$, the IPL group 25.12 ± 3.45 $g/m^2 \cdot h$, and the SSA+IPL group 24.97 ± 3.18 $g/m^2 \cdot h$ [23]. The TEWL decreased progressively in all three groups during the treatment period. By week 4, TEWL had decreased to 21.35 ± 2.87 $g/m^2 \cdot h$ (SSA), 20.98 ± 2.64 $g/m^2 \cdot h$ (IPL), and 19.42 ± 2.31 $g/m^2 \cdot h$ (SSA+IPL); the combination group already differed significantly from both monotherapy groups (FDR-corrected $q < 0.05$) [24]. At week 8, values were 18.76 ± 2.43 $g/m^2 \cdot h$ (SSA), 18.23 ± 2.19 $g/m^2 \cdot h$ (IPL), and 15.87 ± 1.96 $g/m^2 \cdot h$ (SSA+IPL), with between-group differences reaching $q < 0.01$. At week 12, the SSA+IPL group achieved a mean TEWL of 13.24 ± 1.74 $g/m^2 \cdot h$ (−47.0% from baseline; Cohen's d vs. SSA = 2.14, 95% CI: 1.67–2.61; Cohen's d vs. IPL = 2.08, 95% CI: 1.62–2.54), compared with 16.54 ± 2.12 $g/m^2 \cdot h$ (−33.3%) in the SSA group and 16.18 ± 1.98 $g/m^2 \cdot h$ (−35.6%) in the IPL group. Repeated-measures ANOVA showed a significant effect for time ($F = 187.34$, $p < 0.001$), group ($F = 42.67$, $p < 0.001$) and a time × group interaction ($F = 18.92$, $p < 0.001$), namely the combination therapy resulted in better barrier restoration than the two monotherapies [25–27].

Table 1. Comparison of TEWL values across three groups at each time point (g/m^2·h, mean ± SD).

Group	Baseline	Week 4	Week 8	Week 12	F	*p* (Uncorrected)	q (FDR)
SSA (n = 30)	24.83 ± 3.21	21.35 ± 2.87	18.76 ± 2.43	16.54 ± 2.12	98.43	<0.001	<0.001
IPL (n = 30)	25.12 ± 3.45	20.98 ± 2.64	18.23 ± 2.19	16.18 ± 1.98	102.76	<0.001	<0.001
SSA+IPL (n = 30)	24.97 ± 3.18	19.42 ± 2.31	15.87 ± 1.96	13.24 ± 1.74	156.89	<0.001	<0.001
F (between groups)	0.08	4.21	18.54	32.67	—	—	—
p (between groups)	>0.05	<0.05	<0.01	<0.001	—	—	—
q (FDR, between groups)	>0.05	<0.05	<0.01	<0.001	—	—	—

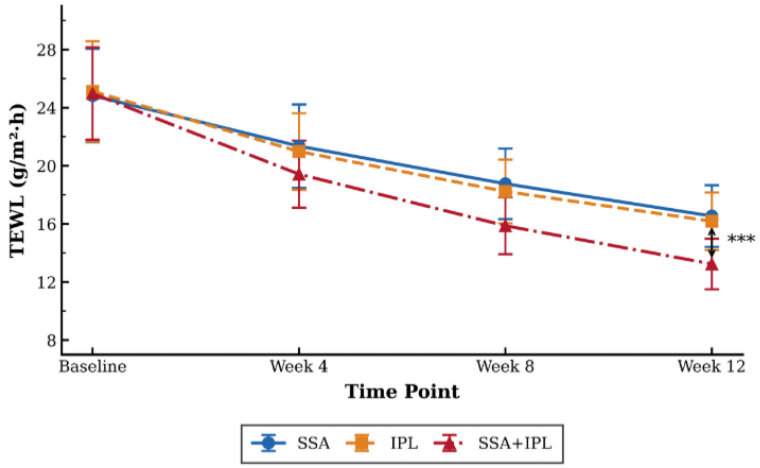

Figure 1. Dynamic Changes in TEWL across Three Groups.

3.2.2. Between-Group Comparison of Stratum Corneum Hydration and Sebum Secretion

Objective parameters that reflect physiology of the skin barrier include stratum corneum hydration and sebum secretion. **Table 2** and **Figure 2** show all three groups were evaluated at baseline, week 4, week 8, and week 12. There were no significant between-group differences at baseline for either of the measures ($p > 0.05$). In all groups, there was a gradual increase in stratum corneum hydration [28]. The SSA group rose from 38.42 ± 4.67 AU at baseline to 52.18 ± 5.23 AU at week 12. The IPL group increased from 37.89 ± 4.52 AU to 53.46 ± 5.11 AU. The SSA+IPL group showed the greatest gain, climbing from 38.15 ± 4.43 AU to 63.72 ± 5.87 AU, a 67.0% increase that was significantly higher than both monotherapy groups (q < 0.001; Cohen's d vs. SSA = 2.06, 95% CI: 1.60–2.52). There was a downtrend of sebum secretion in all groups. The SSA group decreased from 198.35 ± 22.14 μg/cm^2 to 142.67 ± 18.32 μg/cm^2 (−28.1%) [29,30]. The IPL group declined from 201.48 ± 23.67 to 138.54 ± 17.89 μg/cm^2 (−31.3%). The SSA+IPL group fell from 199.72 ± 21.98 to 108.43 ± 14.76 μg/cm^2, a 45.7% reduction substantially greater than either monotherapy group (q < 0.001; Cohen's d vs. SSA = 2.11, 95% CI: 1.64–2.58). For both outcomes, the main effects of time (all q < 0.001), group (all q < 0.001) and their interaction (all q < 0.001) were highly significant, with combination therapy demonstrating superior modulation of cutaneous barrier physiology [31].

3.2.3. Correlation between Skin pH Changes and Microbiome Diversity Recovery

The surface pH is a fundamental factor to keep the acid mantle in good condition and is linked bidirectionally to the composition of the cutaneous microbiome. In acne patients, raised skin pH not only allows C. acnes to multiply more but also allows the lessening of commensal microorganisms diversity, which maintains the immune-inflammatory imbalance. **Table 3** and **Figure 3** show the skin pH and Shannon diversity index of all three groups at baseline, 4 weeks, 8 weeks and 12 weeks. Baseline pH values did not differ significantly among groups ($p > 0.05$): SSA 5.87 ± 0.43, IPL 5.91 ± 0.47, SSA+IPL 5.89 ± 0.45. After 12 weeks, pH declined to 5.42 ± 0.31 (SSA) and 5.38 ± 0.29 (IPL), while the SSA+IPL group reached 5.12 ± 0.24, approaching the normal skin pH range of 4.5–5.5 (between-group differences: q < 0.01). This was reflected by the Shannon diversity index [32,33]. The SSA group rose from 2.14 ± 0.32 to 2.68 ± 0.28 at week 12; the IPL group from 2.11 ± 0.35 to 2.72 ± 0.31; the SSA+IPL group from 2.13 ± 0.33 to 3.24 ± 0.37, a 52.1% increase exceeding both monotherapy groups (q < 0.001; Cohen's d vs. SSA = 1.87, 95% CI: 1.42–2.32).

The Shapiro-Wilk test was used to verify that the magnitude of pH reduction, as well as the Shannon index increment were normally distributed, with $p > 0.05$ for both, so Pearson correlation was used. A strong negative correlation between the pH reduction and Shannon index increase was observed for all 90 participants ($r = -0.726$, $p < 0.001$), suggesting that reduction of pH is an important factor in the recovery of commensal microbiome diversity [34].

Table 2. Comparison of stratum corneum hydration and sebum secretion across three groups (mean ± SD).

Indicator	Group	Baseline	Week 4	Week 8	Week 12	*p*
Stratum corneum hydration (AU)	SSA	38.42 ± 4.67	43.15 ± 4.89	48.36 ± 5.04	52.18 ± 5.23	<0.001
	IPL	37.89 ± 4.52	44.27 ± 4.76	49.52 ± 5.18	53.46 ± 5.11	<0.001
	SSA+IPL	38.15 ± 4.43	48.63 ± 5.21	56.84 ± 5.64	63.72 ± 5.87	<0.001
Sebum secretion (μg/cm^2)	SSA	198.35 ± 22.14	178.42 ± 20.37	162.18 ± 19.45	142.67 ± 18.32	<0.001
	IPL	201.48 ± 23.67	175.63 ± 21.54	158.74 ± 18.97	138.54 ± 17.89	<0.001
	SSA+IPL	199.72 ± 21.98	163.47 ± 18.76	138.25 ± 16.43	108.43 ± 14.76	<0.001

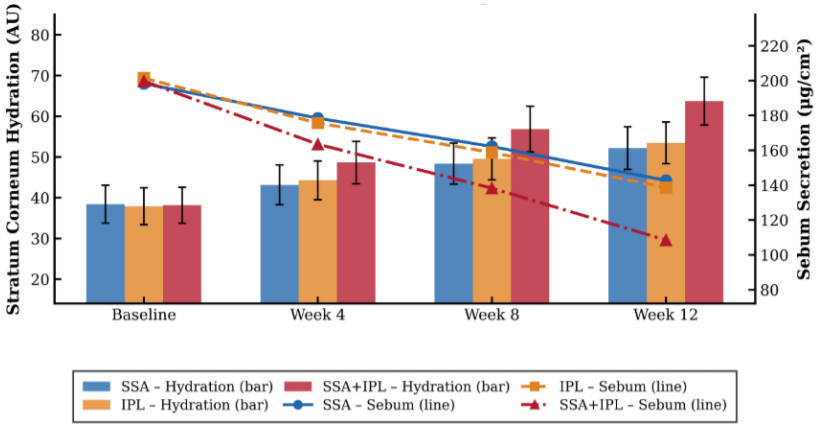

Figure 2. Stratum Corneum Hydration and Sebum Secretion across Three Groups.

Table 3. Comparison of skin surface pH and microbiome Shannon index across three groups (mean ± SD).

Indicator	Group	Baseline	Week 4	Week 8	Week 12	*p*
Skin pH	SSA	5.87 ± 0.43	5.71 ± 0.38	5.58 ± 0.34	5.42 ± 0.31	<0.01
	IPL	5.91 ± 0.47	5.74 ± 0.41	5.54 ± 0.33	5.38 ± 0.29	<0.01
	SSA+IPL	5.89 ± 0.45	5.61 ± 0.35	5.38 ± 0.28	5.12 ± 0.24	<0.001
Shannon index	SSA	2.14 ± 0.32	2.31 ± 0.29	2.51 ± 0.27	2.68 ± 0.28	<0.01
	IPL	2.11 ± 0.35	2.34 ± 0.31	2.54 ± 0.29	2.72 ± 0.31	<0.01
	SSA+IPL	2.13 ± 0.33	2.54 ± 0.34	2.89 ± 0.35	3.24 ± 0.37	< 0.001

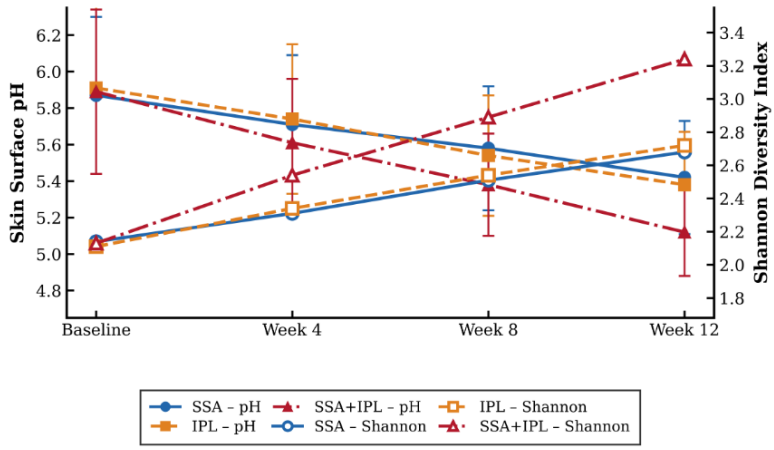

Figure 3. Skin Surface pH and Microbiome Shannon Index across Three Groups.

3.3. Regulatory Effects of Combination Therapy on the Cutaneous Immune Microenvironment

3.3.1. Changes in Local Pro-Inflammatory Cytokine Expression (IL-1β, IL-6, TNF-α)

Acne lesions are associated with an immune microenvironment where there is an excessive production of local pro-inflammatory cytokines. The synergic effect of IL-1β, IL-6 and TNF-α is able to sustain a constant inflammatory process in the involved skin. Their expression was evaluated at baseline, 6th and 12th week using ELISA (**Table 4**, **Figure 4**). There was no difference in the three groups regarding baseline level of cytokines ($p > 0.05$). IL-1β declined from 87.34 ± 9.42 pg/mL to 54.67 ± 7.83 pg/mL in the SSA group, and from 88.12 ± 9.87 to 52.34 ± 7.21 pg/mL in the IPL group. The SSA+IPL group showed IL-1β dropping from 87.76 ± 9.65 to 38.42 ± 5.67 pg/mL, a 56.2% reduction significantly greater than both monotherapy groups ($q < 0.001$; Cohen's d vs. SSA = 2.32, 95% CI: 1.84–2.80) [35]. IL-6 fell from 124.56 ± 13.47 to 78.43 ± 9.32 pg/mL (SSA) and from 126.34 ± 14.12 to 75.67 ± 8.94 pg/mL (IPL). The SSA+IPL group declined from 125.48 ± 13.89 to 52.18 ± 7.43 pg/mL, a 58.4% reduction ($q < 0.001$). TNF-α decreased from 67.23 ± 8.14 to 43.56 ± 6.32 pg/mL (SSA) and from 68.47 ± 8.63 to 41.23 ± 5.87 pg/mL (IPL). In the SSA+IPL group, TNF-α fell from 67.89 ± 8.32 to 28.74 ± 4.56 pg/mL, a 57.7% reduction significantly superior to both comparators ($q < 0.001$; Cohen's d vs. IPL = 2.19, 95% CI: 1.72–2.66) [36,37]. Repeated-measures ANOVA showed highly significant main effects of time, group, and time by group for all three cytokines (all $q < 0.001$) and combination therapy resulted in significantly more suppression of local pro-inflammatory immune responses compared to either monotherapy.

Table 4. Comparison of local pro-inflammatory cytokine levels across three groups (pg/mL, mean ± SD).

Cytokine	Group	Baseline	Week 6	Week 12	*p*
IL-1β	SSA	87.34 ± 9.42	68.45 ± 8.54	54.67 ± 7.83	<0.001
	IPL	88.12 ± 9.87	66.23 ± 8.12	52.34 ± 7.21	<0.001
	SSA+IPL	87.76 ± 9.65	56.34 ± 7.23	38.42 ± 5.67	<0.001
IL-6	SSA	124.56 ± 13.47	98.34 ± 11.23	78.43 ± 9.32	<0.001
	IPL	126.34 ± 14.12	96.45 ± 10.87	75.67 ± 8.94	<0.001
	SSA+IPL	125.48 ± 13.89	82.17 ± 9.45	52.18 ± 7.43	<0.001
TNF-α	SSA	67.23 ± 8.14	54.32 ± 7.23	43.56 ± 6.32	<0.001
	IPL	68.47 ± 8.63	52.67 ± 6.87	41.23 ± 5.87	<0.001
	SSA+IPL	67.89 ± 8.32	44.56 ± 5.87	28.74 ± 4.56	<0.001

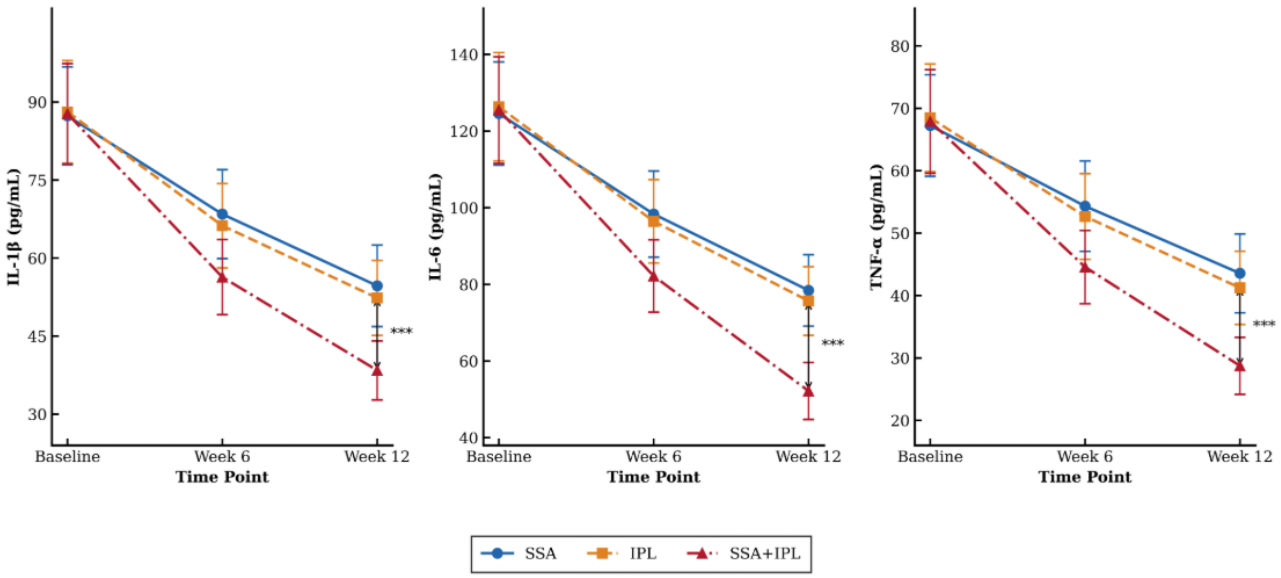

Figure 4. Pro-inflammatory Cytokine Levels across Three Groups.

3.3.2. Upregulation of Anti-Inflammatory Cytokines (IL-10, TGF-β) and Immune Balance Remodeling

IL-10 and TGF-β play important roles as negative regulators of immune homeostasis in the skin. Both cytokines are involved in local immune tolerance and inflammatory resolution, as they inhibit pro-inflammatory signaling

mechanisms, promote regulatory T cell function and inhibit effector immune cell activation. The expressions were measured at baseline, at week 6 and at week 12 (**Table 5**, **Figure 5**). No significant differences between the groups were found at baseline for IL-10 or TGF-β ($p > 0.05$). IL-10 rose from 18.43 ± 3.12 to 32.67 ± 4.54 pg/mL in the SSA group, and from 17.98 ± 2.87 to 34.12 ± 4.78 pg/mL in the IPL group. The SSA+IPL group climbed from 18.21 ± 3.04 to 48.76 ± 5.93 pg/mL, an increase of 167.8% that was significantly higher than both monotherapy groups ($q < 0.001$; Cohen's d vs. SSA = 2.87, 95% CI: 2.33–3.41) [38–40]. TGF-β increased from 24.56 ± 3.87 to 38.43 ± 5.12 pg/mL (SSA) and from 25.12 ± 4.13 to 39.87 ± 5.34 pg/mL (IPL). In the SSA+IPL group, TGF-β rose from 24.83 ± 3.95 to 57.34 ± 6.87 pg/mL, a 130.8% gain ($q < 0.001$). The IL-6/IL-10 ratio declined from 6.87 ± 0.94 to 2.43 ± 0.47 (SSA) and from 7.03 ± 0.98 to 2.24 ± 0.43 (IPL). In the SSA+IPL group, the ratio was lowered from 6.94 ± 0.96 to 1.08 ± 0.21 ($q < 0.001$), indicating a significant change in the microenvironment of this area towards the anti-inflammatory.

Table 5. Comparison of anti-inflammatory cytokine levels and immune balance indicators across three groups (mean ± SD).

Indicator	Group	Baseline	Week 6	Week 12	*p*
IL-10 (pg/mL)	SSA	18.43 ± 3.12	24.87 ± 3.87	32.67 ± 4.54	<0.001
	IPL	17.98 ± 2.87	25.43 ± 4.12	34.12 ± 4.78	<0.001
	SSA+IPL	18.21 ± 3.04	34.56 ± 4.87	48.76 ± 5.93	<0.001
TGF-β (pg/mL)	SSA	24.56 ± 3.87	31.24 ± 4.43	38.43 ± 5.12	<0.001
	IPL	25.12 ± 4.13	32.67 ± 4.87	39.87 ± 5.34	<0.001
	SSA+IPL	24.83 ± 3.95	42.18 ± 5.67	57.34 ± 6.87	<0.001
IL-6/IL-10 ratio	SSA	6.87 ± 0.94	4.02 ± 0.63	2.43 ± 0.47	<0.001
	IPL	7.03 ± 0.98	3.84 ± 0.58	2.24 ± 0.43	<0.001
	SSA+IPL	6.94 ± 0.96	2.43 ± 0.38	1.08 ± 0.21	<0.001

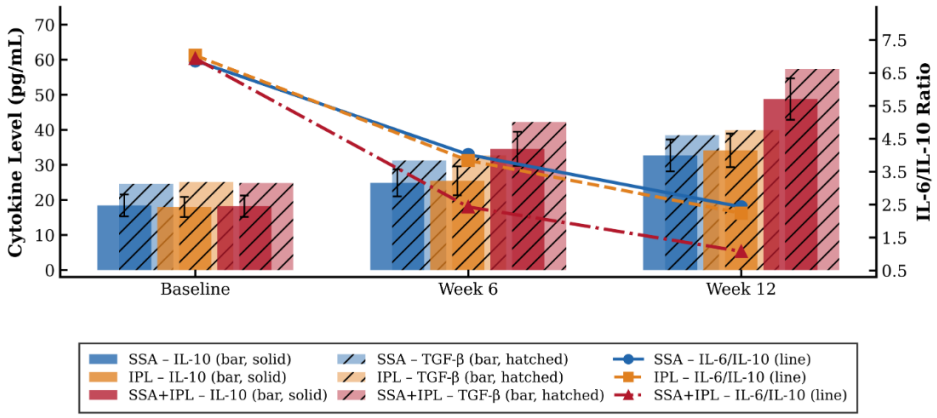

Figure 5. Anti-inflammatory Cytokines (IL-10, TGF-B)and IL-6/IL-10 Ratio across Three Groups.

3.3.3. Dynamic Shifts in Treg/Th17 Cell Ratio and Restoration of Immune Homeostasis

This dynamic balance between Tregs and Th17 is important in the immune homeostasis of the skin and Treg/Th17 imbalance is one of the important immunological mechanisms involved in chronic inflammation in acne. Peripheral blood Treg cells (CD4+CD25+Foxp3+) and Th17 cells (CD4+IL-17A+) proportions were measured at baseline, after 6 and 12 weeks and the Treg/Th17 ratio was calculated (**Table 6**, **Figure 6**). There were no differences at baseline ($p > 0.05$). Treg proportions increased in all groups: SSA from 4.23 ± 0.67% to 6.12 ± 0.84%; IPL from 4.17 ± 0.71% to 6.34 ± 0.89%; SSA+IPL from 4.19 ± 0.69% to 8.47 ± 1.12%, a gain of 102.1%, significantly greater than both monotherapy groups ($q < 0.001$; Cohen's d vs. IPL = 2.21, 95% CI: 1.74–2.68). Th17 proportions declined across all groups: SSA from 8.76 ± 1.23% to 6.43 ± 0.94%; IPL from 8.92 ± 1.34% to 6.18 ± 0.87%; SSA+IPL from 8.84 ± 1.28% to 4.12 ± 0.63%, a 53.4% reduction ($q < 0.001$). The Treg/Th17 ratio increased from 0.49 ± 0.08 to 0.96 ± 0.13 (SSA) and from 0.47 ± 0.09 to 1.03 ± 0.14 (IPL). The ratio was highly increased from 0.48 ± 0.08 to 2.07 ± 0.27 (331.3%) in the SSA+IPL group and was effective in reversing Treg/Th17 immune imbalance ($q < 0.001$). Pearson correlation analysis (normality tested by Shapiro-Wilk with $p > 0.05$ for both variables) showed

that the Treg/Th17 ratio correlated positively with increase of IL-10 (r = 0.783, $p < 0.001$) and negatively with decrease of TNF-α (r = −0.741, $p < 0.001$) in accordance with the systemic immunoregulatory response. It should be stressed that Tregs and Th17 cells were not directly counted in the skin lesion areas but in the peripheral venous blood. Section 4.4 reviews the adequacy of the representation of proportions of infiltrating immune cells in the circulation to the local immune environment of the skin.

Table 6. Comparison of Treg and Th17 cell proportions and Treg/Th17 ratio across three groups (mean ± SD).

Indicator	Group	Baseline	Week 6	Week 12	*p*
Treg cells (%)	SSA	4.23 ± 0.67	5.14 ± 0.74	6.12 ± 0.84	<0.001
	IPL	4.17 ± 0.71	5.23 ± 0.79	6.34 ± 0.89	<0.001
	SSA+IPL	4.19 ± 0.69	6.43 ± 0.94	8.47 ± 1.12	<0.001
Th17 cells (%)	SSA	8.76 ± 1.23	7.54 ± 1.08	6.43 ± 0.94	<0.001
	IPL	8.92 ± 1.34	7.43 ± 1.12	6.18 ± 0.87	<0.001
	SSA+IPL	8.84 ± 1.28	6.34 ± 0.87	4.12 ± 0.63	<0.001
Treg/Th17 ratio	SSA	0.49 ± 0.08	0.69 ± 0.10	0.96 ± 0.13	<0.001
	IPL	0.47 ± 0.09	0.71 ± 0.11	1.03 ± 0.14	<0.001
	SSA+IPL	0.48 ± 0.08	1.03 ± 0.15	2.07 ± 0.27	<0.001

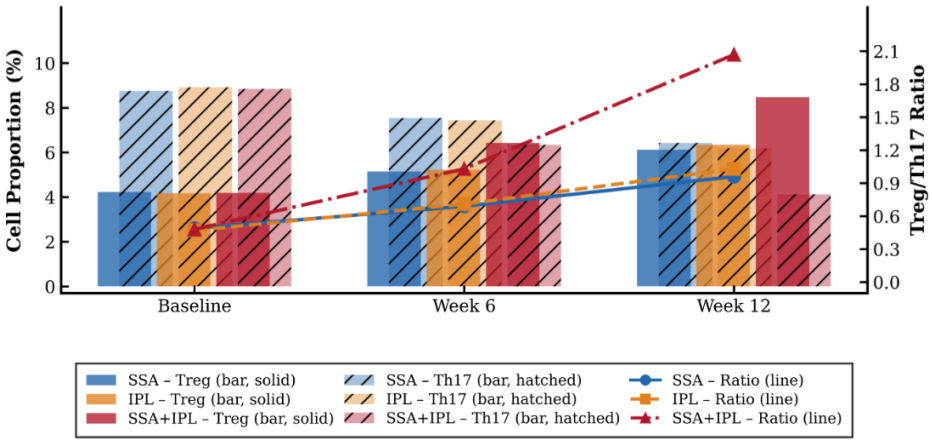

Figure 6. Treg and Th17 Cell Proportions and Treg/Th17 Ratio across Three Groups.

3.4. Comprehensive Clinical Efficacy and Safety Evaluation of Combination Therapy

3.4.1. GAGS Scores and Lesion Counts

The GAGS scores and the number of lesions are the fundamental objective parameters for the severity evaluation of acne and its response. Both the three groups were assessed at baseline, week 4, 8 and 12 as shown in **Table 7** and **Figure 7**. The baseline GAGS score and lesion counts were not significantly different among the groups ($p > 0.05$). All groups had a reduction in GAGS scores. The SSA group fell from 28.43 ± 4.12 to 16.87 ± 3.24 at week 12, a 40.7% decrease. The IPL group declined from 29.12 ± 4.34 to 15.43 ± 2.98, a 47.0% reduction. The SSA+IPL group dropped from 28.76 ± 4.21 to 9.34 ± 1.87, a 67.6% reduction significantly greater than both monotherapy groups (q < 0.001; Cohen's d vs. IPL = 2.43, 95% CI: 1.94–2.92). Inflammatory lesion counts showed a comparable pattern: SSA decreased from 24.67 ± 5.43 to 12.34 ± 3.21 (−50.0%); IPL from 25.12 ± 5.67 to 11.87 ± 2.98 (−52.7%); SSA+IPL from 24.89 ± 5.54 to 6.43 ± 1.76, a 74.2% reduction (q < 0.001). Non-inflammatory lesions followed a similar trend: SSA 18.34 ± 4.12 to 9.87 ± 2.43; IPL 17.98 ± 3.87 to 9.43 ± 2.21; SSA+IPL 18.12 ± 3.98 to 5.12 ± 1.34, a 71.8% reduction (q < 0.001). The overall clinical response rate was 93.3% in the SSA+IPL group (28/30), significantly higher than the SSA group (70.0%, 21/30) and the IPL group (73.3%, 22/30; $\chi^2 = 7.42$, $p < 0.05$). The main effects of time, group and the interactions between time and group were highly significant for each of the three indicators according to the repeated-measures ANOVA (all q < 0.001).

3.4.2. Correlation Analysis between Skin Barrier Repair Indicators and Clinical Efficacy

To quantify the relationships between skin barrier repair indicators and clinical outcomes, Pearson correlation and multiple linear regression analyses were performed. All eight barrier repair indicators showed significant posi-

tive correlations with GAGS score improvement (all $p < 0.001$; **Table 8**). Among these, the Treg/Th17 ratio increase showed the strongest correlation (r = 0.836), followed by IL-10 upregulation (r = 0.812) and TGF-β upregulation (r = 0.784). In the final multiple regression model, three independent predictors were retained after backward stepwise elimination: Treg/Th17 ratio increase (β = 0.412), IL-10 upregulation (β = 0.231), and sebum secretion reduction (β = 0.287), together explaining 76.3% of the variance in GAGS score improvement (adjusted $R^2 = 0.763$). The correlation coefficients (r) and standardized regression coefficients (β) for all indicators are illustrated in **Figure 8**. Adjusted $R^2 = 0.763$ for the three-predictor regression model. S-W = Shapiro-Wilk. Variables excluded from the final regression model by backward stepwise elimination: TEWL reduction, stratum corneum hydration gain, Shannon index gain, TGF-β upregulation, TNF-α reduction.

3.4.3. Adverse Event Rates and Quality of Life (DLQI)

Evaluation of safety and quality of life are crucial variables that can be used to assess clinical feasibility. Systematic adverse events log was kept during the treatment period and DLQI scores were evaluated at baseline and week 12 (**Table 9**, **Figure 9**). Type of adverse events were reported by 27% of the participants in the SSA group as "mild skin dryness" (13.3%), "transient burning sensation" (10.0%) and "mild desquamation" (3.3%). In the IPL group, 7 of 30 (23.3%) reported events: transient erythema (13.3%), mild edema (6.7%), and burning sensation (3.3%). In the SSA+IPL group, 11 of 30 (36.7%) had events: mild erythema (16.7%), transient burning (13.3%), and skin dryness (6.7%). There was no significant differences between the rates of adverse event among the three groups ($X^2 = 1.24$, $p > 0.05$). None were severe and necessitated treatment interruption and all lasted no more than 1–3 days. There have been no serious adverse events. Baseline DLQI scores did not differ among groups ($p > 0.05$): SSA 14.23 ± 3.12, IPL 14.67 ± 3.34, SSA+IPL 14.45 ± 3.21. By week 12, the SSA group declined to 8.43 ± 2.12 (−40.7%), the IPL group to 7.98 ± 1.98 (−45.6%), and the SSA+IPL group to 4.32 ± 1.24 (−70.1%), with the combination group achieving significantly greater improvement than both monotherapy groups ($q < 0.001$; Cohen's d vs. IPL = 2.34, 95% CI: 1.86–2.82). On the subscale analysis, combined group showed improvements in all four the DLQI areas, namely symptoms and feelings (−72.3%), daily activities (−68.4%), leisure and social functioning (−71.2%) and emotional well-being (−69.8%; all between-group $q < 0.01$) [41].

Table 7. Comparison of GAGS scores and lesion counts across three groups (mean ± SD).

Indicator	Group	Baseline	Week 4	Week 8	Week 12	Response Rate
GAGS score	SSA	28.43 ± 4.12	23.67 ± 3.87	19.54 ± 3.43	16.87 ± 3.24	70.00%
	IPL	29.12 ± 4.34	22.87 ± 3.64	18.43 ± 3.12	15.43 ± 2.98	73.30%
	SSA+IPL	28.76 ± 4.21	19.43 ± 3.12	13.87 ± 2.43	9.34 ± 1.87	93.30%
Inflammatory lesions (n)	SSA	24.67 ± 5.43	19.43 ± 4.32	15.67 ± 3.54	12.34 ± 3.21	—
	IPL	25.12 ± 5.67	18.87 ± 4.12	14.98 ± 3.34	11.87 ± 2.98	—
	SSA+IPL	24.89 ± 5.54	15.43 ± 3.43	10.34 ± 2.43	6.43 ± 1.76	—
Non-inflammatory lesions (n)	SSA	18.34 ± 4.12	15.12 ± 3.43	12.43 ± 2.87	9.87 ± 2.43	—
	IPL	17.98 ± 3.87	14.87 ± 3.21	11.98 ± 2.64	9.43 ± 2.21	—
	SSA+IPL	18.12 ± 3.98	12.43 ± 2.87	8.34 ± 1.98	5.12 ± 1.34	—

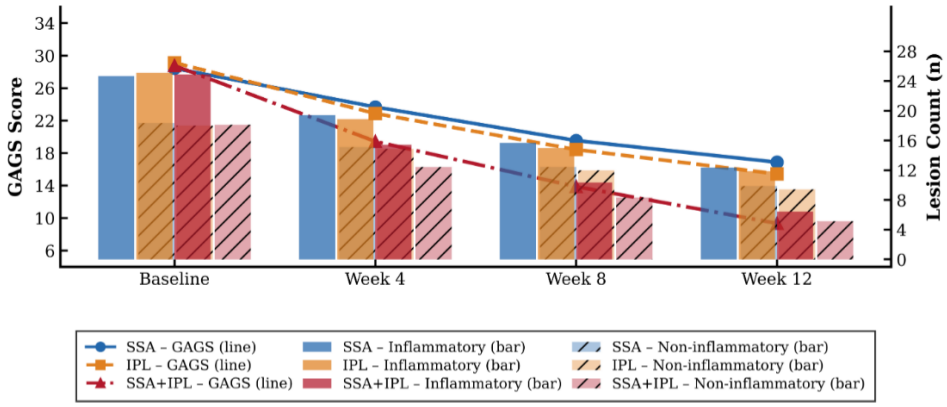

Figure 7. GAGS Scores and Lesion Counts across Three Groups.

Table 8. Correlation analysis between skin barrier repair indicators and GAGS score improvement.

Barrier Repair Indicator	Normality (S-W *p*)	Correlation Method	r	*p*	β	*p* (Regression)
TEWL reduction	0.21	Pearson	0.724	<0.001	0.143	<0.05
Stratum corneum hydration gain	0.18	Pearson	0.698	<0.001	0.127	<0.05
Sebum secretion reduction	0.31	Pearson	0.743	<0.001	0.287	<0.001
Shannon index gain	0.14	Pearson	0.672	<0.001	0.118	<0.05
IL-10 upregulation	0.27	Pearson	0.812	<0.001	0.231	<0.01
TGF-β upregulation	0.22	Pearson	0.784	<0.001	0.198	<0.01
Treg/Th17 ratio increase	0.19	Pearson	0.836	<0.001	0.412	<0.001
TNF-α reduction	0.16	Pearson	0.761	<0.001	0.176	<0.05

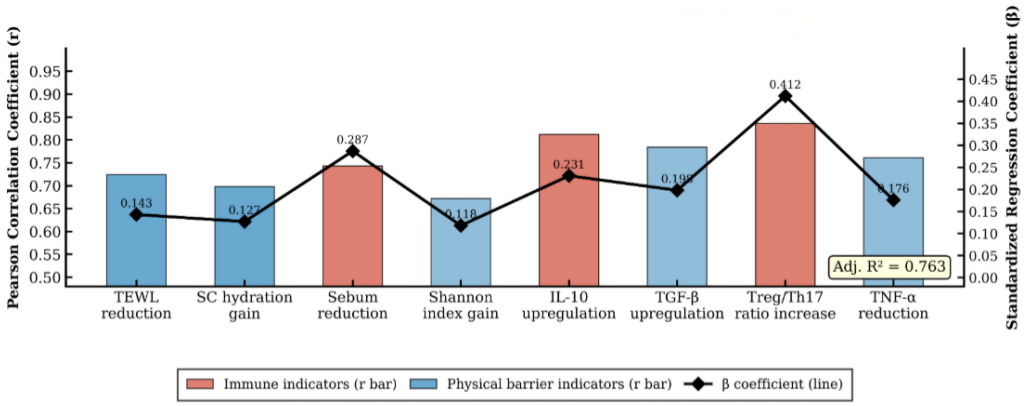

Figure 8. Correlation (r) and Regression (B) Coefficients between Skin Barrier Indicators and GAGS Score Improvement.

Table 9. Comparison of adverse event rates and DLQI scores across three groups (mean ± SD).

Indicator	SSA (n = 30)	IPL (n = 30)	SSA+IPL (n = 30)	*p*
Overall AE rate	26.7% (8/30)	23.3% (7/30)	36.7% (11/30)	>0.05
Mild erythema/burning	10.00%	13.30%	13.30%	>0.05
Skin dryness/desquamation	13.30%	3.30%	6.70%	>0.05
Mild edema	3.30%	6.70%	16.70%	>0.05
DLQI baseline score	14.23 ± 3.12	14.67 ± 3.34	14.45 ± 3.21	>0.05
DLQI week 12 score	8.43 ± 2.12	7.98 ± 1.98	4.32 ± 1.24	<0.001
DLQI reduction (%)	40.70%	45.60%	70.10%	<0.001

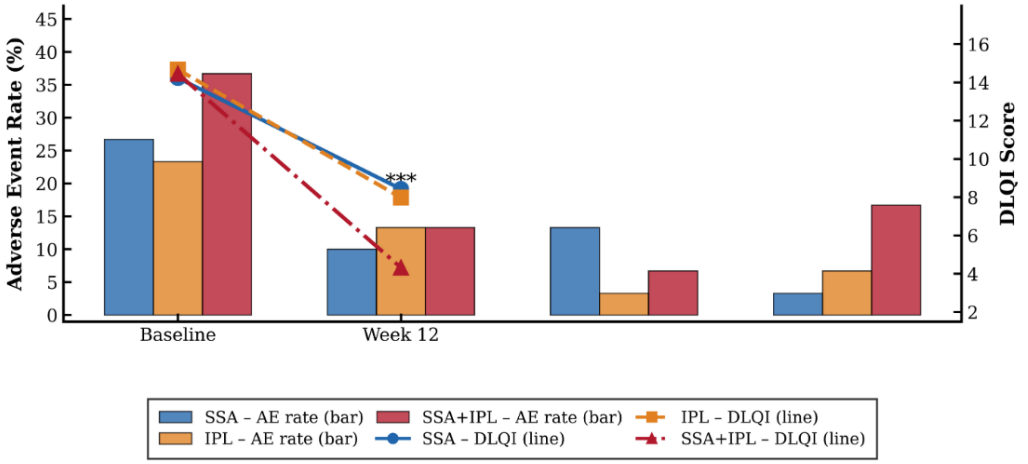

Figure 9. Adverse Event Rates and DLQI Scores across Three Groups.

4. Discussion

4.1. Mechanisms by Which SSA Repairs the Skin Barrier through Innate Immune Modulation

The significant improvements in TEWL, stratum corneum hydration, sebum secretion and local pro-inflammatory cytokine levels in response to SSA monotherapy further reinforces the independent effects of SSA on physical barrier repair and innate immune regulation. Encapsulation of salicylic acid into cyclodextrin complexes using supramolecular inclusion technology allows for controlled, non-destructive release of salicylic acid while retaining its keratolytic efficacy at a lower concentration, eliminating the adverse effect caused by high concentration formulation of salicylic acid in conventional pharmaceutical preparations [42,43]. Evidence exists that salicylic acid inhibits the activity of COX-1/COX-2 enzymes and thus prevents the formation of prostaglandin E2 (PGE2), which is an important factor in the activation of mast cells and macrophages, with the subsequent reduction in the release of IL-1β, IL-6 and TNF-α [44]. Salicylic acid also inhibits the phosphorylation of NF-κB signaling pathways that may be capable of suppression of the upstream innate immune cascade. The sustained-release profile of SSA is thought to provide locally effective therapeutic concentrations for a sustained period of time, with complementary activity against the 5α-reductase enzyme in the sebaceous glands and keratinocyte modulation effects. Although feasible, laboratory studies using immunohistochemistry or Western blot analysis or the use of pathway-specific inhibitors were not possible during this clinical trial and would be an important area for future investigation for the proposed mechanisms.

4.2. Photo-Immunomodulatory Effects of IPL and Its Complementary Interaction with SSA

There were many significant improvements associated with IPL monotherapy. The combination group had significantly more effects on all the indicators measured although this trial did not include formal additivity analysis and no synergy can be proposed. IPL emits broad-spectrum light (515–1,200 nm), which selectively targets C. acnes-generated endogenous porphyrins, to produce singlet oxygen and reactive oxygen species (ROS) that provide damage to bacterial cell membranes, leading to the reduction of the innate immune system activation mediated by TLR2. Other studies have also shown that irradiation with IPL causes a rise in the expression of heat shock protein 70 (HSP70) in keratinocytes and fibroblasts, which could affect the function of dendritic cells and induce differentiation of Treg cells [45]. These molecular pathways are hypothesized as possible mechanisms of action and could be explored at the tissue level in the current patient cohort. If you consider the mechanism, SSA pre-treatment softens keratin and clears the folliculopilosebaceous ducts and might increase the depth of IPL light penetration and the effectiveness of the photothermal. Post-IPL microvascular permeability change may also be an enhancing factor in the absorption of SSA. Combined, these synergistic interactions are proposed to build a multi-level repair system which has yet to be validated in controlled mechanistic studies.

4.3. Mediating Role of the Skin Microbiome in Immune Barrier Repair

The higher Shannon diversity index in the SSA+IPL group (+52.1%) and the significant negative correlation between Shannon diversity index and pH reduction ($r = -0.726$, $p < 0.001$) further suggest that achieving microbiome homeostasis recovery is one of the main mechanisms for immune barrier repair. Commensal flora like Staphylococcus epidermidis also produce antimicrobial peptides and Short chain fatty acids (SCFAs), which serve to keep the surface pH acidic, inhibit pathogen colonization and stimulate IL-10 production. In acne, where the skin pH is increased and the composition of the sebum is altered, C. acnes is able to overgrow and interact permanently with TLR2/TLR4 receptor causing constant production of pro-inflammatory cytokines [46]. Two complementary modes of action, IPL reduces C. acnes bioburden and SSA restores the acidic microenvironment, make Combination Therapy the way to interrupt this cycle. It is thought that the ensuing recovery of the microbiome will then stimulate additional repair of the barrier via competitive colonization of the field by a wide variety of commensals and activation of signaling through GPR41/43, thereby promoting Treg differentiation, and via microbiome-induced upregulation of TJP in keratinocytes. These mechanisms are speculative from the literature, and from the correlational data from this trial; experimental evidence is needed at the pathway level.

4.4. Clinical Implications, Limitations, and Future Directions

These findings demonstrate that combined SSA-IPL therapy could be a clinically useful approach for moderate–to-severe acne as it appears to be more effective than monotherapy and is not accompanied by any increased safety

concerns. A high response rate (93.3%) and high DLQI improvement (70.1%) achieved in the combination group and lack of serious adverse events suggest a favorable benefit-risk profile. Blinding and observer bias: It was not possible to blind participants to allocation to treatment because there were significant sensory and procedural differences between the two interventions. Additionally, clinical assessors were not blinded, a reasonable limitation to keep in mind, since counting the number of lesions and applying the GAG's scores are subjective. To reduce this risk, standardised photography, digital images on a VISIA system and a single trained assessor with a predefined system for grading were used; but it is recognised that some degree of assessor bias may exist. In the future, it would be beneficial to have photographic documentation independently and blindly assessed by others or patient-reported outcome measures as additional co-primary outcome measures evaluated. Peripheral vs. local immune measures: Treg and Th17 cell proportions were measured in peripheral venous blood, instead of in skin biopsies or in biopsies in the areas of the lesions. Immune cell counts in the circulation may not correspond to those found in the local cutaneous immune environment in acne lesions and tissue-resident immune populations and the dermal inflammatory environment may not reflect the systemic environment. These studies reveal suggestive correlation between peripheral Treg/Th17 ratio and the clinical outcomes, but cannot conclude the causality at the tissue level. Future research should include skin biopsy tissues with immunohistochemistry or single-cell transcriptomics for the direct characterization of lesion site immune changes. Targeting all these potential issues, other limitations include: Relatively small size of each group (n = 30) with limitation in generalizability due to single centre design; No relapse data available beyond 12 weeks; Microbiome analysis only using Shannon diversity index, lacking species-level sequencing; Skin type according to Fitzpatrick scale was an inclusion criterion for participants. Future studies should attempt to overcome these limitations and perform a more rigorous interaction testing to distinguish additive from multiplicative effects, and to determine whether benefits on immunoregulation translate to decreased long-term scarring and recurrence.

5. Conclusion

The study showed that combined SSA and IPL therapy yields better restoration of the skin immune barrier function than both SSA and IPL therapy alone in moderate to severe acne: TEWL was decreased by −47.0%, skin hydration by +67.0%, sebum by −45.7% and pH is normalized; pro-inflammatory cytokines were all reduced by 56–58%, while IL-10 increased by +167.8% and TGF-β by +130.8% and Treg/Th17 ratio by +331.3%, and microbiome diversity was restored by +52.1%. For the combination group clinical response rate was 93.3%, GAGS score reduction 67.6%, DLQI improvement 70.1% and adverse event profile was similar to monotherapy. Treg/Th17 ratio reestablishment, sebum reduction and upregulation of IL-10 were found to be independent factors for clinical effectiveness by multiple regression analysis (adjusted $R^2 = 0.763$). These findings can be utilized as evidence for the use of combined SSA and IPL therapy in the treatment of acne. The presented mechanistic pathways are proposed only and need to be confirmed in laboratory, while formal additivity analysis would be interesting in future trials to better describe the nature of the combination effect. Larger multicenter trials with longer follow-up should be performed to confirm the durability and generalizability of these results.

Author Contributions

Conceptualization, X.H. and Z.A.Z.; methodology, X.H.; software, X.H.; validation, X.H. and Z.A.Z.; formal analysis, X.H.; investigation, X.H.; resources, Z.A.Z.; data curation, X.H.; writing—original draft preparation, X.H.; writing—review and editing, Z.A.Z.; visualization, X.H.; supervision, Z.A.Z.; project administration, Z.A.Z.; funding acquisition, Z.A.Z. Both authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

This study received approval from the hospital's Medical Ethics Committee (Approval No.: [UMS.TNCPI/800-3/2/1/2, JKEUUMS2024/0089]). All procedures were carried out according to the Declaration of Helsinki (2013 revision) [World Medical Association, JAMA 2013;310:2191–2194] and national regulations for the ethical review

of life science and medical research involving human subjects [National Health Commission of China, Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects, 2023].

Informed Consent Statement

All participants gave written informed consent before enrolling.

Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions relating to participant confidentiality.

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Conflicts of Interest

The authors declare no conflict of interest.

AI Use Statement

The authors declare that no artificial intelligence (AI) tools were used in the preparation of this manuscript.

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