RESEARCH ARTICLE

Lactiplantibacillus plantarum IS-10506 Supplementation Improves Clinical Outcome and Immunology Markers in Psoriasis Vulgaris Patients: A Randomized Controlled Trial

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Abstract

BACKGROUND: Probiotics may modify the gut microbiome and have been proven to improve psoriasis vulgaris. *Lactiplantibacillus plantarum* IS-10506 is a probiotic strain of Indonesian origin. It offers a safe and effective probiotic for psoriasis patients in Indonesia. This study was conducted to evaluate the effect of *L. plantarum* IS-10506 on clinical and immunology markers in psoriasis vulgaris.

METHODS: This randomized, placebo-controlled, and double-blind trial compared *L. plantarum* IS-10506 (2×10^{10} CFU/day) and placebo in 49 patients mild-moderate psoriasis vulgaris, which were divided into intervention (n=24) and control groups (n=25). The interventions were given twice daily for 12 weeks. Both groups received topical corticosteroid and emollient as standard treatment. Psoriasis area and severity index (PASI), dermatology life quality index (DLQI), interleukin (IL)-10, IL-17, and forkhead box protein (Foxp3) were then assessed.

RESULTS: Mean PASI score for the the subjects in probiotic group was significantly reduced compared to placebo at week-6 (p=0.024), and was sustained until week-12 (p=0.049). At week-12, DLQI scores in the probiotic group were lower than placebo (7.57±5.77 *vs*. 7.79±5.48). IL-17 level was significantly decreased (p=0.013), while the IL-10 and Foxp3 were significantly increased ($p\leq0.001$ and p=0.048, respectively) in probiotic group. Six months after the completion of study, subjects in probiotic group had a lower probability of flares (52.2%) compared to placebo (79.2%). Two subjects receiving probiotics and one receiving placebo noticed changes in defecation frequency, while another subject in the placebo group complained of mild nausea.

CONCLUSION: *L. plantarum* IS-10506 might effectively improve clinical outcomes and immune biomarkers in psoriasis vulgaris patients, potentially acting as an adjuvant therapy.

KEYWORDS: psoriasis, probiotic, clinical severity, immune marker, human and health

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Introduction

Psoriasis is a chronic inflammatory skin disease that is immunologically mediated and associated with a genetic predisposition. The HLA-Cw6 allele has been found to be a significant genetic risk factor for psoriasis vulgaris. Carrying this allele increases the likelihood of developing psoriasis because HLA-Cw6 presents certain peptides that may activate T cells and cause inflammation in the skin.(1) Psoriasis primarily affects individuals in the young and middle age groups and has a substantial negative impact on both their quality of life and their physical and mental well-being.(2) The prevalence of psoriasis is known to range from 0.09 to 11.4% worldwide, with numbers varying across regions.(3,4) In Indonesia, the prevalence of psoriasis ranges from 1–3%, according to reports from several teaching hospitals.(5-8) The manifestations of the disease are well-demarcated, mainly erythema with raised red plaques and a scaly surface, which may afflict the whole body. The lesions are distributed mostly on the scalp and the extensor side of the limbs, although any skin surface can be involved. The skin plaque lesions are characterized by anatomical symmetry.(9) Long term cumulative effects of psoriatic symptoms include a decreased quality of life with concomitant psychological complaints such as depression, stigma, low self-esteem, and depression.(10)

Recent studies indicate that psoriasis results from inflammatory microenvironment initiated by bacterial products, the migration of immune cells such as T cells, macrophages, and neutrophils in the intestines, and the release of cytokines throughout the body.(11,12) The gut microbiome performs numerous essential activities, including preserving the integrity of the intestinal barrier, breaking down and digesting nutrients, synthesizing fatty acids and vitamins, reabsorbing bacterial metabolites, and activating the immune system.(13,14) Dysbiosis, defined as an alteration in the gut microbiota, may lead to the displacement of bacteria from the intestinal lumen, which is associated with compromised integrity of the intestinal barrier or a leaky gut.(15) This phenomenon may result in the detection of bacterial DNA in peripheral blood samples, along with an increase in the levels of inflammatory mediators implicated in the development of psoriasis, such as interleukin (IL)-6, IL-12, IL-1β, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ, without any simultaneous presence of an infectious condition.(16,17) Probiotic supplementation has the potential to exert a beneficial influence on the health of the host, amongst other through changing in the gut microbiota composition or immunomodulation. Enhanced gut health promotes a more regulated and balanced immunological response. Short-chain fatty acids, including butyrate, propionate, and acetate, are produced by microbial fermentation. These metabolites have a direct impact on the differentiation of T cells, increasing the activity of Treg cells, and suppressing pro-inflammatory cytokines secreted by effector T cells. As a result, fewer immune cells migrate to the skin and less inflammation occurred.(18) Therefore, probiotic supplementation could potentially serve as an innovative therapeutic approach for managing clinical manifestation in psoriasis patients.(19) Assessing IL-17, IL-10, and forkhead box protein (Foxp3) as immunological biomarkers for psoriasis might be beneficial for the enrichment of knowledge, since IL-17 is recognized as a crucial cytokine in the development of psoriasis since it is generated by Th17 cells. IL-10 is a cytokine with anti-inflammatory properties that is released by regulatory T cell, whereas Foxp3 is a protein expressed by Treg cells that is used as a marker of their function.(1,9)

Lactiplantibacillus plantarum IS-10506, probiotic strain originating from Indonesia that was isolated from Dadih, a fermented buffalo milk from Western Sumatra (20), is anticipated to offer a safe and effective probiotic option for individuals with psoriasis in Indonesia. Consumption of probiotics is expected to reduce the severity of psoriasis in patients and may improve their quality of life. According to our understanding, this clinical trial was the first research to report the role of *L. plantarum* IS-10506 on psoriasis vulgaris patients. This study was conducted to evaluate the effect of the probiotic *L. plantarum* IS-10506 supplementation on clinical improvement and immune biomarkers of psoriasis vulgaris in a randomized placebo-controlled trial.

Methods

Experimental Design and Study Population

The study was a randomized, placebo-controlled, double-blind trial using a cohort prospective method in patients with psoriasis vulgaris. The research protocol was granted ethical clearance by Dr. Soetomo General Academic Hospital's Ethics Committee for Clinical Research (No. 0315/KEPK/XI/2021).

Outpatients diagnosed with psoriasis who attended the clinic affiliated with the Allergy Immunology Division of the Dermatology and Venereology Department of the Faculty of Medicine at Universitas Airlangga/Dr. Soetomo

General Academic Hospital in Surabaya, Indonesia, were recruited. The requirements for participation in this study were male and female patients with mild-to-moderate psoriasis vulgaris (psoriasis area and severity index (PASI) score <10), with new or old-onset psoriasis, adults aged 18–70 years, and willing to give informed consent. Excluded were subjects receiving immunosuppressive systemic treatment (methotrexate and biological agents) within 3 months before sampling, taking oral antibiotics, laxatives, and proton pump inhibitors (PPI) within 14 days before fecal samples, subjects with malignancy or diarrhea, and oral probiotic consumption within 30 days before sampling.

Participants, Recruitment, and Randomization

In order to calculate the sample size, we used a method specifically designed for an unpaired numerical analytic study.(21) The sample size for this research was calculated referring to a similar clinical trial that had the most resemblance to current investigation and already shown great results, which investigated the effects of *L. plantarum* IS-10506 on individuals suffering from atopic dermatitis. (22) According to the result, the appropriate sample size for each group was 21 subjects. A total of sixty-five psoriasis subjects were screened by dermatologists between March 2022 and April 2023. Fifty subjects aged between 18 and 70 years old with mild-to-moderate psoriasis vulgaris, as measured by PASI, fulfilled the inclusion criteria, but one subject refused to give consent. Forty-nine eligible subjects were then allocated to either the probiotic group or the control group. The two comparison groups were generated by employing simple randomization through the pharmacy department, utilizing a table of random numbers to ensure an equal allocation ratio. A pharmacist was accountable for trial supplement assignment, preparation, and recording. The whole participant flow chart, illustrating the process of enrollment, allocation, and randomization in this study were illustrated in Figure 1.

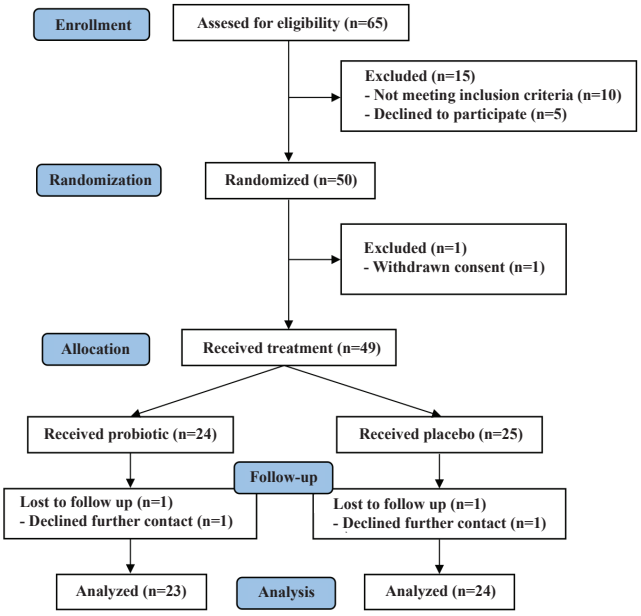

Figure 1. Study's participant flow chart.

Research Protocol

The probiotic used in this research was *L. plantarum* IS-10506 in encapsulated powder form, an original Indonesian probiotic isolated from Dadih.(23) The Department of Food Technology, Faculty of Engineering, Bina Nusantara University, Jakarta, supplied the probiotic and placebo. A probiotic dose of 2×10^{10} CFU/day was given to the intervention group. The control group received a placebo in the form of skim milk in the packaging of an aluminum sachet that resembled the probiotic. Both groups were given the same interval twice daily, every morning and evening before meals. The pharmacy staff systematically concealed drug containers with identical appearance, tamper-proof, and equal weight to ensure allocation concealment for both participants and investigators. All subjects were scheduled to visit at three time points during the intervention: week-0 (baseline), -6, and -12, which marked the conclusion of the treatment. In these three visits, subjects were evaluated clinically with a PASI and dermatology life quality index (DLQI) score by a dermatologist. Blood samples were collected at week-0 and -12 to be utilized for enzyme-linked immunosorbent assay (ELISA) for evaluating serum levels of IL-17, IL-10, and Foxp3. All subjects in both groups were administered desoximethasone cream and emollient as standard treatment for psoriasis vulgaris.

Clinical Outcome Measurement

This research assessed clinical outcomes to identify the response in each intervention group. The parameters measured were PASI and DLQI. PASI is a quantitative index used for assessing the severity of psoriasis. The calculation included assessing the size of the afflicted area and analyzing three characteristic psoriasis lesions in four different body regions (head, upper extremities, trunk, and lower extremities). The lesions evaluated were erythema, induration, and desquamation, which were scaled into four points: 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = significant symptoms, and 4 = extremely significant symptoms. The scores were then combined

using a specific formula to obtain a total PASI score, with a minimum of 0 and a maximum of 72. PASI score was assessed by a doctor through a physical examination.(24)

DLQI is a validated, self-administered survey that assesses the quality of life of patients afflicted with dermatological disorders. The measurement was conducted using a 10-item questionnaire regarding their symptoms, self-consciousness of the disease, daily activities, relationships with others, and treatment received. Subjects were required to answer each question over the previous week using the options 'not at all', 'a little', 'a lot', or 'very much', which are equivalent to scores of 0, 1, 2, and 3, consequently. All of the answers were then summed by researchers, resulting in an overall DLQI score that ranges from 0 to 30.(25)

An additional secondary outcome was post-clinical trial follow-up; this data was obtained after the probiotic or placebo intervention had concluded, as part of an out-of-protocol study. Subjects were monitored and assessed for the duration of the six-month post-intervention outcome period. Each month, a planned chat follow-up was conducted to inquire about the subjects' clinical status, including any occurrences of flare. Flare was defined as the emergence of new lesions or worsening of the symptoms after medication was discontinued. Subjects who disclosed experiencing a flare during this follow-up period were asked to personally visit the outpatient clinic for a re-evaluation.

Assessment of Immunological Biomarkers

In this study, IL-17, IL-10, and Foxp3 were selected as the immunological biomarkers. All three immunology biomarkers were measured with ELISA sandwich kit from Bioassay Technology Laboratory using human IL17 kit (Cat. No.: E0142Hu, BT LAB, Zhejiang, China); human IL10 kit (Cat. No.: E0102Hu, BT LAB, Zhejiang, China); and human Foxp3 kit (Cat. No.: E0692Hu, BT LAB, Zhejiang, China). For this evaluation, we collected serum from venous blood. The serum was then centrifuged at a speed of 2000 to 3000 RPM for 20 minutes in order to get the supernatant without sediment. The assay procedures consist of several steps, after the preparation of the kit, 10 µL of antibody (anti-IL 17/anti-IL 10/anti-Foxp3) was added to the 40 µL supernatant of each sample. The mixture was incubated for 60 minutes at 37°C, washed five times with a wash buffer, and added to 50 µL of substrate solutions A and B. The data was presented in the form of optical density (OD), which was subsequently translated using a standard curve from each sample to obtain cytokines in ng/L units for IL-10 and IL-17, and ng/mL units for Foxp3.

Statistical Analysis

The statistical analyses were performed using the SPSS program version 27 (IBM Corporation, Armonk, NY, USA). In summarizing quantitative variables, means and standard deviations (SD) were utilized, while proportions were chosen to summarize categorical variables. The main outcome of this research was to assess the changes in PASI and DLQI scores, as well as IL-17, IL-10, and Foxp3 serum levels. These potential outcomes between the two arms were compared and the probability of success in each arm along with the 95% confidence interval (95% CI) at each visit were reported. The data for normality and homogeneity of variance was assessed before conducting any analysis or comparisons. For normal distribution data, a paired t-test was used to assess comparisons within the same group. Between-groups analyses were evaluated using an independent t-test, with a p-value<0.05 indicating the statistical significance. The non-parametric statistical approach was applied if the data did not follow a normal distribution.

Results

In this study, 49 mild-to-moderate psoriasis subjects were randomly distributed in a cohort manner into two groups at a 1:1 ratio, resulting in 25 subjects receiving the probiotic intervention and 24 subjects receiving a placebo. Two subjects, one in each group, failed to complete the protocol due to lost to follow-up. Therefore, data analysis was conducted on the remaining 47 subjects (23 subjects in the probiotic group and 24 subjects in the placebo group).

Baseline Characteristics

There were no statistically significant variations between the groups in terms of age, height, body mass index (BMI), and duration of psoriasis (Table 1). However, there was a notable difference in terms of weight (p=0.040). The primary metrics, namely the PASI and DLQI score, as well as immune biomarkers also did not differ significantly between the placebo and probiotic groups at the baseline point, although there was a trend for PASI score to be higher in the placebo group.

***L. plantarum* IS-10506 Supplementation Decreased the PASI Scores**

There were no statistically significant differences observed in the PASI scores between the two groups prior to the implementation of the treatment, although the placebo group tended to have a higher score (Table 1). Following a

Table 1. Baseline characteristics of subjects.

Variable	Probiotic Group (n = 23)	Placebo Group (n = 24)	*p*-value
Age (years)	38.83±14.30	41.50±11.41	0.481[a]
Gender			
Females, n (%)	13 (56.5)	11 (45.8)	
Males, n (%)	10 (43.5)	13 (54.2)	
Weight (kg)	66.04±13.71	74.61±14.05	0.040[b,*]
Height (cm)	162.61±6.94	164.92±6.97	0.261[a]
Body mass index (kg/m^2)	24.82±3.97	27.38±4.61	0.061[b]
Duration of psoriasis (years)	13.27±10.60	14.21±8.72	0.742[a]
PASI score	4.22±2.27	5.68±2.85	0.068[a]
DLQI score	10.09±5.08	9.63±6.47	0.601[b]
Serum IL-17	72.02±24.11	57.80±42.09	0.079[b]
Serum IL-10	238.16±208.40	222.05±208.03	0.151[b]
Serum Foxp3	8.29±4.30	9.90±8.22	0.873[b]

Other than gender, data were presented in mean±SD. [a]*p*-value was obtained using an independent sample t-test, [b]*p*-value was obtained using a Mann-Whitney test; *significant if $p<0.05$.

6 weeks intervention, subjects who consumed the probiotic supplements had a significant and notable decrease in their PASI scores as compared to the placebo group. The improvements at week-6 of follow up were observed to be markedly significant, which was happened in 18 of 23 (78.2%) subjects in the probiotic group and 10 of 24 (41.7%) subjects in the placebo group, with $p=0.024$ for the difference of proportions. PASI scores in the probiotic group at the end of treatment (3.38±3.71) was improved significantly compared to the baseline (4.22±2.27), with $p=0.023$. The end-point PASI scores between the probiotic group (3.38±3.71) and the placebo group (4.29±2.39) also shown statistically significant difference with $p=0.049$ (Table 2).

However, the difference in the placebo group at the end of the trail compared to the baseline was also significant, and the decrease was even higher than in the probiotic-group ($p=0.008$). The details of difference in PASI scores between the probiotic and placebo groups at each visit (week-1, -6, and -12) were presented in Figure 2. An example of the clinical improvements reported in persons who received probiotics was shown in Figure 3.

L. plantarum IS-10506 Supplementation Effects on the DLQI Scores

Neither the probiotic nor placebo groups had a significantly different DLQI score after 12 weeks of treatment compared to the baseline, although the overall trend in both groups showed a decline (Table 2). However, the probiotic group tended to have a wider mean difference in DLQI score than the placebo group.

Table 2. Within group changes in clinical outcome and immune biomarker after 12 weeks of treatment.

Variable	Probiotic Group				Placebo Group			
	Baseline	End-Point	Mean Difference	*p*-value	Baseline	End-Point	Mean Difference	*p*-value
PASI	4.22±2.27	3.38±3.71	0.84±2.77	0.023[b,*]	5.68±2.85	4.29±2.39	1.34±2.26	0.008[a,*]
DLQI	10.09±5.08	7.57±5.77	2.52±6.78	0.088[a]	9.63±6.47	7.79±5.48	1.96±5.73	0.108[b]
Serum IL-17	72.02±24.11	49.91±31.29	22.11±37.57	0.013[b,*]	57.80±42.09	61.88±36.26	4.08±40.01	0.331[b]
Serum IL-10	238.16±208.40	334.94±214.24	96.84±105.85	<0.001[b,*]	222.05±208.03	212.75 ±166.71	9.31± 89.71	0.797[b]
Serum FOXP3	8.29±4.30	10.21±6.44	1.92±3.88	0.048[b,*]	9.90±8.22	8.56±5.88	1.34±6.61	0.331[b]

Data were presented in mean±SD.The *p*-value represents the comparison between pre- and post-intervention outcomes within each group. [a]*p*-value was obtained using a paired sample t-test, [b]*p*-value was obtained using a Wilcoxon test; *significant if $p<0.05$.

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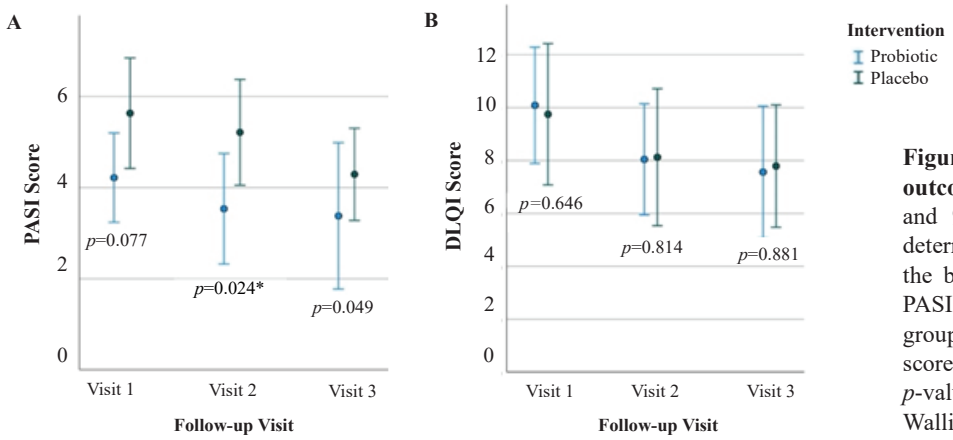

Figure 2. The progression of clinical outcomes between groups. Mean scores and 95% CI for PASI and DLQI were determined at each visit, starting from the baseline. A: Comparison of the mean PASI score between probiotic and placebo groups; B: Comparison of the mean DLQI score between probiotic and placebo groups. *p*-value was obtained using a Kruskal–Wallis test; *significant if $p<0.05$.

L. plantarum IS-10506 Supplementation Decreased the IL-17 Levels

Baseline level of IL-17 was not significantly different between the two groups (72.02±24.11 *vs.* 57.80±42.09, for probiotic and placebo groups, respectively; $p=0.079$), although there was a trend for it to be higher in the probiotic group. After intervention, the level of IL-17 was decreased in the probiotic group and increased in the placebo group. The value was not different between two groups (49.91±31.29 *vs.* 61.88±36.26, $p=0.255$). The decrease of IL-17 level in the probiotic group was statistically significant ($p=0.013$), while in the placebo group IL-17 level was insignificantly increased ($p=0.331$; Table 2 and Figure 4A).

L. plantarum IS-10506 Supplementation Increased the IL-10 Levels

Serum IL-10 level before intervention was comparable between groups (238.16±208.40 *vs.* 222.05±208.03, for probiotic and placebo groups, respectively; $p=0.151$), and after intervention the level of IL-10 was substantial different between groups (334.94±214.24 *vs.* 212.75±166.71, $p=0.004$). In the probiotic group, serum IL-10 was increased significantly after intervention compared to baseline ($p<0.001$). While in the placebo group, IL-10 level was not different compared to baseline (Table 2, Figure 4B).

L. plantarum IS-10506 Supplementation Increased the Foxp3 Levels

Serum Foxp3 level before intervention was comparable between groups (8.29±4.30 *vs.* 9.90±23.70, for probiotic and placebo groups, respectively; $p=0.873$), and after intervention it was not significantly different between groups (10.21±6.44 *vs.* 8.56±5.88, $p=0.360$). In the probiotic group, serum Foxp3 level was increased significantly at week 12, while it decreased in the placebo group (Table 2, Figure 4C).

Post Clinical Trial Follow-up

During the intervention, there were no severe adverse events or unintended effects. Two subjects who received probiotics and one who received a placebo noticed changes in defecation frequency, while another in the placebo group complained of mild nausea. All conditions lasted less than a week without therapy and did not induce them to discontinue the intervention.

Every month subsequent to the completion of the clinical trial, we continued to evaluate all of the subjects to ascertain if they had encountered a flare. In the probiotic group, the average duration between the end of the study and the incidence of a recurrence was 4.2 months, and in the placebo group, it was 2.6 months.

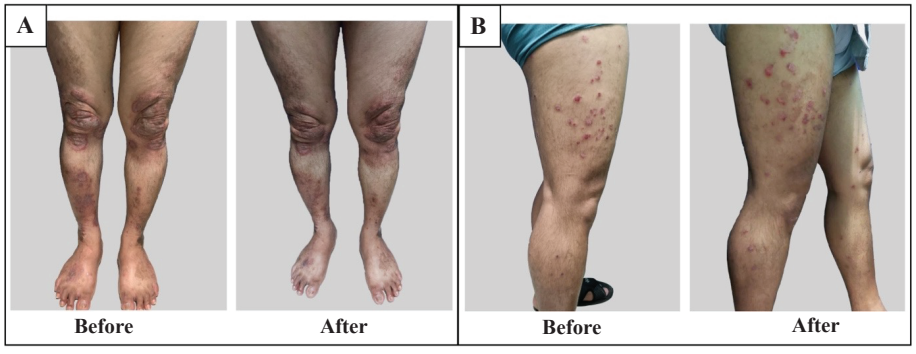

Figure 3. Example of clinical images showing improvement in the probiotic group. A: Before and after 12 weeks of probiotic *L. plantarum* IS-10506 treatment. B: Before and after 12 weeks of placebo treatment.

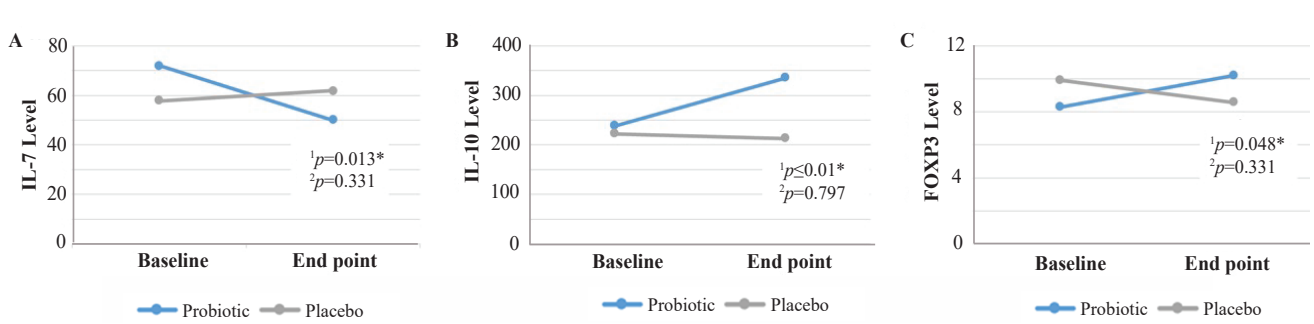

Figure 4. Evaluation results of immune biomarkers. A: Comparison of serum IL-17 level before and after intervention. B: Comparison of serum IL-10 level before and after intervention. C: Comparison of serum Foxp3 level before and after intervention. [1]*p*-value of before-after analysis in probiotic group; [2]*p*-value of before-after analysis in placebo group. *p*-value was obtained using a Wilcoxon test; *significant if $p<0.05$.

During a 6-month post-study follow-up, 12 out of the 23 subjects in the probiotic group experienced a flare (52.2%). Meanwhile, 19 flare-ups out of 24 subjects occurred in the placebo group (79.2%). The difference between groups showed statistically significant differences, with *p*-value for the log-rank test was 0.031 (Figure 5).

Discussion

Probiotics play an essential role in modulating the microbiota through gut-skin axis and serve as a critical therapeutic approach for the treatment of chronic inflammatory skin diseases including psoriasis and atopic dermatitis.(26,27) Previous research studying *L. plantarum* IS-10506 showed excellent results in both animal and human subjects. The administration of *L. plantarum* IS-10506 to the mice, beginning 7 days before allergen exposure and continuing for 27 days thereafter, demonstrated the capacity of this particular probiotic strain to inhibit allergic inflammation in the respiratory tract by significantly enhancing the integrity of the tight junction in the bronchial epithelium.(28) Other studies utilizing this probiotic strain in the Indonesian population with atopic dermatitis also indicated positive outcomes due to its immunomodulatory effect.(29,30) The use of this probiotic showed improvement in clinical and immune parameters for children and adults with atopic dermatitis.(22,32)

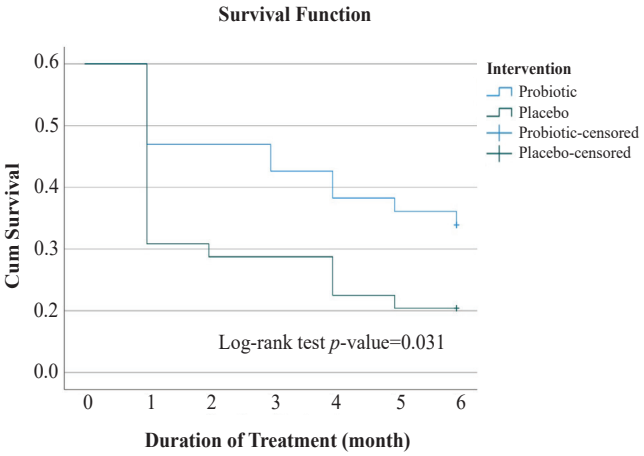

Figure 5. Post-clinical trial follow-up. Proportion of subjects in the probiotic and placebo groups who had not suffered a relapse during the 6-month follow-up period.

In the past few years, the correlation between the gut microbiome and psoriasis has been proven with several types of probiotics already being studied.(32) This research demonstrated that the supplementation of *L. plantarum* IS-10506 as an adjuvant treatment for a duration of 12 weeks has a favorable benefit on relieving the clinical symptoms of psoriasis. The reduction in PASI score in the probiotic group was statistically significant than the placebo group, with evident improvement already seen by the sixth week, showing the mean PASI score for probiotic and placebo was 3.53 and 5.21 ($p=0.024$). This outcome was sustained until week 12 ($p=0.049$). These results indicate a prior enhancement compared to another study which show significant PASI score reduction after given *Lactobacillus* strains for 8 weeks.(33)

In our clinical trial, both the probiotic and placebo groups revealed a statistically significant decrease in PASI after 12 weeks, but not followed by DLQI score. Although at the end of the study, subjects in the probiotic group experienced a greater reduction in DLQI score than subjects in the placebo group, with mean DLQI changes of 2.52 and 1.96, respectively ($p=0.725$). The results of previous study showed no significant mean DLQI changes within the probiotic and the placebo group after 12 weeks of *Lactobacillus rhamnosus* administration.(34) Due to

ethical considerations, all individuals in the probiotic and placebo groups were not deprived of regular psoriasis treatment, including topical corticosteroids, and emollients. Thus, it is anticipated that there would be a certain level of enhancement in both PASI and DLQI, regardless of the use of probiotics. The PASI score is influenced by the investigator's judgement, while the DLQI score is influenced by the patient's perception, which both are susceptible to individual subjectivity. However, this clinical trial is a double-blind study where patients and investigators were deliberately kept unaware of relevant information.

This study also revealed that IL-17 is reduced, while IL-10 and Foxp3 increase significantly after probiotic *L. plantarum* IS-10506 supplementation. IL-17 is considered as a key cytokines in psoriasis pathogenesis. It produced by Th17 cells, the primary immune cells in autoimunity including psoriasis, and stimulates inflammation.(35) Serum and lesional level of IL-17 in psoriasis patients is found to be higher compare to healthy individuals.(36) The decrease of IL-17, confirmed the ability of *L. plantarum* IS-10506 in supressing inflammation. This anti-inflammatory effect may be attributed to the regulatory effect of Treg cells, which is considered to increase with the administration of *L. plantarum* IS-10506 probiotic. This was validated by an elevation in IL-10 and Foxp3 levels following 12 weeks supplementation. IL-10 is anti-inflammation cytokines secreted by Treg, whereas Foxp3 is a protein expressed by Treg cells that is used as a marker of their function. Treg cells are hypothesised to act as regulators, suppressing inflammation and restoring immune cells homeostasis. (35,37)

Six months after the completion of this study, patients who underwent probiotic treatment had a reduced probability of flare compared to those who received a placebo. The skin tissue-residenst memory (TRM) T cells are considered as major driver immune cells in psoriasis relaps.(38,39) In psoriasis, TRM reactivates and produces IL-17 and IL-22 in response to external stimuli, attracting inflammatory cells and promoting relapse.(38) It is proposed that during the inflammation, Th17 can transform into exTh17 displaying a phenotype similar to TRM.(39) It is generally accepted that Th17 and Treg are interconverts, thus increasing the amount and function of Treg may reduce inflammation, diminish Th17 immune response, and restore a Th17-Treg balance. The quantity and function of Tregs must remain stable in order to avoid psoriasis relaps.(40)

The results of this study support the hypothesis that modulation of the gut microbiome via ingestion of *L. plantarum* IS-10506 produces anti-inflammatory effect, clinical improvement, and prolong remision in patients with mild to moderate psoriasis. Psoriasis is strongly linked to an imbalance in the gut microbiota, this imbalance can exacerbate the immune-inflammatory response within the body, thereby contributing to the disease's progression.

Probiotics may assist in restoring balance to the immune system dysregulation in psoriasis by inducing and stabilizing Treg cell responses. Treg cells suppress the inflammatory activity of effector T cells (Th17 and Th1) in psoriasis, therefore promoting immune system balance. Probiotics could produce short-chain fatty acids (SCFA), which subsequently bind to the G-protein-coupled receptors (GPR), such as GPR43, located on the surfaces of Treg cells. The binding of SCFA affects the stability of Foxp3 expression, thereby enhancing Treg cell activity.(18,19) Previous studies conducted in 2017 and 2022 showed that supplementation of *L. plantarum* IS-10506 for children and adult atopic dermatitis had significant effects on the adaptive immune system due to increasing Treg and decreasing proinflammatory T cells.(22,32) Hence, the positive results in this study might be attributed to the immunomodulatory properties of *L. plantarum* IS-10506, which inhibits the expression of proinflammatory cytokines associated with psoriasis.

Unfortunately, this study had small sample size and was restricted of being conducted solely at a single tertiary referral hospital in Indonesia. There are also some probability of risk regarding the bias in subject selection process due to the diversity of immunological characteristics in the wide age range of participants. A larger samples and multicenter research is suggested in the future to further strengthen the findings in this study. Additional research is necessary in the future to enhance the data about the beneficial properties of *L. plantarum* IS-10506 in cases of psoriasis.

Conclusion

The efficacy of the probiotic *L. plantarum* IS-10506 in improving inflammation and clinical outcome among patients with psoriasis vulgaris has been established through the immune biomarkers, PASI, DLQI, and post-clinical trial follow-up. With the potential to prevent recurrence, this probiotic strain could be utilized in conjunction with standard therapy.

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Authors Contribution

MAU was responsible for designing and conducting the research protocol, analyzing the data, and authoring the manuscript. IHH conducted the statistical analysis and data visualization, as well as wrote the manuscript. AE, ISS, and CRSP designing the research protocol and reviewed the manuscript. All authors have finally read and agreed upon the final manuscript.

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