

## ORIGINAL ARTICLE

# Efficacy of probiotic-derived lotion from *Lactobacillus paracasei* MSMC 39-1 in mild to moderate acne vulgaris, randomized controlled trial

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## Abstract

**Background:** Probiotics provide benefits for reducing acne. Previous studies showed an anti-inflammatory effect of *Lactobacillus paracasei*. However, the clinical evidence of topical probiotic lotion and acne treatment is still lacking.

**Objective:** To evaluate the efficacy and safety of probiotic-derived lotion compared with 2.5% benzoyl peroxide in the treatment of mild-to-moderate acne vulgaris.

**Methods:** Topical probiotic-derived lotion was formulated from cell-free supernatant of *L. paracasei* MSMC 39-1. In *vitro* study showed the ability of the supernatant to inhibit both antibiotic-resistance and-susceptibility strains of *C. acnes* and inhibit tumor necrosis factor- $\alpha$ . The patients with mild-to-moderate acne vulgaris on the face were randomized to receive topical probiotic-derived lotion or 2.5% benzoyl peroxide. Acne lesion counts, erythema index, and side effects were assessed after 2 and 4 weeks of treatment.

**Results:** One hundred and four acne vulgaris patients were enrolled. After four weeks of treatment, the inflammatory acne lesion counts and erythema index significantly decreased compared with the baseline in both the probiotic-derived lotion group and 2.5% benzoyl peroxide group ( $p < 0.001$  in both groups) without statistically significant difference between the two groups ( $p > 0.05$ ). However, the comedones were not affected in both groups. Four patients (7.69%) treated with probiotic-derived lotion and 14 patients (26.92%) treated with 2.5% benzoyl peroxide reported treatment-associated side effects.

**Conclusion:** Probiotic-derived lotion is safe and effective for treating mild to moderate acne vulgaris, a comparable outcome with 2.5% benzoyl peroxide. It could be an alternative treatment of acne with more minor side effects.

## KEYWORDS

Acne vulgaris, *Lactobacillus paracasei*, probiotic, topical treatment

## 1 | INTRODUCTION

Acne vulgaris is a chronic pilosebaceous disease that commonly occurs among young people.<sup>1,2</sup> The pathogenesis of acne involves a proliferation of *Cutibacterium acnes* (*C. acnes*), inflammation process, follicular hyperkeratosis, and hyperseborrhea.<sup>3</sup> *C. acnes* is an anaerobic gram-positive bacterium that lives on human skin, especially in the hair follicle of the face and neck. Increased colonization of *C. acnes* contributes to acne because the organism can promote the inflammatory stage by increasing the secretion of many cytokines, tumor necrotic factor-alpha (TNF- $\alpha$ ), and interleukin-1 $\alpha$ .<sup>4,5</sup> The mainstay therapy to diminish *C. acnes* is antibiotic (ATB), but the prevalence of ATB-resistant *C. acnes* strain has recently increased, resulting in an ineffective treatment.<sup>6,7</sup> Overcome those reasons, alternative medications to antibiotics are a growing concern.

Probiotics are live organisms that provide health benefits to the host by maintaining the homeostasis of the gut microbiome and have been widely used in the food industry for centuries. Many probiotic strains, including *Bifidobacterium*, *Saccharomyces*, *Enterococcus*, *Bacillus*, and *Lactobacillus*, have been established for health promotion.<sup>8</sup> According to the gut-brain-skin theory of Stokes and Pillsbury, they hypothesized that emotional stress and depression could disturb gastrointestinal function by altering intestinal microflora, increasing intestinal permeability, and stimulating local and systemic inflammation causing inflammatory diseases.<sup>9</sup> Hence, the link between probiotics and skin has been investigated. Previous studies explored the use of probiotics to treat chronic skin diseases such as atopic dermatitis, psoriasis, and diabetic foot ulcers.<sup>10</sup> However, a limited number of studies on the effect of probiotic use in acne vulgaris were available.

The evidence has shown that *Lactobacillus* and *Bifidobacterium* can modulate inflammation in acne pathogenesis,<sup>11</sup> and *Enterococcus faecalis* has antimicrobial activity to *C. acnes*.<sup>12</sup> Similarly, *Lactobacillus paraplantarum* THG-G10 has anti-bacterial activity against *C. acnes* together with an anti-inflammatory effect.<sup>13</sup> From our published data, *in vitro* study revealed that cell-free culture supernatant of isolates *Lactobacillus paracasei* (*L. paracasei*) MSMC 39-1, *L. casei* MSMC39-3, and *Weissella confusa* MSMC57-1 can decrease TNF- $\alpha$  levels which was proinflammatory cytokine and the most significant inhibitory effect on TNF- $\alpha$  production were found in supernatants of *L. paracasei* MSMC 39-1.<sup>14</sup> Consequently, we hypothesized the potential use of topical probiotic-derived lotion to the treatment of acne vulgaris due to its anti-inflammatory property. Therefore, this study aims to evaluate the efficacy and safety of topical probiotic-derived lotion from *L. paracasei* MSMC 39-1 for treating mild-to-moderate acne vulgaris patients.

## 2 | MATERIALS AND METHODS

### 2.1 | Study population and study protocol

The present study was a single-blinded, parallel design, 1:1 allocation ratio, randomized controlled trial, conducted at Skin Center, Srinakharinwirot University, Bangkok, Thailand, from January

to April 2020. The study protocol was approved by the Clinical Research Ethical Committee of Srinakharinwirot University (SWUEC-339/2562F). Inclusion criteria were patients aged between 18 and 35 years who had mild-to-moderate acne vulgaris according to the Leeds-revised criteria.<sup>15</sup> Participants who had active skin lesion on the face, use of topical treatment for acne such as benzoyl peroxide, retinoid, and antibiotics within 2 weeks before the study, being on anti-acne systemic therapy and contraceptive pill within 6 months before enrollment, being on systemic corticosteroid, and vitamin supplement such as vitamin C, vitamin E, and/or zinc within 6 weeks prior to the study, and pregnancy or breastfeeding were excluded.

The patients were randomized using computer-generated block randomization to receive either topical 2.5% benzoyl peroxide or probiotic-derived lotion. The patients were advised to apply topical 2.5% benzoyl peroxide twice daily for about 15 min on the whole face, then wash it off. In contrast to patients who received probiotic-derived lotion, twice daily application for the entire face after washing and leaving it on were instructed. All patients were also given the same gentle cleanser and moisturizer during the study.

The outcome assessment was acne lesion counts, evaluated by a blinded dermatologist, that included a total number of acne lesions, inflammatory and non-inflammatory acne at baseline, week 2 and 4. The inflammatory lesions consisted of papules, pustules, and nodules, while comedones were counted as non-inflammatory acne lesions. Moreover, the redness of acne was valued by erythema index (a value) using a DSM III Colorimeter (Cortex Technology, Hadsund) at baseline, week 2 and 4. Adverse effects such as erythema, scaling, stinging, and itching were recorded on every visit.

### 2.2 | Formulation of the probiotic-derived lotion

*L. paracasei* MSMC 39-1 was isolated from feces specimens of healthy Thai neonates. Cell-free culture supernatant was prepared as described by Ladda et al.<sup>14</sup> The probiotic-derived lotion was produced by mixing supernatant and cream base until uniform formulation at a ratio of 70:30 according to the result of the cytotoxicity testing. The final probiotic-derived lotion was a uniform, turbid, yellowish color with a mild acetic-like smell. It had a pH between 3.5 and 5.5, similar to normal skin pH. In addition, *in vivo* study of the skin irritation test, under an occlusive patch test in a single application, was done. The positive irritation reactions to the probiotic-derived lotion were statistically significantly less than the positive control ( $p < 0.001$ ) and not significantly different from the negative control ( $p = 0.162$ ).

### 2.3 | *In vitro* study on the evaluation of antimicrobial, anti-inflammatory, and cytotoxic properties of cell-free culture supernatant from *L. paracasei* MSMC 39-1

Before the clinical study, the properties of the cell-free culture supernatant were investigated. The supernatant has an inhibitory

effect on both ATB-susceptibility and ATB-resistant strains of *C. acne*, isolated from Thai acne patients in a previous study.<sup>7</sup> However, no antimicrobial effects were found on skin microflora such as *Staphylococcus epidermidis* and *S. aureus*. Furthermore, the TNF- $\alpha$  inhibition from cell-free culture supernatant was detected, indicating anti-inflammatory property. In terms of safety, the cytotoxicity of the supernatant from *L. paracasei* MSMC 39-1 to the keratinocyte cells was performed using a human keratinocyte cell line. The percentage of the cell viability was not significantly different from the negative control as less than or equal to 70% of supernatant ( $p > 0.05$ ).

## 2.4 | Statistical analysis

Descriptive data were presented as mean with standard deviations (SD) and median with interquartile range (IQR) in normal and non-normal distributions, respectively. Categorical data were demonstrated as proportion with percentages. An independent student *t*-test was used to compare the average mean for the continuous data between the two groups. Pearson's Chi-square test assessed the difference in the categorical data. ANOVA was used to compare the mean change from the baseline at different visits. The statistical data were analyzed by STATA version 15 (Stata Corp, College Station) with intention to treat approach. A *p*-value of  $< 0.05$  was considered a statistically significant difference.

## 3 | RESULTS

One hundred and ten patients were enrolled in the study, and six patients were excluded from meeting the exclusion criteria. A total of 104 patients were randomly assigned to either the probiotic-derived lotion group ( $n = 52$ ) or the 2.5% benzoyl peroxide group ( $n = 52$ ). Three patients in each group did not complete the study protocol and lost to follow-up at fourth week because of the Coronavirus-19 pandemic situation in Thailand. The average mean age of the probiotic-derived lotion group and 2.5% benzoyl peroxide group was

22.2 ( $\pm 4.1$ ) and 22.0 ( $\pm 3.7$ ) years, respectively, and 80% were female in both groups. The baseline number of non-inflammatory lesions, inflammatory lesions, total lesions, and erythema index (a value) was not statistically significantly different between the groups,  $p > 0.05$  (Table 1).

At the baseline, the mean inflammatory acne counts were 7.4 ( $\pm 3.3$ ) on the probiotic-derived lotion group and 6.6 ( $\pm 5.9$ ) on the 2.5% benzoyl peroxide group, which were not statistically different,  $p = 0.39$ . After a four-week treatment, the inflammatory acne counts significantly reduced compared with the baseline; the inflammatory acne counts were 4.8 ( $\pm 3.2$ ) and 4.3 ( $\pm 2.2$ ) in the probiotic-derived lotion and 2.5% benzoyl peroxide group, respectively;  $p < 0.001$  on both groups (Table 2). However, both topical medications reduce inflammatory acne counts without any statistically significant differences when comparing between groups;  $p = 0.23$  (Figures 1 and 2). For the non-inflammatory acne count or comedones, the number of lesions in both groups at week 2 and 4 of treatment were not decreased. Similarly, the total lesion counts did not show any statistically significant reduction from the baseline in both groups. Comparing between treatment groups, the non-inflammatory and total acne lesion counts did not show any statistically significant difference throughout the study,  $p > 0.05$ .

According to the erythema index (a value), the mean baseline value was 22.9 ( $\pm 1.9$ ) on the probiotic-derived lotion group with a significant decrease to 21.4 ( $\pm 2.1$ ) at week 4,  $p < 0.001$ . Similarly, the mean baseline value of the 2.5% benzoyl peroxide group was 23.2 ( $\pm 2.1$ ) with a significant decrease to 22.0 ( $\pm 1.9$ ) at week 4,  $p < 0.001$ . However, there was no statistically significant difference between the two groups,  $p = 0.15$ .

Eighteen patients reported adverse effects during the study, 4 patients (7.69%) in the probiotic-derived lotion group and 14 patients (26.92%) in the 2.5% benzoyl peroxide group. The most common adverse effect in the probiotic-derived lotion group was erythema ( $n = 2$ ), followed by itching ( $n = 1$ ) and scaling ( $n = 1$ ). Similarly, the most common adverse effect in the 2.5% benzoyl peroxide group was erythema ( $n = 7$ ), followed by scaling ( $n = 5$ ), itching ( $n = 1$ ), and a burning sensation ( $n = 1$ ). All side effects which occurred in this study were self-resolved without any treatment.

TABLE 1 Baseline characteristic of the patients

Characteristic	Probiotic-derived lotion	2.5% benzoyl peroxide	<i>p</i> -Value
Sex, <i>n</i> (%)			
Male	12 (23.1%)	10 (19.2%)	0.63
Female	40 (76.9%)	42 (80.8%)	
Age, year (mean $\pm$ SD)	22.2 $\pm$ 4.1	22.0 $\pm$ 3.7	0.78
Comedone count (mean $\pm$ SD)	39.6 $\pm$ 28.0	35.7 $\pm$ 30.5	0.49
Inflammatory acne count (mean $\pm$ SD)	7.4 $\pm$ 3.3	6.6 $\pm$ 5.9	0.39
Total lesion count (mean $\pm$ SD)	47.2 $\pm$ 29.2	42.3 $\pm$ 32.3	0.42
Erythema index (mean $\pm$ SD)	22.9 $\pm$ 1.9	23.2 $\pm$ 2.1	0.50

Abbreviations: *n*, number of patients; SD, standard deviation.

TABLE 2 Outcome of treatment

Outcome measurement	Probiotic-derived lotion	p-Value <sup>a</sup>	2.5% benzoyl peroxide	p-Value <sup>a</sup>	p-Value <sup>b</sup>
Number of inflammatory acnes, mean ± SD					
Baseline	7.4 ± 3.3	Reference	6.6 ± 5.9	Reference	0.23
Week 2	5.5 ± 3.7	<0.001*	4.8 ± 2.9	0.01*	
Week 4	4.8 ± 3.2	<0.001*	4.3 ± 2.2	<0.001*	
Number of comedones, mean ± SD					
Baseline	40.0 ± 28.1	Reference	35.7 ± 30.5	Reference	0.75
Week 2	40.3 ± 27.3	0.78	41.8 ± 27.4	0.02*	
Week 4	39.2 ± 25.9	0.60	36.1 ± 31.5	0.95	
Total lesion count, mean ± SD					
Baseline	47.2 ± 29.2	Reference	42.3 ± 32.3	Reference	0.67
Week 2	46.7 ± 29.1	0.67	47.3 ± 28.5	0.11	
Week z4	44.1 ± 28.3	0.09	41.9 ± 32.7	0.35	
Erythema index, mean ± SD					
Baseline	22.9 ± 1.9	Reference	23.2 ± 2.1	Reference	0.15
Week 2	21.4 ± 2.1	<0.001*	22.1 ± 1.9	<0.001*	
Week 4	21.4 ± 2.1	<0.001*	22.0 ± 1.9	<0.001*	

Abbreviations: n, number of patients; SD, standard deviation.

<sup>a</sup>p-value, compare within treatment group.

<sup>b</sup>p-value, compare between treatment groups.

\*Statistically significant  $p < 0.05$ .



FIGURE 1 Clinical photographs (A) before and (B) after probiotic-derived lotion treatment

## 4 | DISCUSSION

The standard treatment of mild and moderate acne vulgaris includes topical benzoyl peroxide, antibiotics, and retinoid. However, acne medication can cause skin irritation, and antibiotic use has led to an occurrence of antibiotic resistance bacterial strain causing ineffective treatment. An alternative modality has been recently explored. Due to the safety of probiotics in humans having well-known

properties, the trend of oral probiotic supplements in acne vulgaris has been rising. A probiotic can provide antimicrobial substances to protect intestinal pathological microbes, re-balance intestinal microflora, and down-regulate the inflammatory process, which causes reducing inflammatory skin disease, including acne.<sup>16,17</sup> However, the evidence of probiotic use in acne is limited. Previous in vitro studies showed an antimicrobial and anti-inflammatory effect of *L. paracasei*.<sup>14,18</sup> Among many studies exploring the efficacy of the

**FIGURE 2** Clinical photographs (A) before and (B) after 2.5% benzoyl peroxide treatment



oral probiotic *L. paracasei* supplement, no study has been conducted to evaluate the efficacy of topical *L. paracasei* and skin diseases. To the best of our knowledge, this is the first randomized controlled trial to assess the efficacy of probiotic-derived lotion from *L. paracasei* MSMC 39-1 compared with the standard treatment, 2.5% benzoyl peroxide, in mild-to-moderate acne vulgaris. We discovered a comparable result between the probiotic-derived lotion and 2.5% benzoyl peroxide in reducing the inflammatory acne counts after 4 weeks of topical treatment.

The pathogenesis of the acne, *C. acnes*, and inflammatory process played an essential role in causing acne lesions.<sup>3,19</sup> Previous studies indicated dried cell-free supernatant of *L. paraplantarum* THG-G10 could inhibit the proliferation of *C. acnes* and inhibit nitric oxide production.<sup>13</sup> The current study discloses the capability of *L. paracasei* MSMC 39-1, which can inhibit both ATB-sensitivity and resistance *C. acnes* isolated from the Thai population.<sup>7</sup> The results were similar to the clinical trial by Kang et al.<sup>12</sup>; they demonstrated antimicrobial properties of probiotic *E. faecalis* by producing bacteriocin to inhibit *C. acnes* growth isolated from Koreans. Moreover, our study confirmed the ability of *L. paracasei* MSMC 39-1 to inhibit TNF- $\alpha$ , stimulated by human monocytes, which was one of the critical proinflammatory cytokines associated with acne pathogenesis, in line with the previous data.<sup>14</sup> Antimicrobial and anti-inflammatory substances produced from this probiotic were generally secreted into broth medium, also known as supernatant. Then, the probiotic-derived lotion made from the supernatant was formulated and applied to facial acne patients. The therapeutic results revealed that the number of inflammatory acne decreased over time after applying probiotic-derived lotion, similar to topical benzoyl peroxide cream.

Compared with the study of probiotic lotion from *E. faecalis* by Kang et al.<sup>12</sup> the reduction of the inflammatory acne lesions was also demonstrated. However, the percentage of reduction was 55% after 4 weeks, which was higher than the current study; 35.1% in 4 weeks. The discordance results could have been caused by the difference in population and the strain of the probiotics. Furthermore,

they also showed that no effect of either their probiotic lotion or 2.5% benzoyl peroxide on the total and non-inflammatory acne lesion counts after treatment was found, similar to our results.<sup>12</sup> The persistence of comedones might be caused by the short duration of the study since comedones are usually resolved within two-six weeks of treatment.<sup>20</sup>

In terms of safety, this lotion was a safe, in vitro study showed no cytotoxic effect on skin cells. Interestingly, Cha et al.<sup>13</sup> reported the weaker cytotoxic results of supernatant of *L. paraplantarum* THG-G10 than erythromycin, benzoyl peroxide, and ascorbic acid. In addition, no irritation on human skin by occlusive patch test in a single application, and no serious side effect was found in our study. Erythema was the most common side effect followed by scaling and itching, comparable with 2.5% benzoyl peroxide cream. However, these side effects seemed to be even less common in the probiotic-derived lotion. Hence, it could be an alternative for treatment in patients who cannot tolerate benzoyl peroxide due to its irritation.

There were some limitations in the current study. Short treatment duration was done in this study. We initially planned to conduct 2-month research protocol. Unfortunately, the study was interrupted by the Coronavirus-19 pandemic in Thailand. Therefore, the protocol had to be shortened to one month. Second, the study was a single/evaluator-blind, randomized clinical trial due to the difference in the texture and directions of the topical treatment. In addition, we recruited only patients with mild-to-moderate acne. Lastly, the compounds of the supernatant used in this study were not identified. Therefore, further investigation need to analyze and identify the possible substances that inhibit acne pathogenesis, and longer studies are required to support our results.

## 5 | CONCLUSION

The probiotic-derived lotion made from *L. paracasei* MSMC 39-1 could be an alternative therapeutic agent in patients with mild and

moderate acne vulgaris. It is safe and effective, comparable with topical 2.5% benzoyl peroxide, in treating inflammatory acne. The anti-inflammatory and antimicrobial properties of ATB-susceptible and-resistance *C. acne* of topical probiotics were established.

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#### ETHICAL APPROVAL

The study protocol was approved by the Clinical Research Ethical Committee of Srinakharinwirot University with registry no (SWUEC-339/2562F).

#### CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

#### AUTHOR CONTRIBUTIONS

Sunattha Sathikulpakdee (S.S.), Malai Taweechoatipatr (M.T.), and Silada Kanokrungeesee (S.K.) designed the research study. S.S., M.T., and Porntipha Vitheejongjaroen (P.V.) performed the research in vitro. S.S. and S.K. performed the clinical trial research. S.S., Nanticha Kamanamool (N.K.), and Montree Udompataikul (M.U.) analyzed the data and contributed essential materials. S.S., S.K., and M.T. wrote the manuscript. S.K. and M.T. review and edit final manuscript. All authors have read and approved the final manuscript.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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