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Original Article

Investigating the impact of oral probiotic supplementation for acne management: A randomized controlled trial

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ABSTRACT

Background: Acne vulgaris (AV) is a common skin disorder that affects up 10% of the worldwide population. Its pathogenesis involves a complex interplay of factors, leading to the development of cutaneous lesions (papules, pustules, and comedones). This clinical trial aimed to evaluate the efficacy of a specific probiotic formulation composed by *Lactiplantibacillus plantarum* PBS067, *Lacticaseibacillus rhamnosus* LRH020, and *Limosilactobacillus reuteri* PBS072 in improving AV symptoms in adult subject from the APAC region. **Materials and methods:** A double-blind randomized placebo-controlled clinical study was carried out on 64 women supplemented for 56 days plus a follow-up period. Instrumental evaluations of different skin parameters and clinical assessments of lesions were performed at 28 and 56 **da**ys after supplementation (T28 and T56, respectively) and during follow-up (T70). **Results:** A significant increase in skin hydration was achieved by probiotic group compared to the placebo ($p < 0.05$). An improved trend in sebum content and pH resulted in a statistically significant difference with respect to placebo ($p < 0.05$ for the former parameter at T28 and T70; $p < 0.05$ for the latter at T70). A progressive decrement of lesions was demonstrated at each endpoint considered by probiotic supplementation, reaching significant values for non-inflammatory ones at T56 and T70 ($p < 0.05$ and $p <$ s0.01, respectively). **Conclusions:** This specific probiotic formulation may help improving acne symptoms, offering a possible adjuvant therapy to the conventional one and thus overall ameliorating the patient's quality of life.

Key words: Acne vulgaris, Food supplements, Skin disease, Dermatology, Probiotics, Clinical trial

INTRODUCTION

The skin is the largest organ in the body, an impermeable physical barrier that protects from microbes and ultraviolet rays. It is inhabited by various microorganisms, such as bacteria, fungi, viruses, and microeukaryotes that form an intricate ecosystem called the *skin microbiota* [1]. The skin microbial community performs several beneficial functions for the host, including protection from pathogens, degradation of toxins, and boost of the immune system. An imbalance in the qualitative or quantitative profile of the skin microbiota members may result in a variety of cutaneous disorders, such as acne vulgaris (AV), atopic dermatitis, and many others [2].

In this scenario, AV is one of the most common skin disorders concerning the sebaceous glands and hair follicles. It affects the seborrheic areas, mainly those located on the face (99%) yet also on the back and chest (90% and 70%, respectively) [3]. AV patients typically present comedones, papules, and pustules. This skin disorder usually arises with the formation of comedones, resulting from the obstruction of

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pilosebaceous follicles by sebum and dead skin cells. Closed comedones, also known as whiteheads due to their appearance, form when the follicle is completely blocked, while open comedones, or blackheads, occur when the follicle is partially obstructed, resulting in the accumulation of oxidized melanin that gives them a dark pigmentation [4]. Comedones then may evolve into papules, swelling skin lesions, and finally into pustules, inflamed lesions containing pus. In severe cases, patients may experience nodules and cysts, as well as infiltrates causing scars, erythema, and hyperpigmentation [5,6].

Due to its polymorphous clinical appearance, AV may vary in severity, differentiating between acute and chronic forms and its many subtypes. Acne severity may be graded according to rating scales, most of which are poorly validated and may therefore provide inconsistent data, resulting in the use of simplified methods of classifying acne as mild, moderate, or severe in treatment guidelines. The detrimental underestimation of disease severity may often lead to psychological and social distress, further affecting overall well-being [7,8]. Thus, accurate diagnosis and timely and appropriate intervention are crucial, as they may help prevent the worsening of the condition and the scarring associated with more severe outbreaks.

AV usually emerges during adolescence and early adulthood, affecting up to 85% of individuals aged 12 to 24 [9,10]. Although commonly associated with teenagers, AV may occur at any age, subsiding over time. However, AV incidence among adults is increasing, particularly in females, leading to the adoption of the term *adult female acne* for women aged 25 and older [11]. Extensive investigations have been carried out on Caucasian populations, while little is known about populations living in the Asia Pacific region (APAC), which differ in culture, diet, lifestyle, environment, genetic predisposition, and microbiota composition [12-14].

The multifactorial pathophysiology of AV involves hyperplasia of the sebaceous glands, their predisposition toward excessive sebum production, follicular keratosis, *Cutibacterium acnes* colonization, and skin inflammation, contributing significantly to the development of the disease [15]. Hormonal imbalances and genetic predisposition also play a pivotal role [16,17]. Since androgens stimulate sebocyte proliferation and increase intracellular lipid droplet production, the estrogen/androgen ratio affects acne condition [18,19]. In addition, sebaceous glands act as a neuroendocrine organ, indeed, neuropeptides and hormones such as melanocortin and corticotropin-releasing hormone (CRH) may exacerbate sebum production during stressful periods [20]. Furthermore, other evidences correlate acne outcomes with external factors, including environmental pollution, UV exposure, inadequate skin cleaning, and an imbalanced Western diet [21,22]. Foods with high fat and high glycemic index may improve the levels of insulin-like growth factor-1 (IGF-1), which promotes lipogenesis, inflammation, and androgen synthesis [23,24].

It is widely accepted that skin dysbiosis plays a significant role in AV occurrence. *C. acnes* is a commensal bacterium mainly resident in sebaceous skin; it helps in the maintenance of the physiological skin pH and microbial skin eubiosis, preventing colonization by potentially harmful pathogens. However, a reduction in the skin α-diversity and the over-colonization of specific *C. acnes* phylotypes, i.e., phylotype IA1, may lead to acne [25-27]. Acne-related strains may also promote comedogenesis and the production of increased levels of porphyrin, able to trigger inflammation in keratinocytes [28].

Recently, the gut-skin axis has been proposed, linking skin health to gut dysbiosis. Indeed, the intestinal microbiota of individuals with acne differs from that of healthy subjects, with a reduction in the abundance of *Lactobacillus*, *Bifidobacterium*, *Butyricicoccus*, *Coprobacillus*, and *Allobaculum* genera [13]. The intestinal imbalance leads to increased permeability of the gut barrier, potentially facilitating the translocation of microbes and their metabolites into the bloodstream, thereby impacting distant organs including the skin [29]. In particular, gut dysbiosis may impact the mTOR pathway, which regulates cutaneous cell growth and differentiation, leading to systemic inflammation and AV worsening [30].

So far, common interventions to treat acne involved the topical use of retinoids, hydroxy acids, antimicrobial compounds, antibiotics, and hormonal therapy for female subjects [31]. However, despite their effectiveness, many of these treatments have undesirable side effects, ranging from local irritation, skin drying, headache, and nausea to systemic or teratogenic consequences; furthermore, the use of antibiotics may lead to the development of bacterial resistances [32,33]. Consequently, non-pharmacological therapies represent a viable alternative to conventional acne management.

Among the new approaches investigated, restoring a healthy microbial community, by promoting the growth of symbiotic bacteria rather than only inhibiting pathogens, could be promising. Moreover, since multiple factors may be responsible for acne development, possible therapies should involve combined targets, focusing on both skin and gut microbiota modulation [34,35]. Lactic acid bacteria (LAB) are Gram-positive, non-spore-forming, catalase-negative microorganisms; they withstand low pH and are classified in cocci or rods. LAB are traditionally used to enhance gut microbiota balance and functions, and used as probiotics in different fermented foods, such as yogurt and dairy products; they may also be added to functional foods, or be commercially available in drinks, food supplements, or drugs. The probiotic definition was established by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO): "live microorganisms which when administered in adequate amounts confer a health benefit on the host" [36]. In the last years, even more studies have highlighted promising properties of specific probiotic strains for addressing dermatological conditions, due to their ability to trigger beneficial modifications in the gut as well as in the skin microbiota [37,38]. Orally administered probiotics colonize the gastrointestinal tract and exert their functions through different mechanisms, also determining restoration of the skin's biophysical properties and sebum excretion [39,40]. Probiotics support the membrane integrity and produce bacteriocin-like inhibitory substances that modulate the proliferation of *C. acnes*. Furthermore, they show a systemic IGF-1 lowering effect and mitigate inflammation by suppressing IL−1α and stimulating regulatory T cells [38,41,42].

In a previous double-blind randomized placebo-controlled clinical study involving eighty Caucasian adult subjects, an oral probiotic formulation (*Lactiplantibacillus plantarum* PBS067, *Lacticaseibacillus rhamnosus* LRH020, and *Limosilactobacillus reuteri* PBS072) resulted effective in ameliorating AV clinical signs (smoothness and moisturization) and decreasing the levels of skin inflammatory markers. These strains successfully colonized the gastrointestinal tract and exerted long-term effects [43].

This clinical trial aims to assess the efficacy of this specific probiotic strain composition in the improvement of AV status in a population of adult women of the APAC region.

MATERIALS AND METHODS

Study Design, Population, and Products

A double-blind randomized placebo-controlled clinical study was carried out from December 2023 to February 2024 at Complife Beijing Testing Technology Ldt facilities (Beijing, China) in compliance with the Helsinki Declaration (1964) and its amendment. Study protocol and informed consent form were approved by the "Independent Ethical Committee for Non-Pharmacological Clinical studies" of Genova, Italy (ref. IT0006453/23). Study protocol was registered in the ISRCTN registry (ISRCTN16487219).

Subjects were randomly assigned to two groups according to a randomization list previously generated by the study director using an appropriate statistic algorithm ("Wey's urn").

Clinical visits were planned at baseline (T0), after 28 and 56 days of product intake (T28 and T56, respectively), and after 14 days after from the last intake of the products (T70; follow-up period).

Written informed consent as well as permission for using of non-identifiable photographs (part of the face) for publication were obtained from participants before the study. All subjects' images and videos collected throughout the study and concerning any identifiable or private parts (such as the eyes) were treated in privacy by means of coverings.

Sixty-four female subjects, aged between 18 and 45 years old, were enrolled by a dermatologist according to the following inclusion criteria: acne severity from 1 to 3 according to Investigator's Global Assessment (IGA) parameters (Table 1) [44]; subjects who have

Table 1: Acne severity scale based on Investigator's Global Assessment (IGA)

Description	Definition	Grade
Residual hyperpigmentation and erythema may be present.	Clear	0
A few scattered comedones and a few small papules.	Almost clear	1
Some comedones, papules, and pustules; no nodules present.	Mild	2
Many comedones, papules, and pustules; one nodule may be present.	Moderate	3
Covered with comedones, numerous papules and pustules and few nodules and cysts may be present.	Severe	4
Highly inflammatory acne covering the face; presence of nodules and cysts.	Very severe	5

not been recently involved in any other similar study; willingness not to expose to sun/tanning beds throughout the study; no modification in the daily routine or the lifestyle; stable pharmacological therapy (except for the pharmacological therapy in the non-inclusion criteria) for at least one month without any changes expected or planned during the study.

The exclusion criteria were: subjects with a history of allergy or sensitivity to cosmetics, toiletries, solar and/or topical medications, patches, or medical devices; skin conditions or diseases that could interfere with the study or considered by the Investigator as hazardous for the subject, incompatible with the study requirements, and inappropriate for participation; pharmacological treatment (both locally or systemically) that could interfere with the study treatment; consumption of food supplement(s) for skin/hair/nail care containing probiotic at the moment of the enrolment or within the past 12 weeks before the study; pregnant or nursing women.

The probiotic food supplement (probiotic) was formulated in capsules of hydroxypropylmethylcellulose and pectin containing $1x10^9$ colony forming unit (CFU) of *Lactiplantibacillus plantarum* PBS067 (DSM 24937), $1x10^9$ CFU of *Lacticaseibacillus rhamnosus* LRH020 (DSM25568), and $1x10^9$ CFU of *Limosilactobacillus reuteri* PBS072 (DSM 25175) plus excipients (maltodextrin, corn starch, and magnesium salt of fatty acids). The placebo was formulated in identical capsules and contained only excipients.

Subjects were asked to intake one capsule a day of probiotic/placebo for 56 days, away from meals. No specific change in the daily habits or diet were required.

All subjects were provided with a cosmetic cream for the face without any cosmetic claim to be used instead of their habitual facial cream during all the study period to standardize the skin care.

Skin Clinical Parameters

Instrumental evaluations of the skin parameters were carried out at T0, T28, and T56 of product intake. Skin moisturization was measured by the Corneometer® method (Corneometer® CM 825, Courage+Khazaka, electronic GmbH). Sebum level was measured by the Sebumeter® method (Sebumeter 815, Courage+Khazaka GmbH) and expressed as µg sebum/cm^2 of the skin. Skin pH was measured by SKIN pH-METER 905® (Courage + Khazaka GmbH). Clinical assessment was carried out by a dermatologist by counting acne lesions.

Digital pictures of the subjects' face were acquired at each experimental time by means of VISIA-CR (Canfield Scientific, Parsippany, NJ, USA) under standard lighting conditions and used for clinical classification of skin complexion evenness at T0 and by assigning a variation score with respect to the basal classification according to the specific criteria (Table 2).

Clinical evaluation of acne lesions was visually assessed on patients' faces (and by palpation, if necessary) by counting the total number of non-inflammatory (open and close comedones) and inflammatory lesions (papules, pustules, nodules, and cysts).

Statistical Analysis

Instrumental data were submitted to ANOVA test followed by Tukey–Kramer post-test (intragroup analysis); the intergroup statistical analysis was performed on the data variations versus T0 by means of bilateral Student's t-test for unpaired data. Clinical data was analyzed using Mann–Whitney U/Wilcoxon rank-sum Test (two samples). Statistical analysis was performed using NCSS 10 statistical software (NCSS, LLC. Kaysville, Utah, U.S.) running on Windows Server 2008 R2 Standard (Microsoft, U.S.).

For each instrumental parameter under study intra- and inter-group statistical analysis were carried out. Variations were considered statistically significant when $p < 0.05$.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Independent Ethical Committee for Non-Pharmacological Clinical studies of Genova, Italy (ref. IT0006453/23, December 1st 2023). Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

RESULTS

Fifty-five out of the 64 enrolled subjects completed the study, as six subjects from the placebo group and two from the probiotic group no longer intended to

Table 2: Skin complexion evenness criteria based on VISIA-CR images

Skin complexion evenness at T0	Score	Improvement vs. T0	Score
The skin complexion is not uniform, there are discolorations all over the face.	1	No variation	1
The skin complexion of the skin is uneven, there are discolorations on some parts of the face.	2	Slight	2
The skin complexion is quite uniform.	3	Moderate	3
The skin complexion is uniform.	4	Remarkable	4

continue the study and withdrew from it for personal reasons at/before T28; all women well tolerated the food supplement and only one subject from the probiotic group reported a transient mild redness. Therefore, results were statistically evaluated as Per Protocol (PP) and refer to 26 subjects of the placebo group and 29 subjects of the probiotic group. The mean age of the enrolled subjects was 29.1 ± 1.9 years.

Skin Moisturization

Basal levels of skin hydration did not show any significant intergroup difference, supporting the unbiased composition of the two groups. A gradual and statistically significant intragroup increment of the skin hydration was achieved by placebo and probiotic throughout the treatment period ($p < 0.01$ for placebo and $p < 0.001$ for probiotic at T28, respectively; $p < 0.001$ for both groups at T56) (Table 3). Even if a slight decrement in the follow-up period compared to T56 levels was recorded in both groups, the intragroup differences still resulted statistically significant at T70 ($p < 0.001$) (Table 3).

Higher percentage of skin hydration variation with respect to the basal level was achieved by the probiotic treatment compared to the placebo, resulting in a statistically significant difference intergroup until T56 ($p < 0.05$) (Fig. 1a). Such statistically significant amelioration was also maintained in the follow-up period ($p < 0.05$) (Fig. 1a).

Sebum Content

Sebum levels did not show any significant intergroup difference at T0. A progressive decrement of sebum level was measured throughout the probiotic administration period, with the exception of a slight increment at T70, showing a similar trend in comparison with skin hydration ($p < 0.001$) (Table 3). No statistically significant change was recorded at T28 for the placebo group, while a statistically significant intragroup decrement was noted at T56 and T70 ($p < 0.001$ and $p < 0.01$, respectively) (Table 3). Overall, probiotic administration determined an improved trend, resulting in a statistically intergroup difference with respect to the placebo at T28 and T70 ($p < 0.01$ and $p < 0.05$, respectively) (Fig. 1b).

Table 3: Skin hydration, sebum content, pH level, non-inflammatory and inflammatory lesion results are expressed as mean±SEM at each endpoint considered in the study for placebo and probiotic groups. Intragroup statistical analysis is reported. *p<0.05; **p<0.01; ***p<0.001

Parameter	Time	Placebo	Probiotic
Hydration (%)	T0	52.1±1.7	52.6±1.4
	T28	55.2±1.7 **	59.4±1.7 ***
	T56	57.9±1.7 ***	63.4±1.7 ***
	T70	56.0±1.8 ***	60.3±1.5 ***
Sebum content ($\mu g/cm^2$)	T0	95.9±4.8	103.4±5.4
	T28	90.8±4.6	89.7±4.2 ***
	T56	82.1±3.8 ***	81.0±3.6 ***
	T70	86.3±3.8 **	84.5±3.3 ***
pH (arbitrary unit)	T0	5.9±0.1	5.8±0.1
	T28	5.8±0.1	5.6±0.1 ***
	T56	5.7±0.1 ***	5.4±0.1 ***
	T70	5.8±0.1	5.5±0.1 ***
Non-inflammatory lesions (count)	T0	33.3±2.6	27.5±2.5
	T28	31.3±2.6 *	24.2±2.1 ***
	T56	30.5±2.4 ***	22.2±1.9 ***
	T70	29.2±2.5 ***	19.3 ±- 1.6 ***
Inflammatory lesions (count)	T0	9.8±1.0	8.8±1.0
	T28	8.6±0.9	7.3±0.7
	T56	8.7±1.2	6.6±0.7 **
	T70	7.8±1.0 ***	5.5±0.7 ***

Skin pH

Basal skin pH levels did not show any significant intergroup difference; both treatments resulted in a progressive decrement of the respective skin pH levels up to T56 and in a slight increment when measured at T70. However, a statistically significant intragroup decrement was achieved at each checking time by the probiotic group, starting from T28 ($p < 0.001$) (Table 3), whereas the placebo administration resulted in a significant decrement only at T56 ($p < 0.001$) (Table 3). Probiotic treatment showed a higher reduction in pH level with respect to the placebo throughout the study, that resulted in a statistically intergroup difference after the last probiotic intake ($p < 0.05$) (Fig. 1c).

AV Lesions and Their Clinical Assessment

No statistically significant variation in the baseline number of AV lesions was observed between the groups, confirming the unbiased randomization of subjects.

A progressive and statistically significant intragroup reduction of non-inflammatory lesions was achieved throughout the study, that was appreciated also during the follow-up period ($p < 0.05$ and $p < 0.001$ for placebo and probiotic at T28, respectively; $p < 0.001$ for both groups at T56 and T70) (Table 3).

A gradual and higher decrement of non-inflammatory lesions with respect to T0 was shown at each evaluation time by probiotic supplementation compared to the placebo. Indeed, the probiotic group reached a significant reduction at T56 ($p < 0.05$) and the highest intergroup difference at T70 ($p < 0.01$) with respect to the placebo (Fig. 2a). Moreover, placebo treatment resulted in lower number of inflammatory lesions with respect to the basal value, achieving a statistical significant reduction at T70 ($p < 0.001$) (Table 3). The probiotic treatment demonstrated to progressively reduce such lesions throughout the study ($p < 0.01$ at T56) (Table 3). This aspect was highlighted even more in the follow-up period ($p < 0.001$ at T70) (Table 3).

Compared to the placebo treatment, the probiotic group showed a higher percentage of decrement of inflammatory lesions with respect to T0 at each evaluation time, yet no intergroup difference was recorded (Fig. 2b).

Furthermore, the evaluation of the variation of AV severity assessed on facial pictures acquired during the study indicated that both treatments resulted in a progressive improvement of the clinical status of the pathology, reaching highest levels at T70, and with the higher variation achieved by the probiotic treatment (Fig. 2c).

Finally, a similar trend was also observed for skin evenness complexion with respect to the initial score based on pictures acquired by VISIA-CR. Indeed, both treatments resulted effective in achieving a progressive improvement of such parameter (Fig. 3). Thus, an amelioration was highlighted up to T70, especially in the probiotic group (Fig. 4).

DISCUSSION

Among skin diseases, acne vulgaris mainly affects adolescents of both sexes, yet has a higher prevalence in females with respect to males in adult individuals. It is the most common skin disorder in the Western area and the eighth most prevalent disease worldwide, with a prevalence that is broadly consistent globally [45-47]. It is characterized by skin eruptions, mainly in the sebaceous niches, that may be classified as non-inflammatory lesions (open/whiteheads and closed/blackheads comedones), or inflammatory lesions (pustules, papules), or be present at the same time, according to the severity and/or the stage of the disease. The pathogenesis is multifactorial with different etiologic factors including excess sebum production, *C. acnes* colonization, abnormal keratinization of the

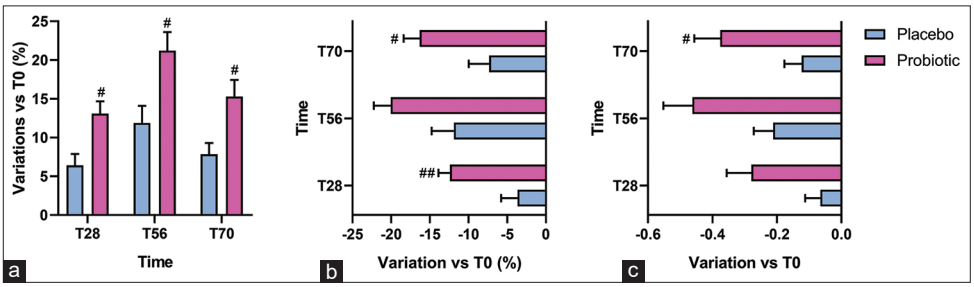

Figure 1: a) Skin hydraton, b) sebum content, and c) pH level at each endpoint considered in the study with respect to T0 for placebo and probiotic groups. The results are expressed as mean ± SEM. Intergroup statistical analysis are reported. # $p < 0.05$; ## $p < 0.01$.

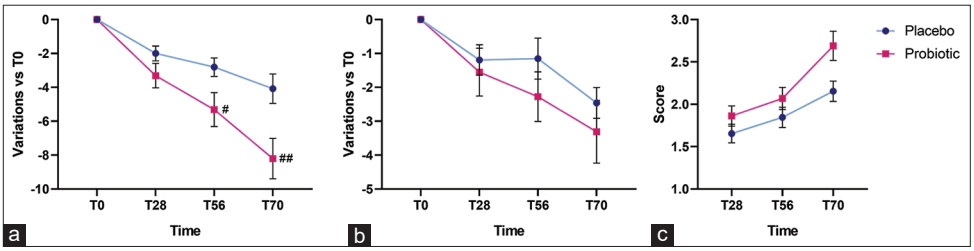

Figure 2: a) Non-inflammatory and b) inflammatory lesion counts at each endpoint for the placebo and probiotic groups. c) Clinical evaluation of AV severity during the study for both groups. # $p < 0.05$; ## $p < 0.01$.

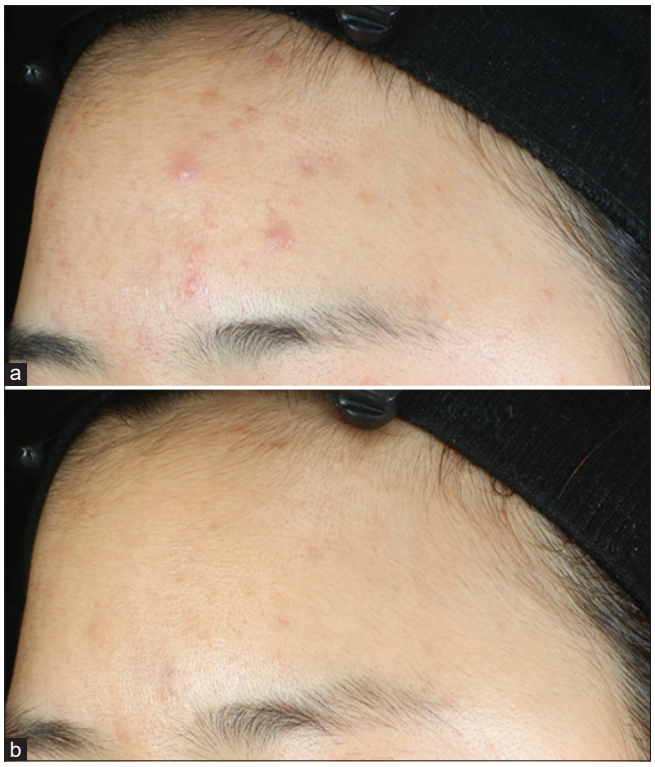

Figure 3: Representative forehead images of a subject enrolled in the study at a) T0 and b) T70.

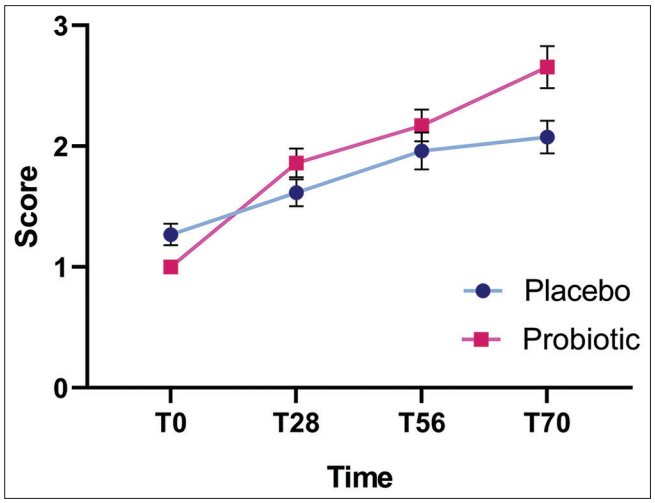

Figure 4: Skin evenness complexion assessment during the study for the placebo and probiotic groups.

sebaceous canals, porphyrin production, genetics, direct immune system stimulation, and release of inflammatory mediators into the skin [48,49]. These factors are often interconnected, as the increased sebum production causes the proliferation of lipophilic bacteria such as *C. acnes*, triggering the development of the disease [49].

First-line AV therapy focuses on the treatment of non-inflammatory comedones or mild inflammatory disease, and it is based on topical agents such as keratolytics, alpha-hydroxy acids, benzoyl peroxide, retinoid analogues, azelaic acid, and topical antibiotics; oral antibiotics are useful for lesions refractory to topical therapy or patients with more severe or extensive disease [50,51]. Such approach, although it has proven to be effective, often shows adverse effects of varying severity, hence alternative or adjuvant therapies have been investigated.

Interestingly, acne has been related to a state of cutaneous dysbiosis. In fact, earlier studies suggested the involvement of *C. acnes* in AV, and recent evidence has shown that dysbiosis of facial microbiota plays a significant role in acne onset and progression [25,34,52-54]. Patients with severe AV displayed a significantly different skin microbiota compared to those with mild grade of this pathology, with increased α-diversity and higher proportions of four Gram-negative bacteria (*Faecalibacterium*, *Klebsiella*, *Odoribacter*, and *Bacteroides*) [55]. Male and female skin microbiota differed, with *Proteobacteria* mainly characterizing the women's skin microbiota, whereas Firmicutes are mostly present in male subjects [56]. Moreover, acne and other skin-related disorders, such as psoriasis, atopic dermatitis, rosacea, alopecia areata, and hidradenitis suppurativa have been associated to gut alteration in terms of microbial composition and abundance [57]. Therefore, probiotics have been investigated either in topical, i.e., cosmetics, or oral formulations to counteract the manifestation of such diseases by the modulation of the gut-brain-skin axis [38].

Gut dysbiosis alters the integrity of the intestinal barrier, the neurotransmitter-based signaling, and the immune system functionality and differentiation; it also determines the production of toxic substances [57]. It is worth of note that in AV-affected patients the gut microbiota differs from non-affected subjects, with a depletion in bacterial diversity, in particular, *Bifidobacterium*, *Butyricicoccus*, *Coprobacillus*, *Lactobacillus*, and *Allobaculum* genera, and an increment of *Proteobacteria* [13,25]. The mechanism by which gut microbiota could influence skin balance has been speculated and is still under investigation. In fact, the existence of an immuno-cross-linking allows the communication between the gut and the skin through different pathways involving the mucosa-associated lymphoid tissues (MALTs), cytokine signaling, and immunoglobulins. Hence, an anti-inflammatory effect is achieved by bacteria through their metabolites [57].

In this context, the oral administration of probiotics facilitates the restoration of the functional activities of the intestinal microbiota. Probiotics, being live microorganisms, may colonize the gut, thereby influencing its microbial composition and exerting a long-lasting effect. By reestablishing the bacterial eubiosis, probiotics contribute to maintain a healthy stratus, which in turn supports immune function. This balance may also extend its influence to the skin microbiota, thereby potentially impacting overall skin health [35].

Recently, it has been demonstrated that orally-administered *L. rhamnosus* could exert a therapeutic effect against AV impacting on tryptophan metabolites and modulating the gut microbiota in an animal model [58]. In a similar way, *L. plantarum* CCFM8661 could alleviate acne symptoms by ameliorating gut microbial unbalance and therefore suppressing cutaneous inflammation, and normalizing hormone metabolism and skin lipids [59]. Moreover, an increase in the anti-inflammatory IL-10 serum level in a small cohort of AV patients was detected after oral consumption of a probiotic formulation for thirty days [60]. Healthy participants supplemented with *Lactobacillus paracasei* NCC 2461 experienced a reduction in transepidermal water loss and skin sensitivity in a controlled placebo-controlled trial [61]. Oral administration of the same probiotic strains used in the present study (*L. plantarum* PBS067, *L. rhamnosus* LRH020, and *L. reuteri* PBS072), in association with a cosmetic treatment based on ectoin, resulted effective in ameliorating acne clinical signs in a randomized controlled trial involving a population of adult Caucasian subjects [43].

Accordingly, this probiotic formulation was investigated in the current study *i)* to confirm its efficacy when administered alone, without any other adjuvant or additive effect (except from the usage of a basal cosmetic cream without any peculiar cosmetic efficacy), *ii)* to check a lasting effect of the treatment after the discontinuation of probiotic intake (follow-up period), *iii)* in a population of adult Chinese female subjects that could possess a different core gut microbiota due to diverse factors, including diet and genetics [62,63]. Clinical signs of acne were improved in two distinct populations, independently from their different diets and lifestyle habits. These results suggest that the colonization of the gut by the timing of probiotic administration could positively modulate the skin microbiota in the two populations. All instrumental parameters (hydration, pH, and sebum content) in subjects with mild acne resulted improved by both treatments throughout the intake period; however, a higher intragroup difference and statistical intergroup significant difference was achieved by probiotic intake compared to the placebo. Such amelioration in the placebo group could be attributable to the controlled use of the cosmetic cream up to T70. Both treatments showed a similar trend in reducing inflammatory lesions, yet the reduction of non-inflammatory lesions by probiotics resulted more effective, and showed a statistically intergroup difference starting from T56 up to T70, confirming a probiotic colonization that exhibit a peculiar effect on such lesions. The probiotic efficacy in lesion reduction confirmed the findings obtained in a prospective, open-label study conducted in subjects with mild to moderate AV [64]. Moreover, the other clinical evaluations (skin complexion evenness and skin status area interested by acne lesions) confirmed the positive trend of the probiotic treatment, that was achieved in shorter time and was observed in higher number of subjects with respect to the placebo.

The study limitations comprise the number of the enrolled subjects. Indeed, a wider study involving a higher number of subjects is desirable. Another limit is the relatively short-term product supplementation: while this research provided valuable insights into short-term effects on a specific population, a longer trial duration would offer a more comprehensive understanding of the probiotics' efficacy. Finally, the analysis of the gut or cutaneous microbiota will help in the understanding of probiotic mechanism of action. Further investigations should be conducted to verify the modulation of the microbiota in terms of species abundance and functions, both at gut and skin level, to better define the interplay between these two distant anatomical sites.

CONCLUSION

Overall, our results showed that the specific combination *of L. plantarum* PBS067, *L. rhamnosus* LRH020, and *L. reuteri* PBS072 can positively impact on acne symptoms in subjects from the APAC region, giving relieve from skin discomforts and offering a possible adjuvant therapy to the conventional one. The gut-skin axis is an intriguing area of study with potential therapeutical implications, highlighting the pivotal role of the microbiota. Deepening the relationship between the microbiota and the host will improve our knowledge of health and disease status.

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Statement of Human and Animal Rights

All the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 2008 revision of the Declaration of Helsinki of 1975.

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