

The Prebiotic Effect of Triple Biotic Technology on Skin Health

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Abstract

Objective: Pre-, pro- and postbiotics are becoming more prevalent as ingredients in cosmetic and personal care products. A novel triple biotic technology has been developed and investigated for its impact on skin flora and skin barrier properties. **Methods:** Growth inhibition/promotion assay was performed to determine the effect on skin bacteria growth, using *Escherichia coli*, *Corynebacterium striatum*, *Staphylococcus aureus*, and *Staphylococcus epidermidis*. A skin penetration assay and skin barrier biomarker measurements were performed using an *ex vivo* human skin explant model. The triple-biotic complex of inulin, 2-butyltolactanol, and a biomimic blend of postbiotics was tested individually as well as part of cosmetic formulations. **Results:** The triple-biotic technology, either as individual components or in a cosmetic formulation, inhibited the growth of undesirable bacteria, in most cases. On the other hand, the growth of desirable bacteria was either promoted or maintained. The cosmetic formulations with the triple-biotic technology demonstrated an enhanced skin barrier and an increase in skin barrier biomarkers. **Conclusion:** A novel triple-biotic technology has been developed and shown to deliver a strong prebiotic effect with demonstrable benefits on bacterial growth, skin barrier properties, and the production of skin barrier biomarkers. This study indicates that triple-biotic technology can be used as a desirable prebiotic ingredient in personal care products to provide skin health benefits.

Keywords

Triple Biotic Technology, Prebiotics, Postbiotics, Skin Microbiome, Skin Barrier

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#Equal contributions.

1. Introduction

The nature of skincare and the cosmetic/personal care industry is rapidly changing with respect to the inclusion of new and novel constituents. Once found strictly in dietary supplements and other nutrient-rich sources, prebiotics and probiotics are becoming more prevalent as ingredients in cosmetic and personal care products. A prebiotic is a “substrate that is selectively utilized by microorganisms conferring a health benefit” [1] [2]. There have been a number of recent articles that have reviewed the impact of prebiotics on skin health [3] [4] [5] [6] [7]. In their review on the impact of prebiotics and probiotics on skin health, Al-Ghazzewi and Tester reported that prebiotics, when applied directly to skin, can selectively increase the activity and growth of beneficial skin microbiota. However, they further stated that little is known about the overall efficacy of this prebiotics [3]. Ouwehand *et al.* concluded in their review that prebiotics had been shown to improve skin health and provide relief to persons with atopic dermatitis [7]. In addition, a clinical study conducted in patients with atopic dermatitis concluded that the use of a topically applied prebiotic was a novel therapeutic approach that could be used to enable normalization of skin microbiota. Many of these articles have focused on the impact of a single prebiotic due to the potential for more than one pre or probiotics to have interactions or increase the complexity of the study.

Plant-based ingredients are commonly used in cosmetics and personal care products. One such ingredient, inulin, is safe and effective [8]. Inulin and inulin-type fructans and galacto-oligosaccharides have demonstrated prebiotic effects in a number of ways, but little is known about its prebiotic effect on skin health when applied topically [9] [10] [11]. Recently, we discovered another cosmetic ingredient, 2-butyloctanol to have a prebiotic effect on the human axillary microbiome by inhibiting undesirable odor-causing corynebacteria while maintaining/promoting skin-friendly staphylococcus [12].

Conversely, probiotics are living microorganisms, which confer a health benefit on the host when administered in adequate amounts [13]. It is difficult, if not impossible, to formulate a cosmetic product using living microorganisms and have them be active throughout the shelf life of the product. Only a few companies have incorporated probiotics into their products [14]. Researchers have gotten around this limitation by using killed probiotics, or postbiotics, which are the byproducts of the fermentation process produced by probiotics, in the product [15]. There are limited examples of topical applications. Guéniche *et al.* have shown *Bifidobacterium longum* sp. extract, formulated at the 10% level in a topical cream, has the potential of decreasing skin reactivity and improving skin barrier function [16]. Another example is the lactobacilli group of bacteria, which have been used successfully as a wound treatment [17]. *Lactobacillus rhamnosus* is a well-known probiotics. It has been shown that oral administration of tyndalized *Lactobacillus rhamnosus* successfully treated atopic dermatitis [18], and a postbiotic derived from *Lactobacillus rhamnosus* GG has a beneficial effect on intestinal barrier function [19]. However, little is known about its prebiotic effect

on skin health topically.

Thus, a triple biotic complex of inulin, 2-butyloctanol, and a biomimic blend of postbiotics, lactic acid and pyruvic acid, that were isolated from *Lactobacillus rhamnosus* fermented with xylitol, has been developed and incorporated into a body wash and a body lotion. These individual ingredients as well products have been compared to their respective placebos in a series of tests that have been designed to evaluate the prebiotic effect of this triple biotic technology.

2. Materials and Methods

2.1. Triple Biotic Technology Development

The triple biotic technology consists of three key actives: inulin, 2-butyloctanol, and a biomimic blend of postbiotics. The biomimic postbiotic blend was generated from the key short chain fatty acids isolated from the fermentation of *Lactobacillus rhamnosus* fed with xylitol.

A pure colony of *L. rhamnosus* LR 32 (Dupont, Wilmington, Delaware) was grown in MRS medium in 5% CO₂ incubator at 37°C overnight. The turbidity of the lactobacillus solution was adjusted to Optical Density = 0.1 (OD) at 610 nm using a UV-VIS Spectrometer (Lambda™ 45, PerkinElmer Inc, Waltham, Massachusetts, USA). Four milliliters of lactobacillus culture (OD = 0.1) was added into 16ml of MRS medium with 2.5% xylitol, and incubated in 5% CO₂ at 37°C overnight. Next day, the turbidity of the lactobacillus culture was adjusted to OD = 1 using sterile distilled water, then centrifuged 12,000 rpm for 10 min. The supernatant was collected and then passed through a 0.22 µm filter. The lactobacillus ferment was stored at 4°C for further usage.

The short chain fatty acids in lactobacillus ferment were analyzed by GC-MS at NIZO food research (Ede, The Netherlands). Lactic acid and pyruvic acid were detected as the main short chain fatty acids. A blend of lactic acid and pyruvic acid at the ratio of 4:1 was generated according to the GC-MS profile, called biomimic postbiotic blend. Sodium pyruvate was used in the formulation to replace pyruvic acid due to hazardous status and issue in shipping.

2.2. In Vitro Micro Test Method

Growth inhibition/promotion assay was performed to determine whether the active or formula inhibit/promote bacteria growth. The test bacteria (VWR, Radnor, PA, USA) were *Escherichia coli* (ATCC 11229), *Corynebacterium striatum* (ATCC 1293), *Staphylococcus aureus* (ATCC 6538), and *Staphylococcus epidermidis* (ATCC 12228).

Solutions of inulin (5%) (The Iidea Company, Jalisco, México) and the biomimic blend (0.6%) were prepared in Tryptic Soy Broth (TSB) medium. A pure colony of individual test bacteria was grown in TSB medium overnight. The turbidity of the bacterial culture solution was adjusted to OD = 0.1 at 610 nm using a UV-VIS Spectrometer. Then 2 ml of the bacteria culture solution was incubated with 2 ml of test neat ingredient at 37°C for 48 h. The bacteria incubated

with medium alone were considered the control. The optical density of each tube was read after incubation using a UV-VIS Spectrometer. Each treatment was evaluated in triplicates.

Test body wash or body lotion products with triple biotic technology as well as their respective placebos (Colgate-Palmolive Company, New York, NY, USA) were diluted to 1% solution in TSB medium. Pure individual colonies of the selected bacteria were grown in TSB medium overnight. The turbidity of the bacterial culture solutions was adjusted to OD = 0.1 at 610 nm using a UV-VIS Spectrometer. Following this, 2 ml of each bacteria culture solution was incubated with 2 ml of a 1% solution each test sample at 37°C for 3 hours. After incubation, each solution was serially diluted 10 times in TSB. A sample of 100 µl of the solution was plated on Tryptic Soy Agar (TSA) plates and incubated at 37°C overnight. The bacterial colonies were counted the next day. Test samples were evaluated in two separate experiments with three replicates each. The data were expressed as log₁₀ colony-forming units (CFU)/ml. The ratio of desirable bacteria to undesirable bacteria was calculated by dividing the log counts of desirable bacteria by the log counts of undesirable bacteria.

2.3. Ex Vivo Skin Test Methods

The *ex vivo* tests were performed by the Padova laboratories of Symrise srl, Milan, Italy.

2.3.1. Skin Preparation

The skin explants were obtained from patients undergoing abdominal plastic surgery, cut into pieces of approximately 8 mm × 3 mm thickness and cultured for three days for the Skin Penetration Assay and for six days for the Skin Barrier Biomarker Measurements.

2.3.2. Application of Body Washes

The skin tissues were gently cleaned with a cotton pad. Afterwards, 4 µl of a 10% diluted solution for the Test and Placebo body washes was applied on top of each tissue, covered with a 6 mm delivery membrane, and left in place for 15 min. Afterwards the skin tissues were gently cleaned until the next application. The application process was performed daily. The tissues were collected at day 3 for the skin penetration assay.

2.3.3. Application of Body Lotions

The skin tissues were gently cleaned with a cotton pad. Afterwards, 4 µl of the Test and Placebo body lotions was applied on top of each tissue, covered with a 6 mm delivery membrane, and left in place for 24 h. The application process was repeated daily. The tissues were collected at day 3 for the skin penetration assay and day 6 for skin barrier biomarker measurements.

2.4. Skin Penetration Assay

Skin tissues (6) were harvested, stained with Rhodamine B, cryo-fixed, and cut

by the cryostat for subsequent image acquisition and analysis. Analysis of Rhodamine B fluorescence (red color) was performed within the epidermis area using Image-J (NIH, Bethesda, MD, USA). For each skin tissue, two sections were selected; fluorescent images acquired, and analyzed for a total of 12 data points. (6 skin samples \times 2 sections = 12 sampling points/data for each tested condition). The values were normalized using the dimension of the selected sections.

2.5. Skin Barrier Biomarker Measurements

Two sections from each of six skin tissues were immunostained with the selected antibody for Filaggrin (SantaCruz Biotechnology, Dallas, TX, USA), Involucrin, Desmocollin 1 and Claudin 1 (Abcam, Cambridge, UK). The amount of the antigen present in each slide was evaluated by estimating the intensity and distribution of the pink/red within the epidermis using Image J (NIH, Bethesda, MD, USA). The values were normalized on the dimension of the analyzed surface expressed in pixels.

3. Statistics

The mean value and standard deviation of optical density or bacteria counts in each tested products were calculated in excel. The statistical significance between the effects of the test products on bacterial optical density or counts was analyzed by one-way ANOVA at the 95% confidence level using Minitab software (Version 17, State College, PA, USA).

For the *ex vivo* test, all quantitative data were summarized in terms of the mean score for each treatment. The measures of variation as standard deviation were applied to the original scores. Statistical significances between groups were evaluated by one-way ANOVA with permutation at the 95% confidence level followed by t-test with permutation using B1SCLASSIC Software (SISSAD snc, Trieste, Italy).

4. Results

The impact of triple biotic technology on skin bacteria growth was investigated individually and in a cosmetic formulation using growth/inhibition assay.

For neat ingredients, in comparison to the control solution, the 5% solution of inulin (**Figure 1**) significantly inhibited the growth of *E. coli*, *C. striatum*, and *S. aureus*, while maintaining the growth of *S. epidermidis*. The 0.6% solution of the biomimic blend (**Figure 2**) significantly inhibited the growth of *E. coli* and *C. striatum*, while maintaining the growth of *S. aureus*. Conversely, it significantly promoted the growth of *S. epidermidis*.

2-butyloctanol works as a smart biotic component in the triple biotic technology. 2-butyloctanol has been shown to preferably inhibit odor causing corynebacterium while maintaining/promoting skin friendly staphylococcus in both *in vitro* and *in vivo* studies in our previous study [12].

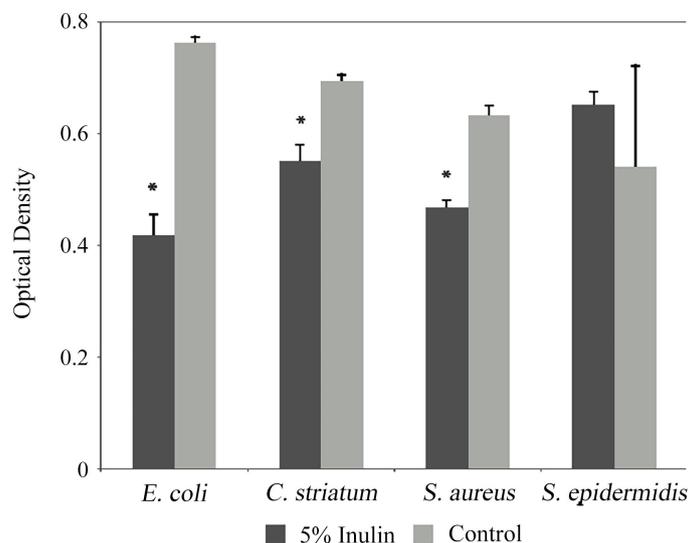


Figure 1. Prebiotic Effect of Inulin (5% solution) on skin bacteria. Inulin (5%) inhibits undesirable bacteria growth (*E. coli*, *C. striatum*, *S. aureus*) and maintains desirable bacterial growth (*S. epidermidis*) *in vitro*. * significant difference compared to control ($p < 0.05$).

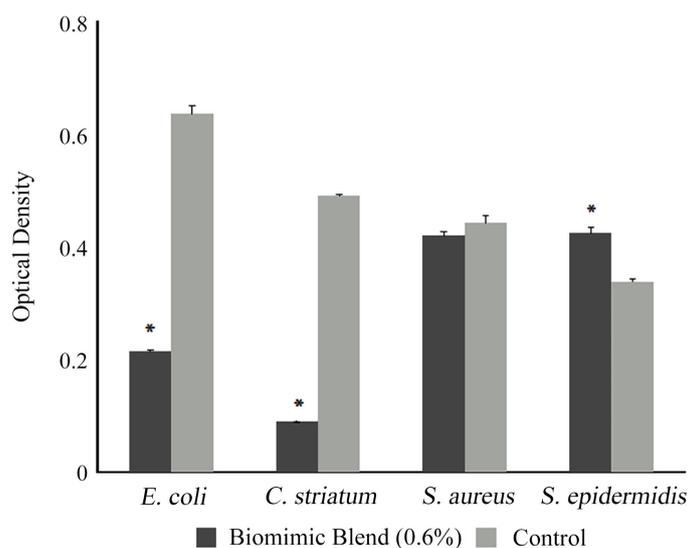


Figure 2. Prebiotic Effect of Biomimic Blend (0.6% solution) on skin bacteria. Biomimic Blend (0.6%) inhibits growth of undesirable bacteria growth (*E. coli*, *C. striatum*), maintains growth of undesirable bacteria (*S. aureus*) and promotes growth of desirable bacteria (*S. epidermidis*) *in vitro*. * significant difference compared to control ($p < 0.05$).

In comparison to the Placebo Body Wash, the Test Body Wash with the triple biotic technology demonstrated a prebiotic effect by inhibiting the growth of *C. striatum* and maintaining the growth of *S. epidermidis* (**Figure 3(a)** and **Figure 3(b)**). These results, expressed in log₁₀ CFU/ml, show a statistically significant difference between the two body washes on *C. striatum* ($p = 0.042$) and non-statistical tendency on *S. epidermidis* ($p = 0.052$). In addition, as seen in **Figure 3(c)**, the Test Body Wash has statistically significantly increased the ratio

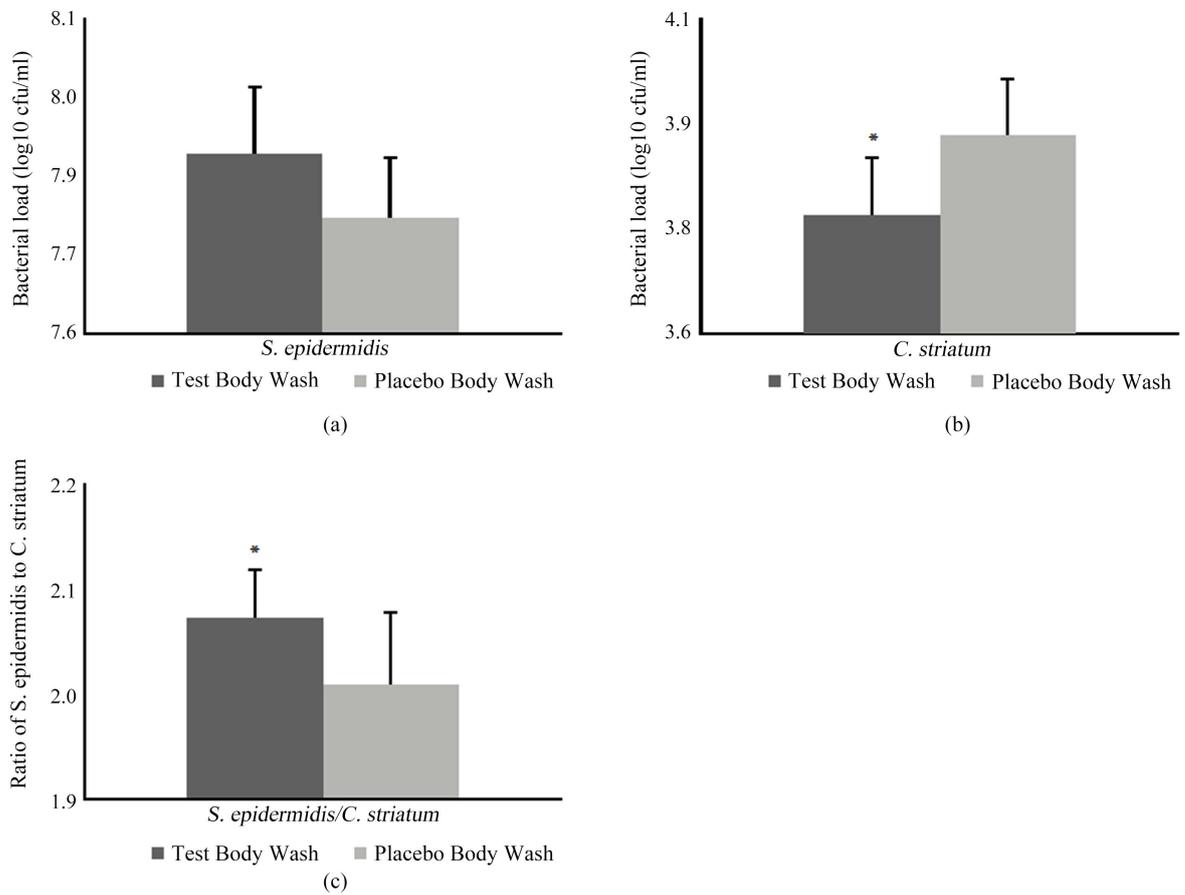


Figure 3. Comparison of Body Wash with and without Triple Biotics Technology of the growth of *S. epidermidis* (3a), *C. striatum* (3b), and the ratio of *S. epidermidis*/*C. striatum* (3c). * significant difference compared to placebo ($p < 0.05$). p value between placebo and test product on *S. epidermidis* is 0.052.

of beneficial bacteria (*S. epidermidis*) to undesirable bacteria (*C. striatum*) ($p = 0.03$). Similarly, the Test Body Lotion with the triple biotic technology demonstrated a prebiotic effect in comparison to the Placebo Body Lotion by maintaining the growth of *S. epidermidis*, while inhibiting the growth of *S. aureus* (Figure 4(a) and Figure 4(b)). These results, expressed as log₁₀ CFU/ml, show a statistically significant difference between the two lotions on *S. aureus* with the Test Body Lotion reducing the bacterial counts in comparison to the Placebo Body Lotion ($p = 0.048$). There was no statistically significant difference between the two body lotions on the counts of *S. epidermidis*. As was seen with the Body Wash, the Test Body Lotion statistically significantly increased the ratio of beneficial bacteria (*S. epidermidis*) to deleterious bacteria (*S. aureus*) ($p = 0.029$). These results are shown in Figure 4(c).

The effect of triple biotic technology on skin barrier property was evaluated in an ex vivo skin tissue model using dye penetration assay and skin barrier biomarkers measurement. Both the Test Body Wash and the Test Body Lotion, each with the Triple Biotic Technology, demonstrated an enhanced skin barrier (Figure 5) in the skin penetration assay. The amount of Rhodamine B fluorescence (red color) penetration into the skin is directly correlated with the barrier

function. The better the barrier, the less dye that penetrates. In comparison to their respective placebos, there is little to no fluorescence dye that has penetrated into the skin for samples treated with either the Test Body Wash with Triple Biotic Technology or the Test Body Lotion with Triple Biotic Technology. The amount of fluorescence was quantified by Image Analysis, and the results are presented in **Table 1**. The Test Body Wash with the Triple Biotic Technology has produced statistically significantly less fluorescence than the Placebo Body Wash indicating much enhanced skin barrier ($p < 0.05$). However, there was not a statistically significant difference in the amount of fluorescence produced by the Placebo Body Lotion and the Test Body Lotion with the Triple Biotic Technology.

Table 1. Intensity of Rhodamine B Fluorescence in skin tissues treated with body wash or body lotion with or without triple biotics technology as Measured by Image Analysis.

	Mean (n = 12)	Std Dev	p-value
Placebo Body Wash	0.17	0.27	<0.05
Body Wash with triple biotic technology	0.0008	0.0029	
Placebo Body Lotion	0.34	0.45	N.S.
Body Lotion with triple biotic technology	0.12	0.14	

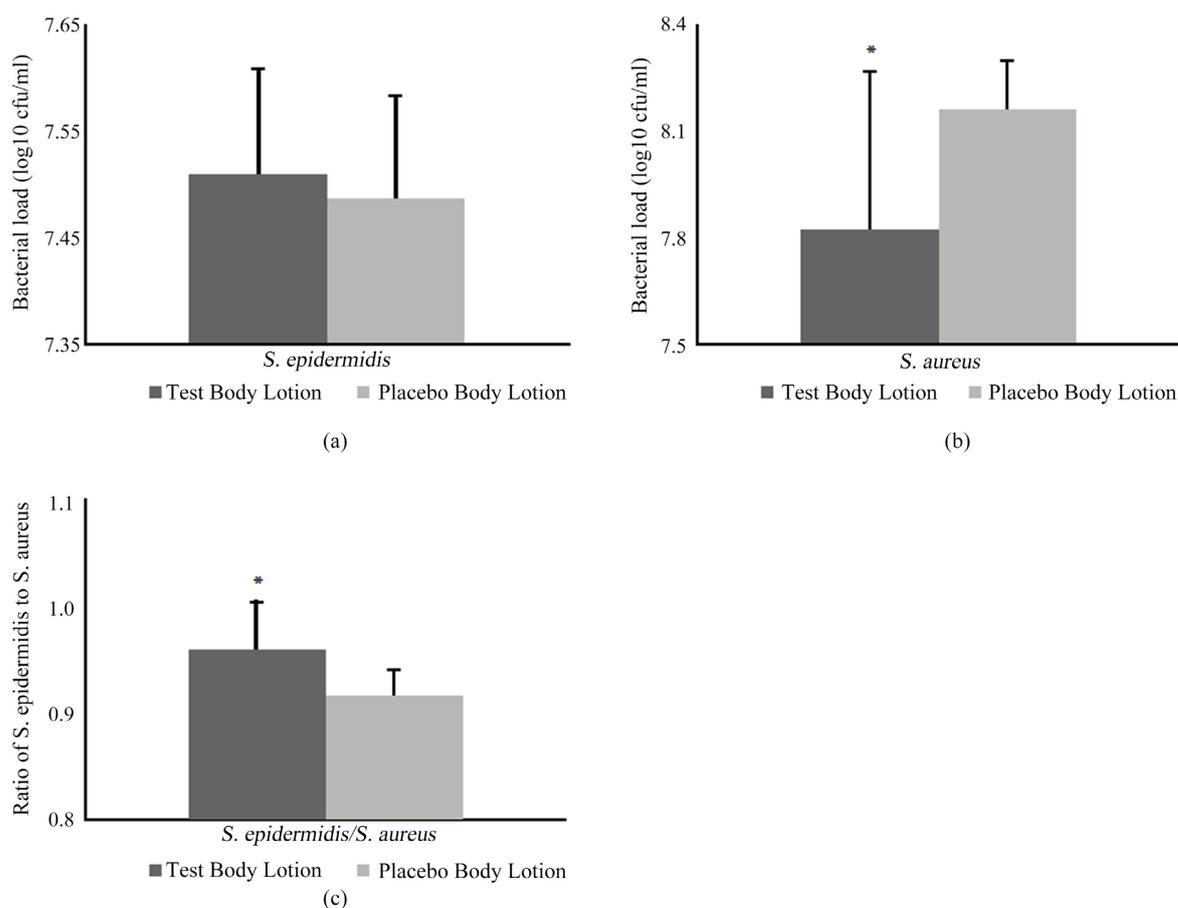


Figure 4. Comparison of Body Lotion with and without Triple Biotics Technology on the growth of *S. epidermidis* (4a), *S. aureus*. (4b), and the ratio of *S. epidermidis*/*S. aureus* (4c). * significant difference compared to control ($p < 0.05$).

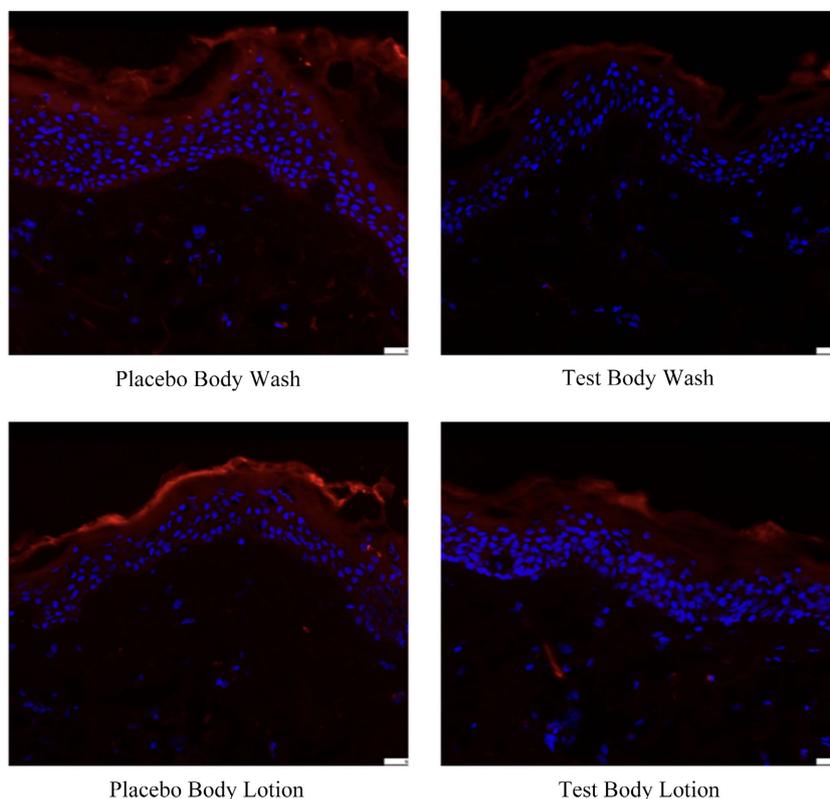


Figure 5. Rhodamine B Fluorescence images of Skin tissues cross sections topically treated with body wash or body lotion with and without triple biotics technology. Red fluorescence is Rhodamine B, blue fluorescence is 4',6-diamidino-2-phenylindole (DAPI) fluorescence.

As shown in **Figures 6(a)-(d)**, application of the Test Body Lotion with the Triple Body Technology has statistically significantly increased specific skin barrier biomarkers ($p < 0.05$), namely, Filaggrin, Involucrin, Desmocollin 1, and Claudin 1, in comparison to the Placebo Body Lotion. Quantitative comparisons were made between products by image analysis of the varying fluorescence levels, as described above for Rhodamine B.

5. Discussion

Prebiotics, probiotics, and postbiotics are emerging technologies that are used in the personal care industry and have a beneficial effect on the skin microbiome [3] [4] [5] [6] [7] [16]. A new proprietary triple-biotic technology consisting of inulin, 2-butyltolactanol, and a novel biomimic postbiotic blend has been developed and evaluated as individual components as well as when formulated into a body wash or body lotion on skin microbiome. We examine the effects on the promotion or inhibition of growth of four common skin bacteria. *S. aureus*, *C. striatum*, *E. coli*, and *S. epidermidis* were chosen as representatives for very specific reasons. *S. epidermidis* was chosen to represent the beneficial bacteria on the skin. Healthy skin is typically populated with coagulase negative staphylococci (CoNS) bacteria along with other bacteria [20] and *S. epidermidis* is the

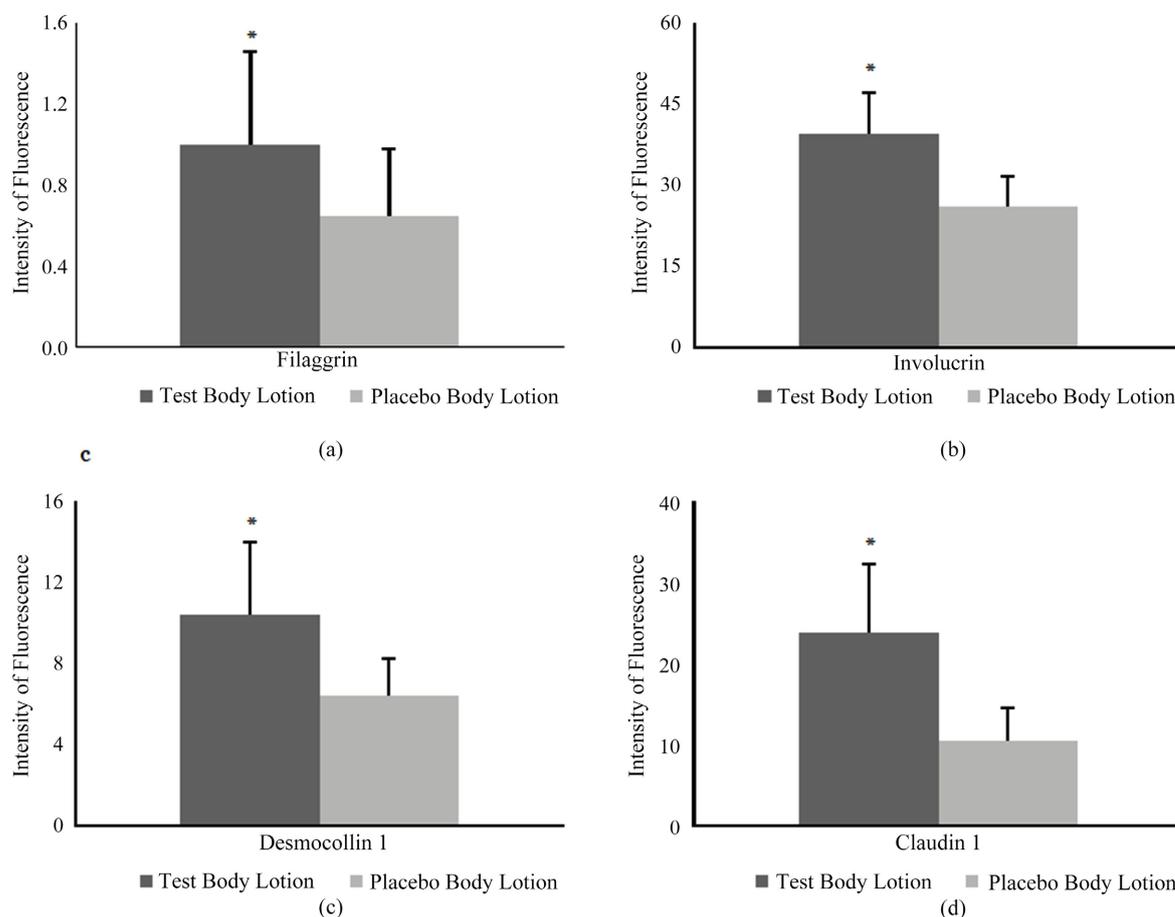


Figure 6. Effect of Body Lotions with and without Triple Biotics Technology on Skin Barrier Biomarkers: Filaggrin (a), Involucrin (b), Desmocollin 1 (c), and Claudin 1 (d). * significant difference compared to control ($p < 0.05$).

beneficial and frequently isolated species [21] [22]. It also can influence the colonization of *S. aureus*, which is one of the deleterious bacteria on the skin [20]. *S. aureus* is also a leading cause of skin infections and is well known for its involvement in atopic dermatitis [23] [24]. *C. striatum* is known to be an odor causing bacterium [25]. *E. coli* has been implicated in skin infections [26].

The first component of this technology, inulin, is a well-known prebiotics that has been widely used in intestinal health to modulate gut microbiome, but little is known with regards to its effect on the skin microbiome [9] [10] [11]. Here we demonstrated in **Figure 1** that inulin has the ability to inhibit the growth of the undesirable bacteria (*S. aureus*, *C. striatum*, *E. coli*) and maintain the growth of desirable bacteria (*S. epidermidis*).

The second component, 2-butyltolactanol, commonly used as an emollient in many skin care products, has been shown to have a prebiotic effect on human axillary microbiome [12]. Using both *in vitro* and *in vivo* studies, the authors determined that 2-butyltolactanol inhibited odor causing corynebacteria while maintaining/promoting skin friendly *S. epidermidis*. The authors postulated that 2-butyltolactanol could be incorporated into cosmetics and personal care products as a complex with other prebiotics, probiotics, and postbiotics.

The third component of our technology, the biomimic blend has been designed to mimic the function of the *Lactobacillus* ferment. According to a recent article, there are at least 50 cosmetic products that claim to contain probiotics. Of these, approximately 50% list *Lactobacillus* ferment as one of the ingredients. The most common claims for these products are improving the skin barrier or “balancing” the skin microbiome [27]. Earlier research has demonstrated that an extract of *Lactobacillus* has been shown to help repair the skin barrier when applied as an oil-in-water formulation [28]. It was also shown to reduce the skin microflora, but no individual bacterial species were identified. In our current study, two short chain acids, lactic acid and pyruvic acid were identified as main components in *Lactobacillus* ferment and prepared in a 4:1 ratio. It is known that the salt of lactic acid, lactate, is a component of the skin’s natural moisturizing factor (NMF) and can comprise up to 12% of NMF [29]. A study by Nakagawa *et al.* suggested that lactate may play a role in maintaining the physical properties of the stratum corneum leading to increased hydration [30]. More recently, the application of colloidal oat in a moisturizer was shown to increase lactic acid production and may help contribute to an improved skin condition in patients with compromised skin conditions [31]. Pyruvic acid is known for its exfoliation benefits [32] [33], but otherwise, there is not any information regarding its impact on the skin barrier. It is well known that lactic acid and pyruvic acid have antibacterial properties [34] [35]. To our knowledge, no data reported on the prebiotic effect of these two acids. In this study, we explored the prebiotic effect of the combination of lactic acid and pyruvic acid in a specific ratio by inhibiting the growth of the undesirable bacteria (*C. striatum* and *E. coli*), while promoting the growth of desirable bacteria (*S. epidermidis*).

In addition to the effect that the individual components have on the skin microbiome, the triple-biotic technology also has a beneficial effect on the skin microbiome when formulated into topical formulations. As noted by Puebla-Barragan and Reid, the use of probiotics, prebiotics, and microbiome by the cosmetic and personal care industry would be encouraging if there was strong scientific claims support and if mechanisms of action were elucidated [27]. We have done just this by identifying the impact of our technology on certain strains of skin bacteria. The recent publication by Liu-Walsh *et al.* evaluated a skin moisturizer containing 1% colloidal oat on skin microbes and demonstrated that it selectively increased the growth rate of *S. epidermidis*, which may also be a major source of lactic acid in the skin [31]. Thus, it is believed that topical application of our triple biotic technology would not have a negative influence on *S. epidermidis* production based on our research and the publication by Liu-Walsh *et al.*

Topical applications of probiotic bacteria have the potential to enhance the natural barrier of the skin [3]. We evaluated the triple-biotic technology formulated into cosmetic formulations using an *ex vivo* skin penetration assay to determine the effect on skin barrier function. The observed decrease in skin fluorescence for the body wash formulation with the triple-biotic technology means

a healthier, more intact skin with a better barrier. On the other hand the body lotion formulation produced a non-statistical decrease in fluorescence. Lack of statistical significance may be due to large variability in the data. Other researchers have also observed that topically applied probiotics can help repair skin barrier function [28] [36] [37] [38].

To further investigate the impact of the triple-biotic technology on skin barrier function, we followed the skin biomarkers, Filaggrin, Involucrin, Desmocollin 1, and Claudin 1, before and after topical application of the body lotion with the triple-biotic technology. Filaggrin is a protein that is known to be fundamental for the function and maintenance of the skin barrier [39] [40]. Involucrin is a protein that is involved with the formation of the cornified envelope of the skin and is crosslinked with keratin filaments along with other proteins [41]. Desmocollin 1 is a calcium dependent adhesion molecule (part of the cadherin family) [42] and is part of the main adhesive structure of the skin. Claudin 1 is another of the skin barrier proteins and has been shown to be less present in the skin of atopic dermatitis patients, who are known to have a poor barrier function, as compared to healthy control patients [43]. We observed statistically significant increases in all four skin biomarkers indicating an improved barrier function by applying a body lotion with triple biotic technology.

There are many products in the marketplace that may incorporate a single biotic or two into their cosmetic formulation to claim either skin or microbiome benefit, however, most of them didn't provide strong scientific evidence publicly. Together with our previous work of Li *et al.* [12], we have shown the combination of three biotic components delivered both microbiome and skin benefits in individual components as well as when introduced into cosmetic formulations.

6. Conclusion

A novel triple biotic technology has been developed and shown to have beneficial effects on the skin microbiome and skin barrier function through the use of *in vitro* and *ex vivo* studies. The benefits have been shown for the components both individually and when formulated into cosmetic formulations. Overall, this novel triple biotic technology was able to deliver a strong prebiotic effect and improve skin health in body wash and body lotion products and can be used as a desirable prebiotic ingredient in personal care products to provide skin health benefits.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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