

Prebiotic Colloidal Oat Supports the Growth of Cutaneous Commensal Bacteria Including *S. epidermidis* and Enhances the Production of Lactic Acid

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Background: Multiple skin conditions have been associated with alterations in the diversity and composition of the skin microbiome, including dry skin and atopic dermatitis. In these conditions, a number of commensal skin bacteria have been implicated in supporting a healthy skin barrier, including *Staphylococcus epidermidis*. Recent clinical studies in patients with mild-to-moderate atopic dermatitis and dry/itchy skin have shown significantly improved skin barrier function and microbial diversity upon treatment with moisturizers containing 1% colloidal oat. We hypothesized that direct use of colloidal oat by skin microbes contributes to these therapeutic benefits.

Methods: Skin bacterial growth was assessed using the BacT/ALERT system. *Staphylococcus aureus* and *S. epidermidis* growth rates and metabolism were compared in an in vitro competition assay. The effect of a 1% colloidal oat-containing moisturizer on lactic acid content of the stratum corneum was clinically assessed in subjects with moderate-to-severe dry skin. *S. epidermidis* gene expression was evaluated by next-generation mRNA sequencing. Short-chain fatty acids were quantified in bacterial culture supernatants.

Results: In vitro, colloidal oat increased the growth rate of *S. epidermidis* vs *S. aureus*, as well as the metabolism of *S. epidermidis*. Colloidal oat also significantly increased lactic acid concentrations in supernatants of both strains and decreased pH, consistent with clinical findings that 6-week use of a 1% colloidal oat-containing lotion significantly increased lactic acid on dry skin. Further analyses suggest that colloidal oat alters the gene expression profile of *S. epidermidis*.

Conclusion: Colloidal oat directly affects the growth, metabolism, lactic acid production, and gene expression of skin commensal bacteria, as shown via in vitro studies. The increased production of lactic acid reflects clinical observations with colloidal oat-containing skin moisturizers. Our findings suggest a new mechanism for colloidal oat as a skin prebiotic, which may contribute to improvements in skin and microbiome diversity in various skin conditions, including dry/itchy skin and atopic dermatitis.

Keywords: atopic dermatitis, dry skin, colloidal oat, skin barrier function, skin microbiome, skin moisturizer, *S. epidermidis*

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Introduction

The skin is the largest organ of the body and home to a vast array of microbes.¹ Phyla that dominate the skin are Actinobacteria, Proteobacteria, Bacteroidetes, and Firmicutes, with more than 60% of the bacterial species belonging to three genera, including

Staphylococcus (Firmicutes); *Corynebacterium* (Actinobacteria), and *Propionibacterium* (Actinobacteria).² Sites rich in sebaceous secretion are preferentially colonized by lipophilic bacteria such as *Cutibacterium acnes* (previously known as *Propionibacterium acnes*), whereas moist locations such as skin folds are favored by *Corynebacterium* spp. and *Staphylococcus aureus*. *S. epidermidis* is one of the most abundant bacterial species of the skin microbiome. It is a mutualistic, Gram-positive, facultative anaerobe that constitutes up to 90% of the aerobic resident flora, and certain strains have been associated with skin health.³

Multiple skin conditions have been associated with alterations in the diversity and composition of the skin microbiome, including atopic dermatitis (AD), dry skin, acne, dandruff/seborrheic dermatitis and psoriasis.^{4–6} For example, atopic dermatitis is commonly associated with colonization of *S. aureus* and a decrease in diversity.^{7–9} Interestingly, in contrast, dry skin is associated with an increase in microbial diversity along with a decrease in microbial load in comparison to more sebaceous areas of the skin.⁶ Acne presents as an excessive growth of pathogenic *C. acnes*,^{10,11} and in dandruff/seborrheic dermatitis there is an uncontrolled growth of *Malassezia* species.^{12,13} While these examples provide ample illustration of the association between skin disease/skin condition and alterations in microbiome composition, the precise role of alterations in these skin states and the events that trigger these alterations are not well understood.

Understanding the overall composition of the skin barrier and how these components of the skin influence or are influenced by the skin microbiota is also pivotal to identifying the role and benefits of the microbiome in the health of the skin.

Lactic acid is one of the natural moisturizing factors (NMF) of the stratum corneum skin barrier that helps to maintain the hydration and slightly acidic pH (ie, “acid mantle”) of the skin surface.^{14–17} Among the NMF components, lactic acid and potassium concentrations are the only ones that have been shown to significantly correlate with the level of skin hydration and skin surface pH (lower lactic acid in dry skin and skin with elevated pH).¹⁵ In this regard, higher lactic acid concentrations and lower skin surface pH have been associated with increased epidermal renewal in healthy skin subjects,¹⁴ and potassium lactate application has been shown to improve skin surface hydration in patients with mild AD.¹⁷ Although it is well accepted that the presence of lactic acid in the skin is crucial for optimal skin

hydration, the precise source of lactic acid on the skin is not well defined.

Prebiotics are a well-established concept in digestive health. They are non-digestible food ingredients that selectively stimulate the growth of beneficial species (mainly bifidobacteria and lactobacilli) of the intestinal microbiota.¹⁸ These bacteria use prebiotics as substrates to produce metabolites and micronutrients that may benefit the host.¹⁹ Although there is no established concept for prebiotics for the skin, we suggest that a topically applied ingredient that is metabolized by members of the skin microbiome and promotes changes in the composition and/or activity of the skin microbiome to benefit the skin may be considered a prebiotic for the skin.²⁰

Oat bran or oat fiber and their main active ingredient, β -glucans, have been well documented to serve as prebiotics in the gut.^{19,21–24} Oat (*Avena sativa*) in colloidal form has been used for centuries as a topical treatment of skin conditions such as AD and other dry, compromised skin conditions.^{25,26} Additionally, in recent clinical studies in patients with mild-to-moderate AD or dry/itchy skin, 2 weeks of treatment with moisturizers containing 1% colloidal oat significantly improved skin barrier properties, including decreasing transepidermal water loss and increasing skin hydration, as well as increasing microbial diversity.²⁷ We hypothesized that the therapeutic benefit of these moisturizers may be related, at least in part, to the prebiotic properties of colloidal oat, which contains 65% to 85% starch, 15% to 20% protein, 3% to 11% lipids, 5% fiber, and 5% β -glucans, as a substrate.^{25,28} To test this hypothesis, we examined the effects of 1% colloidal oat on the growth rate, metabolism, lactic acid production, and gene expression of *S. epidermidis* and *S. aureus* via in vitro studies. Additionally, we clinically evaluated the lactic acid content in the skin barrier after topical application of a 1% colloidal oatmeal-containing moisturizer on subjects with moderate-to-severe dry skin.

Materials and Methods

Bacterial Strains

Bacterial strains were obtained from the American Type Culture Collection (ATCC), including *S. epidermidis* (ATCC 12,228), *S. aureus* (ATCC 6538), and *C. acnes* (ATCC 6919).

Bacterial Growth: Time-to-Detection (TTD) by BacT/ALERT Based on CO₂ Detection

The BacT/ALERT system, which is used extensively in hospital clinical laboratories for the detection of

microorganisms in blood samples,^{29–33} is a fully automated microbial detection system based on the colorimetric detection of CO₂ in sample bottle growth media. A BacT/ALERT prebiotic screening method was developed based on the relative TTD of target microorganism in the absence and presence of potential prebiotic ingredients. In this study, the relative TTD of target microorganisms with and without the addition of 1% colloidal oat was evaluated. The TTD of target microorganisms in the absence of 1% colloidal oat was set at 100% (control), and the relative TTD in the presence of 1% colloidal oat was expressed as a percent of the control. The presence of a prebiotic effect results in a shorter TTD compared with the control and is reported as a relative TTD below 100%.

The target microorganisms to be tested were harvested from BacT/ALERT sample bottles containing overnight stationary phase cultures, which were serially diluted into new BacT/ALERT sample bottles. One-mL aliquots containing approximately 1000 colony-forming units (CFU) were inoculated into designated BacT/ALERT sample

bottles using a sterile 1-mL syringe and 20-gauge needle. Prior to microbial inoculation, 10-mL aliquots of oat suspension were aseptically injected into designated sample bottles using a sterile 10-mL syringe and 18-gauge needle, to obtain a 1% final concentration of colloidal oat. The oat suspension contained 0.51 g resuspended oat per 10 mL volume of sterile filtered water for injection (WFI)-quality water. Control sample bottles inoculated with the designated test microorganisms contained only WFI in the absence of 1% colloidal oat. A negative control containing 1% colloidal oat only was included.

In vitro Bacterial Competition Assay

Co-cultures of *S. epidermidis* and *S. aureus* were inoculated at 1000 CFU/mL in 125-mL sterile flasks containing 50 mL of Tryptic Soy Broth (TSB: 1% tryptone [Difco], 0.5% yeast extract [Gibco-BRL], 0.5% NaCl, 0.1% K₂HPO₄, 0.1% glucose) with or without 1% colloidal oat. Flasks were incubated at 33°C ± 2°C, and samples were taken at 0, 2, 4, 6, and 24 h. Serial dilutions of each sample were plated in duplicate on

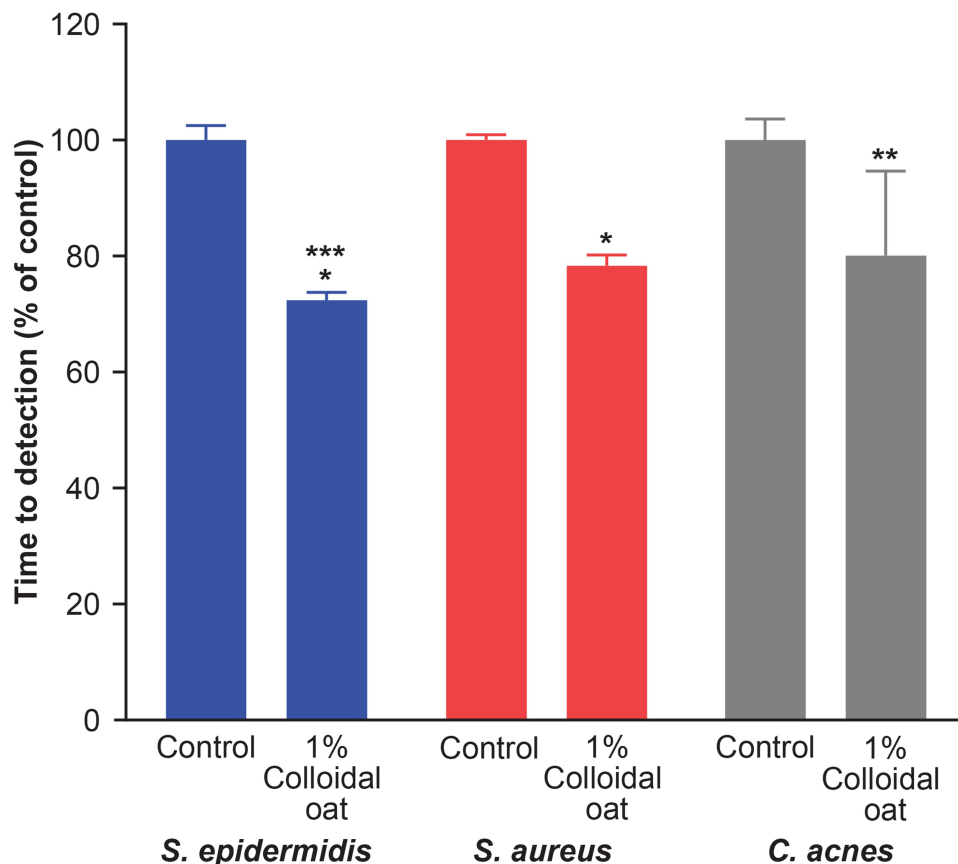


Figure 1 Addition of 1% colloidal oat reduces the time to detection of *S. epidermidis*, *S. aureus*, and *C. acnes* in monoculture. Shown are the means of five replicate assessments (n=5); error bars denote standard deviation. *p<0.01 vs control, **p<0.05 vs control, ***p<0.001 *S. epidermidis* vs *S. aureus* (unpaired two-tailed Student's t-test).

Mannitol Salt Agar plates, and colonies were counted after incubation at $33^{\circ}\text{C} \pm 2^{\circ}\text{C}$ for 48 h. The use of Mannitol Salt Agar allowed for the differentiation of *S. aureus* and *S. epidermidis* on the co-cultured competition assay plates. Mannitol fermentors such as *S. aureus* appeared as yellow colonies with yellow zones in the media while the non-mannitol fermentor, *S. epidermidis*, appeared as clear pink to red colonies with no yellow color change in the medium. For each culture condition and time point, titers were determined from five to eight replicate samples. Non-parametric, two-sided Mann–Whitney tests were used to assess the statistical significance of differences in bacterial concentrations between culture conditions.

Analysis of Short-Chain Fatty Acids

Analysis and quantification of short-chain fatty acids (SCFAs) were performed by gas chromatography followed by mass spectrometry using a 7890A gas chromatograph and a 5975C mass spectrometer (Agilent Technologies). Quantification of lactic acid and succinic acid was performed by high-pressure liquid chromatography (Shimadzu LC-20A System) followed by tandem mass spectrometry (AB Sciex API 4000 with TurboIonSpray® Source). All analyses were performed in triplicate. Unsupervised hierarchical clustering analysis was used to compare metabolic activity (ie, SCFA production) of *S. epidermidis* under different culture conditions.

Gene Expression Analyses

High-throughput RNA sequence (RNA-seq) reads were mapped to the *S. epidermidis* genome using the Rockhopper pipeline.³⁴ A negative binomial model (edgeR) was used to evaluate differential gene expression, with read counts normalized using the weighted trimmed mean of M-values method, and dispersions estimated using the Cox-Reid-adjusted likelihood approach. Differential expression analyses were performed using features with detectable expression in at least two of six samples involved in a given comparison. A feature was considered to have detectable expression in a sample if the count per million mapped reads estimate was greater than 0.20. The StringDB database was used for the functional analysis of differentially expressed genes.³⁵

Clinical Study of Colloidal Oat-Containing Daily Moisturizer in Subjects with Dry Skin

A single-center clinical study was conducted on 18- to 65-year-old female subjects with Fitzpatrick skin type

I–IV who had clinically determined moderate-to-severe dry skin on the lower leg and used moisturizer at least one to three times per week (registered at Clinicaltrials.gov NCT04510103). One objective of the study was to determine the impact of a daily moisturizing lotion containing 1% colloidal oat on the amount of lactic acid, a natural moisturizing factor, within the stratum corneum skin barrier. The lotion was applied twice a day for 6 weeks after a 3-day washout period with a gentle skin cleanser that was continued for the study duration. At baseline and after 6-weeks use of the lotion, two consecutive D-Squame Standard Sampling Discs (CuDerm Corporation, Dallas, TX) were collected from the designated test site. The first tape, collected from the uppermost layer of the stratum

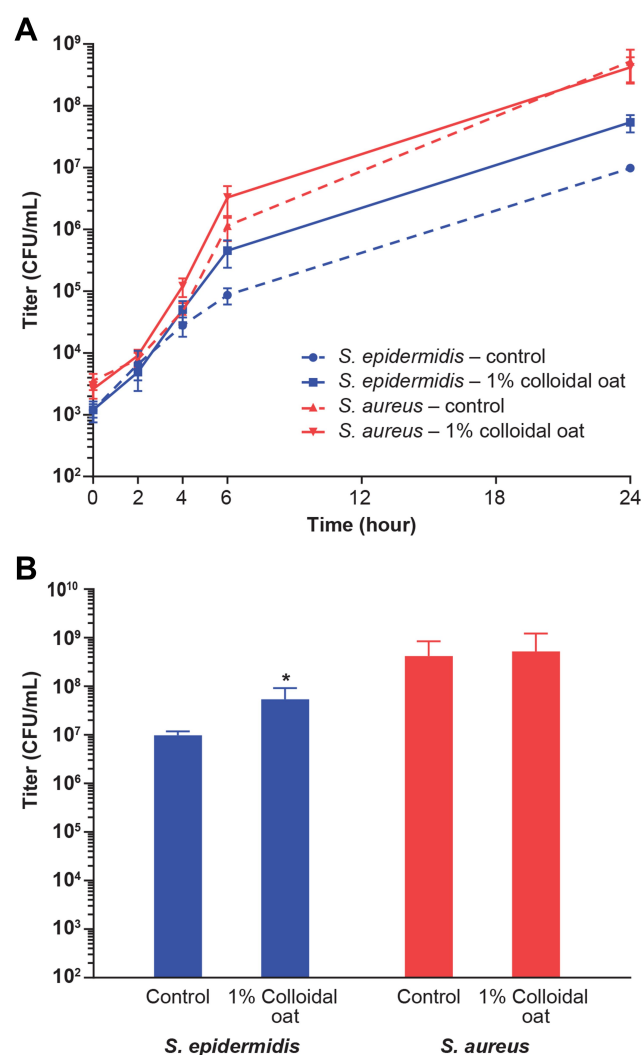


Figure 2 Addition of 1% colloidal oat selectively increases the growth rate of *S. epidermidis* versus *S. aureus* in an in vitro competition assay. Shown are the time course of bacterial growth (mean with standard error) over 24 hours (A) and final titers (mean with standard deviation) after 24 hours (B). * $p < 0.05$ vs control (two-tailed Mann–Whitney test).

corneum, was used to quantify the degree of skin flakiness by image analysis. The lactic acid content in the second tape was extracted, quantitated via colorimetry, and normalized by total protein content (Synelvia SAS, Labège, France). A paired *t*-test was performed to compare the lactic acid

content at baseline and after 6 weeks of treatment for six subjects. The trial was conducted in accordance with the Declaration of Helsinki. Each participant provided informed consent. The IntegReview Institutional Review Board (Austin, TX) approved the study.

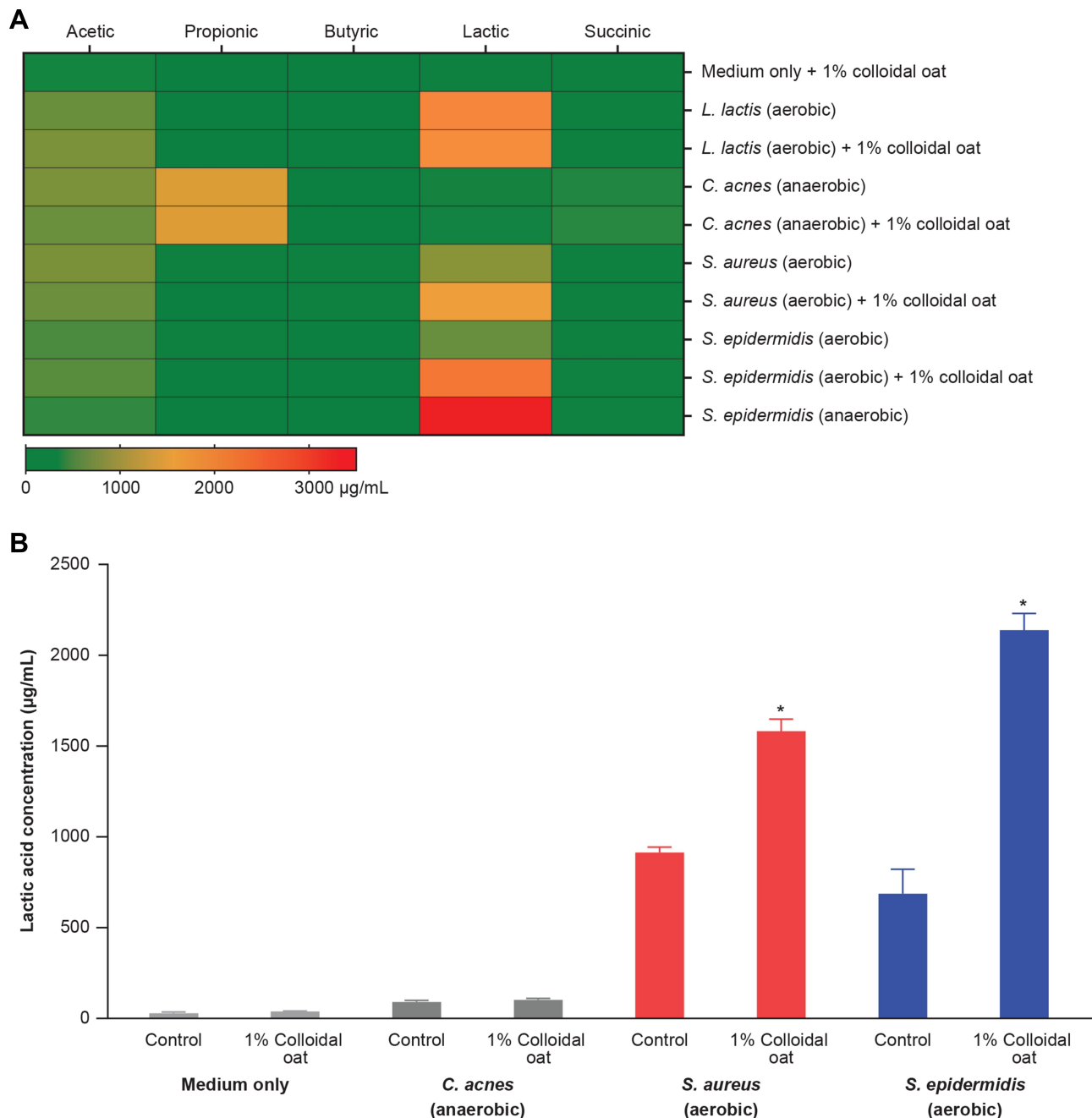


Figure 3 SCFAs (**A**) and lactic acid (**B**) in supernatants of monocultures of skin bacteria. Heat map and bar graph show mean values of analyses performed in triplicate. Error bars denote standard deviation. * $p < 0.01$ vs control (unpaired two-tailed Student's *t*-test).

Abbreviation: SCFAs, short-chain fatty acids.

Results

Differential Effects of 1% Colloidal Oat on the Growth of Members of the Skin Microbiome

Using the BacT/Alert system for detection of *S. epidermidis*, *S. aureus*, and *C. acnes* grown in bacterial monocultures, we found that addition of 1% colloidal oat to the culture medium significantly reduced the TTD compared with cultures grown in the absence of 1% colloidal oat (control) (Figure 1). On average, TTD of *S. epidermidis*, *S. aureus*, and *C. acnes* grown with 1% colloidal oat was 72%, 78%, and 80% that of the corresponding time in control cultures. Importantly, the increase in growth rate obtained with 1% colloidal oat was significantly greater for *S. epidermidis* than *S. aureus* ($p < 0.001$). This suggests that the beneficial effects of moisturizers containing 1% colloidal oat observed in patients with AD or dry/itchy skin^{28,36} may be attributable, at least in part, to the effects of 1% colloidal oat on the increase in diversity of the microbiome overall, along with the increase in the relative abundance of *S. aureus* and *S. epidermidis* species. To explore this possibility further, we tested the effect of 1% colloidal oat on the growth of *S. aureus* and *S. epidermidis* in an in vitro competition assay. In the absence of oat (control), *S. aureus* grew faster than *S. epidermidis* (Figure 2A and B). However, although the addition of 1% colloidal oat to the culture

medium had no substantial effect on the growth of *S. aureus* (mean titer after 24 h, 4×10^8 CFU/mL vs 5×10^8 CFU/mL without oat), it selectively increased the growth rate of *S. epidermidis* (mean titer after 24 h, 5×10^7 CFU/mL vs 1×10^7 CFU/mL without oat; $p = 0.012$, two-tailed Mann-Whitney test; Figure 2A and B).

Effects of 1% Colloidal Oat on *S. epidermidis* Metabolism and Lactic Acid Production

Metabolism of 1% colloidal oat in mixed cultures of *S. aureus* and *S. epidermidis* (1:1 ratio) resulted in significant decreases in the pH of the culture media from a mean value \pm standard deviation of 7.61 ± 0.29 to 7.15 ± 0.38 ; $p < 0.001$.

A previous study showed that fermentation of oat by fecal bacterial generated significantly more butyric acid than fermentation of other grains, such as corn and wheat.³⁷ Interestingly, in our study fermentation of 1% colloidal oat by the tested skin bacteria did not yield detectable levels of butyric acid (Figure 3A). Propionic acid was generated only by *C. acnes* (among the tested bacterial strains), and its concentration was not significantly affected by the presence of 1% colloidal oat (1459.8 ± 35.4 $\mu\text{g/mL}$ without 1% colloidal oat and 1470.5 ± 4.5 $\mu\text{g/mL}$ with 1% colloidal oat). Under aerobic conditions, 1% colloidal oat altered the

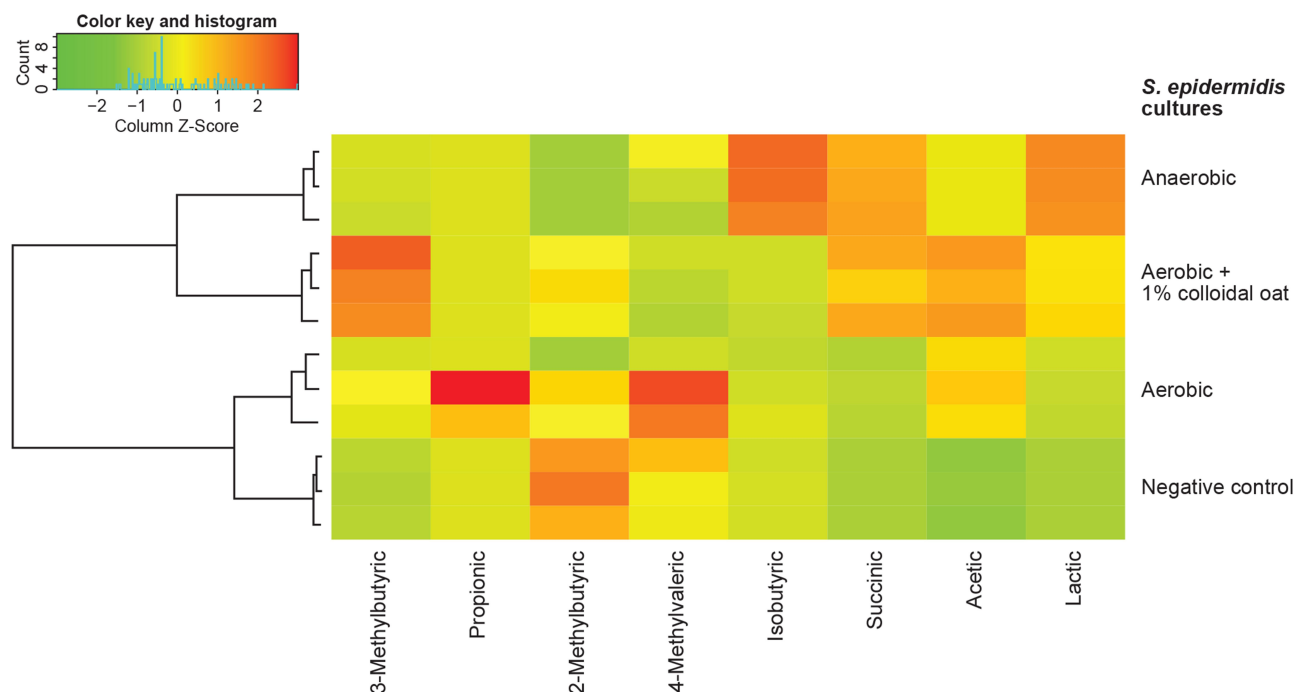


Figure 4 Unsupervised hierarchical clustering analysis of *S. epidermidis* metabolic activity under different culture conditions.

metabolite composition of both *S. aureus* and *S. epidermidis*, with significantly increased production of lactic acid by factors of 1.7 (from 913.4 ± 30.0 $\mu\text{g/mL}$ to 1581.5 ± 66.7 $\mu\text{g/mL}$, $p=0.0001$) and 3.1 (from 687.2 ± 134.4 $\mu\text{g/mL}$ to 2137.7 ± 92.2 $\mu\text{g/mL}$, $p=0.0082$), respectively (Figure 3A and B). The levels of lactic acid produced by *S. epidermidis* in the presence of 1% colloidal oat were particularly high and very similar to those produced by *Lactococcus lactis* (used as a positive control for lactic acid production) in the presence or absence of colloidal oat. The highest levels of lactic acid were produced by *S. epidermidis* under anaerobic conditions (Figure 3A). Unsupervised hierarchical clustering analysis further showed that the metabolic activity of *S. epidermidis* under aerobic conditions and in the presence of 1% colloidal oat is more similar to that under anaerobic conditions than that under aerobic conditions in the absence of 1% colloidal oat (Figure 4).

To support the results of the in vitro studies, clinical evaluations with a moisturizer containing 1% colloidal oat demonstrated the mean lactic acid content in vivo was significantly increased (by a factor of 1.9; $p<0.05$) in moderate-to-severe dry skin after 6 weeks of twice-daily application (Figure 5). This suggests that 1% colloidal oat might contribute to the production of SCFAs, including lactic acid, by various skin bacteria.

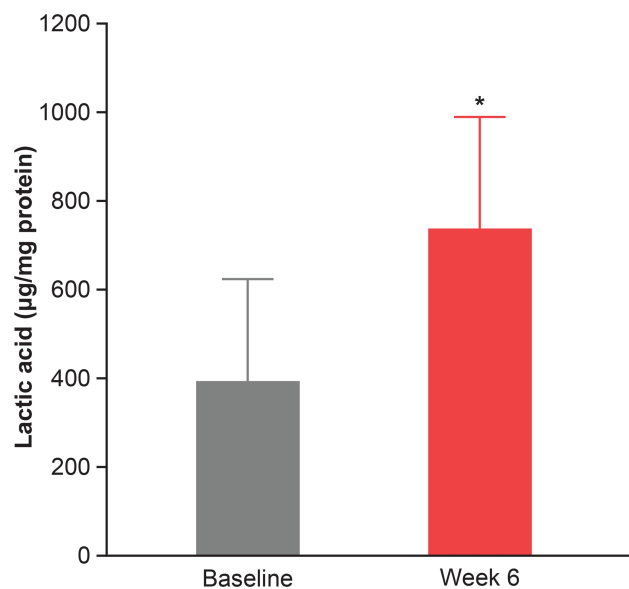


Figure 5 Treatment with a daily moisturizing lotion containing 1% colloidal oat significantly increased the lactic acid content in moderate to severe dry skin ($n=6$). Error bars denote standard deviation. * $p < 0.05$ vs baseline (paired t-test).

Effects of 1% Colloidal Oat on *S. epidermidis* Gene Expression

The gene expression profiles of *S. epidermidis* treated with and without 1% colloidal oat were evaluated using RNA-seq. *S. epidermidis* was grown in TSB media under aerobic conditions at 33°C. Overall, 418 genes were significantly upregulated ≥ 2 -fold, and 335 genes were significantly downregulated ≥ 2 -fold when treated with 1% colloidal oat (Supplementary Materials). Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed with genes significantly upregulated or downregulated to dissect the molecular pathways affected by treatment with 1% colloidal oat. Significantly enriched KEGG pathways and associated genes that were differentially expressed with versus without 1% colloidal oat are shown in Table 1.

The top enriched KEGG pathway of genes significantly downregulated was the glycolysis pathway; six of 10 key enzymes in the glycolysis pathway were significantly decreased when 1% colloidal oat was present in the medium, suggesting a shift in bacterial metabolism from simple sugars in the culture medium to the complex carbohydrates in oat. Genes significantly upregulated in the presence of 1% colloidal oat included genes important for cell proliferation, DNA synthesis, and adenosine triphosphate (ATP) metabolism, consistent with the observed increased growth of the *S. epidermidis* in the presence of oat. In addition, alpha-D-1,4-glucosidase and sucrose-6-phosphate hydrolase, enzymes involved in breaking down starch, were significantly upregulated. KEGG pathway analysis further revealed that bacterial infection pathway were enriched significantly, including the genes *dltA*, *B*, *C* and *D*, which are part of the same operon.

Discussion

Our findings demonstrate that 1% colloidal oat is used by skin bacteria and influences their growth rate, metabolism, production of lactic acid, and gene expression. Specifically, in an in vitro competition assay, 1% colloidal oat selectively increased the growth rate of *S. epidermidis*, a commensal skin resident associated with skin health, versus *S. aureus*.

Our in vitro data suggest that skin bacteria, including *S. epidermidis*, may be one of the major sources of lactic acid, and that metabolism of 1% colloidal oat increases lactic acid production by skin bacteria. The observed increase in lactic acid production with

Table 1 Enriched KEGG Pathways of *S. epidermidis* Differential Gene Expression in the Presence of 1% Oat

Description	Count (DEGs)	Count (Non-DEGs)	Raw p-value	FDR	DEG List
Decreased DEGs					
Glycolysis/Gluconeogenesis	9	27	0.00	0.00	SE0557 SE0558 SE0559 SE0560 SE0561 SE0658 SE1913 SE2042 SE2156
Galactose metabolism	2	10	0.02	0.08	SE1913 SE2042
Carbon metabolism	8	74	0.03	0.09	SE0346 SE0557 SE0558 SE0559 SE0560 SE0561 SE0658 SE2156
Increased DEGs					
Lipoic acid metabolism	2	1	0.01	0.09	SE0617 SE1217
Riboflavin metabolism	2	1	0.01	0.09	SE1438 SE1440
C5-Branched dibasic acid metabolism	4	4	0.01	0.09	SE0924 SE1659 SE1660 SE1661
Bacterial infection	5	6	0.01	0.09	SE0624 SE0625 SE0626 SE0627 SE2400

Abbreviations: DEGs, differentially expressed genes; FDR, false discovery rate; KEGG, Kyoto Encyclopedia of Genes and Genomes.

1% colloidal oat was greater with *S. epidermidis*, a commensal bacterium, than with *S. aureus*, an opportunistic pathogen. Clinical evaluation with a 1% colloidal oat-containing moisturizer supported these in vitro results, demonstrating an increase in the lactic acid content in the skin barrier. Additionally, our in vitro results showed that the bacterial strains tested do not produce major amounts of butyric acids, which is beneficial for the gut but can be harmful to the skin.^{38,39} Propionic acid was generated only by *C. acnes*, and 1% colloidal oat had no significant influence on its production.

Under anaerobic conditions, *S. epidermidis* grows faster than *S. aureus* (data not shown). Comparison of metabolite profiles including hierarchical clustering analysis revealed that *S. epidermidis* grown under aerobic conditions in the presence of 1% colloidal oat displayed a metabolic profile more similar to that under anaerobic conditions than to that under aerobic conditions in the absence of oat, suggesting a shift in metabolic pathways.

Analysis of differential gene expression revealed that the addition of 1% colloidal oat under aerobic conditions rendered large changes in the gene expression profile of the *S. epidermidis*. Gene expression profiling through mRNA sequencing identified 2665 genes expressed in *S. epidermidis*. Among those, 418 genes were significantly

upregulated and 335 genes significantly downregulated upon 1% colloidal oat treatment.

As expected, oat significantly changed the metabolism of the *S. epidermidis*. Of note, six of 10 key enzymes in the glycolysis pathway were decreased significantly. The TSB medium *S. epidermidis* was grown in a nutrient-rich medium with high concentrations of simple sugars such as glucose. Our findings suggest that in the presence of 1% colloidal oat in the medium, *S. epidermidis* relied less on glycolysis of simple sugars and more on metabolism of the complex carbohydrates in colloidal oat. Consistent with this interpretation, alpha-D-1,4-glucosidase and sucrose-phosphate hydrolase, enzymes involved in breaking down starch (a major ingredient of colloidal oat) were significantly increased in the presence of 1% colloidal oat. Consistent with the growth assay, genes related to bacterial growth, such as those involved in DNA synthesis, amino acid synthesis, and ATP metabolism, were upregulated when 1% colloidal oat was present in the growth medium.

KEGG pathway analysis revealed that *dltA*, *dltB*, *dltC* and *dltD*, which are from the same operon, were co-upregulated. This group of genes has been shown to be involved in the metabolism of D-alanine, a component of bacterial cell wall peptidoglycan. Interestingly, *dltA* has been shown to help bacteria to persist on human skin through evasion of cutaneous innate defense by cationic skin-derived antimicrobial

peptides.⁴⁰ Thus, *dlta* may help *S. epidermidis* to outcompete opportunistic skin pathogens, such as *S. aureus*.

In summary, taken together these findings suggest direct effects of 1% colloidal oat on the growth rate, metabolism, lactic acid production, and gene expression of commensal skin microbes. These effects may contribute to the therapeutic benefits and increased microbial diversity observed in various skin conditions, such as dry/itchy skin and atopic dermatitis, upon application of 1% colloidal oatmeal-containing skin moisturizers.

Data Sharing Statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

Some of the research described in this report involved a study in human participants. The trial was conducted in accordance with the Declaration of Helsinki. The study was approved by IntegReview Institutional Review Board (Austin, TX). Each participant provided informed consent.

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Disclosures

All authors are employees and own stock of Johnson & Johnson. The authors report no other potential conflicts of interest for this work.

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