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 ORIGINAL ARTICLE

Effects on the Skin Microbiome by a Moisturizer Formulated for Eczema-Prone and Sensitive Skin

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ABSTRACT

Background: Cutaneous dysbiosis contributes to the pathophysiology of atopic dermatitis and potentially that of sensitive skin; regulation of the bacterial communities through skincare products is an emerging management strategy. Previous studies have highlighted the utility of ingredients that function as prebiotics, are anti-inflammatory, and have barrier-repairing properties to help shift species richness and composition toward more eubiotic states.

Methods: In a single-site open-label study, a moisturizer containing colloidal oatmeal, *Ophiopogon japonicus* root extract (AD-Resyl®, SILAB, France), and a patented filaggrin protein byproduct was evaluated for its effect on the bacterial communities of eczema-prone and sensitive skin (n=12). Skin swab samples from participants' cheeks were collected before and after applying the moisturizer twice daily for 21 days. Measures of alpha diversity (richness, Shannon diversity index) and beta diversity were calculated using paired, comparative analyses of sampled bacterial loads.

Results: Bacterial species richness was significantly increased in 10 participants ($P<0.05$) without dysbiotic shifts in overall microbial composition.

Conclusion: These results support the use of a moisturizer containing anti-inflammatory and skin barrier-repairing ingredients for managing atopic dermatitis and add to our knowledge of the skin microbiome in sensitive skin.

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INTRODUCTION

Atopic dermatitis (AD) is a common, chronic inflammatory skin disease for which cutaneous dysbiosis is a core component of disease pathophysiology.[1,2] AD-associated dysbiotic changes in the skin microbiome composition include an increased abundance of *Staphylococcus aureus* (*S. aureus*), *S. epidermidis*, and *S. haemolyticus*, decreased bacterial species diversity, and reduced colonization of the fungal genus *Malassezia*.[3] Regulation of the skin microbiota is an emerging strategy for managing AD, and monitoring could be a biomarker for disease activity and treatment success.[4-6] Cosmetic skin care products may be tools for microbial manipulation through barrier restoration and foundational support for diverse cutaneous flora. Even simpler, anti-inflammatory ingredients could theoretically augment the microbiota through this mechanism alone and enhance AD treatment and management.

Colloidal oatmeal is an often used ingredient in skin care products for AD for its anti-inflammatory, anti-pruritic, and barrier repair properties and is listed in the US Food and Administration monograph as a skin barrier protectant and irritation-relieving ingredient for skin irritation due to eczema; notably, colloidal oat also acts as a prebiotic, encouraging the balanced growth of commensal bacteria.[7-10] Additionally, extracts from the plant *Ophiopogon japonicus* have demonstrated immunoregulatory activity in an AD mouse model[11] and clinically improved AD symptoms and patient's quality of life compared to placebo.[12] Finally, filaggrin, an essential protein for maintenance of the epidermal barrier, is reduced in atopic skin.[13] Reduced levels of filaggrin metabolic byproducts such as pyrrolidone carboxylic acid (PCA) correlate with disease severity,[14] thus topical replenishment of PCA may improve the defective skin barrier in AD. Despite these findings, the impact of these combined ingredients on improving dysbiosis has not been well elucidated to date.

Sensitive skin syndrome (SSS) is a condition of increased skin reactivity to innocuous exposures and is associated with an impaired skin barrier like AD. Although the skin microbiome of sensitive skin is not well understood, it is suspected that this impaired skin barrier contributes to the abnormal neurosensory responses of this condition.[15–17]

Therefore, the authors sought to investigate the activity of a moisturizer containing colloidal oatmeal, *O. japonicus* root extract (AD-Resyl®, SILAB, France), and a patented filaggrin technology (Restoraderm Technology™, sodium PCA, and arginine) on the skin microbiome of eczema-prone and sensitive skin.

MATERIALS AND METHODS

An open-label, in-use study (SPR.205147) was conducted at a single site to investigate a moisturizer (Restoraderm Cream Fla#1808) containing 2% colloidal oatmeal, Ad-Resyl, and the filaggrin technology for its effects on the skin microbiome composition of eczema-prone and sensitive skin. Study participants (n=12) were 18 to 60 years old with eczema-prone (self-perceived mild to moderate persistent dry, pruritic, and flaky skin) and sensitive skin (identified as a score >13 using a clinical questionnaire, Table 1). Subjects underwent the following washout period before starting the study: no new

TABLE 1.

Questionnaire for Selection of Subjects With Sensitive Skin to be Completed by a Dermatologist				
1. Do you regularly use cosmetic products dedicated to sensitive skin?				
The answer "yes" is not mandatory. *Yes * No				
2. Inclusion Questionnaire				
Severity: from 1 to 3: mild, from 4 to 7: moderate, and from 8 to 10: severe 0=0 none				
3. When you do NOT use your usual products", do you have discomfort sensations triggered by cosmetic products?		**Yes**	**No**	**If yes, severity rated on a scale from 1 (Not severe) to 10 (very severe)**
Cosmetic CARE products (1)	Do you have or did you have abnormal and repeated discomfort* sensations on your face/body skin linked to SKIN CARE PRODUCTS (cream, serum, essence, lotion…)?	--	--	I _ _ I
Toiletries products (2)	Do you have or did you have abnormal and repeated discomfort* sensations on your face/body skin linked to TOILETRIES (cleanser, soap, make up remover…)?	--	--	I _ _ I
4. Do you have discomfort sensations triggered by Environmental/External conditions?		**Yes**	**No**	**If yes, severity rated on a scale from 1 (Not severe) to 10 (very severe)**
Temperature change (3)		--	--	I _ _ I
Cold (4)		--	--	I _ _ I
Wind (5)		--	--	I _ _ I
Pollution (6)		--	--	I _ _ I
Limestone/Chlorine (7)		--	--	I _ _ I
5. Are these sensations regularly associated to?		**Yes**	**No**	**If yes, severity rated on a scale from 1 (Not severe) to 10 (very severe)**
Redness (8)		--	--	I _ _ I
Dryness (9)		--	--	I _ _ I
Redness (8)		--	--	I _ _ I
4. Do you have discomfort sensations triggered by Environmental/External conditions?		**Yes**	**No**	**If yes, severity rated on a scale from 1 (Not severe) to 10 (very severe)**
Temperature change (3)		--	--	I _ _ I
Cold (4)		--	--	I _ _ I
Others (precise) (10): _____ _____		--	--	I _ _ I
5. To be included as a subject with a sensitive skin a positive answer should be given for:				
CARE products with a minimum score of 2 or TOILETRIES products with a Minimum score of 4		*Yes	* No	--
AND AT LEAST 2 OF THE LISTED ENVIRONMENTAL CONDITIONS with a minimum score of 3		*Yes	* No	--
CONCLUSION: INCLUSION OF THE SUBJECT (11)		*Yes	* No	--

*Discomfort sensations: prickling, tightness, itching, stinging, burning sensation, heat sensation, pain of skin.
( ): numbers referring to template data entra- specific excel file

skincare product application 3 days before D0 and no application of any skincare products on day 0 (D0). Skin swab samples were collected from the cheeks of study participants before (D0) and after (D21) the 3-week intervention in which all participants applied the cream to their face and body twice daily. In total, 24 skin swab samples were collected, and samples were analyzed by V3V4 16S rDNA PCR sequencing for bacterial microbiome assessments. Using amplicon sequence variants (ASVs) data, bacterial taxonomic profiles to, at minimum, the genus level were created for each sample. To assess changes in the skin microbiome before and after the intervention, measures of the alpha diversity – richness (number of different taxa) and Shannon diversity index (abundance evenness of different taxa) – and beta diversity (overall microbiome composition) were calculated.

Statistical Analysis

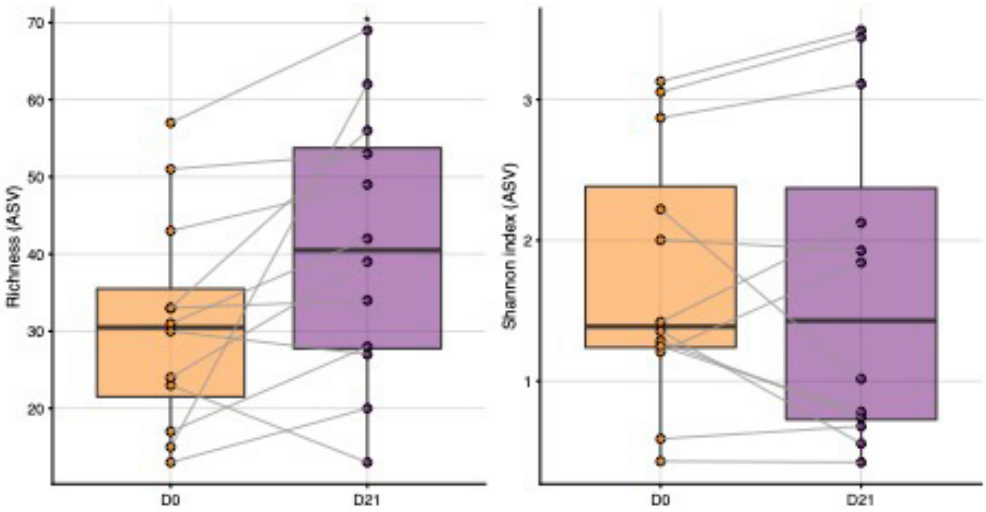
For the in-use skin microbiome analysis, the Benjamini-Hochberg (BH) method was used to control the false discovery rate (FDR) at 10%. Statistical analyses for the visit and subject variable effects were performed using permutational multivariate analysis of variance (PERMANOVA) tests; for changes in taxa abundance and prevalence, Mann-Whitney U tests (Wilcoxon signed rank tests) and exact McNemar's tests were performed, respectively.

RESULTS

Bacterial Analysis

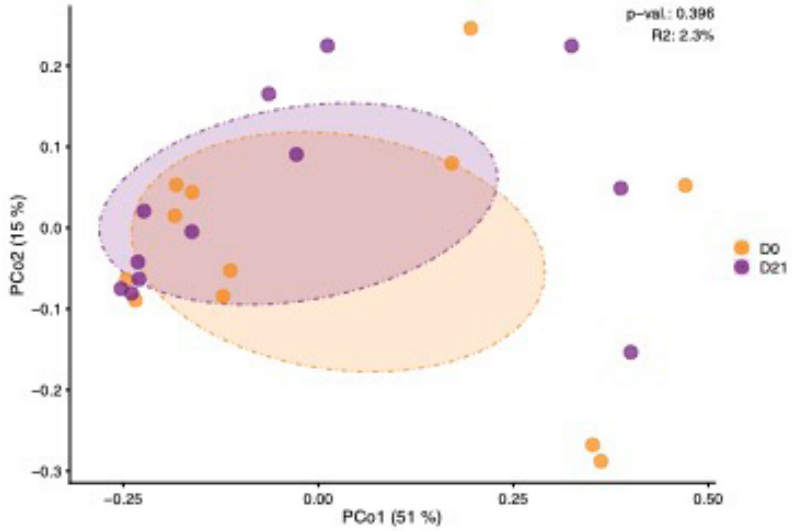
16S sequencing data was obtained for all 24 samples (average 104750 high-quality read pairs per sample, median 65342, minimum 8963), and ASVs of expected, commensal bacteria species were observed (eg, *S. epidermidis* and *Cutibacterium acnes*). A comparison of the phylum, genus, and species taxonomic profiles showed that intra-subject profiles were similar from D0 to D21, and inter-subject profile variation was greater than that of intra-subject profiles. Paired comparisons of alpha diversity measurements showed a significant increase in richness from D0 to D21 in 10 of 12 subjects (*P*-value < 0.05) but no significant effect on the Shannon diversity index (Figure 1). Dissimilarity measurements (Bray Curtis, weighted UniFrac, and unweighted UniFrac) calculated to assess the overall microbiome composition (beta diversity) showed that the participant variable (*P*-value=0.002) but not the visit variable (*P*-value=0.396) had a significant effect. Thus, participants maintained overall similar microbiome compositions before and after the intervention (Figure 2). Moreover, paired abundance/prevalence tests showed no taxon was significantly different between D0 and D21 samples. Sub-analysis of *Staphylococci* species found no significant changes in the abundance of four species (*S. epidermidis*, *S. capitis*, *S. hominis*, and *S. aureus*), consistent with other results. Of note, *S. aureus* was only detected in low abundances in two D0 samples. Overall, the intervention significantly increased bacterial species richness but did not impact the species evenness and overall microbiome composition.

FIGURE 1. Alpha diversity measures calculated from ASV relative abundances (paired data, same participant connected by gray line). Richness values increased significantly. No significant changes were detected for the Shannon index.



Asterisks refer to *P*-values of paired Mann-Whitney U tests (*: *P*-value < 0.05).

FIGURE 2. A PCoA plot is shown based on weighted UniFrac dissimilarities calculated from ASV relative abundances (N=24; grouped by visits D0 vs D21).



The ellipses cover one standard deviation of the mean of the group centroids. The x- and y-axis labels indicate the variance explained by the first two principal coordinates. The visit variable had no significant effect on the overall microbiome composition of the samples (*P*-value of PERMANOVA test after adjustment for subject variable = 0.396; effect of participant variable was highly significant with a *P*-value of 0.002 and a R2 of 70.3%).

DISCUSSION

The clear link between AD and dysbiosis requires understanding how topical products and their ingredients impact the skin microbiome. Herein, a moisturizing cream including ingredients beneficial for AD was investigated for its effect on the skin microbiota to provide further insight into the mechanism of clinical impact.[7,9,12-14,18]

Compared to that of AD, the skin microbiome of adults without skin disease has overall stable and established microbial communities over time, regardless of changes in the external environment.[19-21] The composition of bacterial communities is largely determined by the unique microenvironments created by the cutaneous physiologic features of skin sites.[19,21] Sebaceous, moist, and dry are the 3 main cutaneous biogeographic habitats, and each varies in their respective microbial diversity and biomass.[22] In comparison to bacterial communities, the composition of fungal communities is largely determined by body location as a function of environmental exposure (ie, high fungal diversity on feet and toenails) rather than biogeographic habitats, and across most sites fungi of the genus *Malassezia* predominate.[19,23] Furthermore, for both bacterial and fungal community composition, intrapersonal variation is smaller than interpersonal variation.[21,23]

The bacterial species identified and the variation of the taxonomic profiles were consistent with the expected skin microbiome patterns discussed above. Firstly, *S. epidermidis* and *C. acnes* were collected from the cheeks of participants, which are 2 species commensal to this sebaceous skin site.[19,22]

Also, as expected, intra-participant taxonomic profiles were more similar than inter-participant profiles. Together, these results increase confidence in the study's ability to detect true significant differences before and after the intervention. Our results showed increased bacterial species richness following application of the moisturizer, a potentially beneficial effect since AD skin is associated with decreased bacterial diversity.[24,25]

Throughout this study, *S. aureus* was infrequently detected, and its presence was not significantly affected post-intervention. The presence of *S. aureus* detected on D0 for 2 participants suggests they were currently experiencing an AD flare since exacerbation of disease is correlated with increased abundance of *S. aureus*.[24] Overall, a study limitation was the absence of clinical scoring of AD severity and activity in participants; future studies investigating this moisturizer could be improved by documenting current AD activity as the relative abundance of *S. aureus* is increased during a flare and associated with worse disease.[2,24]

Multiple factors underlie the complex pathogenesis of AD, namely skin barrier defects, aberrant immune system regulation, environmental exposures, and dysbiosis.[26] Certain ingredients in skin care products may impact the skin microbiome and simultaneously the aforementioned factors as they are closely interrelated. The studied moisturizer was formulated with several ingredients that could have led to the observed effects on the skin microbiome, specifically the significantly increased bacterial species richness and decreased *S. aureus* colonization.

A proprietary form of PCA was a key ingredient in the moisturizer studied. PCA is a filaggrin byproduct and major component of natural moisturizing factor (NMF), an essential humectant found in the stratum corneum. Loss-of-function mutations in the gene encoding filaggrin (FLG) are a well-established predisposing factor of intrinsic skin barrier dysfunction in some, but not all, patients with AD.[27] Those without FLG mutations are also found to have defective epidermal barrier function, reduced filaggrin levels, and altered ceramide levels in the stratum corneum.[13,27] Filaggrin deficiency in AD skin regardless of FLG genotype may be due to the downregulation of filaggrin expression by T2 cytokines or decreased activity or protein expression of proteases that sequentially process profilaggrin to NMF.[27] Notably, evidence supports the defective stratum corneum caused by filaggrin deficiency alters the skin microbiome and may lead to AD-associated dysbiosis.[28] It is thus plausible topical delivery of PCA contributed to the improved bacterial diversity seen in this study by reinstating a normal stratum corneum barrier and improving its physiologic function. By improving moisture retention, keratinocyte maturation, and maintenance of an acidic pH, epidermal homeostasis is restored and hospitable to eubiosis.[27] Finally, regarding the decreased detection of *S. aureus* at conclusion of the study, although non-significant this may have been due to the addition of the proprietary PCA technology. PCA and urocanic acid (UCA), another filaggrin byproduct and major component of NMF, are antimicrobial and, importantly, low levels of NMF in the skin strengthen *S. aureus* binding to corneocytes.[27]

The natural active ingredient, *O. japonicus* root extract, was also included in the studied moisturizer formulation. This extract is rich in immunomodulating polysaccharides, which decreased T2 inflammatory cytokines in an AD-mouse model.[18,29] In AD, increased T2 cytokines inhibit the expression and function of a key antimicrobial peptide against *S. aureus* thus, this anti-inflammatory effect of *O. japonicus* may impact the skin microbiome.[30] Additionally, cosmetic products rich in polysaccharides like those found in *O. japonicus* increase alpha- and beta-diversity of bacterial communities on the skin, possibly due to prebiotic properties.[31] Taken together, the significantly increased bacterial diversity and reduction in *S. aureus* colonization following application of the moisturizer possibly resulted from the anti-inflammatory and prebiotic properties of O. japonicus root extract.

Colloidal oatmeal has many properties beneficial to AD skin, including richness in barrier-repairing lipids and fatty acids, plus anti-inflammatory, anti-pruritic, and anti-oxidant activities.[8] Most notable for this study, colloidal oatmeal is a known prebiotic that is metabolized by commensal bacteria and subsequently promotes their growth. Previous studies found increased microbial diversity and promotion of *S. epidermidis* growth compared to *S. aureus*; these effects are thought to result from colloidal oat's prebiotic properties encouraging commensal bacteria growth and restoration of the epidermal barrier through increased hydration and maintenance of an acidic pH deterring pathogenic colonization.[7,9] Our study found a similar increase in bacterial diversity, and this could result from the colloidal oat properties discussed above; however, a significant differential impact on *Staphylococcal* species growth was not observed, perhaps due to the rare presence of pathogenic *S. aureus* throughout the study.

Notably, this moisturizer was studied in eczema-prone individuals with concomitant sensitive skin. Sensitive skin syndrome (SSS) is a condition of increased skin reactivity to innocuous exposures – such as temperature changes, stress, or cosmetic products – and is characterized by abnormal stinging, pruritus, burning, pain, dryness, and often erythema; notably, SSS is not attributable to another skin condition.[17] A direct link between sensitive skin and the skin microbiome has yet to be elucidated.[16] Despite this, it is theorized the skin microbiome impacts the aberrant activity of the cutaneous nervous system underpinning the pathophysiology of SSS. Commensal or pathogenic bacteria interact with the epidermis and dermis and can directly stimulate cutaneous nociceptors, transducing sensations of pain, itch, and temperature.[32,33] Antimicrobial peptides produced upon pathogenic bacteria detection may also stimulate mast cell degranulation and promote the release of interleukin 31, the pruritus-mediating cytokine.[34] Moreover, substance *P* and calcitonin gene-related peptide, two key neuroinflammatory peptides expressed in the skin and involved in SSS, also impact the skin microbiome.[35,36] Finally, SSS is linked to an impaired skin barrier, including lower PCA levels and bleomycin hydrolase activity, two components of filaggrin metabolism also dysregulated in AD.[15] Considering these relationships, the skin microbiome of SSS may be distinct from non-sensitive skin, yet few studies have investigated this with conflicting results.[37,38] This study adds to our knowledge of the skin microbiome in SSS and how a moisturizer containing anti-inflammatory and skin barrier-repairing ingredients may impact it.

This study was limited by its uncontrolled design and small number of participants. It is also unknown if participants were experiencing active eczema flares before or during the study, which may have impacted the skin microbiome composition. Finally, this study sampled microorganisms from a single body site; thus, alterations in the microbiome at other sites were undetermined. Future investigations would be improved by analyzing changes in fungal species and sampling multiple body sites of lesional and non-lesional skin across time, as this would provide greater insight into lesion-associated, temporal, and regional changes in the skin microbiome and mycobiome.

CONCLUSION

In conclusion, an in-use, open-label study found a moisturizing cream formulated with AD-beneficial ingredients positively affects the skin microbiome of eczema-prone and sensitive skin by increasing bacterial species richness and not causing dysbiotic shifts in the overall microbial composition. These results support its use as part of a topical product regimen for managing AD with concomitant sensitive skin.

DISCLOSURES

CW's work is funded through an independent fellowship grant from Galderma; SAA's work is funded through independent fellowship grants from Eli Lilly and Pfizer. NJT and NL are employees of Galderma. AF is an advisor for and has received independent research grants from Galderma. This article discusses proprietary technology owned by Galderma. Patent: U.S Pat. No 8,7957,05 to Voegel J. et al.

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