

From Probiotic to Prebiotic Using Thermal Spring Water

Joshua Zeichner MD^a and Sophie Seite PhD^b

^aMount Sinai Hospital, New York, NY

^bLa Roche-Posay Dermatological Laboratories, Levallois-Perret, France

ABSTRACT

Background: La Roche-Posay Thermal Spring Water (LRP-TSW) exhibits both probiotic and prebiotic properties enhancing the diversity of the skin microbiota.

Methods: A review was undertaken to explore the role of LRP-TSW as a topical probiotic and prebiotic therapy in improving the diversity of the skin microbiota and reducing dryness and pruritus in inflammatory skin diseases.

Results: The concentration of minerals and non-pathogenic microbes in LRP-TSW may explain its therapeutic benefit when used for inflammatory skin diseases. Clinical studies have shown that topical LRP-TSW treatment results in increases in Gram-negative bacteria with reduction of Gram-positive bacteria, and improvements in skin microbial diversity. At the same time skin condition in atopic dermatitis, psoriasis, and general dryness in otherwise healthy skin, has been shown to improve.

Conclusions: Enhancement of skin microbiota diversity using topical LRP-TSW may offer a valuable option for the treatment and maintenance of inflammatory skin diseases.

J Drugs Dermatol. 2018;17(6):657-662.

INTRODUCTION

Thermal water has been used for its medicinal benefits since Roman times. It has been reported to benefit a variety of diseases across dermatology, pulmonology, hematology and gastroenterology.¹⁻³ La Roche-Posay Thermal Spring water (LRP-TSW) from France has been useful in treating skin diseases including atopic dermatitis and psoriasis.^{1,2} The LRP-TSW Thermal Center serves as a hospital staffed by 8 Dermatologists treating over 8,000 patients per year, 25% of whom are children. Patients at the Center are treated with therapeutic baths, known as balneotherapy (BPT). The regimen consists of an 18-day treatment with a daily high-pressure filiform shower (15 bars for 3 minutes) using crude thermal spring water.

This review discusses the role of TSW as a probiotic and prebiotic therapy in enhancing the diversity of the skin microbiota in inflammatory skin diseases as well as the clinical improvements in signs of these diseases using LRP-TSW balneotherapy.

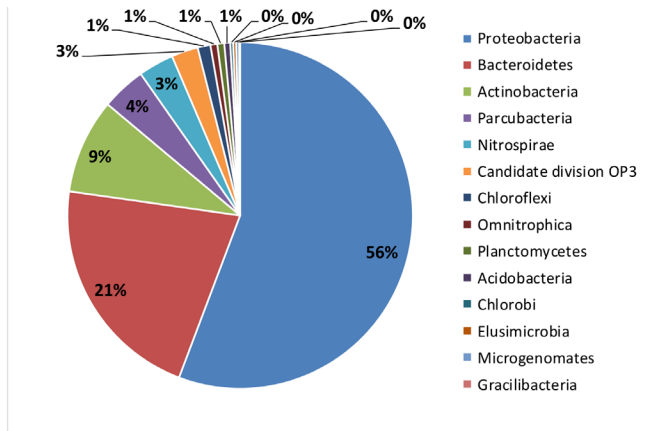
Mineral and Microbial Composition of Thermal Spring Water and Its Chemical and Physical Properties

LRP-TSW is comprised of specific minerals and non-pathogenic microbes.^{1,2} The low mineral and silicate concentration gives LRP-TSW its name in French, "L'eau de velours" or velvet water. LRP-TSW is oligotrophic meaning that it contains a low concentration of nutrients (<1 g/L). However, the presence of elements like selenium (Se) and strontium (Sr) play an important role in its biological activities.² Selenium salts are necessary for cellular functions including enzyme activity like glutathione peroxidase, thioredoxin (a class of small redox proteins) reductase, and deiodinases. Those elements also influence bacterial growth and can

impact the body's global microbiota.³ Since decades the reactions catalyzed by formate dehydrogenase of bacteria, or glycine reductase of clostridia, have been described.³ The common denominator of these selenium-dependent processes is that they are all oxidation-reduction reactions.³ The antioxidant properties of LRP-TSW may help improve skin condition by reducing skin dryness and pruritus of patients affected by chronic dermatoses such as atopic dermatitis and psoriasis.² The effect of selenium on lipid peroxidation has been studied in cultured human skin fibroblasts.² A reduction of thiobarbituric acid reactive substances (TBARS), an index of lipid peroxidation and oxidative stress, was noticed if the cells were cultured in a medium supplemented with Se or with LRP-TSW compared to the control medium with demineralized water.² Together, selenium-dependent glutathione peroxidase (Se-GSH.Px) activity and cell viability were significantly increased.²

LRP-TSW is rich in non-pathogenic micro-organisms that play a major role treating various skin diseases. The microbial composition of LRP-TSW has been characterized with a metagenomics approach using an Illumina next-generation sequencing (NGS) of the V1-V3 hypervariable regions of the 16S rRNA genes. A global bacterial picture of LRP-TSW was determined² and is shown in Figure 1. The main bacterial characteristics of crude LRP-TSW are:

- A high bacterial diversity (Da Silva Database)
- A very low bacterial concentration
- A majority of Gram-negative bacteria

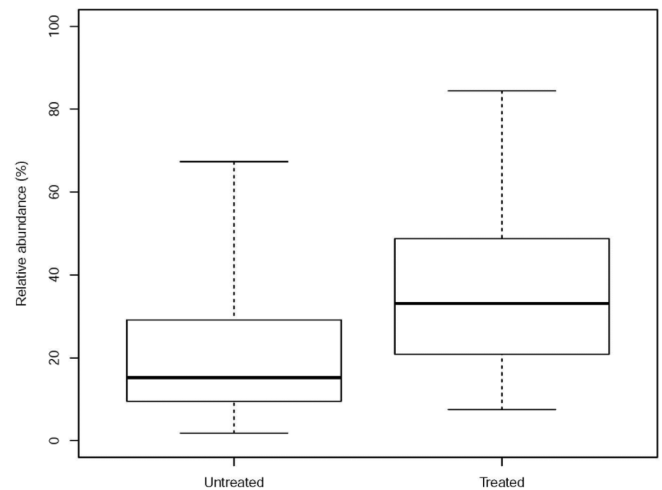
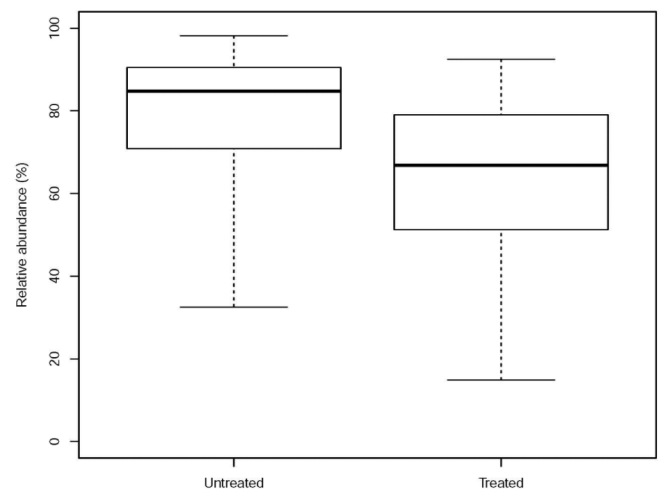
FIGURE 1. The bacterial landscape of LRP-TSW crude water at phyla level.

As LRP-TSW contains live bacteria that impact the skin's microbiota, the water itself is considered to be a probiotic.²

In discussing the safety of drinking water, the World Health Organization (WHO-2006) recommends that "Water entering the distribution system must be microbiologically safe," meaning that it should not be contaminated by pathogenic microorganisms. However, the WHO does not contend that drinking water is microorganism free, and in fact, bacteria are present in relatively high numbers (10^2 to 10^4 cells/ml) in drinking water.⁴⁻⁶

Probiotic versus Prebiotic Water

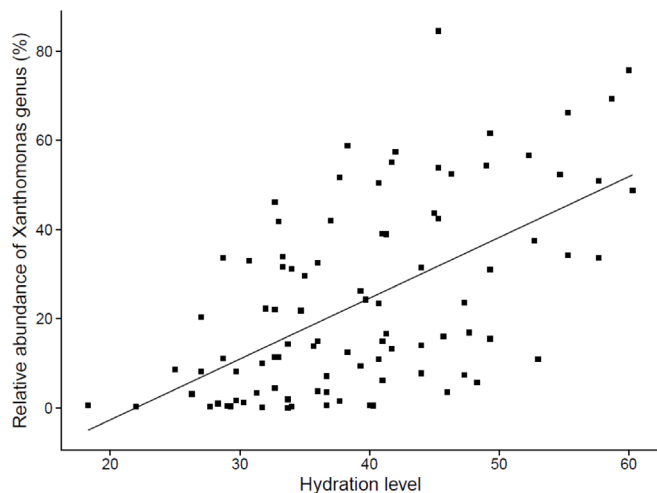
While a probiotic is a product containing live microorganisms, a product containing an ingredient or nutrient that selectively stimulates or inhibits the growth or activity of commensal skin bacteria, is considered a prebiotic.⁷ Filtered LRP-TSW, that does not contain living bacteria can be considered a prebiotic. The product has a low mineral content (<1 g/L) and specific trace elements like Se and Sr, which are necessary for cellular functions including enzyme activity. Intrinsically its major biological properties are free radical "scavengers", anti-inflammatory and toxic heavy metals protection. Prebiotic TSW has been shown to be beneficial in subjects with dry but otherwise healthy skin.⁷ The effect of LRP-TSW using a commercial spray (2 sprays per application) twice a day for 14 days on inner forearms, was evaluated in 70 healthy subjects with dry skin (corneometry measurement ≤ 50 au).⁷ Thirty minutes after the last application of LRP-TSW microbiome sampling of the treated and nearby untreated skin was performed to determine bacterial community composition. Treatment resulted in a significant increase in Gram-negative bacteria and a decrease of Gram-positive bacteria on the skin surface of treated skin areas versus nearby untreated areas was noted (Figure 2). Interestingly, topical application of a moisturizer containing LRP-TSW in a similar protocol demonstrated a significantly increased level of *Xanthomonas* genus correlated with increased skin hydration levels (Figure 3).

FIGURE 2. Relative abundance of Gram-negative (A) and Gram-positive (B) bacteria at the skin surface of healthy subjects untreated (Untreated) and treated with LRP-TSW twice a day for 14 days (Treated). For Gram-negative bacteria, Wilcoxon rank sum test with continuity correction ($W = 3742$, $P\text{-value} = 7.349 \times 10^{-8}$) and for Gram-positive bacteria Wilcoxon rank sum test with continuity correction ($W = 1158$, $P\text{-value} = 7.349 \times 10^{-8}$).**(A)****(B)**

Effect of Balneotherapy on the Skin Microbiome in Some Inflammatory Skin Diseases

The microbiota is the collection of microorganisms that live on and in our bodies. The complex diversity and composition of microbial communities on the skin vary by skin region⁵ and between individuals.^{5,6} The skin microbiota is composed of around 80% Gram-positive and 20% Gram-negative bacteria. Firmicutes and Actinobacteria for Gram-positive bacteria, while Proteobacteria and Bacteroidetes are the main phyla of skin Gram-negative bacteria. The bacterial diversity is mainly driven by Gram-negative bacteria, and abundance by Gram-positive

FIGURE 3. Correlation between *Xanthomonas* genus relative abundance level at the skin surface and skin hydration level measured by corneometry in healthy subjects after treatment with a moisturizer containing 100% of LRP-TSW. Significant positive correlation (P -value < 0.05) with a correlation coefficient of 0.58 was measured.



bacteria. Several diseases such as atopic dermatitis and psoriasis have been found to be associated with changes in the composition of the skin microbiota.⁸⁻¹¹ Balneotherapy using probiotic LRP-TSW water has been shown to improve the skin microbiota in a variety of inflammatory skin conditions.

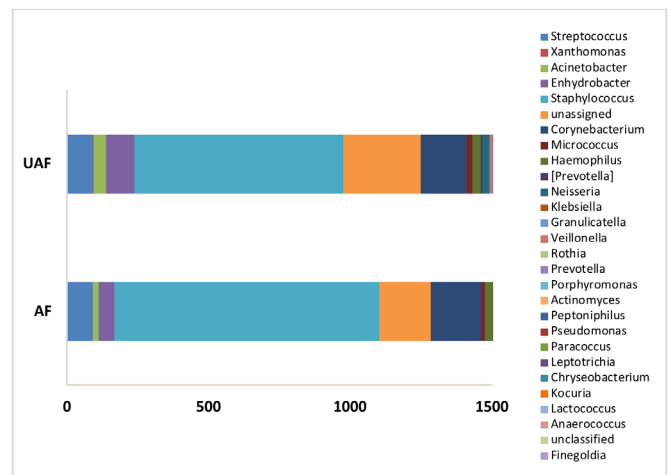
Effect of LRP-TSW on Atopic Dermatitis

The effect of LRP-TSW balneotherapy on the microbiome has been evaluated in patients with atopic dermatitis. Microbial samples were taken from 31 patients with atopic dermatitis on both affected and adjacent unaffected skin. Repeat samples were taken after 21 days of balneotherapy to analyze microbiota diversity (Shannon index), bacterial phyla, and genus abundance. At baseline, Shannon diversity was lower in the lesional AD skin as compared to adjacent clinically normal skin. After balneotherapy, Shannon diversity index increased in the lesional areas and became similar to what was observed in the clinically normal appearing skin. In addition, balneotherapy resulted in a reduction of Firmicutes organisms mainly *Staphylococci*, along with an increase in other bacterial phyla. Additionally, an increase in the amount of *Xanthomonas* genus was also observed (Figure 4). The increase in bacterial diversity after balneotherapy was correlated with a significant increase in Gram-negative bacteria and a significant decrease of Gram-positive bacteria on the skin (Figure 5).

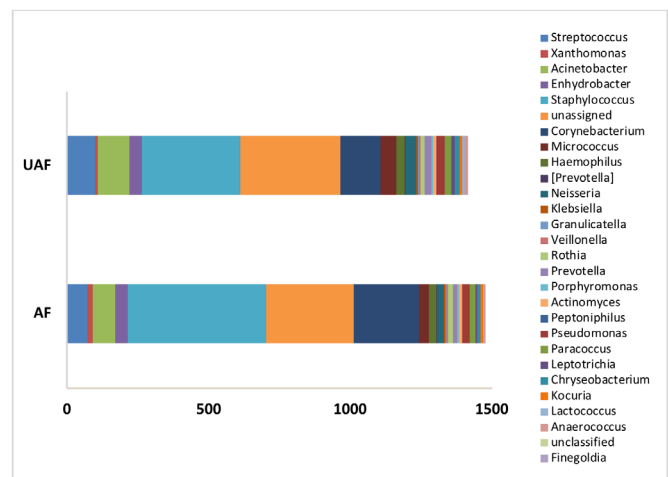
In a 2014 study, 100 patients suffering from chronic AD were treated with LRP-TSW balneotherapy at the LRP Treatment Center.¹² After treatment, SCORing Atopic Dermatitis (SCORAD) scores significantly ($P < 0.0001$) improved in 90% of subjects, with a mean decrease of 38% from 46.8 (SD±1.9) to 27.8 (SD±1.5). Mean

FIGURE 4. Average taxonomic composition (30 main genera) of the skin surface microbiome associated with AD prior (A) and post (B) balneotherapy on unaffected (UAF) and affected (AF) skin areas.

(A)



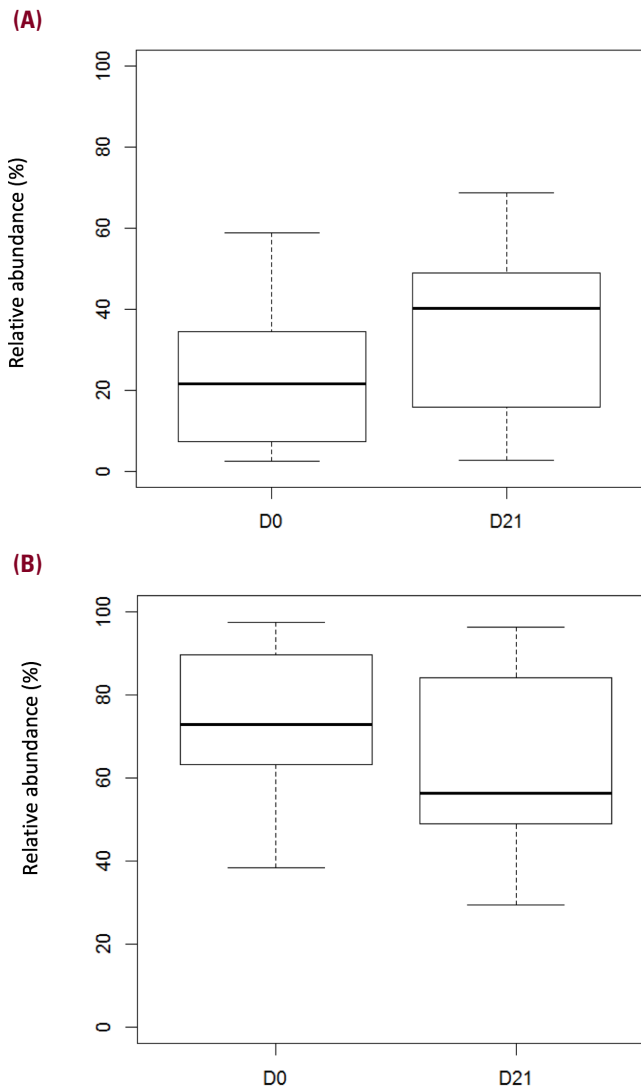
(B)



EASI (Eczema Area and Severity Index) scores also significantly ($P < 0.0001$) improved in 82% of patients from 9.3 (SD±0.8) to 4.6 (SD±0.6). Clinical efficacy correlated with significant improvements in quality of life measures, as Dermatology Life Quality Index (DLQI) and Children's DLQI (CDLQI) (both $P < 0.0001$). There was a mean reduction in DLQI scores of 8.1 (SD±1.0) to 4.1 (SD±0.7) and a 28% reduction in CDLQI scores of 7.5 (SD±0.7) to 4.5 (SD±0.5). Balneotherapy was reported to provide long-lasting results, with clinical and quality of life improvements maintained for an average of 6 months.¹²

LRP-TSW based skincare products have also been shown to improve the diversity of the skin microbiome in eczema patients, after three months of applying an emollient containing at least a 50% concentration of LRP-TSW¹² and a supplement with a

FIGURE 5. Relative abundance of Gram-negative (A) and Gram-positive (B) bacteria at the surface of affected and unaffected skin of patients affected by AD prior (D0) and post (D21) balneotherapy. For Gram-negative bacteria, a significant Wilcoxon rank sum test with continuity correction ($W=163.5$, $p\text{-value}=0.06711$) was measured as well as for Gram-positive bacteria ($W=320$, $P\text{-value}=0.06887$).



biomass of non-pathogenic Gram-negative bacteria such as *Vitreoscilla filiformis* (LRP-VFB).¹³ Improvements were observed in the microbiome of the skin of AD patients with an increase in microbial diversity.

Psoriasis Vulgaris

The skin microbiome has been evaluated in patients with moderate to severe psoriasis vulgaris at the LRP thermal care center. Similar to studies performed in AD, bacterial swabs were taken from affected and nearby unaffected skin before and after three weeks of TSW balneotherapy.¹⁴ While balneotherapy resulted in significant improvements in clinical signs, as measured by Psoriasis Area and

Severity Index (PASI) scores, no significant change in the Shannon diversity index was observed. The average taxonomic composition of skin bacterial communities associated with the unaffected and affected skin of psoriatic patients post-balneotherapy showed a significant increase in the level of *Xanthomonas* genus and, to a lesser extent, *Corynebacterium* genus.¹⁴ The *Xanthomonas* genus belongs to the main Xanthomonadaceae family found in LRP-TSW and also, at a low concentration, on the naturally healthy skin.¹⁴ This is associated with a decrease in *Staphylococcus* genus. Additionally, in this patient group after balneotherapy, there was a significant increase of skin surface Gram-negative bacteria and a significant decrease of Gram-positive bacteria observed (Figure 6). Two studies have been performed specifically to evaluate the therapeutic benefits of balneotherapy in treating psoriasis. In 1995, 92 patients with moderate plaque psoriasis were treated with balneotherapy. After treatment, there was a mean reduction in PASI scores of 47% (from 5.5 ± 0.5 to 2.9 ± 0.3 , $P < 0.001$), 8% of patients were completely clear and 48% improved by more than 50%. While the clinical significance is unknown, an increase in the mean Se plasma level (from 77.1 ± 2.1 to 90.4 ± 2.7 $\mu\text{g/L}$, $P < 0.01$) was noted after treatment and correlated with the reduction of PASI ($r_s=0.31$, $P < 0.01$).³

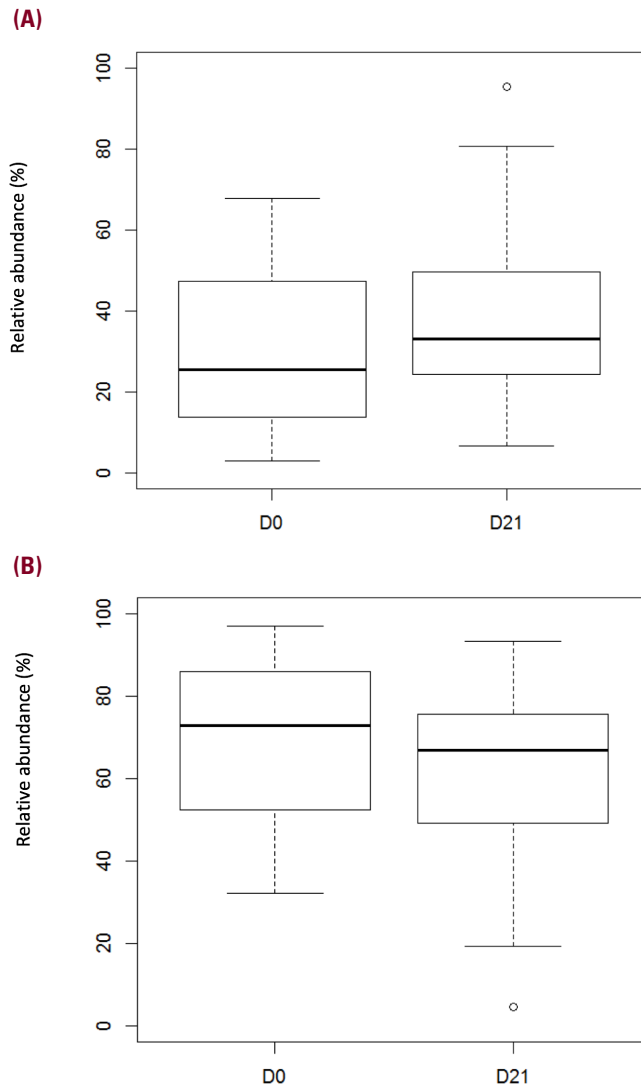
In 2012, 199 patients with severe plaque psoriasis (74.4%) or guttate psoriasis (12.1%) were treated with balneotherapy. After treatment, mean PASI scores were reduced by 57% (from 17.6 ± 0.9 to 7.8 ± 0.5 , $P \leq 0.0001$), 96% of patients showed some degree of improvement in PASI scores, 26% achieved a PASI 75, and 64% of patients achieved a PASI 50 response, 78% of patients experienced improvement in DLQI (from 5.9 ± 0.2 to 3.4 ± 0.15 , $P \leq 0.0001$). Among these patients, 75% had previously received balneotherapy with an average of 8 ± 9 treatments (max=57 - min=1). Patients reported that balneotherapy continued to improve their quality of life for 7 ± 3 months and gave a sustained remission of psoriasis for an average of 6 ± 3 months following treatment.

DISCUSSION

Healthy human skin normally consists of a mix of Gram-positive and Gram-negative bacteria of at least 19 phyla. *Actinobacteria*, *Firmicutes*, *Proteobacteria*, and *Bacteroides* are the predominant bacterial phyla in the human skin, regardless of body site.^{9,10} Within these phyla, the 3 most abundant genera are: *Propionibacterium*, *Corynebacterium*, and *Staphylococcus*.^{9,10}

A variety of inflammatory skin diseases are associated with abnormalities in the microbiota with a loss of diversity.⁷ There is an overrepresentation of Firmicute organisms, like *Staphylococci* sp. and an underrepresentation of Actinobacteria, Proteobacteria, and Cyanobacteria.¹² Treatment of AD with LRP-TSW has been associated with improvements in diversity of the microbiota in patients with AD as well as clinically meaningful improvements in signs of the disease itself.¹²⁻¹⁴

FIGURE 6. Relative abundance of Gram-negative (A) and Gram-positive (B) bacteria at the surface of affected and unaffected skin of patients affected by psoriasis prior (D0) and post (D21) balneotherapy. A significant Wilcoxon rank sum test with continuity correction was measured for Gram-negative bacteria, ($W=1341.5$, $P\text{-value}=0.01622$) and for Gram-positive bacteria ($W=2243.5$, $P\text{-value}=0.02006$).



LRP-TSW may be considered a probiotic, as it naturally contains a low concentration of bacteria, with a high microbial diversity and more Gram-negative than Gram-positive bacteria. Clinical studies indicate that balneotherapy with probiotic LRP-TSW stimulates the growth of Gram-negative bacteria, particularly on Xanthomonadaceae, at the expense of Gram-positive bacteria at the skin surface improving microbial diversity associated with decreased severity of inflammatory skin conditions.¹²⁻¹⁴ Without the use of an antibiotic, LRP-TSW can modify the microbiota on human skin. Decreases in *Staphylococci* sp. have been observed along with increases in Gram-negative Xanthomonadaceae levels, even after topical application of LRP-TSW.¹²⁻¹⁴ Moreover, these improvements

in microbiota have been correlated to clinical improvement of the skin in conditions like AD. Although the therapeutic mechanisms of balneotherapy are not completely understood, in addition to a probiotic effect LRP-TSW may have anti-inflammatory effects as well. Finally, it exhibits a prebiotic effect on Gram-negative bacteria and on the Xanthomonadaceae family, as patients treated with prebiotic demonstrate improvements in dryness and skin barrier function.⁷

LIMITATIONS

Skin microbiome studies are challenging and costly. Currently results are a discussion of in-vivo data that demonstrated microbiome alterations correlated with skin condition improvement when using balneotherapy at the source with probiotic LRP-TSW, topical filtered LRP-TSW, and skincare containing more than 50% LRP-TSW. More comparative studies using TSW with different mineral compositions are needed to better understand the mechanism(s) of action.

CONCLUSION

LRP-TSW exhibits both prebiotic for its mineral composition and probiotic properties for its bacterial diversity. LRP balneotherapy has been shown to effectively treat inflammatory skin conditions including AD and psoriasis. An abnormal microbiota is associated with skin disease and improvements in microbial diversity correlated with clinical improvements in the severity of the skin disease itself. LRP-TSW has been shown in clinical studies to improve skin microbiome diversity as well as the decreased severity of active lesions in skin diseases like AD, psoriasis, and general dryness in otherwise healthy skin. The concentration of minerals and non-pathogenic microbes likely explain its therapeutic benefit and make it an attractive option for treating inflammatory skin diseases.

DISCLOSURES

Joshua Zeichner has served as an advisory board member and consultant to La Roche Posay. Sophie Seité is an employee of La Roche-Posay, France.

ACKNOWLEDGMENTS

The author would like to thank Dr. Andriessen of RBC Consultants for writing assistance. Her support was funded by La Roche-Posay Dermatological Laboratories, France.

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AUTHOR CORRESPONDENCE**Joshua Zeichner MD**

E-mail:..... joshzeichner@gmail.com