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Yogurt: Using Positive Associations in the Consumer's Mind

B. Walzel, A. Herrmann, U. Bätz, B. Senti, T. Shah, S. Bänziger

abstract

Consumers prefer clear messages that match prior knowledge and experience – a perfect example is yogurt: Yogurt, as a probiotic food, is a success – it's healthy, it's nutritious, it's tasty. These positive consumer associations are the perfect starting point for developing cosmetic concepts. Lipoid Kosmetik has rediscovered yogurt's beneficial properties for the treatment of sensitive skin and developed a 100% natural, prebiotic, spray-dried yogurt concentrate derived from Swiss milk. As an active ingredient, the yogurt concentrate strengthens the skin's microbial and physical barrier, it calms and soothes sensitive skin.
The power of pre-existing associations was demonstrated in a consumer survey, where yogurt provided an instant sensation of skin refreshment that was triggered by consumer expectations.

Yogurt – a popular food associated with health benefits

What is tasty and has a lot of health benefits? Yogurt! In most grocery stores yogurt has practically taken over the dairy section. In fact, the health benefits of yogurt are impressive, and many health-conscious people make it a daily habit.

Yogurt is made from milk. In a fermentation process, probiotic bacteria convert milk into yoghurt. When eaten, probiotics provide health benefits by supporting digestion and by boosting the function of the immune system [1] [2].

Although yogurt has been part of the human diet for several millennia, the raise of conscious living, healthy nutrition, and active lifestyle has given yogurt's popularity a boost. The interest in probiotics is also fueled by scientific and public interest in the human microbiome – the interacting ecosystems of bacteria and other microorganisms found throughout the body [3]. This trend has now expanded to the cosmetics industry because the microbiome of our skin is as important to our health as is the microbiome of our gastrointestinal system [4].

The interplay between skin microbiome and skin sensitivity

The complex ecosystem of microorganisms that live on our skin is crucial for the way the skin looks, feels, and functions. With approximately one million bacteria per square centimeter of skin, our skin microbiome builds a strong microbial barrier, and plays a vital role in keeping our skin healthy, free from sensitivity and even disease [4].

Fig. 1 Positive associations in the consumer's mind – yogurt is linked to health benefits and an active lifestyle.

Skin hydration and natural sebum production provide nutrients for bacteria – they are important factors for colonization of the human skin by microorganisms. Populated by both, 'good' and 'bad' bacteria, these microbial communities communicate with skin cells to boost immunity and strengthen the skin's physical barrier [5]. This way, a highly populated, balanced, and diversified microbiome builds a strong microbial barrier that actively prevents normal skin from being colonized by opportunistic pathogens.

Many factors can reduce the skin microbiome, from certain skin care products and washing habits, to pollution, UV-radiation, and lifestyle factors such as diet and stress. Once the microbial barrier is weakened, potentially harm-

ful microbes can accumulate and disturb the skin's physical barrier. This in turn favors penetration of environmental aggressors, skin irritation and moisture loss [6]. Dehydrated skin is a poor habitat for bacteria, which further reduces the skin microbiome. Hence, skin sensitivity, dryness, itchiness, irritation, inflammation, and redness are all signs of a potentially weakened microbial barrier **(Figure 2)**.

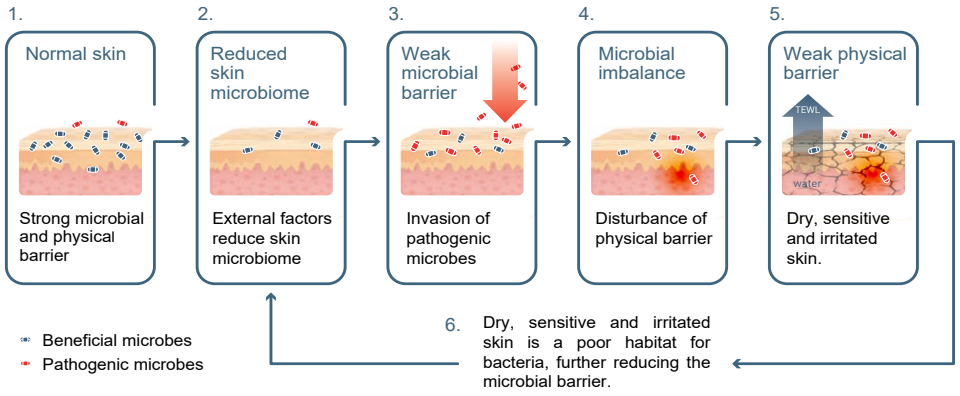

Fig. 2 The interplay between the skin microbiome, physical skin barrier function and skin sensitivity. A reduced microbial barrier disturbs the physical barrier leading to dry and sensitive skin. Dry and sensitive skin further reduces the microbial barrier.

Prebiotic food for the skin microbiome

A strong microbial barrier is a prerequisite for a strong physical barrier. The skin microbiome can be restored with the help of prebiotic skin care products. Prebiotics are naturally occurring nutrients that act like fertilizers – creating an ideal environment for skin microbes.

Yogurt itself is a perfect, ready-to-use prebiotic cream gel – a light formulation, full of vitamins, minerals, and proteins. It is the ideal environment for skin microbes to grow. Yogurtolin® is a spray-dried yogurt concentrate derived from fermented Swiss milk, free of additives and preservatives (hereafter referred to as yogurt concentrate). It is certified as microbiome-friendly, it is COSMOS-approved, and it is of 100% natural origin. Hence it is particularly helpful in recovering a low-level skin microbiome that is typical for sensitive skin.

Yogurt invokes positive associations in cosmetics – a consumer survey

A study was designed to find the most relevant claims for yogurt-based cosmetic concepts. To this end, we analyzed the strength of positive associations linked to yogurt in the consumer's mind. In a survey, 54 volunteers (32 women, 22 men) were asked if they would associate certain attributes to yogurt as a cosmetic ingredient. In total, 25 properties were rated on a scale from 0 to 100 **(Figure 3)**.

As a result, consumers have very clear expectations of yogurt as a cosmetic ingredient: They associate yogurt-based cosmetic products as natural, healthy, microbiome strengthening, calming, gentle and refreshing. Based on these associations, yogurt offers ample opportunities for building cosmetic concepts. In the following, we could substantiate these consumer expectations by several studies.

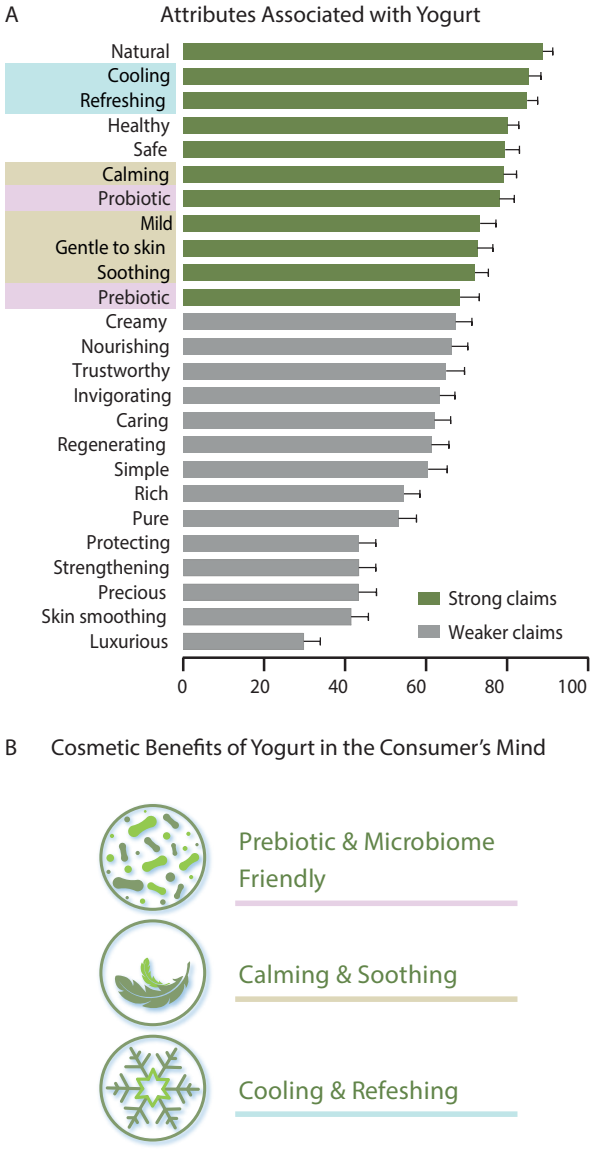

Fig. 3 Yogurt evokes strong pre-existing associations for cosmetic concepts. In a survey, consumers rated their associations with yogurt in cosmetics on a scale from 0 (= no association) to 100 (= strongest association). We consider the top pre-existing consumer association as very useful claims for yogurt-based cosmetic concepts. N = 54, Mean + SEM.

The world's first active ingredient certified as 'microbiome-friendly'

While the number of cosmetic products with microbiome claims is rising, there exist no common standards, nor criteria for microbiome related claims. Many products selectively focus on either microbial balance, diversity, or growth behavior. What's more, consumers know about the importance of the skin microbiome but often lack the scientific knowledge to make purchasing decisions. In summary, communication and substantiation of microbiome-related claims is difficult.

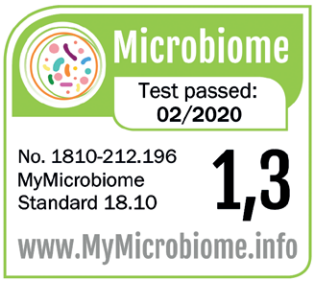

Fig. 4 Yogurt concentrate, a certified microbiome-friendly active ingredient. The quality seal 'microbiome-friendly' uses a conclusive and transparent rating bringing clarity to customers: 1 = Microbiome-friendly; 2 = Microbiome neutral; 3: = Microbiome damaging.

The independent, third-party certification label 'microbiome-friendly' provides a concise and convincing approach to give consumers orientation and to build trust in cosmetic products with microbiome claims. As an independent expert organization, MyMicrobiome issues certificates that make microbiome-related claims transparent and comparable in between products.

The standardized testing procedure covers all aspects of the microbiome, including:

- The microbial quality of the product
- The influence of the product on microbial diversity
- The influence of the product on the growth behavior of specific microbes.

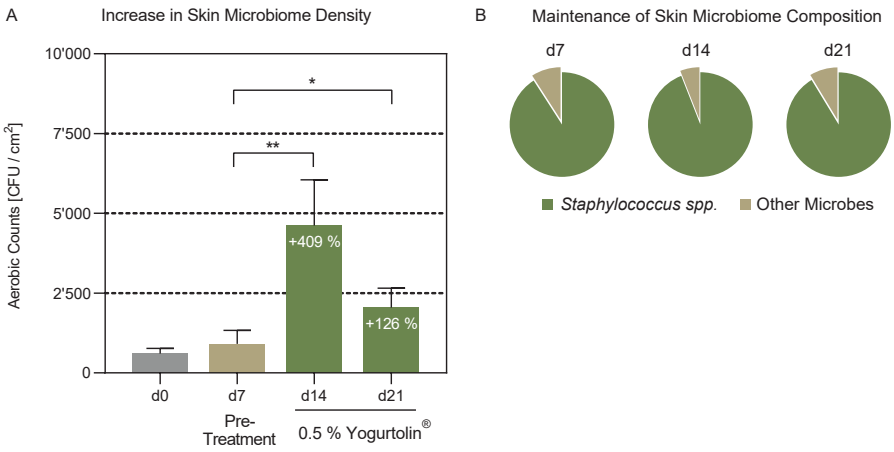

Fig. 5 Yogurt concentrate increases microbe quantity while preserving the microbiome composition. 15 volunteers with dry and sensitive skin and low levels of microbes applied a test formulation with 0.5 % yogurt concentrate twice daily to facial skin. **Fig.5A:** Skin has low levels of microbes before treatment (d0). After pre-treatment, using a formulation without yogurt concentrate, the microbe number slightly raised (d7). Subsequent treatment with yogurt concentrate increased the microbe number (d14, d21). **Fig.5B:** The overall skin microbiome composition was maintained before (d7), during (d14) and after (d21) treatment with yogurt concentrate. No microbial imbalance occurred. N = 15; Mean + SEM; Student's paired test; * = $p < 0.05$; ** = $p < 0.01$.

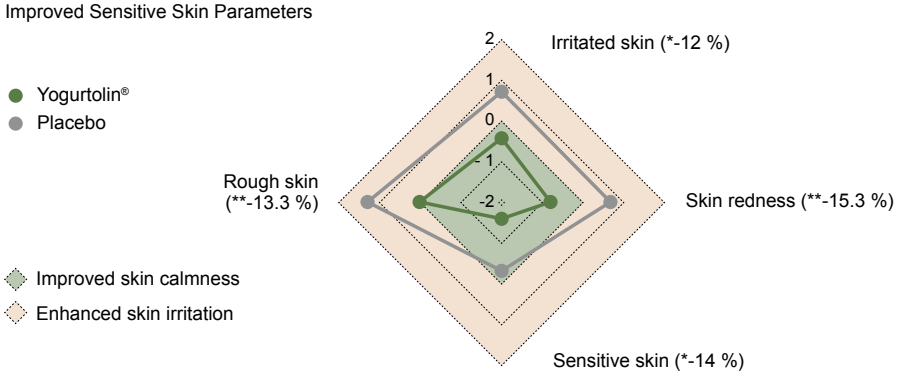

Fig. 6 Consumers experience a relief of sensitive skin with yogurt concentrate. Consumers applied a cream gel with 0.5 % yogurt concentrate or without (placebo) for seven days. They were asked to rate sensitive skin parameters on a 10-degree-scale, before the first and after the last application. The data points show changes in absolute numbers (changes > 0 indicate a worsening, whereas changes < 0 indicate an improvement of the condition). Percentual changes between yogurt cream and placebo at the end of the study are indicated in brackets. N = 15; Mean; Student's unpaired t-test between treatments at d7; * = $p < 0.05$; ** = $p < 0.01$.

Finally, the standard uses a simple and transparent rating that makes products comparable for consumers:

1 = 'microbiome-friendly',
2 = 'microbiome neutral',
3 = 'microbiome damaging'.

(*www.mymicrobiome.info*)

The yogurt concentrate successfully passed the objective test criteria and got certified as 'microbiome-friendly' according to the MyMicrobiome Standard 18.10. Of note, it received an excellent rating of 1.3 = 'microbiome-friendly' **(Figure 4)**.

Re-establishing the skin microbiome – an *in vivo* study

To substantiate the consumer expectation of 'prebiotic and microbiome friendly', we analyzed the impact of a yogurt cream on the quantity and composition of microbes on dry and sensitive facial skin. The total quantity and types of aerobic microbes was monitored by taking swabs from the forehead, followed by a quantification of the total microbe number using cell culture techniques. Microbe types were identified by MALDI-TOF-MS (Matrix Assisted Laser Desorption Ionization - Time of Flight - Mass Spectrometry).

As a result, the yogurt concentrate has prebiotic functionality. It reestablishes and stabilizes a disturbed skin microbiome and thereby helps to strengthen the skin's microbial barrier. This will make skin more robust to external challenges and reduce symptoms of sensitive skin.This finding supports the pre-existing consumer expectation of yogurt being a prebiotic, microbiome-strengthening ingredient.

Calming sensitive and irritated skin – a consumer study

To substantiate the consumer expectation of 'calming and soothing' a placebo-controlled consumer study was performed.

A test panel of two groups of 15 female volunteers with sensitive skin applied a test cream gel formulation with 0.5% yogurt concentrate or without (placebo) to their faces, twice daily for seven days. Volunteers rated skin parameters according to a questionnaire before and after application.

As a result, yogurt concentrate calms and soothes sensitive skin and reduces the redness and irritation level typical for sensitive skin. This finding supports the pre-existing consumer expectations of yogurt being calming and soothing.

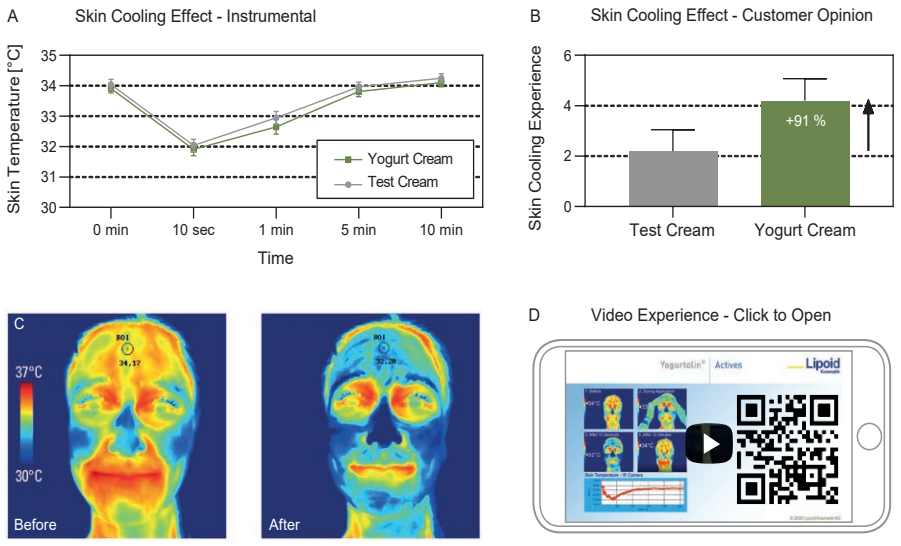

Fig. 7 Subjective sensation of skin cooling with yogurt concentrate. (A) Time course showing that, objectively, both creams reduce skin temperature without a significant difference. N = 15; Mean (B) Subjectively, consumers experienced a 'yogurt cream' to be twice as refreshing than a 'test cream'. Consumers rated their immediate skin cooling experience on a 10-degree-scale (0 = lowest effect; 10 = highest effect) after applying a 'Test Cream' or a 'Yogurt Cream'. (C) Representative infrared thermal images of the skin temperature before and after application of a cream with 0.5% yogurt concentrate. (D) Open the video and experience how a cream with yogurt concentrate can instantly refresh the skin.

Providing a subjective sensation of refreshment

To substantiate the consumer expectation of 'cooling and refreshing' we investigated the instant cooling effect on facial skin after the application of a cream gel with and without yogurt concentrate. To demonstrate real temperature changes on the skin surface, we monitored skin temperature with an infrared thermal camera immediately after application.

To demonstrate the subjective cooling effect associated to yogurt, we asked consumers to rate their cooling experience on a scale from 0 to 10 in a self-evaluation questionnaire. For this experiment, test products were labelled either 'Yogurt Cream' or 'Test Cream'.

As a result, the instrumental assay measured an approx. 2°C drop in skin temperature with no difference between 'Yogurt Cream' or 'Test Cream'. However, the subjectively experienced cooling effect was 91% stronger when the product was labelled "Yogurt Cream". This underlines the principle that "You feel what you expect to feel". Yogurt concentrate supports refreshing cosmetic concepts due to the power of consumer expectations.

Conclusion: Yogurt concentrate is an ideal treatment for sensitive skin

Lipoid Kosmetik has rediscovered yogurt's beneficial properties for sensitive skin and makes use of pre-existing consumer associations linked to yogurt.

- **Prebiotic functionality –** Sensitive skin is characterized by low levels of skin microbiota. Yogurt concentrate is a natural, prebiotic ferment that reinforces the skin's microbial barrier by creating a favorable environment for a balanced skin microbiome.
- **Improvement of sensitive skin –** Sensitive skin is characterized by dryness and irritation. Yogurt concentrate regenerates the physical skin barrier and reduces skin discomfort: it calms and soothes sensitive skin.
- **The power of associations –** The value of yogurt concentrate as a skin care ingredient is not only based on its efficacy, but also on its pre-existing, positive consumer associations (e.g., yogurt is associated with cooling and refreshing properties). These associations add value by reinforcing product experience of yogurt-based cosmetic concepts.

Taken together, Yogurtolin® is a powerful prebiotic and natural concentrate derived from fermented Swiss milk. It builds on pre-existing, positive consumer associations, and allows to create product concepts with clear messages that match prior knowledge and experience. It is best suited for sensitive skin care products that restore the microbial and physical skin barrier and add an instant sensation of skin refreshment and cooling to irritated skin.

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Caring and Strengthening: the Global Skin Moisturization Strategy

L. Schmidt, M. Kujawa-Autié, M. Reichenbach

abstract

Moisturization is a very well-known and essential need for skin care. Nowadays, classic hydration strategies are supplemented with new approaches to support the skin in achieving its moisturizing mechanisms. In this article, we present an overall strategy based on two pillars: caring and strengthening the skin. Thereby, we will elucidate the roles of Natural Moisturizing Factors, hyaluronic acid, ceramides and filaggrin within this overarching strategy on the basis of four specific products from the Symrise portfolio acting on these essential components: Hydroviton® PLUS, SymGlucan®, SymRepair® 100 and SymReboot™ L19.

Introduction

The very nature of skin care formulations e.g. emulsions of oil and water, is to provide a hydrolipidic film similar to the skin's own sebum, fatty substances and sweat, which contribute to skin hydration. That's why, hydration has been a key cosmetics concern at the core of marketing claims since the early 20th century (the first moisturizing skincare product is believed to be "Secret de Bonne Femme" by Guerlain in 1905).

Historically, the first generation of moisturizers formed an occlusive layer of lipids on the skin's surface to reduce Trans Epidermal Water Loss (TEWL). Later, the next generation of moisturizers was supposed to capture ambient water with hygroscopic hydrophilic molecules. These classic strategies lack support of skin's own function and sustainability. Thus, today's state-of-the-art skincare strategies present a more disruptive and sustainable approach to strengthen the skin's natural capacities and regulate its own hydration. In addition to properties considered standard, these new active ingredients not only help the skin to improve its hydrating powers but also its own defenses.

A caring strategy

One solution to punctually fight dehydration disorders consists of using active ingredients that support the molecules naturally synthesized in the skin, thus 'watering' *in situ*.

Caring from outside or how to maximize skin moisture

The skin secretes endogenous molecules contributing to hydration by cleavage of filaggrin- a protein associated to keratin filaments- thereby forming an essential component of the natural moisturizing factors NMFs. These NMFs consisting of free amino acids, urea and sugars absorb atmospheric water into the skin and, at the same time, retain water transported from deeper layers subsequently increasing the hydration reservoir. Due to the loss of NMFs by the daily washing routine the skin hydration decreases, what is even more aggravated during aging [1]. This phenomenon results in skin tightness, impaired desquamation, and loss of suppleness. By providing hygroscopic molecules that attract and capture water into the *Stratum Corneum* (SC), moisturization on the skin surface is temporarily increased but this artificial approach lacks sustained effects on the skin.

That is why a cocktail of natural sugars and biomimetic moisturizers that mimic the NMFs was designed as a natural and endogenous approach to foster prolonged skin hydration. Hydroviton® PLUS (INCI: Water (Aqua), Pentylene Glycol, Glycerin, Fructose, Urea, Citric Acid, Sodium Hydroxide, Maltose, Sodium PCA, Sodium Chloride, Sodium Lactate, Trehalose, Allantoin, Sodium Hyaluronate) provides an optimal amount of sugars and moisturizers to compensate loss of NMFs naturally and thus brings immediate and long-term skin moisturization (*in vivo* study, **Figure 1**). Further, Hydroviton® PLUS contains filmogenic molecules like hyaluronic acid derivative that reduce water loss therewith fighting age-induced dryness.

Caring from inside or how to maximize water storage capacity

Skin contains about 50% of a total body's hyaluronic acid (HA). This glycosaminoglycan (GAG) is a key molecule

involved in skin moisture with a unique capacity to bind and retain water molecules. Besides its natural degradation within the skin, HA level also decreases with age and the size of the HA polymers is reduced as well [2].

This lack of HA is partly responsible for dryness, loss of elasticity and wrinkles as HA is known for its extremely high water -binding capacity. Two Symrise active ingredients have proven their ability to enhance the HA synthesis within the skin. Indeed, in this caring approach, SymGlucan®, an active ingredient made of premium oat fractions (INCI: Water (Aqua), Glycerin, Beta-Glucan, 1,2-Hexanediol, Caprylyl Glycol), and SymReboot™ L19, a new generation of skin microbiome active containing a specific processed Lactobacillus strain with an intact bacterial cell wall (INCI: Maltodextrin, Lactobacillus Ferment), can improve the skin's ability to retain water as a result of HA stimulation in the skin. Thus, SymGlucan® enhances HA synthesis by both keratinocytes and by fibroblasts *in vitro* (data not shown) [3]. It is also proven *in vivo* to improve moisture, smoothness, firmness and elasticity of the skin in two weeks. The combination of these effects enhances skin regeneration *in vivo* **(Figure 2)**.

SymReboot™ L19 significantly promotes HA production according to an ex vivo study **(Figure 3)**.

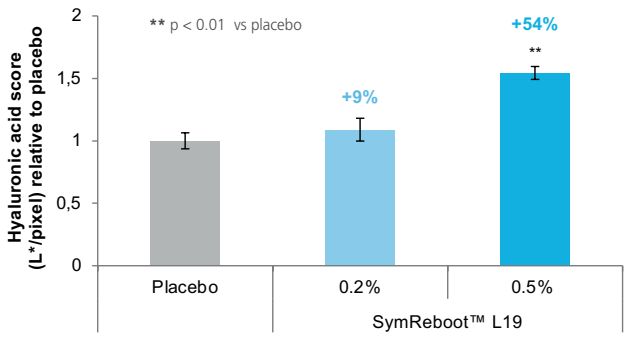


Fig. 3 Support of hyaluronic acid production by SymReboot™ L19 in *ex vivo* human skin explants after topical treatment of tested compounds in hydrodispersion gel.

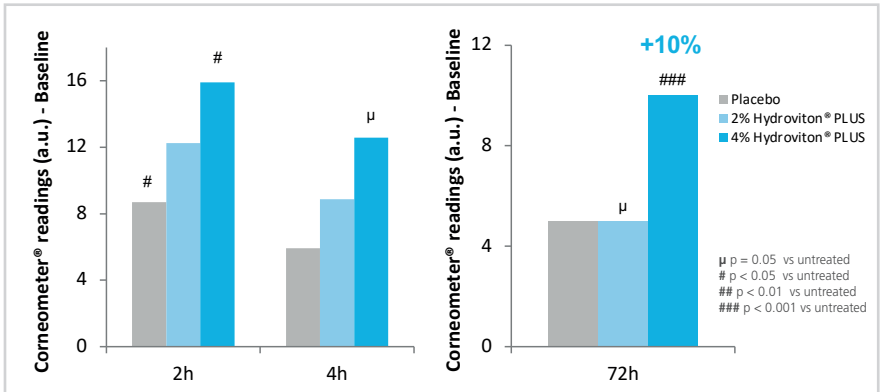


Fig. 1 Immediate and long-term improvement of skin moisturization after one single application of O/W emulsion with Hydroviton® PLUS *in vivo*.

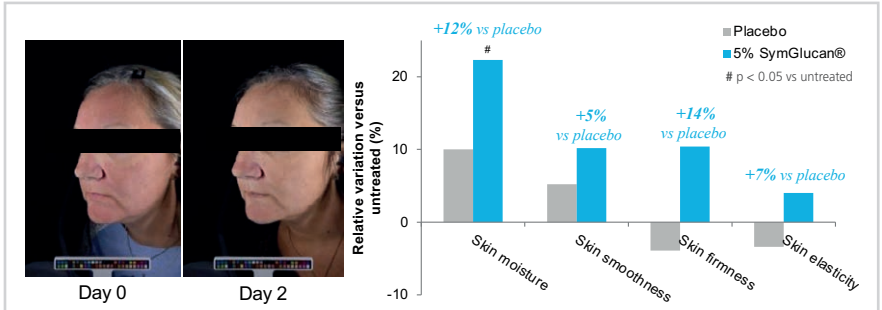


Fig. 2 *In vivo* evaluation of skin regeneration after a laser dermabrasion test. Visible enhancement ofepidermal reconstruction after 2 days of treatment with 5% SymGlucan®: skin becomes less red over time & appears regenerated.
Improvement of skin aspect and texture (moisture, smoothness, firmness and elasticity) after 2 weeks of treatment with 5% SymGlucan® *in vivo*.

A strategy to strengthen the skin barrier function

Intrinsic factors (age, psychological stress, etc.) and external aggressors, both physical (UV rays or temperature) and chemical (detergents, pollutants, etc.), weaken the epidermis barrier function's capacities. In order to counter this imbalance, the solution is to strengthen the skin's natural protective functions.

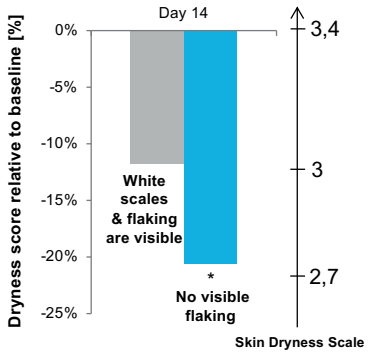
Today, this strategy is evolving towards a more sustainable alternative.

Strengthening from outside or how to minimize water permeability

Indeed, factors such as environmental pollutants and/or chemicals alter the quality and quantity of components of the SC responsible for the skin barrier function (lipids, NMF, proteins, etc.). This phenomenon leads to damages of the skin surface, making the skin even more dehydrated

and sensitive to external aggressors. This vicious circle further weakens the skin barrier.

It is well-known that, on one hand, an intact skin barrier and appropriate hydrolipid film work together to limit the penetration of harmful substances and prevent the excess of water loss. On the other hand, 50% of the total lipids comprising the 'mortar of the skin' in the intercellular space of corneocytes are represented by ceramides [4,5]. Therefore, another level of protection against dehydration is to supply the skin with pseudo-ceramides and other lipids. This helps to restore the lamellar structure of skin lipids in the *strateum corneum* and limit both penetration of harmful substances and excess of water loss [6,7].



Grade	Skin Dryness Scale
5	Extremely dry skin with deep or extensive cracking and evidence of bleeding
4	Extremely dry skin, extensive scaling and pronounced separation of scale edges, some evidence of cracking
3	Severely dry skin, **pronounced scaling visible to the naked eye**, definite uplifting of edges or scale sections surface may have a whitish appearance
2	Moderately dry skin, fairly uniformly distributed scale, but no wide spread uplifting and flaking
1	Slightly dry skin, occasional scale, not necessarily uniformly distributed
0	Smooth, no evidence of dryness

Placebo
SymRepair® 100
* p < 0.05 vs placebo

Fig. 4 Significant improvement of the visual aspect of extra-dry skin after 14 days of treatment with 4% SymRepair® 100 in O/W emulsion *in vivo*

SymRepair® 100 (INCI: Bisabolol, Cetylhydroxyproline Palmitamide, Stearic Acid, Brassica Campestris (Rapeseed) Sterols) is a biomimetic association made of three restructuring compounds of skin lipid bilayer combined with an instant soothing agent. It restores damaged dry skin in 7 days by reinforcing skin barrier integrity. SymRepair® 100 significantly improves skin hydration in 5 days and consequently improves the visual aspect of extra-dry skin *in vivo* **(Figure 4)** [8].

Strengthening from inside or how to enhance skin's instinctive defenses

A key element for barrier integrity is the presence of filaggrin monomers in the SC. These monomers directly bind to keratin, resulting in thickened and aggregated keratin filaments condensing the keratinocyte cytoskeleton. They are part of the 'skin barrier' together with lipids and cornified layer proteins, forming the "brick" of the barrier. As mentioned above, the degradation of filaggrin monomers into free amino acids and derivatives, such as urocanic acid (UCA) and pyrrolidone carboxylic acid (PCA), participates in the NMF composition [9]. That is why it is important to maintain high levels of filaggrin within the skin.

SymReboot™ L19 completes this strategy for better moisturization in a smarter and more sustainable way, by enhancing filaggrin production in the skin (*ex vivo* study, **Figure 5**) and HA stimulation **(Figure 3)**. This microbiotic solution supports the regulation of skin microbiota pathways. SymReboot™ L19 is also proven to sustainably reduce skin dryness *in vivo* (**Figure 6**) [10,11].

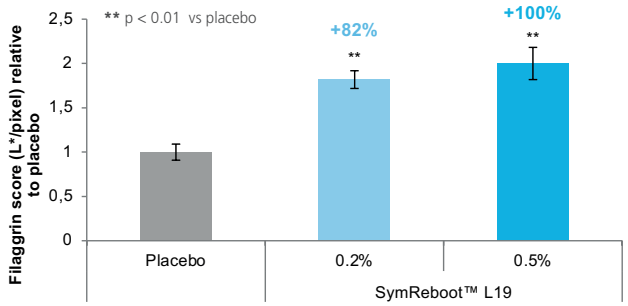


Fig. 5 Support of filaggrin production in ex vivo human skin explants after topical treatment of tested compounds in hydrodispersion gel.

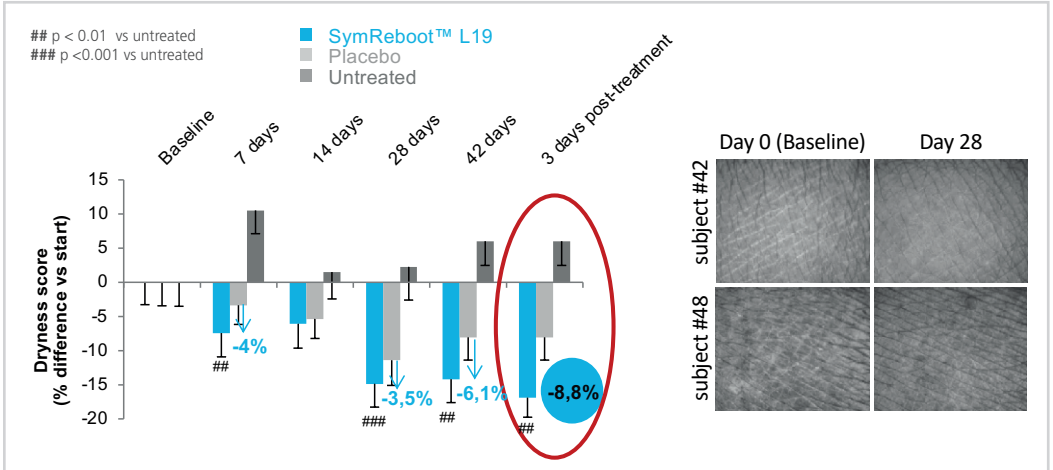


Fig. 6 Significant and sustainable reduction of visible skin dryness after 42 days of treatment with 0.5% SymReboot™ L19 in O/W emulsion *in vivo* and effects on visual signs of skin dryness at baseline (day 0) and after 28 days of treatment.

SymReboot™ L19

True Biotic

Restores the instinctive defenses of sensitive skin & scalp

Based on a novel patented technology, Symrise introduces its first processed probiotic. The membrane of the bacterium is kept intact, thus delivering its full specific benefits to the skin & scalp.

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Conclusion

Today, there is a strong market requirement for moisturizing solutions that have an added value to achieve a holistic and sustainable action. Symrise developed a strategy with smart associations to provide immediate care and, at the same time, promote the skin's innate capacities. Thereby, skin can regain balance by reactivating the means to defend itself in an intelligent, optimal, and sustainable way.

Therefore, this 21st century broad moisturization strategy makes it possible to instantly and lastingly fight against the visible and perceptible signs of skin dehydration.

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New Microbiotic Care with Bacterial Lysate against Dry Skin

H-J. Müller, E. Jaspers, A. Hecht

*Additional figures and tables can be downloaded at: https://www.sofw.com/images/a-symbio-2106-e.pdf **

abstract

This application study examined *in vivo* the effect of a microbiotic care product (**SYMBIO®** DERMAL) on dry skin prone to atopic dermatitis. The microbiotic care contained a complex of lysed, non-pathogenic *Escherichia coli* and *Enterococcus faecalis* bacteria additionally to nourishing substances. It thus follows the "emollients plus"-principle as described in the current European guidelines for treatment of atopic dermatitis [5]. Before and after applying the microbiotic care for four weeks, the following tests were carried out on defined skin testing areas: **(i)** determination of the transepidermal water loss (TEWL); **(ii)** determination of hydration, **(iii)** evaluation of dryness/flaking by *in vivo* touching evaluation, **(iv)** clinical-dermatological assessment with final questionnaire and **(v)** patch safety test. As shown after four weeks of application, the microbiotic care reduced transepidermal water loss by an average of around 22%, increased skin moisture by an average of almost 50% and reduced dryness/flaking by an average of almost 50%. Consequently, the microbiotic care supported the barrier function of dry skin. Previously performed *in vitro* studies also proved immunomodulatory properties of the bacterial lysate complex. According to clinical-dermatological test criteria, the microbiotic care was very well tolerated. It received the 5-star-rating ("clinically tested" &"very good") from Dermatest.

1. Introduction

The human skin is one of the largest and most versatile organs in the human body. On the one hand, it has barrier function and prevents invasion of harmful substances like toxins and pathogenic microorganisms. Additionally, the human skin helps to maintaining body's water balance.

Epidermal lipids (horn fats) seal the intercellular spaces between the keratinocytes and form a diffusion barrier. The density of this lipid- and cell network is a basic requirement for a healthy and resilient skin that retains sufficient moisture. Impaired horn fats promote water loss and subsequent xerosis. Dry skin solely can already promote inflammation, for instance the "eczéma craquelé" in elderly people [4]. Additionally, a disturbed skin barrier sets the course for atopic dermatitis (neurodermatitis).

The physiological skin microbiota supports barrier function: By providing colonization resistance, the microbiota protects the skin from microbial infections. The skin microbiota also interacts with the immune system of the host. For instance, *Staphylococcus epidermidis* inhibits the release of proinflammatory cytokines from keratinocytes [2]. *S. epidermidis* also increases gene expression of antimicrobial peptides like human β-defensin 2 [2] and stimulates resident skin T-lymphocytes [3]. *S. epidermidis* thereby enhances the skin's immune defense and thus contributes to skin protection and health.

In most skin dysfunctions and diseases, the skin microbiota has changed. In atopic dermatitis, for example, more pathogenic *Staphylococcus aureus* colonise the skin, which can cause infections. At the same time, the skin produces fewer antimicrobial peptides, which promotes the infection process [1].

This application study examines the effect of a new microbiotic skincare on dry skin prone to neurodermatitis. In addition to different lipids, which act as emollients, the product contains inactivated (lysed) apathogenic *Escherichia coli* and *Enterococcus faecalis*. As shown by preliminary *in vitro* studies, the bacterial lysate complex can modulate immunological skin reactions.

The new microbiotic skincare follows the new principle "emollients plus" in the basic care for atopic dermatitis as described in the current European guideline for the treatment of atopic dermatitis [5]: Active components like plantlet extracts or bacterial lysates are added to the emollients [5]. The lysates of certain bacteria can improve lesions and influence the skin microbiota as well as the skin's immune system [5,9].

2. Material & Methods

2.1 Skincare products

We tested a new type of water-in-oil emulsion (cosmetic Symbio® DERMAL, SymbioPharm GmbH). Beside other skincare ingredients, it contained lysed *Escherichia coli* (*E. coli*)

and *Enterococcus faecalis* including their metabolites produced up to their lysis.

Ingredients: *E. coli*/*Enterococcus faecalis* fermented lysate, caprylic/capric triglyceride, squalane, pentylene glycol, glycerine, Simmondsia chinensis oil, Prunus Amygdalus Dulcis oil, Cetyl PEG/PPG-10/1 dimethicone, Persea Gratissima castor oil, Oenothermal oil Panthenol, Butyrospermum Parkii Butter, Tocopheryl Acetate, Cera Alba, Aqua, Betaine, Cetyl Palmitate, Sodium Gluconate, Sodium Hyaluronate, Sodium Lactate, Ceramide-NP, Cholesterol, Glyceryl Dibehenate, Phytosphingosin Acid, Tocopherol, Ceramide 6 II.

For comparison and control, the identical skincare without bacterial lysate and untreated control areas on the left forearm were used, respectively.

2.2 Application study

Institutions involved

- **RSC Pharma GmbH & Co. KG,** Gleibergring 23, 35396 Gießen, Germany (contract researcher),
- **Dermatest® GmbH**, Engelstrasse 37, 48143 Münster, Germany (assessor),
- **SymbioPharm GmbH**, Auf den Lüppen 10, 35745 Herborn, Germany (product development)

Study participants

20 male and female adults between the ages of 23 and 66 years meeting the inclusion criterion were enrolled **(Table 1 (download at https://www.sofw.com/images/a-symbio-2106-e.pdf))**. The inclusion criterion was very dry skin or skin prone to neurodermatitis, but not in need of medical treatment. In the test and control areas, all test subjects initially showed dry or very dry, sometimes atopic skin.

Exclusion criteria were severe or chronic skin inflammation; severe internal or chronic diseases; medication that might affect skin reaction such as glucocorticoids/antiallergics/topical immunomodulators; application of skincare products or substances containing active ingredients 7-10 days before start of studies, severe allergies or any previous severe side effects from cosmetics; sunbathing or solarium visits during the study, cancer.

Study design

Preliminary *in vitro*-studies (cytotoxicity test prior to marketing authorization according to ISO 10993 and "Skin Irritation Test" using a reconstituted epidermis (Epi Derm™)) had confirmed the safety of the bacterial lysate (unpublished data).

The Ph. Eur. 5.1.-test for adequate antimicrobial preservation passed the microbiotic care with "Criterion A". The microbiotic care showed *in vitro* inhibitory effects on several pathogens, including *Staphylococcus aureus* (unpublished data).

The bacterial lysate modulated *in vitro* the release of cytokines Interleukin (IL)-6 and IL-8 in a TNF-α provoked inflammation of epidermal skin cells (HaCaT cell line).

The subsequent application study included:
(i) determination of the transepidermal water loss (TEWL),
(ii) determination of hydration
(iii) assessment of dryness/flaking,
(iv) clinical-dermatological evaluation with final questionnaire and
(v) patch safety test.

Each subject had a dry, partially atopic test area on the extremities of each body half **(Table 1 (download at https://www.sofw.com/images/a-symbio-2106-e.pdf))**. The subjects applied the microbiotic care to the test areas on the right body half. The product without bacterial lysate was applied to the test areas on the left body half. Both occurred daily in the morning and evening for four weeks. The application was double-blinded. The control areas remained untreated. The use of any other products in the test areas was prohibited.

2.2.1 Determination of the transepidermal water loss (TEWL)

Transepidermal water loss (TEWL) is a measure of skin barrier function. The evaporimeter probe with two sensors was used to measure the vapor pressure gradient arising within the chamber and between the skin and the surrounding air. TEWL in the test areas was measured using the Tewameter® evaporimeter (Courage + Khazaka electronic GmbH). Decreases in TEWL indicate an improvement in skin barrier function such that less water is lost through the skin barrier.

Both test areas as well as the control areas had a diameter of approximately 3 cm each. 20 TEW measurements were taken at each test area, out of which an average value was calculated.

Measurements were performed before and after the four-week application period.

2.2.2 Determination of skin hydration

Changes in skin capacitance were used to study epidermal hydration *in vivo*. The Corneometer CM 825 (Courage and Khazaka electronic GmbH) was used to measure the electrical capacitance of the skin. Prior to the measurement, the test subjects were standardized for 45 min in a 22°C room

with a relative humidity of 60%. Measurements were performed before and after the four-week application period, ten to twelve hours after product application. Three replicate measurements were taken on three different points within each test and control area, which each had a diameter of approximately 3 cm. Out of each of the three measurements an average value was calculated.

2.2.3 Evaluation of dryness and flaking

Specially trained dermatologists assessed the parameters dryness and flaking visually and by touching the skin (*in vivo*-touching evaluation). For this, they used an analog scale that ranged from "no intensity" (0.00) to "maximum intensity" (100.00). Intensity 0 corresponds to excellent skin conditions without any dryness or flaking. Very dry, flaky skin has an intensity of 100 **(Figure 1).** The evaluations were performed before and after the four-week application period. The diameter of the test areas was extended to approximately 5 cm. Control areas were not considered as this evaluation method by default only assesses treated skin.

Fig.1 Analog scale for the evaluation of dryness and flaking

2.2.4. Clinical-dermatological assessment with final questionnaire

Before and after the four-week application period, the subjects were dermatologically examined. Additionally, each subject could daily refer to the dermatologists if necessary.

Dermatological assessment criteria were as follows:
(i) redness,
(ii) flaking and
(iii) dryness.

At the end of the study, each subject completed two questionnaires, each for the microbiotic skincare and the lysate-free care. Here, they answered general question about the skincare products and about how the skin subjectively felt after applying the products **(Tables 5a, 5b** (download at https://www.sofw.com/images/a-symbio-2106-e.pdf) **and Figure 5a)**.

2.2.5 Patch safety test

After four weeks of application; the skincare products were applied in concentrations of 5 mg/15µL to patch test strips (Curatest® F Adhesive Strip, Lohmann & Rauscher GmbH & Co. KG, REF 30062). Two discs remained uncoated (control), one disc was coated with the microbiotic care, another disc was coated with the skincare without bacterial lysate. The strips were applied to healthy skin of the upper back.

Under standardized lighting, evaluation of possible skin reactions was performed after 24, 48 and 72 hours of exposition 30 min after the tapes were detached.

3. Results

3.1 Transepidermal water loss (TEWL)

After four weeks of application, the microbiotic care had reduced TEWL by 26,7% on average, compared to the start. The skincare without bacterial lysate reduced TEWL by 17,75% on average. In control areas, TEWL was reduced by 4,85% on average **(Tables 2a, 2b and 2c** (download at https://www.sofw.com/images/a-symbio-2106-e.pdf) **and Figure 2)**.

3.2. Hydration

After four weeks of application, the microbiotic care increased skin moisture by 51,37% on average, compared to the start. The skincare without bacterial lysate increased skin moisture by 53,67%. In control areas, skin moisture increased by 5,23% on average. **(Tables 3a, 3b and 3c** (download at https://www.sofw.com/images/a-symbio-2106-e.pdf) **and Figure 3)**.

3.3. Dryness and flaking

After four weeks of application, the microbiotic care improved dryness and flaking by 47,94% on average, compared to the start. The skincare without bacterial lysate improved dryness and flaking by 46,46% on average **(Tables 4a and 4b** (download at https://www.sofw.com/images/a-symbio-2106-e.pdf) **and Figure 4)**.

3.4. Clinical-dermatological assessment with final questionnaire

No irritation or sensitivity effects were reported in any subject during and after the four-week application period. Correspondingly, none of the subjects consulted the dermatologist. No test interruptions or medical treatments were needed. The microbiotic skincare as well as the skincare without bacterial lysate were very well tolerated.

In the finale questionnaire, the subjects adressed several criteria related to the microbiotic skincare and the skincare without bacterial lysate. The criteria were as follows: consistency,

skin feeling, relaxation of skin tension, spreadability, tolerance, suitability for sensitive skin, skin soothing and suitability for very dry skin prone to neurodermatitis. The majority of the subjects rated both skincare products in the criteria-order listed as "exactly right", "(very) pleasant", "I (fully) agree", "(very) quickly absorbed", "very good and good", "I totally/tend to agree" and "I totally/tend to agree". (details see **Tables 5a, 5b (download at https://www.sofw.com/images/a-symbio-2106-e.pdf) and Figure 5a**)

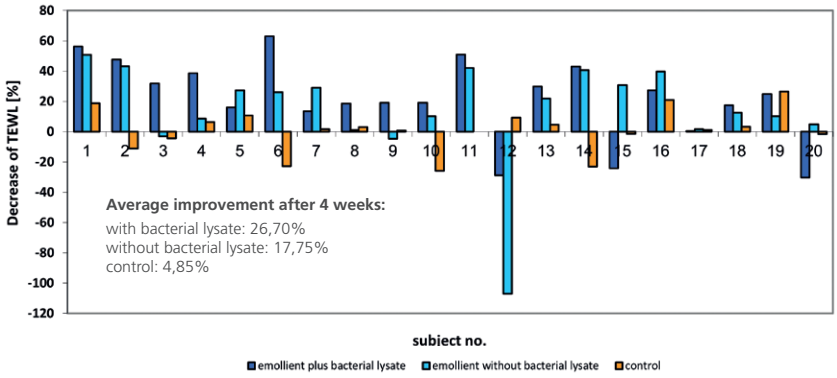

Fig. 2 Decrease in transepithelial water loss (TEWL) after four weeks of applying the microbiotic care and the skincare without bacterial lysate.

3.5. Patch safety test

The patch test results did not reveal any sensitivity or irritation from the test products – neither in the test areas nor in the control areas **(Tables 6a, 6b, 6c (download at https://www.sofw.com/images/a-symbio-2106-e.pdf))**.

It received the 5-star rating ("clinically tested" & "very good") from Dermatest.

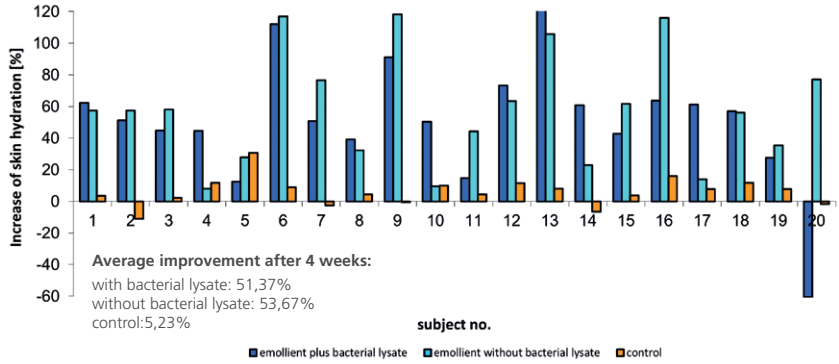

Fig. 3 Increase in skin hydration after four weeks of applying the microbiotic care and the skincare without bacterial lysate.

4. Discussion

Altered skin conditions are often associated with an impaired quality of the patient's daily life. Beside skin diseases like atopic dermatitis or acne also dry skin is problematic. Patients need to apply special skincare to prevent exacerbation of dryness and flaking and to maintain skin's barrier function.

Filaggrin gene mutations are the highest risk factor for developing atopic dermatitis [7]. The protein filaggrin is part of the *stratum corneum* and helps to connect the keratinocytes with each other. Then the skin barrier is intact and the *stratum corneum* is sufficiently hydrated. However, mutated filaggrin genes do not produce enough filaggrin molecules. In consequence, the skin's barrier function is disturbed which increases transepidermal water loss. This promotes dry skin and eczema [7]. Dry skin is also likely to promote penetration of allergens that lead to allergenic sensitization, asthma and hay fever [7]. Reducing skin dryness is the key to reduce the frequency, duration and severity of inflammation in atopic dermatitis [7].

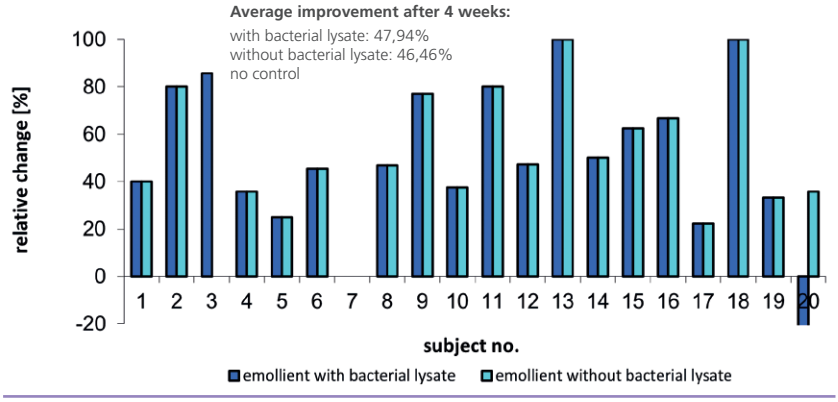

Fig. 4 Decrease in skin dryness and flaking after four weeks of applying the microbiotic care and the skincare without bacterial lysate. An assessment of untreated skin areas as a control was not performed.

The current European guideline for the treatment of atopic dermatitis describes emollients as "extremely helpful for AE (atopic eczema = atopic dermatitis) patients". It recommends using emollients twice a day to reduce skin dryness [5,7]. In recent years, so called "emollients plus" products for topical treatment have been developed. Beside emollients they also contain active components. The current European guideline recommends emollients plus for the basic therapy of atopic dermatitis. Often these products are neither fulfilling the definition of nor needing a license as a topical drug [5].

They are cosmetics such as Aderma Exomega Control and Avene XeraCalm A.D. They contain plant saponins, flavonoids and riboflavins or bacterial lysates from *Aquaphilus dolomiae* or *Vitreoscilla filiformis* [5] as active components. In general, live bacteria as especially the lactid acid bacteria *Lactobacillus paracasei*, *L. brevis* and *L. fermentum* influence the skin positively. They support growth of the health promoting skin-bacterium *Staphylococcus epidermidis* and inhibit growth of undesired skin-bacteria like *Staphylococcus aureus*. In cosmetics, however, the use of inactivated bacteria as lysates or extracts is more common [1]. *Aquaphilus dolomiae* and *Vitreoscilla filiformis* extracts have been scientifically investigated for beneficial properties for skin health. *In vitro* studies and clinical research have shown their immunomodulatory properties. For example, the modulate the release of interleukin-8 or induce the expression of human beta-defensin (HBD)-2 [8,9]. Many human epithelial tissues produce beta-defensins. They fight pathogenic bacteria without eliciting inflammatory immune responses. The skin epithelia express HBD-1 constitutively; HBD-2 is additionally induced when inflammation occurs [1]. Keratinocytes increase their HBD-2-expression when exposed to *Staphylococcus aureus* [1]. In atopic dermatitis, high levels of HBD-2 in the *stratum corneum* are associated with impaired skin barrier and the severity of the disease [12]. They are "fight indicators", demonstrating how the skin epithelial cells fight potentially pathogenic bacteria of an aberrant skin microbiota. Therefore, substances which promote HBD-2-formation support the epithelial immune defense.

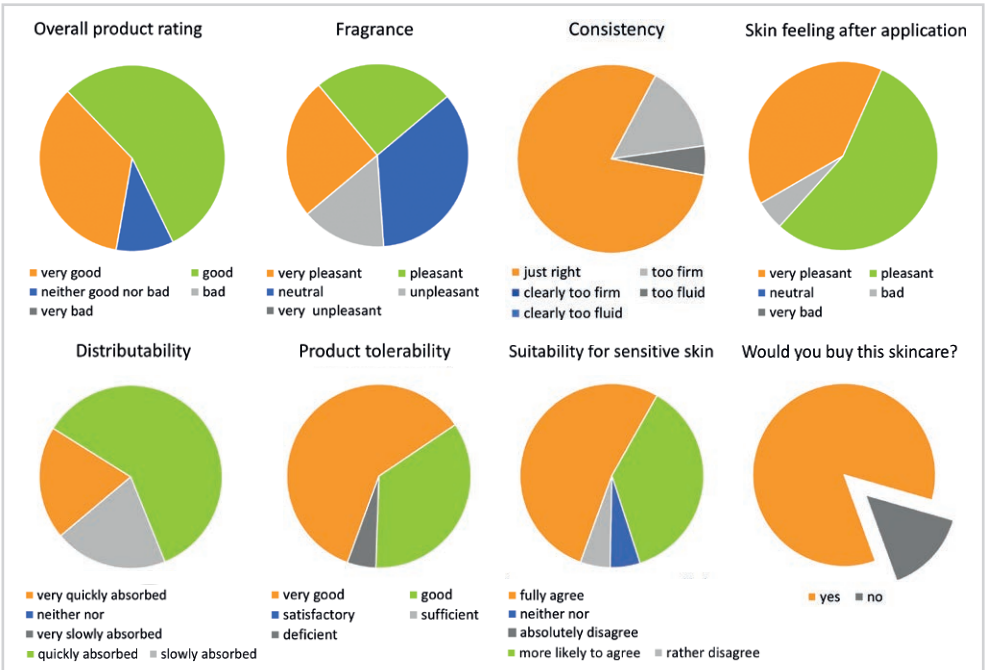

Fig. 5a Results (graphics) of the questionnaire on the application of the microbiotic care (right half of the body) - corresponding to **Table 5a** (download at https://www.sofw.com/images/a-symbio-2106-e.pdf).

This application study shows that a complex of lysed, non-pathogenic *E. coli* and *Enterococcus faecalis*-bacteria helps to improve dry skin or skin prone to neurodermatitis: 40% of the TEWL-reduction was achieved by the bacterial lysate complex. The nourishing ingredients brought about the further 60% of the TEWL-reduction. TEWL is one of the most important parameters to evaluate the epidermal permeability barrier function of the skin. Low values of this parameter are the main characteristic of the healthy skin which is capable of retaining moisture. Consequently, substances which reduce TEWL improve epidermal barrier function of the skin.

The nourishing ingredients exhibited further positive effects: Within for weeks, they decreased skin's dryness and flaking, while in parallel skin moisture was increased. Consequently, the new microbiotic skincare supports the epidermal skin barrier of dry skin and skin prone to neurodermitis, following the new principle of "emollients plus". The risk factor "impaired epidermal skin barrier" for developing atopic dermatitis is therefore reduced.

Beside an impaired skin barrier, an immunological imbalance is believed to contribute to the inflammatory lesions of atopic dermatitis [7]. Especially in the case of acute excema inflammation is strong [7]. The close interaction between microbes and human immune system is known for the intestinal microbiota and also occurs between the skin microbiota and the skin's immune system [1]. Inactivated bacteria (lysates or extracts) can possibly contribute to the immunomodulatory effects of the skin microbiota. The complex of lysed, non-pathogenic *E. coli* and *Enterococcus faecalis* bacteria used in Symbio® DERMAL exhibited *in vitro* immunomodulatory capacities like modulating cytokine-responses. This might support improvement of skin conditions. As one example, the lysed *E. coli* and *Enterococcus faecalis*-bacteria reduced the interleukin-8 release, much like lysed *Aquaphilus dolomiae* [8] does. Interleukin- 8 is considered to be a mediator of inflammation in psoriasis [11]. Interleukin-8 recruits neutrophils and promotes their degranulation [10]. Therefore, the lysed *E. coli* and *Enterococcus faecalis* used in this study can probably have a positive effect on the risk factor "immunological imbalance", which increases susceptibility to inflammation.

Beside health effects, tolerance is another important aspect for daily use of a skincare product for dry skin. According to clinical-dermatological test criteria, the microbiotic care was very well tolerated. No irritation or sensitivity effects were reported. The subjects were very content: As shown in the results of the questionnaires, 85% of the subjects would buy the microbiotic care.

5. Conclusion

According to dermatological assessments, the microbiotic care Symbio® DERMAL supports dry skin prone to neurodermatitis in multiple ways: It increases skin moisture, reduces dryness and flaking and – with special contribution of the lysed *E. coli* - and *Enterococcus faecalis* - bacterial strains - reduced TEWL. As shown in preliminary *in vitro* studies, the complex of lysed bacterial strains can modulate the immune system to promote antiinflammatory reactions. Consequently, the newly developed microbiotic skincare has positive impacts on a disturbed skin barrier and probably also to an inflammatory immunological imbalance - two risk factors for the development of atopic dermatitis.

Conflict of interest:

- Dr. Hans-Jörg Müller is employed as Director Business Development by the SymbioPharm GmbH.
- Dr. Elke Jaspers (mikroLogos GmbH) is working as scientic consultant for the SymbioPharm GmbH.
- Angelika Hecht is employed in the Public Relation Department of the SymbioPharm GmbH.

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*** Annex Download:**

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Boosting the Anti-viral Defense of the Skin

C. Pickel, F. Wandrey, F. Zülli

abstract

The body's immune system recognizes infections with pathogens and reacts towards them in a two-phasic response. In particular, the anti-viral response has caught attention throughout the past year, in which SARS-CoV2 (severe acute respiratory syndrome coronavirus-2) has kept the world in suspense. Training the immune system can have beneficial effects and allows for a faster reaction towards infections, and it was shown that β-glucan promotes trained immunity. CM-Glucan Forte, the water-soluble version of β-glucan combined with magnesium, was previously shown to balance the skin's immune system, alleviating signs of atopic and stressed skin. New data indicate that CM-Glucan Forte is further able to stimulate the anti-viral defense of keratinocytes by upregulating a set of genes that support skin cells' reaction upon infection with a virus and thereby contributing to the anti-viral defense of the skin.

Virus infections and the viral replication cycle

Viruses are submicroscopic infectious organic structures which exploit eukaryotic cells to amplify themselves and spread. For this, it is important to understand that the replication of a virus is not possible without a host cell which provides the machinery for multiplication of the virus genome and synthesis of the structural proteins that make up the virus envelope and capsid. In this way, the virus goes through a replication cycle every time a host cell is infected.

This cycle consists of several steps:

- **Viral entry:** Through specific interaction of a protein on the surface of the virus with a protein (often a receptor) on the surface of the host cell, the virus can attach to the cell surface. The virus is subsequently taken up by the host cell and its genome is released.

- **Replication:** On the one hand, the viral genome is multiplicated by DNA or RNA polymerases (depending on the type of virus) and on the other hand, it is transcribed to mRNA which codes for the proteins making up the virus. These are then produced by the cellular ribosomes.

- **Assembly:** Once all of the viral proteins as well as copies of the viral genome are available, viral particles are assembled within the cell.

- **Release:** The fully assembled viral particles are released into the extracellular fluid, while the infected cell continues to produce new viruses.

The cellular anti-viral defense

The immune system is the body's protection system from infections with bacteria, viruses and foreign bodies that could harm the body. It consists of two parts that work closely together: the innate (general) immune system and the adaptive (specialized) immune system. The innate immune system is often the body's first line of defense and reacts quickly, but non-specifically, towards pathogens that enter the body. However, it has limited power in preventing the spread of viruses or bacteria and therefore activates the adaptive immune system for further support. The role of the adaptive immunity is the targeted elimination of the pathogen by recognizing the type of germ that causes the infection and specifically attacking it through production of neutralizing antibodies and cytotoxic T-cells that eliminate bacteria or cells infected with a virus. While this is usually a slower process due to the need to first identify the pathogen, it offers the advantage of forming an immune memory which allows for a faster reaction the next time the body encounters the same pathogen.

As part of the innate immune system, most cells of the body are able to detect viruses both at their cell membrane and in the cytoplasm though recognition of viral nucleic acids and proteins by so-called pattern recognition receptors (PRR). Binding of viral DNA or RNA to specific PRRs triggers a signaling cascade which results in the secretion of signaling molecules known as inflammatory cytokines and interferons, which attract immune cells that help to fight off the infection and warn neighboring cells of the threat of a potential viral infection, respectively. In response to interferons, surrounding cells upregulate the expression of interferon-stimulated genes (ISGs), a large group of genes which help the

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- **Alleviate skin discomfort in less than one week**

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cells to prepare for a viral infection. The protein products of these genes control virtually all steps of the viral replication cycle, for example through blocking the attachment and entry of the virus into the cell, by preventing the import of viral nucleic acids into the host cell nucleus, by inhibiting synthesis of viral proteins or through preventing the assembly and release of the viral particles [1].

In addition to increasing the antiviral defense locally, cytokines and interferons also attract immune cells to the site of infection. These recruited immune cells help to clear infected cells and amplify the immune response by involving the adaptive immune system. For this, specific cells, broadly termed antigen presenting cells (APCs), process the virus in order to subsequently present parts of it on their surface to activate other types of immune cells. Once the APCs have found and activated immune cells that specifically recognize the infecting virus, these start the second phase of the immune response, consisting of antibody production and targeted elimination of infected cells **(Figure 1)**. In this way, circulating viruses can be neutralized and destroyed before infecting further cells, while cells already infected with the virus can be cleared und ultimately tissue repair can be initiated. These mechanisms occur in most tissues of the body, and are particularly important in the skin, which is our first line of defense against all kinds of infections as it is in constant contact with the outside world.

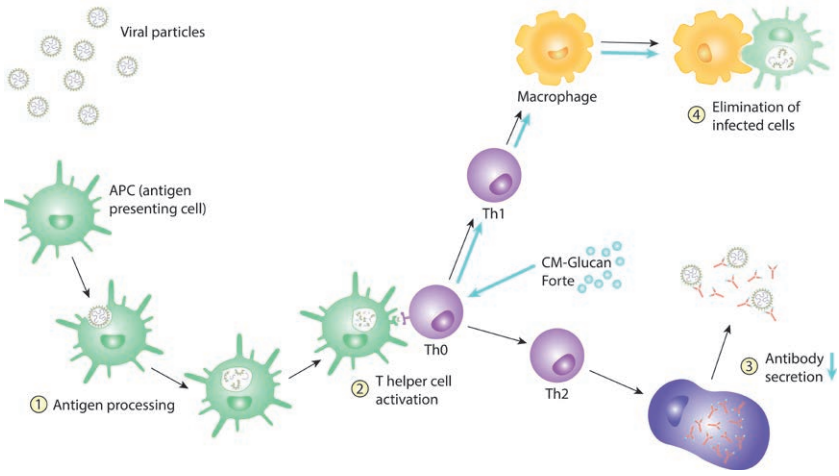

Fig. 1 Immune responses to viral infections.

Very quickly after the beginning of the pandemic, it was shown that on the molecular level, SARS-CoV2 attaches to cells by docking to the angiotensin converting enzyme 2 (ACE2) using the spike protein on its surface, and thereby initiates its uptake into cells **(Figure 2)**. Once inside, the virus uses the cell's replication and protein production machineries to produce new viral particles. When fully assembled, these can exit the host cell and spread within the body or, for example, through sneezing or coughing, to other people.

Despite its actual function in regulating the blood pressure, ACE2, the cell surface receptor for SARS-CoV2, is not only expressed in the cells lining the blood vessels. As the respiratory disease caused by SARS-CoV2 suggests, this molecule is also present on the cells lining the nasal cavities and the lung, and therefore allows the virus to infect these cells [2]. Quite surprisingly, ACE2 is also highly expressed in various other tissues, including the kidney, heart, gastrointestinal tract and the skin [3]. There, it was recently published to be

SARS-CoV2 and the ACE2 Receptor

One specific virus, namely the coronavirus family member SARS-CoV2 (severe acute respiratory syndrome coronavirus-2), has rushed the whole world off its feet for most of the past year. An infection may lead to the severe respiratory disease termed COVID-19 (coronavirus disease 2019) which has caused hundreds of thousands of deaths worldwide until now. Ongoing research is focusing on the development of both vaccines and pharmaceuticals to prevent the spread of the virus and to treat the progression of this serious disease, respectively. Further, the molecular events taking place during viral infection are being studied extensively by researchers all over the world.

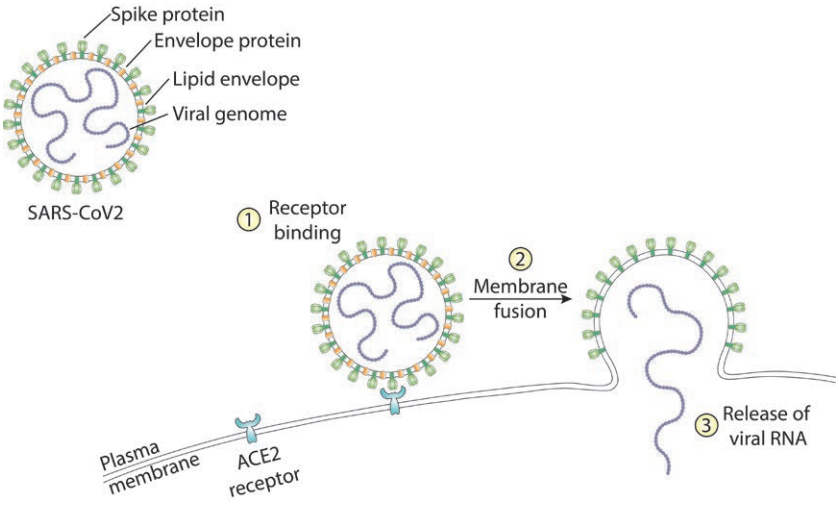

Fig. 2 SARS-CoV2 binding to the ACE2 receptor.

present on keratinocytes, particularly in the basal cell layer of the epidermis, and to be enriched around hair follicles and in cells from sweat and sebaceous glands [4,5]. Further research on the skin as a potential route of entry into the body for SARS-CoV2 would thus be of big interest.

Modulation of the immune response by CM-Glucan Forte

Boosting the antiviral immunity of the skin might be a beneficial strategy, particularly in these times of increased need for protection. This might for example be achieved by topical application of CM-Glucan Forte, a carboxymethylated and thus water-soluble version of β-glucan combined with magnesium. It was shown that β-glucan induces trained immunity, a process which prepares immune cells for an infection by setting them in an alert state and therefore allows them to react faster and stronger when encountering a pathogen [6]. In addition, we have shown that CM-Glucan Forte balances the skin's immune response. Ideally, the activation of a specific type of cells termed T helper (Th) cells by APC initiates the differentiation to both Th1 and Th2 cells that in turn activate a cellular and antibody-mediated immune response, respectively. However, especially in atopic dermatitis, the normally balanced ratio is shifted towards a Th2 response resulting in the production of immunoglobulin E (IgE) antibodies that induce the degranulation of mast cells. This causes the typical symptoms of allergies such as itching and inflammations. In this setting, CM-Glucan Forte acts as a "personal trainer" for the skin and helps it to regain its natural Th1/Th2 balance. It suppresses the allergy related Th2 response and reduces the expression of IgE antibodies which mediate hypersensitivity reactions. By redirecting the immune response to a Th1-mediated reaction, the skin can be additionally supported to react towards viral infections. Therefore, CM-Glucan Forte offers not only relief for already stressed skin, but it additionally supports the skin by preparing it to defend itself from pathogens such as viruses or bacteria.

New insights into the effect of CM-Glucan Forte on anti-viral immune responses

To further investigate whether CM-Glucan Forte can support the immune response in the skin in fighting off potential viral infections by inducing the antiviral response, a study was performed in epidermal keratinocytes obtained from an aged donor. This model was of particular interest as it is known that the anti-viral response is generally impaired in the aged population [7]. For this study, normal human epidermal keratinocytes (NHEK) from a 55-year old donor were incubated with 2 mg/ml CM-Glucan Forte for 48 hours prior to analysis of several ISGs and anti-viral genes.

Treatment with CM-Glucan Forte stimulated the expression of the ISGs ADAP2 (ArfGAP with dual PH domain 2) and GBP1 (Guanylate binding protein 1) by 442% and 202%, respectively. During viral infections, ADAP2 blocks the entry of RNA viruses into the cells, while GBP1 promotes autophagy of viral replication complexes, thereby effectively contributing to clearance of the viral particles from the cytoplasm and helping to prevent the further spread of the virus.

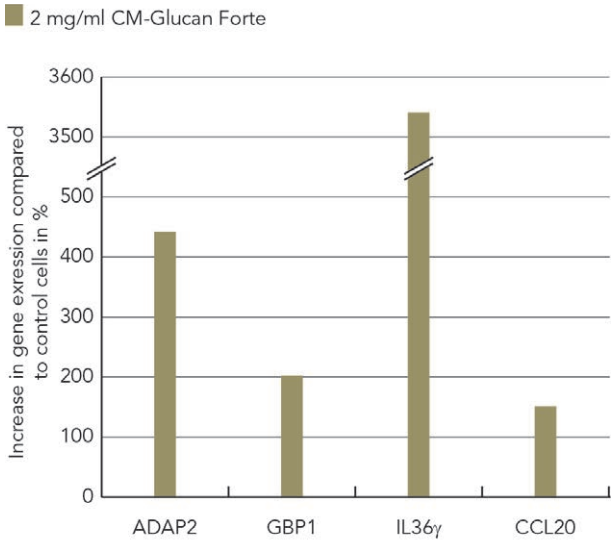

Fig. 3 CM-Glucan Forte upregulates the anti-viral immunity in NHEK.

The expression of IL36γ (Interleukin 36 gamma), an interleukin which participates in the anti-viral response and which counteracts viral immune evasion strategies around the related IL-1, was stimulated by 3541% upon treatment with CM-Glucan Forte. In addition, the chemokine CCL20 (Chemokine (C-C motif) ligand 20), that is involved in the antiviral response by attracting immune cells to the site of infection, was upregulated by 151% upon treatment of NHEK with CM-Glucan Forte. These proteins therefore help the keratinocytes to activate the adaptive immune system for further clearance of a potential viral infection.

Overall, the changes in gene expression of ISG and anti-viral genes indicate that CM-Glucan Forte supports the immune system of the skin by preparing the cells for fending off a viral infection.

Conclusion

Supporting the immune system has become a trend in health care and nutrition. Especially the skin as our first line of defense is exposed to numerous threats from pathogens such as bacteria and viruses. CM-Glucan Forte is able to boost the anti-viral immunity of epidermal keratinocytes, preparing them for a potential viral infection.

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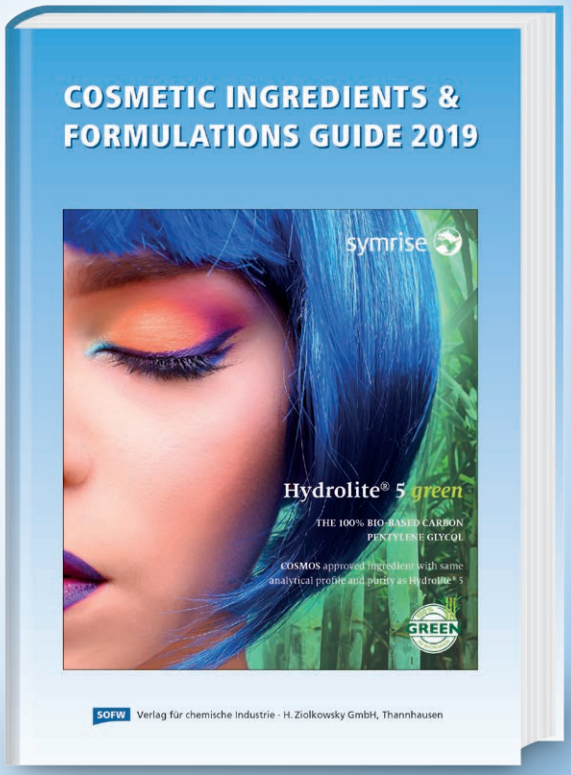

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Piroctone Olamine – Advancing Anti-dandruff Care & More

Efficient and safe scalp care for new formats & applications

K. Kita, F. Caravieri, S. Birkel

abstract

Demand for anti-dandruff hair care is increasing, with research showing dandruff and scalp related issues are particularly common when heat and moist, humid conditions are at play. Safe active ingredient Piroctone Olamine, an established cosmetics preservative, is proven also to be effective at controlling microorganisms responsible for flaking and irritation, reducing dandruff and scalp itch. Furthermore it offers efficient formulating advantages that support application of anti-dandruff action to modern formats such as clear liquid formulas, dry shampoos and leave-on hair repair tonics. We demonstrate its performance as a viable solution for formulators looking to meet hair care demands, with even broader scope of application from anti-acne skin care to deodorants.

Background and market demand

Heat and humidity are recognized contributors to oily scalp [1] and provide the ideal breeding environment for microorganisms known to trigger dandruff. By feeding on the scalp lipids, the microorganisms reduce the strength of the scalp, making it more vulnerable to external pollutants. Existing dandruff, dry scalp and scalp irritation, such as that initiated also by seborrheic dermatitis, is consequently exacerbated, creating a vicious circle for affected consumers.

A prevalence of dandruff and related scalp issues among men and women in hot countries compared to those in Western Europe and the USA underlines this experience. Consumer studies by Clariant Kantar-TNS [2] rank dandruff and itchy scalp as the top hair-related issues for respondents from China, Asia and SE Asia. Oily scalp, itself often indication of seborrheic dermatitis, affects 49% of men and 35% of women in China, as opposed to 18% men and 20% women in France and 10% men and 13% women in the US [3]. Dandruff and itchy scalp are big themes for women in Indonesia and Malaysia with 37% and 79% respectively suffering from dandruff.

Scalp issues are also common among wearers of a hijab, which could be attributed to the heat- and moisture-trapping environment created under the material. Hijab wearers in Turkey, Indonesia and Malaysia rank oily scalp, itchy scalp and dandruff as their top two hair care issues. In Turkey, 59% of hijab wearers experience scalp issues with sensitive and dry scalp a frequent occurrence. 72% of hijab wearers in Indonesia experience scalp issues with dandruff becoming worse when the hijab is worn over wet/moist hair. 80% of Malaysian women experience scalp issues and those who wear the hijab over wet/moist hair more often experience itchy scalp.

These findings suggest significant regional and country-specific demand for effective anti-dandruff scalp care; points of interest for marketeers in the context of the growing global demand for specialized products driving the shampoo segment. "Anti-dandruff" is expected to be the fastest growing segment within the global shampoo market that is projected to grow with a CAGR of approx. > 3.5% during the forecasted period 2020-2025 [4].

With increasing regulatory scrutiny on anti-dandruff active ingredients likely to restrict choice for shampoo formulators, Clariant offers the industry a good compromise between safety, performance and formulation to support future product development.* Intended to treat seborrheic dermatitis and dry scalp specifically, Piroctone Olamine has a proven ability to control the growth of microorganisms and reduce dandruff and scalp itch. It also has a low environmental impact. Piroctone Olamine is not sensitizing nor mutagenic. It is particularly suitable for formulating both shampoos and the wider hair / scalp care formats preferred by today's consumers, such as answering trends for transparent and dry shampoo products, and leave-on hair repair tonics. Furthermore, it is multifunctional, doubling as a preserving agent, and offering properties of interest to the wider Personal Care application areas of anti-acne skin care and deodorants.

This technical paper presents clinical studies and activity testing that demonstrate the ingredient's anti-dandruff performance. They underline its value as an alternative easy-to-use solution for formulating anti-dandruff scalp care relevant to modern requirements, and touch on its suitability as a one-ingredient solution for multiple purposes.

* The anti-dandruff active Piroctone Olamine is available globally, however it is recommended to check regulations in specific regions.

Introducing Piroctone Olamine

Piroctone Olamine is marketed under the registered tradenames Octopirox® and Octopirox® Plus. It has the chemical name 1 Hydroxy-4-methyl-6-(2.4.4 trimethylpentyl)-2(1H)–pyridone, 2-aminoethanol salt, **(Figure 1)**. The minimum 99% active ingredient has good solubility between 1-10% in aqueous surfactant systems as well as alcohol/water mixtures, giving a pH of 9-10 which can be adjusted using organic acids like citric acid or lactic acid. This makes it a versatile ingredient for a variety of cosmetic products.

Despite the anionic character of its molecule, Piroctone Olamine can be used together with most cationic surfactants (quaternary ammonium compounds), cationic active ingredients, and typical additives used in cosmetics. It has a long shelf-life of at least five years if stored correctly in its original sealed container at ambient temperature protected from moisture.

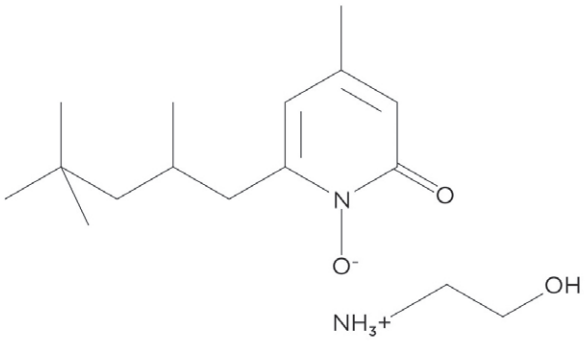


Fig. 1 Molecular structure of Octopirox® and Octopirox® Plus (INCI: Piroctone Olamine)

Dandruff and scalp care – experiments, results and discussion

Seborrheic dermatitis is widely believed to be caused by the Malassezia fungus. Microorganisms such as *Malassezia furfur* produce enzymes which decompose fats into their respective fatty acids. These and other products of decomposition, such as lipo-peroxides, irritate the scalp. As a result, mitosis and production of keratinocytes increase, leading to desquamation and parakeratosis [5].

Piroctone Olamine is an ethanolamine salt of piroctone that is known to be particularly effective against these fungi [6]. It is thought to inhibit fungal cells from using energy. It has been observed to successfully reduce the level of fungi and change the composition of lipid and fats on the scalp.

Its ability to effectively control the growth of microorganisms and reduce the occurrence of dandruff and scalp discomfort is demonstrated here through clinical studies and laboratory testing.

Dandruff and flake free

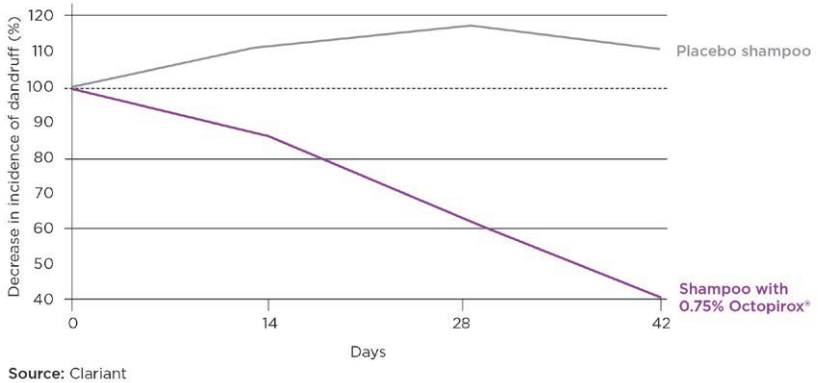
The following clinical study indicates the performance of Piroctone Olamine as an effective anti-dandruff active ingredient [7].

A shampoo formulated with Piroctone Olamine as an active was compared to a placebo shampoo. **Figure 2** highlights the efficacy of the ingredient at a concentration of 0.75% over the course of 1.5 months, showing a clear decrease of dandruff compared to the placebo.

Further testing has determined that use concentration for anti-dandruff applications can be chosen between 0.1 and 1.0%, depending on the desired finished product. For shampoo, this information was obtained through a double blind study conducted with 88 volunteers in which quantity of flakes and flake size were evaluated before, during and after treatment over five visits during an eight-week period.

STUDY: ANTI-DANDRUFF ACTION IN SHAMPOOS

In a study over the course of 1.5 months, a formulation with Octopirox® at a concentration of 0.75% showed clear decrease of dandruff compared to a placebo shampoo.



Source: Clariant

Fig. 2 Anti-dandruff action

Itch free scalp

Scalp itch is a condition mostly caused by dandruff irritating the scalp. As the skin sheds its outer layer in a bid to get rid of the irritant, it causes the familiar discomfort and itchy sensation. The Clariant Kantar TNS [8] study showed that of the approximately 500 people interviewed in each country – Brazil, Switzerland, France, USA and India - up to 10% suffer from itchy scalp.

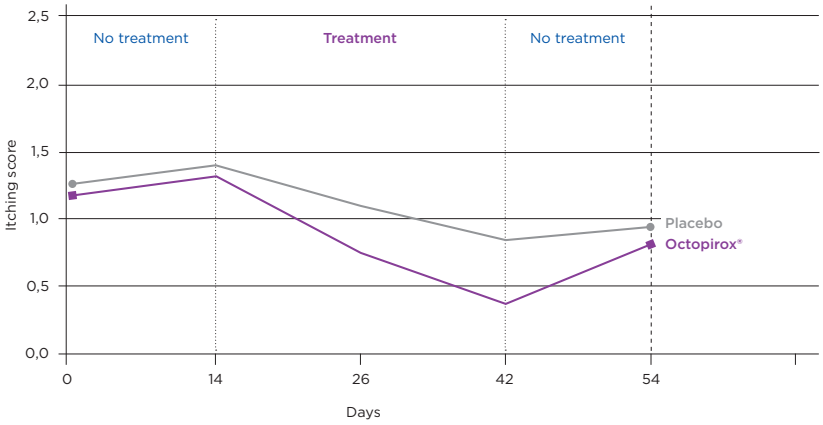
The following double blind, randomized placebo-controlled study on the efficacy of a Piroctone Olamine treat-

ment applied after 14 days (2 weeks after start of evaluation; 4 weeks treatment (from day 15 till day 42) shows that Piroctone Olamine at a concentration of 0.5% helps relieve the itching within days and after the treatment it holds several days. A reduction in itching is experienced compared to the placebo during the treatment.

Even though anti-dandruff shampoo is the largest format within scalp care area, potential other scalp care products such as conditioners / treatments, dry shampoo and cream rinses can be formulated with Piroctone Olamine. In the following sections, we highlight the particular formulation characteristics of Piroctone Olamine and indicate its suitability for achieving formats offering anti-dandruff properties that support latest consumer trends.

STUDY: ITCHING REDUCTION WITH SHAMPOO PIROCTON OLAMINE TREATMENT

In a comparison with a placebo it has been shown that a 0.5% concentration of Octopirox® helps relieve the itching within days.



Source: Doctorate thesis 2005, Marcus Blömer, 262/5000, Double-blind, randomized, placebo-controlled.

Fig. 3 Itching reduction with anti-dandruff treatment containing 0.5% Piroctone Olamine and 0.35% $ZnCl_2$ [9]

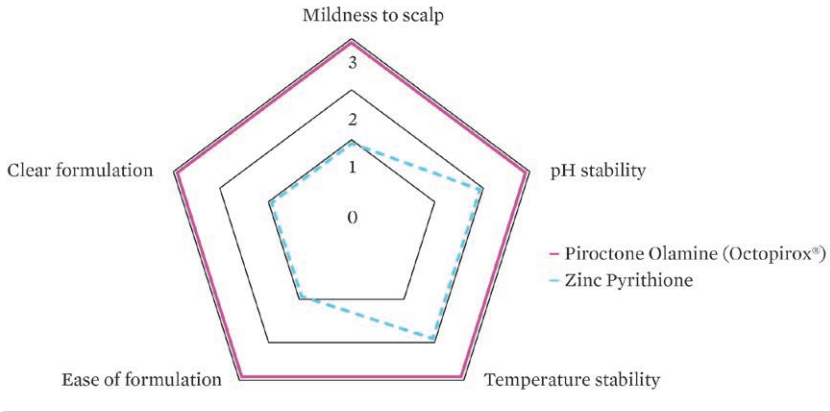


Fig. 4 Anti-dandruff action

Formulating With Piroctone Olamine

Piroctone Olamine shows a number of formulation advantages, as illustrated in the spider graph **(Figure. 4)**, which can contribute to an easy formulation process. Formulating with Piroctone Olamine is seen to be easier and more efficient than with Zinc Pyrithione. Factors such as compatibility with cosmetics raw materials, influence on viscosity in surfactant systems, pH and temperature stability, and solubility create formulation freedom for the Personal Care industry.

Formulation Stability

Piroctone Olamine makes stable formulations with no addition of a stabilizer. This is an advantage over ZnPTO, which, as a particulate material, is insoluble in water and requires a suspending agent to disperse. In some surfactant systems Piroctone Olamine may cause an additional increase in viscosity, which can be considered beneficial in order to economize on consistency modifiers during formulation development.

Influence of pH value and thermal stability

With a pKa value of ca. 7.4 Piroctone Olamine is present as free acid in neutral solutions and is chemically stable over a wide pH range, from pH 3 to pH 9. in which are typical formulation conditions for Personal Care products.

Low dosage requirements

The following typical concentrations have been determined through internal testing and indicate the low dosage requirements of the active ingredient:

- Hair shampoo 0.3-1.0%
- Hair tonics 0.05-0.1%
- Hair conditioners 0.1-0.3%
- Setting lotions / hair gels 0.05-0.2%
- Hair creams 0.1-0.3%

Application in trend formats

Our formulation development team has taken the reduction in dandruff and scalp itch benefits of Piroctone Olamine as well as its formulating characteristics into consideration to create several example product concepts that tie in with consumer format and performance preferences. The following

shampoos and leave-on treatment for scalp care combine anti-dandruff action with ingredients offering specific conditioning and, where relevant, foaming behaviours.

Transparent anti-dandruff shampoo

Consumer association between purity and transparency is leading to a rise in demand for transparent, cosmetics products. Piroctone Olamine's good solubility makes the active ingredient especially suitable for the formulation of clear products. This is of potential significance to the anti-dandruff shampoo segment, where most take the form of white viscous liquids. This is due in part to the difficulty in formulating a transparent shampoo because of the large particles and white appearance of the Zinc Pyrithione, the most common anti-dandruff agent.

To demonstrate the suitability of Piroctone Olamine for answering the market trend in this application segment, 0.5g of the ingredient (0.5% of the formulation) was used in a transparent anti-dandruff shampoo formulation with good conditioning performance.

Phase	Ingredients (trade name | INCI name)	Function	% w/w
A	Water		q.s.
	Genapol® LRO paste (Clariant) *Sodium Laureth Sulfate*	*Anionic surfactant*	**9.00**
	Genagen® SC 35 (Clariant) *Sodium Laureth Sulfate, Cocamide MEA, Aqua*	*Surfactant*	**2.00**
	Genagen® CAB 818 (Clariant) *Cocamidopropyl Betaine*	*Amphoteric surfactant*	**12.00**
B	**Octopirox® (Clariant)** *Piroctone Olamine*	*Active ingredient*	**0.50**
	Water		5.00
C	Sodium Chloride	*Consistency factor*	1.30
	Water		15.00
D	Citric Acid	*pH regulator*	q.s.

Procedure
I. Prepare phase A by adding the listed ingredients
II. Prepare phase B by ispersing Octopirox® and add to I.
III. Adjust viscosity with phase C and pH with phase D (around 5.0-6.0)

Results
pH 5.00
Viscosity (Brookfield, 20°C 20 rpm): 18000 mPa s
Stability: 3 months at 4°C, RT, 37°C, 45°C
Appearance: transparent liquid
Preservation: challenge test according to European Pharmacopoeia, pass A

Formulation 1: Transparent Anti-Dandruff Shampoo Basic formulation suitable for the mass market. Genagen® SC 35 is an effective and easy-to-use thickener, which is activated in the presence of salt. It does not contain DEA, which makes the product safe from nitrosamines. Octopirox® is not only an effective anti-dandruff agent, but also an efficient preservative for cosmetic products.

Dry anti-dandruff shampoo

It is estimated that by 2025 half of the world's population will be living in water-stressed areas [10]. The value of water is changing how young, sensible and environmentally-conscious consumers shop. They love nature and strive to protect it. To help the beauty sector to find new ways to formulate without water and offer anti-dandruff action, Clariant has successfully applied 0.5% Piroctone Olamine to a concept dry shampoo powder formulation.

Phase	Ingredients (trade name | INCI name)	Function	% w/w
A	Agenajel 21287 *Zea Mays (Corn) Starch*	*Consisency factor*	45.63
	Hostapon® SCI 85 P (Clariant) *Sodium Cocoyl Isethionate*	*Anionic surfactant*	**29.41**
	Polyglykol® 3350 P (Clariant) *PEG-75*	*Humectant*	**10.00**
	Sodium Bicarbonate	*pH regulator*	6.20
	Allantoin (Clariant) *Allantoin*	*Active ingredient*	**0.50**
	Hostapon® TPHC (Clariant) *Sodium Methyl Oleoyl Taurate*	*Anionic surfactant*	**2.00**
	Octopirox® (Clariant) *Piroctone Olamine*	*Active ingredient*	**0.50**
	Coguar 113 (Clariant) *Hydroxypropyl Guar Hydroxypropyltrimonium Chloride*	*Conditioning agent (hair)*	**0.30**
	Citric Acid	*pH regulator*	5.00
B	**Patauá Oil (Beraca)** *Oenocarpus Bataua (Pataua) Fruit Oil*	*Conditioning agent (hair)*	**0.20**
C	Fragrance 'Silk & Velvet' (Bell)	*Fragrance*	0.20

Procedure
I. Mix the components of A and blend for 5 minutes (if possible grind for 5 minutes).
II. Add B drop by drop and blend for another minute.
III. Add C drop by drop and blend for another minute.

Results
pH (1% in water) 6.5-7.0
Viscosity (Brookfield, 20°C 20 rpm): n/a
Appearance: off-white fine powder
Stability: 12 weeks at RT and 40°C

Formulation 2: BLUE GOLD Dry Shampoo Hostapon® SCI 85 and Hostapon® THPC are solid surfactants that create a generous foam when activated with water. Coguar® 113 is ideal to bring conditioning benefits on wet hair. Pataùa oil and Allantoin® Premium both care for tired scalp by promoting hydration and improving the removal of squams. Finally, the anti-dandruff property of this powder shmapoo is achieved by Octopirox®.

Its ingredients create a generous foam when activated with water and bring conditioning benefits on wet hair, in addition to the anti-dandruff properties and improving the removal of squames.

Leave-on treatment for scalp care

Similarly to specialized skin care, where ampoules and single-dose products have won consumers' hearts for applications in target areas and offer highly concentrated products promising premium performance, some scalp care product manufacturers rely on leave-on formats offering the most efficient solutions. In line with the quest for specialized, cosmeceutical-like solutions, Clariant offers a leave-on treatment formulation for scalp care, containing 0.05% Piroctone Olamine to overcome dandruff, as well as conditioning ingredients to have favourable effect on the hair. Reinforced with vitamins, the formula is intended to care for both scalp and hair, and to help consumers target the application frequency and areas of concern according to their specific, individual needs.

Phase	Ingredients (trade name | INCI name)	Function	% w/w
A	Propylene Glycol	*Solvent*	0.70
B	**Octopirox® (Clariant)** *Piroctone Olamine*	*Active ingredient*	**0.05**
C	Carbopol® 980 *Carbomer*	*Polymer (thickening/ suspending)*	0.60
D	**Genamin® KDMP (Clariant)** *Behentrimonium Chloride*	*Cationic surfactant*	**0.20**
	Genamin® CTAC (Clariant) *Cetrimonium Chloride*	*Cationic surfactant*	**0.50**
	Starch (Wheat)	*Consistency factor*	0.50
	Dimethicone Copolyol Acetate	*Silicone*	0.80
	Dimethicone Copolyol	*Silicone*	0.50
E	Water		Ad 100
	Panthenol	*Active ingredient*	0.20
	Polyquaternium-4	*Conditioning agent*	0.10
	Benzophenone-4	*Sun filter*	0.05
	Nicotinamide	*Active ingredient*	0.30
	Tocopheryl Acetate	*Ingredient protectant*	0.10
	Caustic soda (50% in water)	*pH regulator*	0.80
F	Guar Hydroxypropyltrimonium Chloride	*Polymer (conditioning/ additive)*	0.20
G	Fragrance	Fragrance	q.s.

Procedure

I. Mix the components of A and blend for 5 minutes (if possible grind for 5 minutes).
II. Add B drop by drop and blend for another minute.
III. Add C drop by drop and blend for another minute.
IV. Add I to III
V. Heat IV to about 80°C
VI. Add C to II and add V directly
VII. Stir until cool
VIII. Add the components of G at about 35°C

Formulation 3: Instant Anti-Dandruff Vitamin Hair Repair Leave-On

Antimicrobial action in wider application areas

Further to its antimicrobial action of relevance to hair and scalp care, Piroctone Olamine is proven to offer broad spectrum activity against yeast, mould, and gram positive and gram negative bacteria. This, in combination with its long shelf life and good formulation compatibility, has supported its 30 year-use in cosmetics as a preservative, both solo and in blends.

The antimicrobial action extends benefits to wider application areas with the active ingredient able to substantiate claims of interest to anti-acne treatment products, a globally growing market, and to provide differentiation to deodorants. For example, internal testing by Clariant indicates activity against Propionibacterium acnes, a gram-positive human skin commensal that prefers anaerobic growth conditions and is involved in the pathogenesis of acne, suggesting the suitability of Piroctone Olamine as an active ingredient in gel, lotion and cleanser anti-acne products. Typical concentrations in leave-on anti-acne products is a low dosage level of up to 0.2%

Its efficacy in a deodorant formulation and applicability in enhancing performance has also been demonstrated against triclosan. Piroctone Olamine is shown to offer better deodorancy when each is used at 0.1% dosage in a sample roll-on deodorant formulation. Typical concentrations of Piroctone Olamine in deodorants, established through internal testing, is low dosage of 0.1-0.3%

CONCLUSION: performance with formulation freedom for scalp care and more

The effective anti-microbial action, safety profile and formulation freedom offered by active ingredient Piroctone Olamine combine together to deliver new possibilities for formulators to create differentiated anti-dandruff scalp care products.
This technical paper has highlighted its scalp care-related benefits and features at low-dosage:

- Dandruff and flake-free
- Itch-free and mild to scalp
- Non-irritating and non-allergenic
- Suitability for transparent formulations
- Formulation ease: compatibility with cosmetics ingredients; processing stability; and solubility.

Furthermore, its proven, effective performance extends to multiple applications in deodorant and anti-acne skin care products. Piroctone Olamine is also a highly-valued broad spectrum preservative. Taking all this into account, the active ingredient presents Personal Care formulators with a versatile, low-dosage one-tool solution that can save on inventory. Importantly, it also offers the industry an alternative to existing actives currently under market scrutiny.

For more information on formulation specifics and to obtain a sample of Octopirox, visit **www.clariant.com/octopirox** or scan the QR-Code:

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The Study of a Palmitoyl Oligopeptide Complex: a 3D Anti-aging Theory

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abstract

Skin is a multifunctional organ but, alongside every other organ system, is subject to both intrinsic and extrinsic aging. Whilst both ageing processes are associated with phenotypic changes in cutaneous cells, the major functional manifestations of ageing occur as a consequence of structural and compositional remodeling of normally long-lived dermal extracellular matrix proteins, flattened dermal-epidermal junction (DEJ), and weaker epidermal function. Many researchers revealed that dermal fibroblast which mainly synthesis the collagen and elastin in dermis, while the epidermal keratinocyte and DEJ are lesser described, especially for peptides. A new palmitoyl oligopeptide complex PTC, which consists of hydrolyzed collagen and oligopeptide, was identified in both keratinocyte and fibroblast, and finally verified in human skin. All data suggest PTC had a 3D theory against skin aging: from epidermal keratinocyte to dermal fibroblast, especially containing the structural proteins of DEJ.

Introduction

Skin is a multifunctional organ but, alongside every other organ system, is subject to both intrinsic (chronological) and extrinsic (environmental) aging. Skin function is mediated primarily by the structure of the epidermal and dermal layers. The epidermis as well as the dermis is becoming thinner and the dermal epidermal junction flattens in skin aging [1]. Many researchers revealed that dermal fibroblast which mainly synthesis the collagen and elastin contribute to maintaining the skin's elasticity and inhibit wrinkling of skin *in vitro* and *in vivo* [2-4], while the epidermal keratinocyte and dermal-epidermal junction (DEJ) are lesser described, especially in palmitoyl oligopeptides, a kind of raw material, largely applied in cosmetics.

Many peptides have functions such as maintaining skin elasticity, strengthening joints and retaining moisture, including collagen and elastin [5, 6]. Due to the large size of the collagen molecule unable to absorb, oligopeptides were been widely used recently, especially the palmitoyl oligopeptides, including tripeptide to six peptide. We combined two high throughputs screening methods focus on cell proliferation and type collagen I synthesis which is the common factors related to aging, to validate lots of active ingredients from different plants and peptides, and finally got a palmitoyl oligopeptide complex PTC, which consists of hydrolyzed collagen and oligopeptide. Then the anti-aging effect of PTC was identified in both keratinocyte and fibroblast, and finally verified in human skin. All data suggest a new 3D theory for anti-aging effect of PTC: 1st layer, to accelerate keratinocyte proliferation and stimulate transforming growth factor β1 (TGF-β1) expression; 2nd layer, to improve synthesis of 3 key proteins in DEJ; 3rd layer, to repair dermal reticulate structure.

Methodology

PTC Preparation

The palmitoyl oligopeptides (ZPC peptide, China) were mixed with different proportions and dissolved in 1, 2-hexanediol (CAS No. 6920-22-5), followed by hydrolyzed collagen added into the liquid. Finally, PTC solution was obtained through filtration

Maintenance of Cells

Normal human epidermal keratinocytes (NHEK) and human dermal fibroblast from adult (HDF-a) were procured from Sciencell company. NHEK cells were cultured in Dulbecco's modified Eagle's medium (DMEM; Invitrogen, CA) high glucose medium, with 10% fetal bovine serum (FBS; Invitrogen, CA), penicillin and streptomycin (100 µg/ml; Invitrogen, CA). HDF-a cells were cultured in FM medium (Sciencell, China) completed with 10% FBS, 1% FGS including insulin and penicillin-streptomycin solution (100 µg/ml; Invitrogen, CA). Both cell lines were mantainced at 37°C in a humidified CO_2 (5%) chamber (Thermo Fisher Scientific, USA).

Cell Proliferation Experiments

NHEK keratinocyte and HDF-a fibroblast was used to detect the proliferation effect in epidermis and dermis according to literatures [6-8]. Briefly, NHEK and HDF-a cells were seeded in the 96-well plate at a density of 5000 cells/well. When cultured overnight in DMEM or FM media with

10% FBS, the cells were continually incubated with various concentrations of PTC (0.004-1%) in the medium without FBS for 24 to 72 hrs. respectively. Cells treated with vehicle served as a control. The cell proliferation rate was estimated by MTT (Sigma, USA) assay at 492 nm after incubation using the Multiscan FC microplate reader (Thermo Fisher Scientific, USA). From the values obtained, the percentage proliferation was calculated from the following equation:

$$\text{Viability (\%)} = OD492_{treatment}/OD492_{control} \times 100\%$$

DEJ Proteins ELISA Detection

The DEJ composition proteins such as laminin 5, intergrin β1, type IV collagen and type VII collagen were detected on NHEK and HDF-a cells by ELISA assay [9, 10]. NHEK and HDF-a cells were seeded into 12-well plates (50000 cells/well). The cells were treated with PTC (0.004-1%) similar with proliferation assay described above. After incubation period, the supernatant and cells were collected respectively. Laminin 5, intergrin β1, type IV collagen and type VII collagen content was estimated using commercially available ELISA kits (Elabscience, China) according to its manual. The percentage rate of growth was calculated from the following equation:

$$\text{Growth rate (\%)} = OD450_{treatment}/OD450_{control} \times 100\%$$

Dermal Proteins Detection

The synthesis of type I, type III collagen and the dermal extracellular matrix (ECM) component fibronectin were detected on HDF-a cells by ELISA assay [11]. HDF-a cells were treated with PTC (0.004-1%) similar with proliferation assay. After incubation period, the supernatant and cell lysates were collected respectively. Type I collagen (Takara, Japan), type III collagen (Elabscience, China) and fibronectin (R&D, USA) content was estimated using commercially available ELISA kits according to its manual. The percentage rate of growth was calculated as described above.

For visualization of type I and III collagens, PTC treated HDF-a cells were firstly fixed with cold methanol (CAS No. 67-56-1; Sinopharm, China) at 4°C for 10 min, and then 0.5% triton X-100 (Sigma, USA) was incubated with cells for 15 min. After washing, cells were blocked with 3% BSA for 1.5 hrs at room temperature. Finally cells were stained with anti-collagen I and III antibody (Abcam, CA) at 4°C overnight and anti-rabbit IgG Alexa Fluor(R) 488 antibody (CST, USA) was used to detect the fluorescence. The nuclei were stained with DAPI (Abcam, CA) and the images were captured using fluorescence microscope (Leica, GER) [12].

TGF-β1 ELISA Detection

NHEK and HDF-a cells were treated with PTC (0.004-1%) similar with proliferation assay. After incubation period, the supernatant were collected and TGF-β1 content was estimated using commercially available ELISA kits (Neobioscience, China) [13]. The percentage rate of growth was calculated as described above.

Skin Wrinkles Evaluation

A clinical study of 20 subjects (the average age was 41.5) was performed to evaluate the effects of PTC on facial wrinkles and roughness [14, 15]. During 8 weeks treatment, participants applied 2 mg/cm2 test formula (contained 5% PTC) and vehicle around the left and right eye every morning and evening after cleansing. Photo were taken and analyzed by visioscan VC98 (CK company, GER) using SELS multi parameter analysis at the following time points: baseline (T0), after 2, 4, 6 and 8 weeks of use (Tw). The reduction of skin wrinkle and roughness was calculated from the following equation:

$$\text{Reduction (\%)} = (SELS_{Tw}/SELS_{T0})\ \text{test formula} / (SELS_{Tw}/SELS_{T0})\ \text{vehicle} \times 100\%$$

Statistical Analysis

All experiments were repeated at least three times with different batches of cells. Data were evaluated statistically using Student's t-test. Statistical significance was set at $P<0.05$.

Results and Discussion

PTC improves the proliferation of NHEK and HDF-a

Cellular senescence plays a vital role in regulating cellular aging both *in vitro* and *in vivo*. The aging cells are identified with a distinct phenotype, which includes flat morphology, bulged cell size, slowed proliferation rate and changes in protein and gene level [7, 16]. The cells treated without FBS for 72 hrs, appeared as aging cells under the microscope **(Figure 1A and B, control w or w/o FBS)**.

When treated with PTC (0.06% to 0.25%) without FBS for 24, 48 and 72 hrs, the cell number was significantly increased in comparison to the untreated control cells **(Figure 1A and B)**. Meanwhile 0.5% and 1% PTC showed no toxicity on cell morphology and cell number (data not shown).

MTT results showed that the highest cell viability rate were 239.4% after 0.016% of PTC treatment for 72 hrs on NHEK cells **(Figure 1C)**, while for 24 and 48 hrs PTC at low concentrations still significantly improved the cell viability. On HDF-a cells, the cell viability was maximum induced to 155.3% after 0.25% of PTC treatment for 72 hrs on NHEK cells **(Figure 1D)**. It verified the proliferation efficacy of PTC in epidermal keratinocytes and dermal fibroblasts.

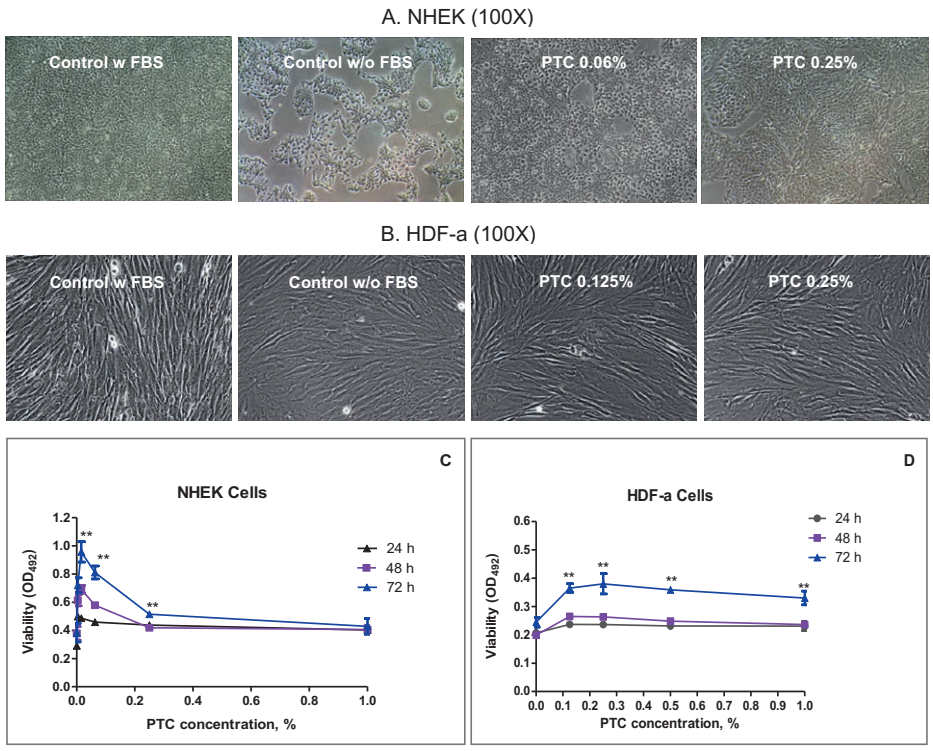

Fig. 1 Proliferation effect of PTC on keratinocyte and fibroblast cells. (A-B) Cells were incubatedwith PTC for 72 hrs. The image was taken under a light microscope magnification. (C-D). The cell viability was measured by MTT results when treated with PTC from 24 to 72 hrs. Data represent mean±SD of at least three individual experiments (**P<0.01 by Student's t-test vs.control).

PTC improves the expression of DEJ proteins

The presence of both keratinocytes and fibroblasts is crucial for an optimal localization of DEJ components. Several proteins produced by keratinocytes such as integrins, nidogen, type IV collagen, type IV collagen and laminin-5. Fibroblasts were required for correct deposition at the DEJ of type VII collagen and laminin-5 [10].

We tested the expression of different proteins from 24 to 72 hrs using the supernatant and cell lysates on NHEK treated with PTC (0.063% to 1%). Results indicated when treatment for 48 and 72 hrs, the intercellular and extracellular amount of type VII collagen were significantly increased in comparison to the untreated control cells, with a maximum rate of growth to 813.2% and 378.0% respectively **(Figure 2 A and B)**. Only the extracellular amount of type IV collagen was regulated from 375.9 to 1063.6 pg/ml by PTC at 72 hrs **(Figure 2C)**, and the maximum rate of growth of intergrin β1 was moderately upregulated to 162.5% compared to untreated cells **(Figure 2D)**, while laminin 5 was not changed with data not shown.

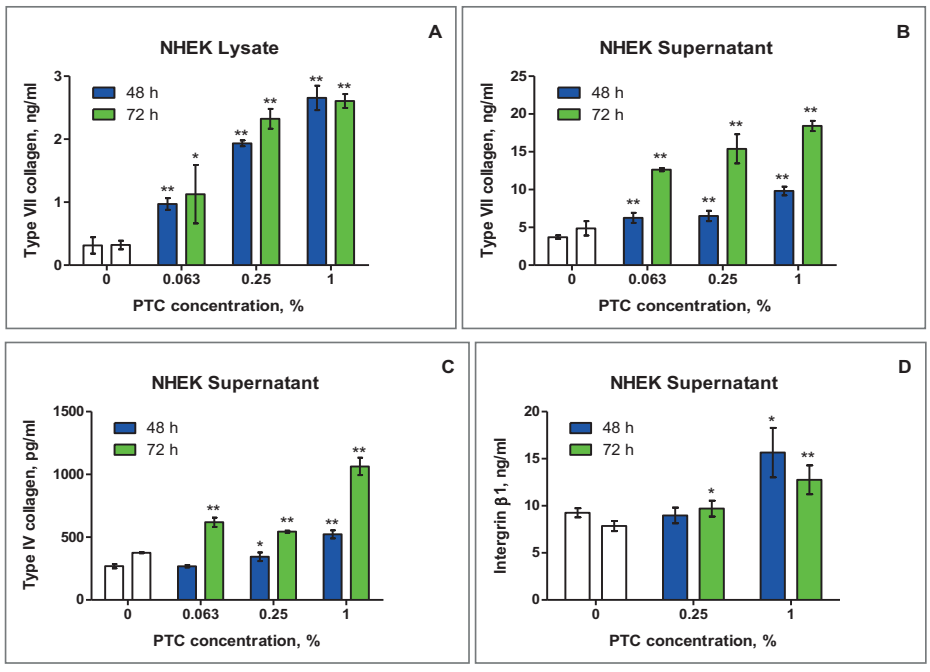

Fig. 2 PTC increases the expression of DEJ proteins on NHEK cells. (A-D) ELISA assays. Data represent mean±SD of at least three individual experiments (**P<0.01,*P<0.05 by Student's t-test vs. control).

The extracellular and intercellular amount of type VII collagen, type IV collagen and laminin 5 was detected on HDF-a cells either. But PTC wasn't significantly affecting the synthesis and secretion of these proteins when treatment for 24, 48 and 72 hrs (data not shown). The correct deposition will be verified on the reconstructed full skin models in future.

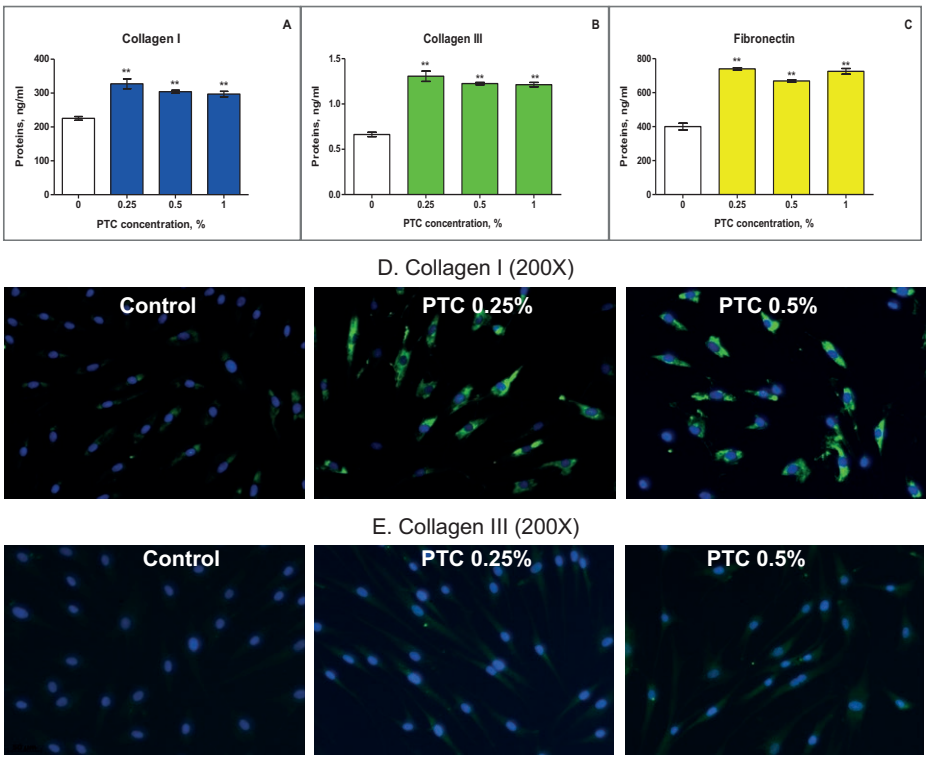

Fig. 3 PTC increases the expression of collagens and fibronectin on HDF-a cells. (A-C) The extracellular amount of proteins treated by PTC for 48 hrs was detected by ELISA assay. Data represent mean±SD of three individual experiments (**P<0.01 by Student's t-test vs. control). (D-E) Collagens were measured by immunofluorescence assay. The image of cells was taken under a fluorescence microscope (Green for target proteins; Blue for DAPI).

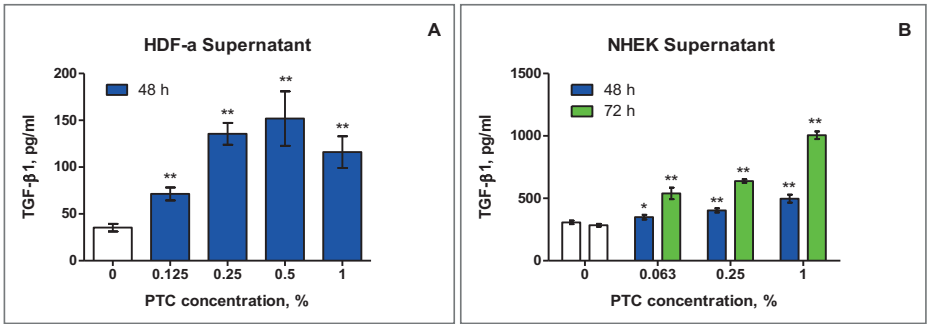

Fig. 4 PTC increases the expression of TGF-β1 on HDF and NHEK cells. (A-B) ELISA assays. Data represent mean±SD of three individual experiments (**P<0.01,*P<0.05 by Student's t-test vs. control).

PTC induced the synthesis of collagens and ECM proteins

Dermal fibroblasts are thought to be responsible for synthesising the three major groups of dermal ECM proteins including fibrillar collagens, elastic fibres and proteoglycans [2]. The efficacy of PTC was verified in dermis further.

Skin HDF-a fibroblast treated with PTC synthesized more type I collagen, type III collagen and fibronectin than untreated control cells from 24 to 72 hrs in our studies. When cells were treated with 0.25% PTC for 48 hrs, the extracellular amount of type I collagen synthesis was increased from 225.4 to 327.4 ng/ml and type III collagen synthesis increased from 0.66 to 1.31 ng/ml; the fibronectin was also increased from 400.3 to 785.7 ng/ml **(Figure 3 A to C)**. The maximum growth rate of collagen I, collagen III and fibronectin was reached to 145.2, 198.5% and 196.3% respectively. Immunofluorescence data confirmed this result **(Figure 3 D and E)**.

PTC upregulated TGF-β1 expression

TGF-β1 is the cytokine that contributes primarily to the biosynthesis of collagen associated with cutaneous aging [17]. It also acted as an important modulator of cell growth, inflammation, matrix synthesis and apoptosis [18].

We firstly detected the expression of TGF-β1 on HDF cells to illustrate the mechanism of collagen synthesis when treated with PTC. As shown in figure 4A, after treatment for 48 hrs, the amount of TGF-β1 was significantly improved compared to untreated cells, from 35.3 to 151.9 pg/ml at 0.5% concentration. Further, we also measured the expression of TGF-β1 on NHEK to confirm a hypothesis: PTC promotes the epidermal cells releasing TGF-β1 to enhance cell proliferation and biosynthesis of collagens to against skin aging. Results showed in Figure 4B, when treated NHEK cells with PTC for 48 and 72 hrs, the extracellular amount of TGF-β1 were maximally regulated to 1005.1 pg/ml at 1% concentration. The growth rate was reached 353.7% compared to control.

PTC reduced the wrinkles and roughness of human skin

The clinical trial results indicated a higher incidence of improvement with PTC than with the placebo **(Figure 5)**. When applied with formulas (5% PTC) for 8 weeks, the surface evaluation of wrinkles (SEw) and surface evaluation of roughness (SEsm) was reduced from 100% to 80.6% and 86.3% respectively. Macrophotography of the left side of the face also showed a reduction in lines and wrinkles.

Conclusions

We confirm that PTC, a palmitoyl oligopeptide complex, exhibits anti-aging effects based on a 3 Dimension Theory: 1st layer, to rejuvenate epidermis by improving the proliferation rate of keratinocytes; 2nd layer, to rebuild DEJ by increasing the synthesis of DEJ proteins such as type IV collagen, type VII collagen and integrins; 3rd layer to regenerates dermis by regulating the fibroblast proliferation, biosynthesis of collagens and ECMs, to against skin aging. A schematic diagram of PTC's therapeutic mechanisms based on whole experimental results is illustrated in **Figure 6**.

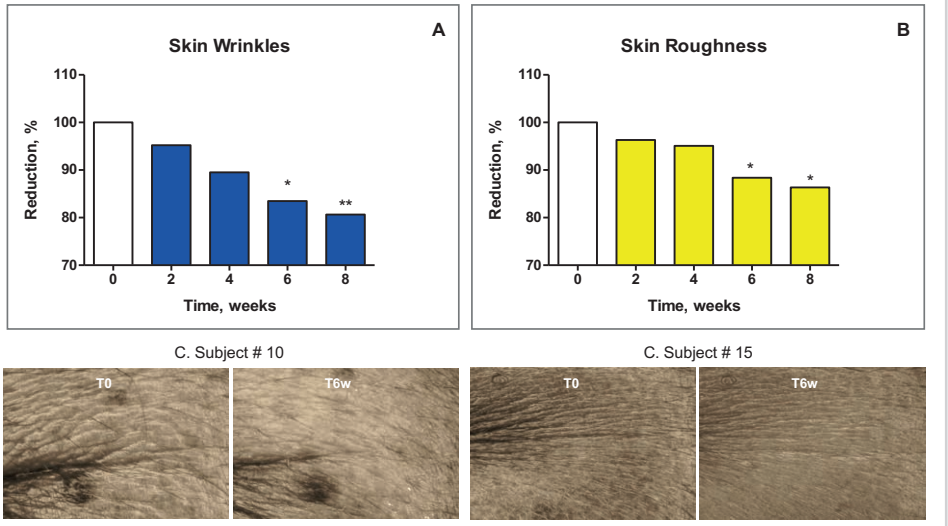

Fig. 5 PTC improved the skin wrinkles and roughness. (A-B) The reduction of skin wrinkles and roughness was detected by VC98. (C) The photo was taken by VC98 in two subjects (Subject #10, 47 old-years; Sebject #15, 32 old-years.)

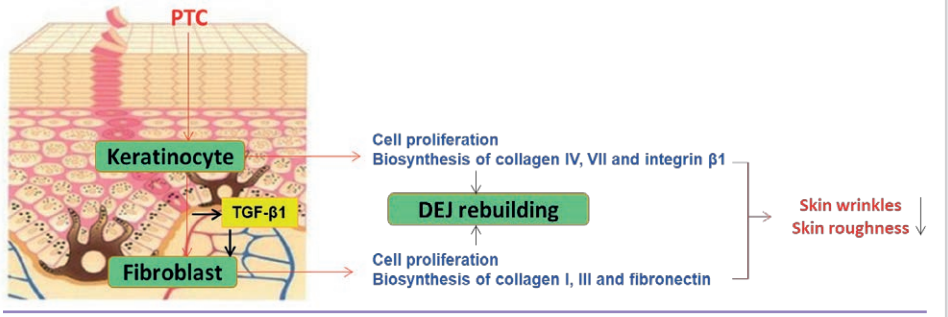

Fig. 6 Possible therapeutic mechanisms based on our results. These mechanisms could elucidate the efficacy of PTC against skin aging.

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Affiliations

The authors declare no conflict of interest.

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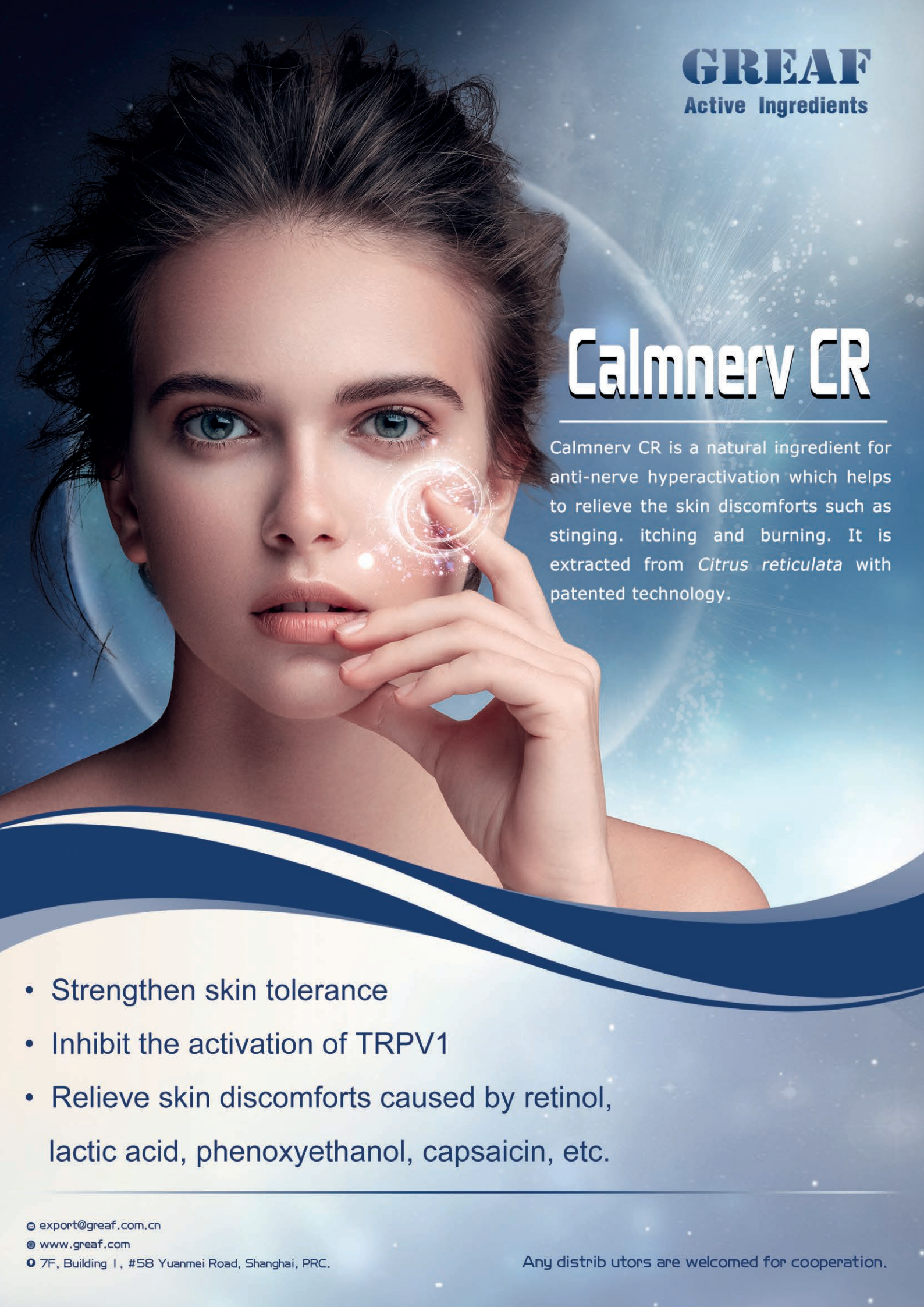

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Disinfectant with Prolonged Efficacy against Microorganisms without Leaving Chemical Deposits on the Surface

K. Henning

abstract

A disinfectant composition having prolonged activity against microorganisms contains a biocide, particularly chlorhexidine or biguanide such as polyhexamethylene biguanide, in combination with a film-forming component including polyvinyl alcohol, polyvinyl pyrrolidone or polyalkylene glycol, and optionally a tertiary amine. The disinfectant composition forms a film on a hard surface that is abrasion resistant and exhibits biocidal activity over an extended period of time while being fully dispersible in water.

Effectiveness of disinfectants

Commercially available disinfectants usually have a good killing effect of microorganisms on surfaces when applied, but for many disinfectants this effect decreases rapidly after application. Most importantly, the disinfectant cannot remain on the surface for any length of time and be persistently effective. The disinfectant either degrades rapidly, evaporates, or tends to be physically removed from the surface by repeated touching or wiping with a cloth. Consequently, if the surface becomes re-contaminated, the disinfectant must be reapplied with a cloth to kill the deposited microorganisms.

The various disinfectants used so far contain alcohols such as isopropyl alcohol and ethanol, copper compounds, silver compounds, aldehydes, oxidizing agents such as sodium hypochlorite and the like.

Ideally, a disinfectant has broad-spectrum activity against all types of microorganisms at different pH levels. The disinfectant should also have high efficacy so that a minimal amount of the antimicrobial agent can be used to save costs and avoid or reduce potential adverse effects caused by the antimicrobial agent. It is also desirable that the disinfectant be stable to any temperature changes that occur during manufacturing, packaging and transportation, and storage. Furthermore, an ideal disinfectant is physically and chemically compatible with components of different application systems so that the antimicrobial agent can be incorporated into different products.

Disinfectant with rapid microbial elimination and sustained efficacy

In this respect, there is a need for a disinfectant that provides rapid initial antimicrobial elimination and also exhibits residual protection and long-lasting efficacy. The disinfectant should not discolour a surface or make it sticky despite long-lasting efficacy. In addition, the prolonged effectiveness against microorganisms should not create chemical deposits on the surface.

Composition

The disinfectant composition contains at least one biocide in combination with a film-forming component. The film-forming component acts synergistically in conjunction with the biocide to not only kill a broad spectrum of microorganisms, but also forms a thin coating or clear film over the surface that has antimicrobial properties over an extended period of time. Of particular advantage is the thin coating or clear film formed on the surface, which is non-sticky and relatively invisible. The dried disinfectant can be redissolved in water or in further applications of the disinfectant. This makes the disinfectant resistant to chemical deposits over time, which allows repeated use of the composition on the same surface.

The disinfectant can be used in any commercial sector or in other suitable areas. For example, the disinfectant can be used in the food and beverage sector. It may include, for example, a hard surface disinfectant, a hand sanitiser, a sterilising or high-level disinfectant, an instrument disinfectant cleaner, and the like.

Biocide

The biocide contained in the disinfectant may be an amine, a chlorhexidine, a biguanide, or a mixture thereof. These biocides can also be used in combination with a quaternary ammonium cation. Further, the biocide is combined with a

film-forming component. This may be a polyvinyl alcohol, a polyvinyl pyrrolidone, a glycol such as polyethylene glycol, or mixtures thereof. The biocide and the film-forming component are combined and mixed with a liquid carrier. The liquid carrier may be, for example, water. The amount of water in the disinfectant composition may be > 40% by weight, > 50% by weight, > 60% by weight, or > 70% by weight.

In one embodiment, the disinfectant composition comprises an amine, in particular a tertiary amine. For example, the biocide may be a tertiary alkyl amine having from 8 to 16 carbon atoms. Examples of amine biocides include N,N-bis(3-aminopropyl)-dodecylamine, N-(3-aminopropyl)-N-dodecylpropane-1,3-diamine,N-(3-aminopropyl)-N-decyl-1,3-propanediamine, N-(3-aminopropyl)-N-tetradecyl-1,3-propanediamine, or mixtures thereof.

The biocide may be present in the disinfectant composition in an amount of 0.1 to 2 wt%, such as 0.2 to 2.0 wt%, or such as 0.3 to 1.5 wt%.

Film-forming component

The film-forming component included in the disinfectant composition is a polyvinyl alcohol alone or in combination with another film-forming component.

For example, the polyvinyl alcohol may have a degree of hydrolysis of at least 80 mol%, such as 90 mol%, 95 mol%,or 97 mol%.

In one embodiment, the composition includes a first polyvinyl alcohol and a second polyvinyl alcohol. The first polyvinyl alcohol may have a degree of hydrolysis that is greater than the degree of hydrolysis of the second polyvinyl alcohol. For example, in one embodiment, the first polyvinyl alcohol may have a degree of hydrolysis of 98 mol%. On the other hand, the second polyvinyl alcohol may have a degree of hydrolysis of 90 mol% to 97 mol%, such as 96 mol%. The first polyvinyl alcohol may be present in the composition in a weight ratio of 1 : 1 to 4 : 1, such as 1.5 : 1 to 3 : 1, with respect to the second polyvinyl alcohol.

The total amount of film forming compoents present in the disinfectant com-position may generally range from 1 to 10 wt%,such as 2 to 8 wt% or 3 to 7 wt%.

Evaporant

The disinfectant composition may also include an evaporant that has a boiling point < 90 °C, preferably < 85 °C, at 1 atm. For example, the evaporant may include an alcohol such as isopropyl alcohol.

Other components

The disinfectant composition may contain various other components and ingredients such as chelating agents and/or a surfactant. For example, the surfactant may be an alkoxylated alcohol.

The disinfectant may be applied to a surface using a wipe or by spraying. Likewise, the use of a disposable substrate pre-impregnated with the disinfectant composition is possible.

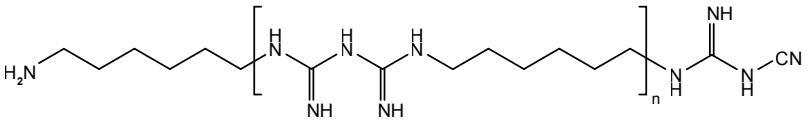

Fig. 1 Polyhexamethylene biguanide (PHMB)

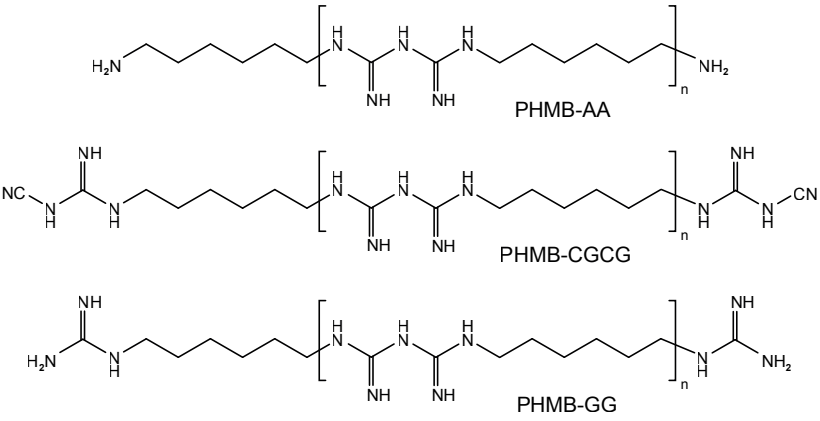

Fig. 2 PHMB-AA, PHMB-CGCG, PHMB-GG

Biguanides

A suitable biocide is polymeric biguanide, also known as polybiguanide, or a salt, analogue or derivative thereof. The polybiguanide no be a copolymer or a heteropolymer. It may be linear, branched, circular and/or dendrim. The number of repeating polymer units may vary from 2 to 1000, such as from 5 to 750, from 10 to 500, from 25 to 250, from 50 to 100 repeating units. In a specific embodiment, the polybiguanide may include polyhexamethylene biguanide (PHMB), polyhexamethylene monoguanide (PHMG), polyethylene biguanide (PEB), polytetramethylene biguanide (PTMB), polyethylene hexamethylene biguanide (PHMB), polymethylene biguanides (PMBs), poly(allylbiguanidine). Coallylamine, poly(N-vinyl biguanide), polyallyl biguanide, etc. The biocide can be polyhexamethylene biguanide hydrochloride (PHMB), which is also known as polyaminopropyl biguanide (PABP).

PHMB is usually represented by the following structural formula, although it is known to exist as a complex mixture of polymeric biguanides with various terminal groups including guanidine (not shown).

In particular, PHMB may be a mixture of different biguanide polymers, which may include different combinations of end groups, e.g., amine, cyanoguanidine, and guanidine.

Based only on these three end groups, there may be at least six possible biguanide polymers. There can be a biguanide polymer with two terminal amine groups, referred to as PHMB-AA, one with two terminal cyanoguanidine groups, referred to as PHMB-CGCG, and one with two terminal guanidine groups, referred to as δ-PHMB-GG (see below). There are also the three possible biguanide polymers with a combination of two different end groups. The above end groups again include amine-cyanoguanidine (PHMB-ACG), amine-guanidine (PHMB-AG), and guanidine-cyanoguanidine (GCG). Accordingly, a sample of PHMB may comprise a mixture of polymeric biguanides having the three mentioned end groups. In addition, a portion of the composition may contain in-chain polymeric guanide (not shown). The subscript "n" represents the average number of repeating groups. A distribution of polymer length exists for each of the polymers shown below, wherein n can be 1 to 50, such as 1 to 10.

Polyhexamethylene biguanide, such as polyhexamethylene biguanide hydrochloride, has a broad antimicrobial range and acts rapidly. Furthermore, the antimicrobial agent is stable over a wide pH range.

Chlorhexidine

Another suitable biocide is chlorhexidine or its derivatives or salts.

The chlorhexidine salt can be chlorhexidine gluconate, chlorhexidine hydrochloride or chlorhexidine acetate.

Quaternary ammonium cation

The disinfectant composition may additionally contain a quaternary ammonium cation. This may be a bicarbonate, halide or propionate salt of a quaternary ammonium cation. The amount in the composition is < 0.5 wt%, such as < 0.3 wt% or < 0.1 wt%.

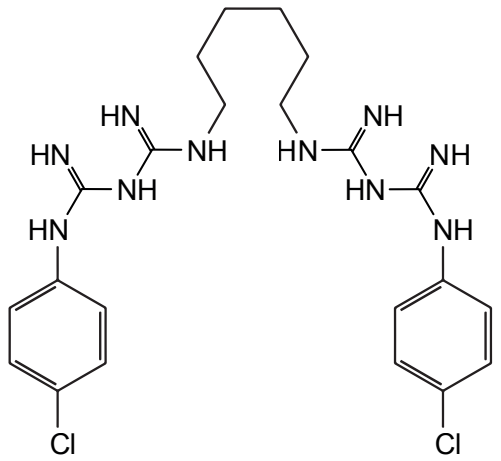

Fig. 3 Chlorhexidine

Disinfectant content

One or more of the above biocides are present in an amount of > 0.1% by weight, such as > 0.2% by weight, or > 0.3% by weight, or in an amount of < 4% by weight, such as < 2% by weight, < 1% by weight, 0.8% by weight, or < 0.5% by weight.

Ingredients	Parts (wt.-%)							
	A	B	C	D	E	F	G	H
PVOH-98[1]	5.2	-	-	-	-	3.4	3.4	3.4
PVOH-96[2]	-	5.2	-	-	-	1.8	1.8	1.8
PVP[3] K-60	-	-	5.2	-	-	-	-	-
PVP K-90	-	-	-	5.2	-	-	-	-
Polyethylene glycol (PEG) (3350 Mn)	-	-	-	-	5.2	-	-	-
Isopropyl alcohol	19.2	19.2	19.2	19.2	19.2	19.2	5.26	-
Water, deionised	75.6	75.6	75.6	75.6	75.6	75.6	89.54	94.8
Total	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.00**	**100.0**

[1]Polyvinyl alcohol, 98% hydrolysed I [2]Polyvinyl alcohol, 96% hydrolysed I [3]Polyvinylpyrrolydone

Tab. 1 Components of the polymer base formulations.

Formulations	Parts (wt.-%)					
	A	B	C	D	E	F
Polymer basis A	95.0	95.0	95.0	95.0	-	-
Polymer basis F	-	-	-	-	95.0	-
Polymer basis H	-	-	-	-	-	95.0
Alkyldimethyl-benzylammonium chloride	0.5	-	-	-	-	-
N,N-bis(3-amino-propyl) dodecyla-mine	-	0.4	-	-	0.4	0.4
Chlorhexidine digluconate	-	-	-	-	0.4	-
PHMB	-	-	2.0	-	-	0.5
EDTA-Na_4	-	-	-	-	-	0.1
Water, deionised	4.5	4.6	3.0	4.6	4.6	4.0
Total	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

Tab. 2 Components of the polymer base formulations.

Examples

Preparation of Formulation

Polymer Base Formulations

The base formulations were prepared using different polymers and different concentrations of isopropyl alcohol as shown in **Table 1**. The polymer base formulations were mixed at room temperature, except for the base formulations containing polyvinyl alcohols (PVOH), which were prepared by mixing the ingredients and stirring at 50 to 60 °C until complete dissolution of the PVOH. The base formulations were cooled to room temperature before further formulation with the biocides.

Biocide/polymer-based formulations

A biocide/polymer formulation was prepared by adding biocides to the polymer base formulations. Examples of such biocide/polymer formulations, reproduced in **Table 2**, contain 0.4% active biocides.

Micro-efficacy test

As an example, microtests to determine the efficacy of the biocides against *P. aeruginosa* are shown in **Table 3**. Approximately 30 mg of the biocide/polymer-based formulation was applied to the 1 in^2 area of a stainless steel coupon, air-dried overnight. The dried stainless steel test samples were submitted to a microlab for efficacy testing for *P. aeruginosa* ATCC 15442 according to a modified version of residual self-sanitising activity on hard, non-porous surfaces (EPA protocol # 01-1A). Test samples were not subjected to the abrasion process. Samples were inoculated with the test organism and subjected to a contact time of 5 minutes. Three replicates were tested for each sample. Test results are shown in **Table 3**.

Another series of tests consisted of comparing the efficacy after an abrasion process. 30 mg of the test formulation was applied to the 1 in^2 area of a stainless steel coupon. The samples were divided into two groups: one group was exposed to no friction and the other group to 12 dry frictions. No re-inoculation was done between frictions. The test results are shown in **Table 4**.

Finally, a determination of residual efficacy after 8 and 12 hours was carried out according to EPA Protocol No. 01-1A with proportional reduction of abrasion numbers and inoculation numbers.

The formulation is shown in **Table 5** and the test results for residual effectiveness are given in **Table 6**.

Active ingredients	Active substance content (wt.-%)	Film	Germ reduction (log 10 levels)
Alkyldimethylbenzyl-ammonium chloride	0.4	PVOH	3.85
N,N-bis(3-aminopropyl) dodecylamine	0.4	PVOH	≥ 4.85
N,N-bis(3-aminopropyl) dodecylamine	0.4	PVP	4.05
Chlorhexidine digluconate	1.0	PVOH	≥ 4.85
PHMB	0.4	PVOH	3.56

Tab. 3 Screening test results to determine the efficacy of the biocides against *P. aeruginosa*

Formulation	Active substance content (wt.-%)	Film	Germ reduction (log 10 levels)	
			no friction	12 frictions
Alkyldimethylbenzyl-ammonium chloride	0.4	PVOH	3.56	3.48
N,N-bis(3-aminopropyl) dodecylamine	0.4	PVOH	5.22	4.77
Chlorhexidine digluconate	0.4	PVOH	5.42	5.04
PHMB	0.4	PVOH	1.97	2.24

Tab. 4 Screening test results against *P. aeruginosa* without and after 12 dry frictions

Reference:

"Disinfectant composition having residual biocidal properties"

Patent-No.:
WO 2018/089761
Publication:
17/05/2018
Applicant:
Lonza Inc.
90 Boroline Road
Allendale
New Jersey 07401
USA

Ingredients	Parts (wt.-%)
N,N-bis(3-aminopropyl)dodecylamine	0.4
PVOH-98	3.3
PVOH-96	1.7
Isopropyl alcohol	18.0
Water, deionised	76.6

Tab. 5 N,N-bis(3-aminopropyl)dodecylamine/PVOH formulation

Time after application (h)	Contact time (h)	Testing conditions			Testing conditions (log 10 levels)		
		Dry abrasion	Wet abrasion	Reinoculation	*S. aureus*	*P. aeruginosa*	*E. aerogenes*
8 hours	10	2	2	3	4.90	-	-
	5	2	2	3	-	5.49	3.72
12 hours	5	3	3	3	3.57	5.57	-

* Required efficacy standard to pass the hygiene test is ≥ 3 log 10

Tab. 6 Germ reduction *P. aeruginosa* after 8 or 12 hours waiting time after treatment with formulation according to **Table 4**.

contact

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VINCENTZ

The Full Power of Organic Centella Asiatica with TALADVANCE™ with New Clinical Data for Healthy Skin

Fanny Tanaka - Wesource Product Manager, Seppic

Centella asiatica

In an increasingly hectic world, consumers are switched on to adapt, cope with stress and find back their inner peace. A group of ingredients lately creates buzz in the health and wellness space: the adaptogenic ingredients. Moreover, in their quest of better balance of body and mind, consumers give an importance to skincare. Then, although they are still niche, these superherbs slowly pop up in skincare jars and tubes thanks to their natural and holistic attributes.

One leading adaptogen in skincare is Gotu Kola "Fountain of Youth" in India, a little herb also known as *Centella asiatica*. Eaten as a green leafy vegetable or drunk in decoction, its leaves are praised as an adaptogenic ingredient for their remarkable properties of calming anxiety and improving memory and concentration.

Also for many centuries until the advent of Western Medicine, African traditional medicine (ATM) was the only available source of health care. The preventive and curative secrets of African medicinal plants like *Centella asiatica* have been transferred orally from family to family and community to community. Today, traditional medicine is still often termed alternative or complementary medicine in many countries. Herbal treatments are the most popular form of traditional medicine and 70% to 80% of the Region has used a form as primary health care [1].

At wesource™, Seppic's dedicated brand for active ingredients, we ethically harvest wild Centella asiatica organic leaves within our sustainable supply chain on high plateaus in Madagascar in compliance with the Union for Ethical BioTrade (UEBT) and the Nagoya protocol.

From those leaves is extracted **TALADVANCE™ (Cosmos certified and preservative free)**. With a composition in triterpenes & polyphenols close to the molecular content of the native plant Centella asiatica, TALADVANCE™ have significant effects on skin radiance & healthy glow and gives a smooth & supple skin with its action during day & night.

For a healthy skin, and in order to protect all biological processes, the skin homeostasis needs to be maintained & restored if damaged, our cells need to be resynchronized, and our skin needs to be protected during the day and repaired at night.

Many intrinsic or extrinsic factors in our lifestyle like a lack of sleep, bad diet and/or an overexposure to UV light, but also our genetics can desynchronize our cells & deregulate our circadian rhythms…

As a result, the skin loses its homeostasis making the skin rough & dull, lacking homogeneity, luminosity, radiance & even suppleness, which can affect the skin appearance and overall skin health.

New clinical datas with TALADVANCE™ demonstrates a significant *in vivo* improvement of +11% on skin suppleness after 28 days with 2% of TALADVANCE™, additionally from its in vivo results on immediate & long term effects on skin radiance, after 30 min with 5% of TALADVANCE™ & after 28 days with 2% of TALADVANCE™ respectively.**

A new *in vitro* model in chronobiology was also developed internally, to highlight the fact that TALADVANCE™ can re-synchronize fibroblasts and participate in the restoration & maintenance of the skin homeostasis, and so restore the skin circadian rhythm when deregulated.

TALADVANCE™, an ingredient ethically sourced from Madagascar and based on the famous CICA hero plant, acts on skin homeostasis in order to reach the "Healthy skin you are looking for" and get a beautiful skin with radiant glow & improved suppleness.

Literature

[1] https://www.afro.who.int/health-topics/traditional-medicine

>> Watch our video

Seppic in brief

A company of Air Liquide Healthcare, Seppic has been designing, producing and distributing for more than 75 years a wide range of specialty ingredients for health and beauty. Present in 100 countries through its subsidiaries and its network of distributors, Seppic employs more than 820 people worldwide, including 110 employees dedicated to innovation. **www.seppic.com**

About wesource™

wesource™ is Seppic's dedicated brand to gather a global and innovative offer of 100 cosmetic active ingredients. Based on marine biotechnologies, botanical extraction and plant chemistry, these actives are unique by the inspiring stories they carry, their technicality and efficiency, and create solutions that truly empower Beauty. **www.wesourcebeauty.com**

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Skin Microbiota Care:
How to Prevent Skin Discomforts Respecting Skin Biodiversity

Interview with Mr. Andrea Maltagliati,
Market Manager – Personal Care, ROELMI HPC

ROELMI HPC aims to enhance human's life-quality linking science and environmental preservation in the best way possible. This is your company vision. How is skin care part of this philosophy?
At ROELMI HPC, we aim for added values in creating a sustainable partnership with our customers. The development of high-technological and sustainable ingredients are here linked in the innovative attitude to help customers in transforming their needs into safe and performing formulas. We make tangible the magic in your dreams with a strict commitment in sustainable development.

A term you use in connection with microbiota protection is "Exposome". What do you want to express with it?
Skin is one of the largest body district, which the main function is to isolate and protect human body from the external environment. Acting as a strong barrier, it is capable of preventing water loss and avoiding the entry of foreign pathogens. All that is true, but incomplete!

In fact, the skin is the result of a complex ecosystem of microorganisms living in peaceful coexistence with the host, benefiting from the sheltered ecological niche and playing an active role in host defense. Skin microbiota is as important as delicate; what is essential to guarantee its vitality and activity is a state of health characterized by balance and equilibrium of the different species composing it, this reflects in what is commonly known as Microbiota Eubiosis.

Many environmental and host factors can alter the ecosystem of the skin, leading to dysbiosis alterations with resulting changes in skin conditions and consequent topical distresses. The term "Exposome" describes, in fact, the ensemble of all the exposures to which an individual is subjected in a lifetime.

What affects the skin and consequently life quality aversively?
As mentioned above, we are exposed to phenomena that can daily damage skin ecosystem and this is the reason why more than 80% of skin aging condition is caused by EXPOSOME.

So, the following question is: how exposome can cause irreversible damages to our skin?

It is important to distinguish among factors that come from Solar exposure, chemicals and other markers that include the urban environment, such as pollution. UVB rays can lead to the formation of superficial damages such as erythema and sunburn while UVA rays are even more dangerous and can penetrate deeper into the skin inducing damages that can lead to skin spots formation. Another relevant factor related to the skin Exposome is Pollution. It is clearly demonstrated that heavy metals (Pb, As, Cd, Ni …) inside the polluted air, could alter our skin barrier making it more sensitive and more permeable causing all those related skin disorders as acne, atopic dermatitis and sensitive skin.

What is your approach to prevent and contrast the Skin Exposome?
At ROELMI HPC, we have developed science-based active ingredients aimed at counteracting and mitigating the negative effects of Skin Exposome involved in accelerating skin aging. Several approaches have been adopted in the research:

1. To support the reparative processes of inflamed skin with **Plerasan® Sun**, able to prevent damages induced by UV rays exposure by stimulating and improving the natural immune defenses of fragile skin, by reducing the erythema of irritated and sensitive skin.

2. To maintain skin barrier integrity with PhytoSerene, the extremely pure β-sitosterol that mimics the function of cholesterol, naturally present into the skin. Showing high compatibility with natural skin matrix, **PhytoSerene** is able to reduce the inflammatory processes and related skin redness and concurs to prevent skin damage against chemical stresses (i.e. aggressive cleansing products or environmental stresses).

3. To restore skin ecosystem balance with **ÆCtive®**, the guardian for skin microbiota able to interact directly with the microenvironment around the skin microflora membrane, balancing and improving the correct water content inside and outside our commensal bacteria

You call one of your actives Skin Guardian. Why and what is it?

Starting from its deep knowledge of probiotics, ROELMI HPC has developed different approaches to interact with localized microbiota. First, by investigating the effects of probiotics in nutraceutical applications exploring cutting-edge technologies for a new era of ingredients application on gut microbiota.

As a step forward, ROELMI HPC moved to a different market, from nutraceutical to cosmetics, designing specific ingredients for skin care applications. First by investigating whether cosmetic preservatives, which are known and used for their antimicrobial efficacy, could have any impact on the microbial population inhabiting our skin, then by developing dermobiotic ingredients aiming to rebalance the skin microbiota affected by external stresses.

Dermobiotics innovation is targeted to keep the perfect balance for the skin microbiota survival. By working on Microbiota research, ROELMI HPC developed the most outstanding ingredient to maintain eubiosis in order to achieve skin health.

ÆCtive® is a biotech active ingredient (a cyclic amino acid derivative with osmolytic properties) which concurs to avoid dysbiosis and related skin distresses demonstrating a proved efficacy rate in improving hydration, elasticity and sebum control as a unique result of skin microbiota care. By means of metagenomic tests, **ÆCtive®** has demonstrated the ability to re-establish the Eubiosis among different populations of microorganisms. An *in-vivo* test in extreme climatic conditions has been performed by enrolling volunteers living in Beijing (where the environment is heavily characterized by high pollution rate) and demonstrated that **ÆCtive®** is able to prevent microbiota dysbiosis, above all by countering the damage induced by pollution. Acting positively on the microbiota, it helps to counteract the damage induced by skin Exposome, improving skin complexion and preventing all potential correlated skin disorders.

Clean Beauty is a key issue in the marketing of products. How do you approach this subject?

Thanks to the adoption of a new technological approach focused on ethics, sustainability and transparency. Our network of expertise permits us to bring specific solutions giving the possibility to customers to express all particular activities or needed target. On selected product lines, we applied our **SAF-e-CACY®** concept of excellence. Aimed at reaching maximal efficacy maintaining highest safety results, the concept includes a repetitive efficacy control on every production batch.

Andrea Maltagliati

In your opinion, how will the pandemic influence the cosmetic industry over the next years?

The current period underlined the extreme need to pursue responsible actions towards civil society, environment and business. In light of that, ROELMI HPC has activated an adaptive model versus the contingencies of every day. The future awaits us with new challenges, considering the evolution of purchasing behavior from traditional to digital, the greater attention to multifunctional products that respect skin microbiota and growing attention to sustainability. Particular attention towards the so-called make-care (skin-care claims associated with make-up applications), and multi-functional products with innovative delivery system.

Tell us a little bit about the history of ROELMI HPC

ROELMI HPC is the partner company committed to driving innovation in the Health & Personal Care markets. Expertise roots lie in the Mediterranean area, where the company still finds concepts and innovation-driven technologies. ROELMI HPC is focused on research, planning, development and production of functional and active ingredients. Our activities spring through cutting-edge technologies driven by innovation in green chemistry and are guided by the will of building high-performing models of circular economy. Our forefront formulations respect the principles of sustainability through the preservation of biodiversity and the use of renewable resources, following our corporate sustainable program **NIP®:**

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Natural Green Body Mask

L098-8.6-1020

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Phase	Ingredients	Manufacturer	% w/w
A	Water, deionized		57.70
	Glycerin 99,5%, Ph. Eur. (Glycerin)	Cremer Oleo GmbH & Co.KG	4.50
	dermofeel® PA-3 (Sodium Phytate; Aqua; Alcohol)	**Evonik**	**0.10**
	Xanthan Gum FEDCS-PC (Xanthan Gum)	Jungbunzlauer Ladenburg GmbH	0.80
B	Phytosqualan, refined, Olive based (Squalane)	Henry Lamotte	5.00
	Phytosphingosine (Phytosphingosine)	**Evonik**	**0.20**
B1	**symbio®muls GC MB** (Glyceryl Stearate Citrate; Cetearyl Alcohol; Glyceryl Caprylate)	**Evonik**	**8.00**
	TEGIN® M Pellets MB (Glyceryl Stearate)	**Evonik**	**2.00**
	KahlWax 8104 (Cera Alba)	KahlWax	2.00
	KahlWax 6614 (Camellia Sinensis Leaf Extract)	KahlWax	2.00
	Sheabutter, refined, organic (Butyrospermum Parkii Butter)	Henry Lamotte	2.00
	Almond Oil, refined (Prunus Amygdalus Dulcis Oil)	Henry Lamotte	5.00
	Avocado Oil, refined (Persea Gratissima Oil)	Henry Lamotte	3.00
	Apricot Kernel Oil, refined (Prunus Armeniaca Kernel Oil)	Henry Lamotte	2.00
	dermofeel® Toco 70 non GMO (Tocopherol; Helianthus Annuus (Sunflower) Seed Oil)	**Evonik**	**0.20**
	dermofeel® TocoSkin (Tocopherol; Helianthus Annuus (Sunflower) Seed Oil)	**Evonik**	**1.00**
C	**TEGO® Turmerone** (Curcuma longa (turmeric) root extract)	**Evonik**	**0.50**
	Pumpkin seed (Kürbiskern) organic extractive P- 00025487 (Helianthus Annuus Hybrid Oil; Cucurbita Pepo Seed Extract; Rosmarinus Officinalis Leaf Extract)	Botanica	0.50
	dermosoft® 1388 eco NaL (Glycerin, Aqua, Sodium Levulinate, p-Anisic Acid, Sodium Hydroxide)	**Evonik**	**3.50**

DIY concept: Add peeling particle as you like and create a scrub Rich cream-formulation with a combination of actives for the skin.
Natural content cn: 77.4%, Natural origin content cno: 100% (incl. water, ISO 16128)

Processing
1. Mix phase A and heat up to 78°C. Disperse phase A1.
2. Mix phase B and heat up to 90°C until a clear solution is obtained.
3. Heat phase B up to 78°C. Add components of phase B1 to B.
4. Emulsify phase B/B1 into phase A/A1 while stirring.
5. Homogenize.
6. Start to cool down slowly under medium stirring.
7. Add phase C below 40°C under stirring.
8. Adjust pH-value to 5.0-5.3, if necessary.

Appearance:
Light green cream.
Viscosity:
150000 - 200000 mPa.s (Brookfield (21°C): TD94; 5rpm / helip.)
pH Value: 5 - 5.3.
Stability: Proven
Microbiological Safety: Challenge test passed

Super Primer with Alpine Rose Active*

Clearing "zombie cells" in the skin

mibelle GROUP biochemistry

Phase	Application / Trade Name	INCI	% w/w
A1	Aqua	Aqua / Water	80.4
	Konjac Mannan Gel Powder (GfN-Selco)	Amorphophallus Konjac Root Extract	0.1
	Xanthan Gum FNCSP-PC (Jungbunzlauer International AG)	Xanthan Gum	0.1
	GeoGard Ultra™ (Lonza)	Gluconolactone (and) Sodium Benzoate	2.0
A2	**Alpine Rose Active**	**Rhododendron Ferrugineum Extract (and) Glycerin (and) Aqua / Water**	**2.0**
	Panthenol	Panthenol	5.0
	Glycerin	Glycerin	5.0
	Resplanta Phyto Pomegranate MB (Res Pharma Industriale)	Punica Granatum Seed Oil Polyglyceryl-4 Esters	1.0
B	CEGESOFT® PFO (BASF)	Passiflora Incarnata Seed Oil	0.5
	symbio®solv clear plus MB (Evonik Operations GmbH)	Caprylyl/Capryl Glucoside (and) Aqua (and) Sodium Cocoyl Glutamate (and) Glyceryl Caprylate (and) Citric Acid (and) Polyglyceryl-6 Oleate (and) Sodium Surfactin	3.5
	Perfume True Rain Blossom CO (Essencia AG)	Sodium Benzoate	0.2
C	Ronastar Red Lights (Merck KGaA)	Alumina (and) Titanium Dioxide (CI 77891) (and) Tin Oxide	0.1
	YuraQ (Döhler)	Phytelephas Aequatorialis Seed Powder	0.1

Alpine Rose Active is a natural active ingredient based on an extract of organic alpine rose leaves and acts as a so-called senolytic. That means it specifically targets the senescent cells and not the healthy cells in the skin.

* Formulation based on COSMOS approved ingredients.

Manufacturing Procedure:
1. Mix phase A1 under agitation until completely homogenous.
2. Add **Alpine Rose Active** and the other raw materials from A2
3. Stir until everything is dissolved.
4. Mix phase B separately and then add it to phase A1 / A2 .
5. Very important: stir slowly. Do not homogenize!
6. Add components of phase C one by one under agitation.
7. If necessary, adjust pH to 5.0 - 5.5 using NaOH or citric acid.

SKIN OASIS Hydrating Dewy Cream

vytrus biotech

Phase	INCI (Trade Name)	% w/w
A	Hydrogenated Ethylhexyl Olivate (And) Hydrogenated Olive Oil Unsaponifiables (NATURA-TEC PLANTSIL™)	5.00
	Coco-Caprylate/Caprate (MASSOCARE® CCC)	5.00
B	Potassium Cetyl Phosphate (MASSOCARE® CPH-K)	0.70
	Cetyl Alcohol	4.00
	Glycerin	10.00
	Propanediol	5.00
	Hydrogenated Lecithin (NIKKOL LECINOL S-10)	0.50
C	Arginine	0.35
	Water	20.00
D	Water	to 100
	Pentylene Glycol, Levulinic Acid, Glyceryl Caprylate (VERCATECH PENTYFORCE)	4.00
E	**NECTARIA LITHOPS**	**1.50**
	Fragrance/Parfum	CSP

Highly hydrating emulsion that actively improves cutaneous texture providing immediate moisturizing properties and leaving an ultra-soft and protective non-greasy film on the skin.

This dewy cream is specially formulated to allow the water retention in deep skin layers. Thanks to NECTARIA LITHOPS the skin shines from the inside out: water reserves are replenished, and the skin structure is deeply improved allowing an efficient synthesis and storage of vitamin D. Plumped cheeks and hydrated turgid skin. Vegan and respectful with the skin and the environment.

Procedure:

1. Mix and heat the components of phase B to 60°C. Ensure a homogenous dispersion is formed.
2. Mix the components of phase C and heat the mix to 60°C.
3. Add phase C over B gradually under continuous stirring until a homogenous mixture occurs.
4. Let the mix cool down to room temperature.
5. Add phase D over B+C and stir until homogenous.
6. Heat phase A to 60°C and incorporate it under homogenization over B+C+D during 5-10 mins to emulsify the two phases.
7. Add phase E components consecutively.

DISCLAIMER:
The information contained herein is meant to demonstrate how our products can be used. The given data, including claims and procedures, are suggestions without any guarantee, aimed at supporting customers' development. Any product manufactured corresponding to the present recipe is used at own risk and may require additional testing prior to marketing in order to comply with local regulations. **www.vytrus.com**

AWARD

HPCI CEE 2020 Poster Session Winner

Warsaw | Poland

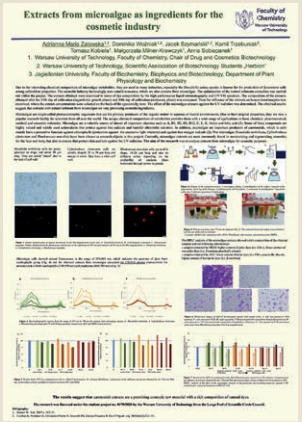
For the first time the Poster Session "*Innovative Cosmetic Raw Materials and Biologically Active Compounds in Cosmetology*" was organised by **The Warsaw College of Health and Engineering in Warsaw** as part of the **Home and Personal Care Exhibition and Conference (HPCI) Central and Eastern Europe**. Due to the Covid-19, in 2020 the session took place online. Winning poster was awarded by publication in **SOFW Journal.**

Winning Poster

The winning poster is: "*Extracts from Microalgae as Ingredients for the Cosmetic Industry*" presented by A. M. Zalewska, D. Wozniak, J. Szymanski, K. Trzebuniak, T. Kobiela, M. Milner-Krawczyk and A. Sobiepanek from **Warsaw University of Technology** and **Jagiellonian University**.

"*The winning poster presents students' study on the possibility of use and efficacy of microalgae extracts in the cosmetic industry. Under the supervision of their tutors, young researchers conducted an advanced scientific project of high practical interest, utilizing modern assessment tools (cell cultures, simulation of the UV-B based stress, MTT assay, etc.) The presentation of the results is clear and complete, giving the full view of the problem to the viewer. Apart from technical aspects of poster presentation, the main reason why this study won was practical side of the topic proposed by very young scientists*" said **Dr. Katarzyna Pytkowska**, HPCI Organizers Expert and jury member.

Next **HPCI CEE Poster Session** will take place on **September 22-23, 2021** in Warsaw, Poland.


Extracts from microalgae as ingredients for the cosmetic industry

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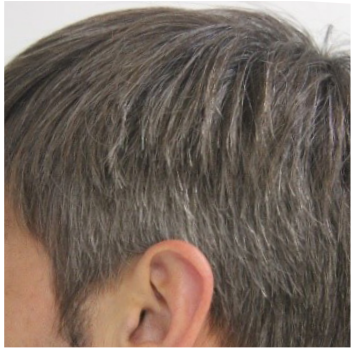

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