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A Psychobiological Approach for a Positive Skin Aging: Target Senescence Cells to Boost Emotion

Sandie Gervason[1], Assia Dreux-Zhiga[1], Justine Demangeon[1], Caroline Lazzarelli[2], Jean-Yves Berthon[1], Edith Filaire[1,3]

[1] Greentech. Biopôle Clermont-Limagne 63360 Saint Beauzire, France

[2] Deinove. 1682 rue de la Valsiere, 34790, Grabels, France

[3] University Clermont Auvergne, UMR 1019 INRA-UcA, UNH (Human Nutrition Unity), ECREIN Team, 63000 Clermont-Ferrand, France

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INTRODUCTION

According to demographic studies, 2020 will be a turning point when individuals 60 years and older will outnumber children younger than five. Moreover, centenarians are a commonplace today, with more than 70,000 in the United States alone, and individuals expecting to live longer and in good health without deleterious effects associated with aging. From this trend a new dermocosmetic concept emerged, well aging, which focuses on wellness in order to maintain health capital. At the same time, women are aware that they have wrinkles and that these will not go away and like millennials, they do not want any more "overpromising".*Brousse et al.* [1] reported that beauty then becomes more integrative; it will globalize well-being, the silhouette, the lifestyle, and sleep or relaxation practices... resulting in a freer feminine look expecting new codes and expressions. In line with this evolution more and more studies suggest a relationship between cosmetics use, self-esteem and self-perceived attractiveness [2]. *Nash et al.* [3] studied the correlation between makeup and women's mental health and reported that the use of cosmetics helped in the manifestation of emotional benefits such as having a good mood, reflecting a positive self-evaluation, and showing a significant escalation in the confidence level.

Even though these psychological parameters included in the wellness concepts currently have conquered the cosmetic industry and because wellness relates to subjective perception, it is difficult to prove that a product positioned in this way is not simply marketed as such but actually induces a perceivable enhancement in the consumer's well-being. Besides subjective reports used in the psychology area, objective noninvasive psychophysiological measurements can be used to record the effect of certain active ingredients on cognitive and emotional states in humans. To account for this challenge, it is possible to use a psychophysiological approach based on measurement of parameters such as skin conductivity, biomechanical properties or stress hormones [4].

Slowing down aging by acting on the senescence process may be beneficial to overall health, and the development of specific interventions that target senescent

Abstract

Using a psychobiological approach, we evaluated in vivo the effect of Sphingomonas extract on self-esteem (Rosenberg Scale), mood (Profile of Mood State), and the biomechanical properties (isotropy and suppleness) of the skin in 24 females (60-70 years old). An aging full-thickness skin equivalent model, treated or not with the bacteria extract systemically for 42 days, was used. p21 and p16 and senescence-associated galactosidase activity were evaluated.

Sphingomonas extract significantly suppressed senescence associated with b-galactosidase activation. It also significantly inhibited the expression of cell cycle inhibitors (p21 and p16). At the same time, the bacteria extract had a significant positive impact on the tissue by increasing the expression of versican and fibrillin-1. Significant improvements in self-esteem and mood were reported after 56 days of Sphingomonas extract application. These psychological benefits were accompanied by a significant improvement in skin suppleness and isotropy.

Sphingomonas extract delayed the intrinsic skin aging process and also was able to restructure the skin. These beneficial physiological effects had a positive influence on self-esteem. Because skin aging causes emotional distress, Sphingomonas extract can serve as an anti-aging cosmeceutical agent and help to build better psychological health and advantageously impact aging.

cells may serve as a therapy to delay aging, including skin pathologies and mood [5]. The cosmetics industry has focused on bioactive substances derived from natural products such as plants, mushrooms, and marine algae. Besides these products, bacteria such as the Lactoccus lactis strain may prevent immunosenescence and decelerates individual senescence [6]. Another genus, the genus *Sphingomonas* hallmarked by its oligotrophic nature and plasticity in manmade environments, has been intensively exploited for its metabolic properties relevant to biotechnological importance [7]. *Sphingomonas sp.* belongs to the proteobacteria phylum and is a Gram-negative bacterium. It has the capability to degrade a variety of organic compounds, such as PAHs, suggesting that they adapt well to contaminated environments and play important roles in bioremediation [8]. They mainly employ abundant oxygenases to degrade these xenobiotics. They can synthesize carotenoids which protect cells from reactive oxygen species produced during degradation processes [9]. The second specificity of these bacteria is that they contain glycosphingolipids in their cell envelopes instead of the lipopolysaccharides observed in other Gram-negative bacteria. The glycosphingolipids appear to act as a barrier to bactericidal substances [9].

Sphingomonas strains have been isolated from a variety of environments, including both aqueous (both fresh- and seawater), terrestrial habitats and plant root systems [10]. The widespread distribution in the environment is due to their ability to utilize a wide range of organic compounds and to grow and survive under low-nutrient conditions. Due to their biodegradative and biosynthetic capabilities, these bacteria have been used for a wide range of biotechnological applications, from bioremediation of environmental contaminants to production of extracellular polymers such as sphingans (e.g., gellan, welan, and rhamsan) used extensively in the food and other industries [10].These bacterial species described in the environment may play a role in skin homeostasis. This is the One-Health concept, which recognizes that the health of humans is connected to the environment [11]. Based on its rich and unique composition, *Sphingomonas sp.* represents an innovative source for the development of new skin care solutions.

The aim of this investigation was to determine whether *Sphingomonas* extract application in old women could slow down the cell senescence mechanism and have a positive effect on mood. We used a psychobiological approach to evaluate *in vivo* the effect of *Sphingomonas* extract on self-esteem, mood, and the biomechanical properties of the skin as well as *ex vivo* experiments in order to evaluate the effect on *Sphingomonas* extract on senescence markers. Because *Sphingomonas* hydrophobicum contains glycosphingolipids acting as a barrier to bactericidal substances, we put forward the hypothesis that *Sphingomonas* extract not only imparted anti-aging effects but also has a synergistic sense of emotion.

EXPERIMENTAL

Bacterial strains and culture conditions

Sphingomonas hydrophobicum was isolated from water samples of a site located in Tartras (Aquitaine, France) and kept in the Deinove's collection (Montpellier, France).

Sphingomonas hydrophobicum was cultivated on Complex Medium Glucose: 10 $g.L^{-1}$ of glucose, 5 $g.L^{-1}$ of yeast extract, 2g. L^{-1} of bacto-peptone, 5.74 mM K_2HPO_4, 10 % v/v 3-(N-morpholino) propanesulphonic acid (MOPS) buffer mixture (400 mM MOPS, 200 mM NH_4Cl, 100 mM NaOH, 100 mM KOH, 2.76 mM Na_2SO_4, 5.28 mM $MgCl_2$ and 5 lM $CaCl_2$), The MOPS buffer mixture added was sterilized by filtration. The initial pH was adjusted to 7 with NH_4OH. The culture conditions were defined as follows: temperature 30 °C, pH 7, in a rotary shaker at 250 rpm for 21 h.

The *Sphingomonas hydrophobicum* starting culture was used to inoculate a bioreactor containing 20 L of Complex Medium Glucose. The culture conditions were defined as follows: temperature 30 °C, pH 7, impellor speed from 300 to 900 rpm and aeration rate between 0.25 and 1 vvm. A batch strategy of 48 h of fermentation was performed to achieve the highest yield of biomass using a 5 % v/v inoculum. After 48 h of production the culture was centrifuged to recover the bacterial cells with a dry matter of approximately 15 % (m/m). The recovered biomass was mixed with ethanol 96 % at a ratio of 10:1 (ethanol:biomass (m/m)), heated at 60 °C for 30 min and then incubated at room temperature for 30 min. The extract obtained was filtered on filter paper, mixed in propanediol and placed in a rotary evaporator until the ethanol had evaporated. Finally, the extract was filtered at 0.2 μm and the dry matter adjusted to obtain 2 % (m/v).

The polyphenols, malic and lactic acid, coenzyme Q10 and the sphingolipids were used for characterization of our *Sphingomonas hydrophobicum* extract.

MTT cell viability assay

An aging full-thickness skin equivalent model with 57-year-old normal human dermal fibroblasts (NHDF) was used and treated with the bacterial extract at different concentrations in a systemic way for 42 days. As a preliminary evaluation, cytotoxic analysis on cell culture monolayers was conducted to select the highest noncytotoxic concentrations and to avoid any cumulative deleterious effect on the 3D reconstructed skin model.

Immunohistological analysis

Several immunohistological analyses were performed to study the elasticity of the dermal compartment based on determination of the expression of the fibrillin and versican proteins. Finally, the fibroblast senescence was investigated by analysis of p16, p21 expression and ß-galactosidase.

In vivo study

Twenty-four subjects aged 60 to 70 were included. The study duration was 56 days. *Sphingomonas* extract formulated at 1 % was applied twice a day *vs.* placebo.

Inclusion criteria were:
1) subject with loose skin on the face, person with wrinkles and fine lines on the face, 2) subject with dry skin on the face (cutaneous hydration rate < 70 A.U.) on jaws checked by corneometer (CK Electronic GmbH, Germany)

Exclusion criteria were:
1) cutaneous pathology on the face,
2) subjects having used on the studied zone an anti-wrinkle product (or product in action on the skin's surface) or having stopped use less than 1 week previous to the study, and
3) subjects having done facial injections and/or a palpebral lifting or use during the previous weeks of topical or systemic treatment liable to interfere with assessment of the cutaneous acceptability of the studied product.

Isotropy, biomechanical measurements and psychological tests were done at the beginning (D0) of the study and after 56 days of *Sphingomonas* extract application (D56).

Isotropy

The orientation of the lines in the cutaneous relief, allowing the evaluation of the restructuring effect on cheek, was measured using the "3D PRIMOS Lite" (Canfield Scientific, Parsippany-Troy Hills, USA) was measured at the beginning and after 56 days of *Sphingomonas* extract treatment. This technique consists in calculating a phase image from images with interference fringe projection. The parameter evaluated was the isotropy, which defines the orientation of the lines in the cutaneous relief.

Biomechanical properties of the skin

Mechanical properties of the skin were determined with a noninvasive suction skin elasticity meter (Cutometer MPA 580, Canfield Scientific, Parsippany-Troy Hills, USA). A 2 mm diameter measuring probe was used, which applied a constant suction of 350 mbar in the time/strain mode (Mode 1) for 18 s followed by a relaxation time of 2 s, with two repetitions. Measurements were made on a single site on the face. The cutometer generated a graph depicting immediate deformation or skin extensibility (Ue).

Anti-wrinkle effect

A VISIA CANFIELD® imaging system (Canfield Scientific, Parsippany-Troy Hills, USA), which allows taking pictures with different types of illumination, was used to evaluate the anti-wrinkle effect on crow's feet.

Psychological parameters

Self-esteem was investigated using the Rosenberg test, which is a widely used self-report instrument [12]. It is a 10-item scale that measures global self-worth by assessing both positive and negative feelings about the self. All items were assessed using a 4-point Likert scale format ranging from strongly agree to strongly disagree. It appeared that self-esteem had a strong relation to happiness [13, 14]. The measure demonstrated good internal consistency (Cronbach's alpha reliability coefficient was 0.85).

The profile of mood states (POMS), which is a psychological rating scale used to assess transient, distinct mood states was also determined in the same period [15]. It measures six different dimensions of mood swings over a period of time. These include: tension or anxiety, anger, vigor, fatigue, depression and confusion. A five-point scale ranging from »not at all "to extremely" was administered by the investigator to subjects to assess their mood states. A positive mood state was a positive outlook on life [15].

Life situations were evaluated using a visual analogic scale (VAS) at the beginning (D0) and end of the investigation (D56). The viasual analogic scale was a 100 mm long horizontal line with verbal descriptors (word anchors) at each end to express the extremes of feeling. Subjects were instructed to mark the point on the line that best corresponded to their life situation (bad or good) by putting a cross on the straight line at the point that most accurately expressed their degree of agreement.

Statistical Analysis

All statistical analyses were performed using the SPSS program. All values were expressed as the mean ± SD. The Mann–Whitney U test was performed because of non-Gaussian distributions. A p value < 0.05 was considered statistically significant.

RESULTS

Ex vivo study

Effect of *Sphingomonas* on senescence-related proteins

Retinoic acid and *Sphingomonas* extract treatment at a concentration of 0.1% decreased β-galactosidase expression compared with the untreated control. The decreases were 78% *versus* the untreated condition ($p < 0.01$).

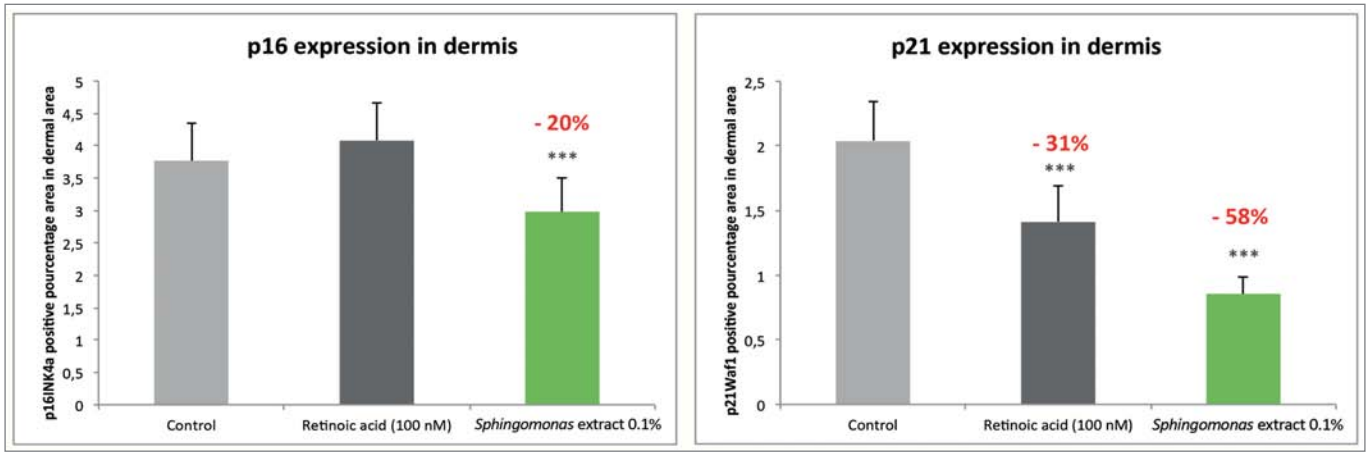

Figure 1 p16 and p21 expression quantification normalized by the total dermal area. Automatic analysis of staining with "ImageJ" software (*** $p < 0.001$ *vs.* control).

Sphingomonas extract decreased p21 expression in the dermis of reconstructed skin. This decrease was about 58 % ($p < 0.001$) *versus* the untreated condition ***(Figure 1)***. We also noted a significant decrease in p16 expression. This decrease was 20 % *versus* the untreated condition ($p<0.001$).

Expression of fibrillin-1 and versican

Treatment with *Sphingomonas* extract increased significantly fibrillin-1 expression in the dermis of reconstructed skin (22 % : $p < 0.001$). This treatment also induced a significant increase in versican expression (7 %; $p < 0.05$) ***(Figure 2)***.

In vivo study

After 56 days of application, *Sphingomonas* extract induced a significant improvement in isotropy (+14 %: $p < 0.02$), while application of placebo induced an isotropy decrease.

Significant improvement in the average roughness (-9 % $p < 0.05$ *versus* D0, with a positive effect for 68 % of subjects) and average relief (-8 % $p < 0.05$ *versus* D0, with a positive effect for 64 % of subjects) was noted ***(Figure 3)***.

A significant increase in the Ue parameter (reflecting the suppleness evaluated using the deformation and immediate extensibility of the skin) of 12 % on average e ($p < 0.001$ *versus* D0) was reported; this effect was observed in 70 % of the subjects. At the same time, the placebo induced a non significant increase of 4 % ***(Figure 4)***.

Using the VISIA CANFIELD® imaging system, which allowed taking pictures with different types of illumination and very rapid capture of images, we could observe that the active ingredient induced an anti-wrinkle effect on crow's feet ***(Figure 5)***.

Concerning the psychological status, there was a significant increase in self-esteem and mood were from D0 to D56 ($p < 0.001$; $p < 0.003$, respectively). No changes in the VAS score were noted between D0 and D56.

DISCUSSION

At what age do we get old? The question should be: when do we begin to accept ourselves serenely as we are? But it is unfortunately not enough to stay young in your head,. The search for eternal youth has now been forgotten in favor of showing off one's real age. According to this concept, women beyond their 50s are less interested in looking younger; they want to look healthy. This positive and optimitisc outlook on aging contrasts with the well-known fact that women attach self-esteem to their body image, which is associated with beauty, femininity and youth. In accordance with this latest new trend in cosmetic and skincare products, the aim of this investigation was to evaluate whether Sphingomanas extract application for 56 days in old women could slow down the

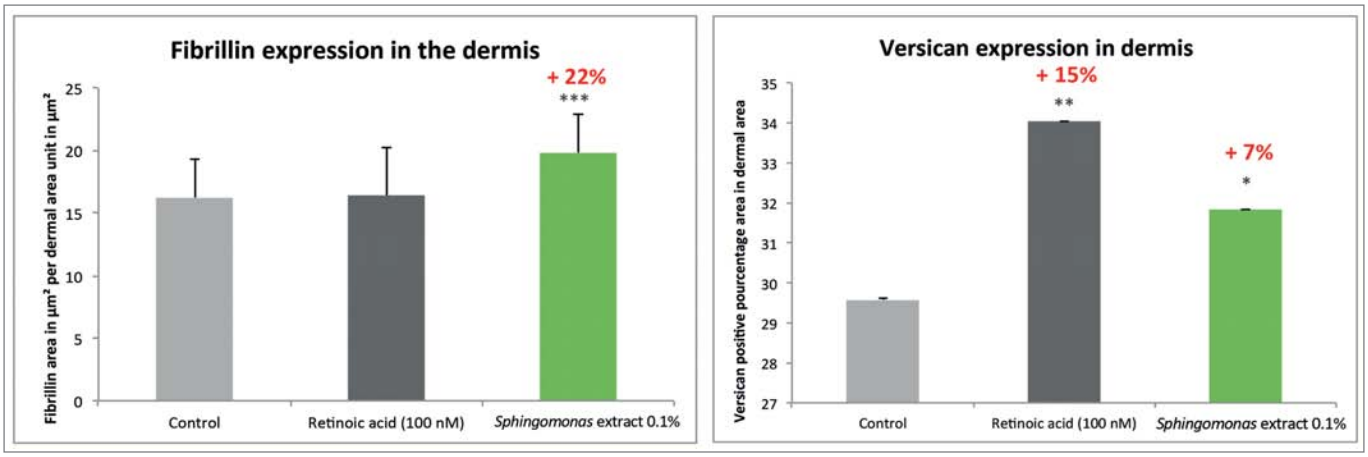

Figure 2 Effect of Sphingomonas extract on fibrillin and versican in the 3D reconstructed full-thickness model (***$p<0.001$, **$p<0.01$, *$p<0.05$).

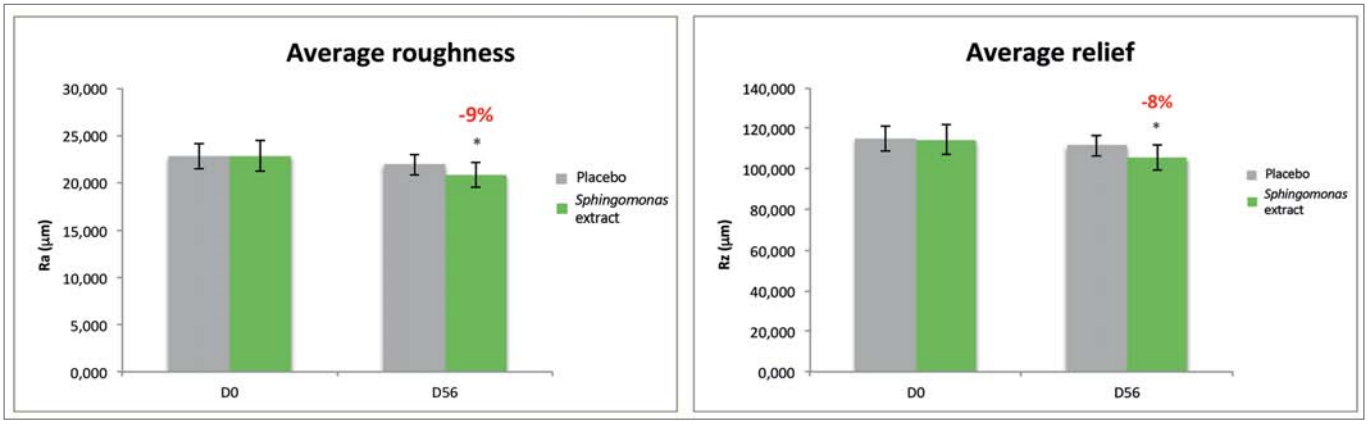

Figure 3 Roughness and average relief measurements at D0 and D56 (*, $p<0.05$).

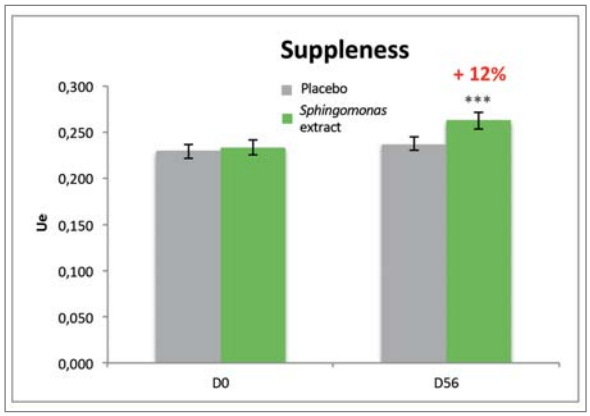

Figure 4 Suppleness measurements at D0 and D56 (***, p<0.001 *vs.* D0).

Figure 5 Pictures of a volunteer at the beginning (D0) and end (D56) of the investigation.

cell senescence mechanism and have a positive effect on mood. The main results showed that this active has three types of action on the skin:
1) a structural action by strengthening the deep architecture,
2) an anti-aging effect through impact on senescence cell pathways and
3) an emotional action by improving mood and self-esteem. Mood was evaluated using the POMS, which is an tool to measure psychological well-being [16].

All these data show that a skincare cream can improve wellness, with the effect being quantified using scientifically validated tests.

More precisely, for the first time, we have reported the beneficial effect of an extract from *Sphingomonas hydrophobicum* bacteria acting on senescence, reflecting the potential of environmental bacteria for skin care applications. Vitreoscilla filiformis was one of the first bacteria isolated from thermal spa water reported for topical therapy of inflammatory skin disorders [17]. More recently, Bacillus methylotrophicus has also been proposed as a new type of anti-acne preparation to cure or prevent acne [18]. Our results demonstrate that *Sphingomonas* extract attenuates cellular senescence by suppressing senescence-associated β-galactosidase and the expression of cell cycle inhibitors (p21 and p16) ***(Figure 1)***. p21 is a cyclin-dependent kinase (CDK) inhibitor. Suppression of CDK activity triggers activation of the retinoblastoma protein pRB. p16, another CDK inhibitor, acts via the retinoblastoma pathway, inhibiting the action of the cyclin-dependent kinases leading to G1 cell cycle arrest [19]. These data might reflect the proliferation-promoting and anti-senescence effects of *Sphingomonas* extract.

Normal skin aging is characterized by an alteration of the underlying connective tissue with measurable consequences on global skin biophysical properties and increasing changes in the skin relief. In fact, the cutaneous lines change from a relatively isotropic orientation to a highly anisotropic orientation [20]. This reorganization of the skin relief during the aging process might be due to a modification of the skin's mechanical properties, and particularly to a modification of the mechanical properties of the dermis. Our data indicated that *Sphingomonas* extract application for 56 days restored skin flexibility and counteracted the deleterious effect of aging by significantly increasing the isotropy orientation. All the above improved the clinical appearance of patients' skin and conclusively improved their view of their body image and the associated self-esteem, as we noted. Appearance is important in our society and influences the way in which we are perceived by others. The skin is the most visible organ of the body and determines, to a large extent, our appearance. It has been shown that in women the signs of aging on the skin are perceived as being symptomatic of a loss of femininity, social power and social visibility [21]. As suggested by Baker [4], physical changes between the ages of 50 and 60 years affect one's physical attractiveness and disrupt self-esteem. People with high self-esteem claim to have better relationships and to make better impressions on others.

CONCLUSION

Recently, probiotic bacterial fermentation has emerged as one of the crucial processing tools in cosmetic technologies to enhance absorption into the skin and improve desirable pharmacological activities [22]. In contrast to probiotic extracts, little has been done on other microorganisms. To our knowledge, we are the first to identify that *Sphingomonas* extract delays the intrinsic skin aging process by not only attenuating cellular senescence through reduction of p21 and p16 expression but also increasing the expression of fibrillin-1 and versican. By acting on the biomechanical skin properties all these processes improve self-esteem and mood. The psychophysiological approach undoubtedly offers new innovation opportunities for the cosmetics industry. However, brands and suppliers will have to take care to strongly substantiate their claims as part of a more holistic conception of beauty.

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Corresponding Author
Edith Filaire
Greentech
Saint Beauzire
France
edithfilaire@greentech.fr

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