

## Research and Development

**Shiseido discovers a new function of "pure retinol" that suppresses progression of wrinkles from the surface to deep layers of the skin by softening the stratum corneum**

- Approach to addressing the hardening of the stratum corneum, which leads to the progression of the "gap between the two skin layers," the root cause of wrinkles -

Using the "internal and external skin elasticity 3D imaging system"<sup>\*1</sup>, a technology uniquely developed by Shiseido, the company confirmed that the hardening of the stratum corneum increases mechanical stress<sup>\*2</sup> applied to the dermis when the skin moves with facial expressions, etc., leading to the progression of the "gap between the two skin layers (stratum corneum and dermis)"<sup>\*3</sup>, the root cause of wrinkles. It also discovered that "pure retinol,"<sup>\*4</sup> an active ingredient with confirmed efficacy and effect on wrinkle improvement, has an effect of softening the stratum corneum, revealing a new function of the ingredient that prevents the progression of wrinkles from the surface of the skin to its deeper layers (Figure 1). While pure retinol is highly effective in improving the skin, it is easily degraded by oxygen, heat, light, etc. Therefore, it takes some ingenuity to keep the ingredient stable and ensure that it gets delivered to the skin in order to fully demonstrate its effects. Through over 30 years of research on retinol, Shiseido has developed a unique technology, "Shiseido Retinol TripleLock Technology," to create products formulated with pure retinol in a stable manner, and this has realized the delivery of the effects of "pure retinol" to the skin with absolute certainty.

The results of this research were partly presented at "The 31st International Federation of Societies of Cosmetic Chemists (IFSCC)<sup>\*5</sup> Congress 2020 Yokohama (Oct. 21-30, 2020)," and also, at the 48th Convention of the Japanese Cosmetic Science Society (Jun. 23, 2023).

<sup>\*1</sup> Patented technology jointly developed by Shiseido, Honda Electronics Co., Ltd., and Toyohashi University of Technology. This technology, which converts the reflected ultrasonic signals from the inside of the skin into the modulus of elasticity, was developed for the first time in the world.

Shiseido Succeeds in Visualization of Internal Skin Elasticity (2018)

<https://corp.shiseido.com/jp/news/detail.html?n=00000000002422>

<sup>\*2</sup> A force present during deformation. The force that is exerted due to the hardness of the stratum corneum on the inside of the skin is calculated from the compression simulation of the multilayer structure. Joint research with Toyota Technological Institute.

<sup>\*3</sup> Shiseido Discovers that Balance of Internal Skin Elasticity is Root Cause of Wrinkles (2021)

<https://corp.shiseido.com/en/news/detail.html?n=00000000003074soude>

<sup>\*4</sup> Among retinols, it refers to pure vitamin A and not a derivative. Compared with retinol derivatives having modified chemical structures of vitamin A, the effect of pure retinol is high, although it is easily degraded. Shiseido is the only company in Japan that has been approved to blend in pure retinol (vitamin A) as a quasi-drug active ingredient.

Recognition of effect and efficacy in improving skin wrinkles with retinol acting ingredient acquired for the first time in Japan (2017)

<https://corp.shiseido.com/jp/news/detail.html?n=00000000002135>

<sup>\*5</sup> IFSCC: The International Federation of Societies of Cosmetic Chemists

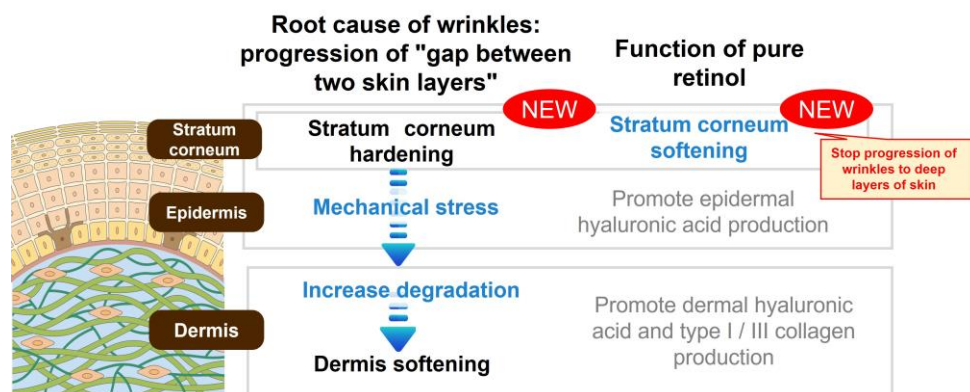


Figure 1. The root cause of wrinkles and the overall effects of "pure retinol" on all layers of skin

### Research background

Based on results from over 30 years of retinol research<sup>\*6</sup>, Shiseido's claim on the effect of the active ingredient "pure retinol" in improving wrinkles was recognized for the first time in Japan by the Ministry of Health, Labour and Welfare. This effect is reproducible, and the function that leads to wrinkle improvement in each layer of the skin—from the superficial layer (epidermis) to the deep layer (dermis)—has been clearly demonstrated, including its effect on the wrinkles of the neck.<sup>\*6</sup> While it has a clear improving effect, since it takes several weeks for the physiological changes of the skin to appear, the company has also been studying the mechanical structure of the skin, getting to the root of wrinkles, in search of even more efficient wrinkle improvement. Shiseido has developed the "internal and external skin elasticity 3D imaging technology" for the first time in the world, which has made what had been considered impossible by the conventional mechanical measurement possible: to measure the elasticity (repulsion when compressed) of each microscopic region of the skin in three dimensions. This development led to a discovery that the stratum corneum hardens with age, whereas the dermal layers become softer, and that this gap in hardness is the cause of wrinkle formation, i.e., "the root cause of wrinkles."

This time, we advanced our research with a focus on the hardening of the stratum corneum, which is related to the "root cause of wrinkles," with the aim of developing faster and more reliable methods to prevent and improve wrinkles.

<sup>\*6</sup> "Shiseido Discovers New Effect of Improving Neck Wrinkles, Results in 8 Weeks—New effects of retinol confirmed: Stimulates the production of collagen and hyaluronic acid in the dermis (2018)

<https://corp.shiseido.com/jp/news/detail.html?n=00000000002518>

### Effects of stratum corneum hardening on the dermis

To get a clearer picture of how the hardening of the stratum corneum affects wrinkles, we constructed a model that reflects the actual skin structure on a computer, and simulated the deformation caused by compression when the stratum corneum was soft vs. hard. Results revealed that, in the model of hard stratum corneum, the dermal deformation increased, and the mechanical stress applied to the dermis increased (Figure 2). Previous studies have shown that mechanical stress on the dermis promotes the production of collagen-degrading enzymes<sup>\*7</sup>. Therefore, when the stratum corneum is hard, the mechanical stress applied when the skin moves during facial expressions, etc., increases, which induces softening of the dermis; this is considered to lead to the progression of the "gap between the two skin layers (stratum corneum and dermis)," i.e., the root cause of wrinkles. In other words, these findings suggest that the hardening of the stratum corneum leads to the progression of wrinkles from the skin surface to the deep layers of the skin, and revealed that keeping the stratum corneum soft is an important care for wrinkle improvement.

<sup>\*7</sup> Skin Research and Technology 2014;20: 399–408

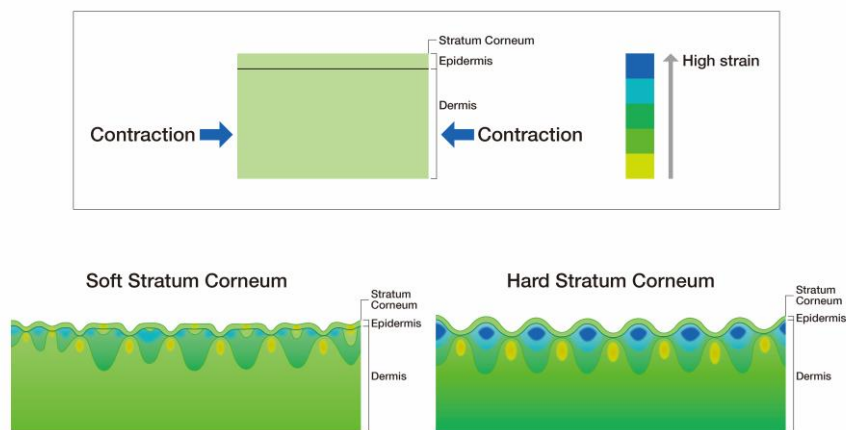


Figure 2. In the skin with hard stratum corneum, mechanical stress on the dermis due to skin deformation increases

### The stratum corneum softening effect of pure retinol

In accordance with the "Guideline for Evaluation of Anti-Wrinkle Products for Obtaining New Efficacy"<sup>\*8</sup> formulated by the Japanese Cosmetic Science Society, a continuous use study was conducted to evaluate changes in the hardness of the stratum corneum when a cream containing pure retinol was applied to one side of the face for 12 weeks in 35 healthy Japanese women with shallow to slightly deep wrinkles in the outer corner of the eyes. Results showed that the stratum corneum was significantly softer after 4 weeks of continuous use of the pure retinol-containing cream compared with before (Figure 3). Moreover, by continuing the use, the softness of the stratum corneum was maintained, with a consequent reduction in the area of wrinkles (Figure 4).

\*8 Journal of Japanese Cosmetic Science Society Vol. 30, No. 4, pp. 316-332 (2006) (jcss.jp)

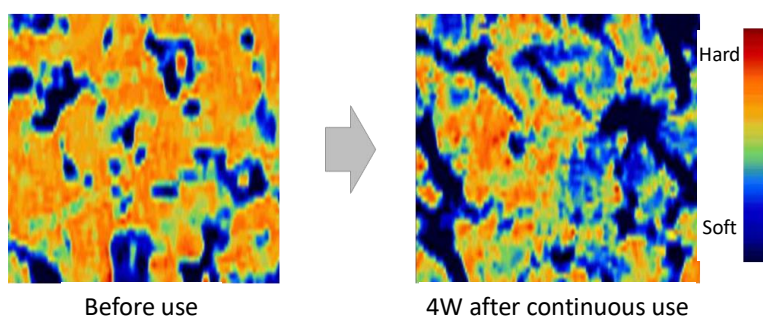


Figure 3 Measurement using the internal and external skin elasticity 3D imaging technology: 4 weeks of continuous use of the pure retinol-containing cream softened the stratum corneum

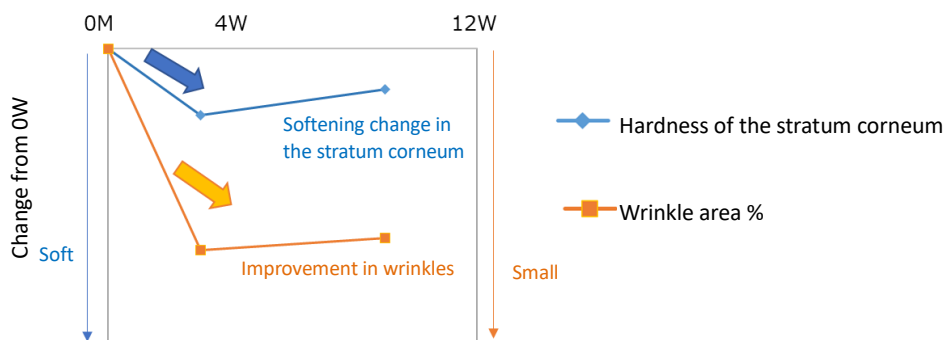


Figure 4. Changes over time of the hardness of the stratum corneum and the area of wrinkles after continuous use of the pure retinol-containing cream

## Rapid stratum corneum softening effect achieved by blended ingredients of complex oil

We showed that pure retinol has the effect of softening the stratum corneum physiologically and fundamentally, but since it requires a few weeks before any physiological changes are brought about, we also examined ingredients that can soften the stratum corneum in a short period of time and lead to prevention of wrinkles. When we checked the modulus of elasticity of the stratum corneum immediately after applying blended ingredients of complex oil containing castor oil and bis-diglyceryl polyacyladipate-2, etc., to a stratum corneum sheet, we found that the application of these ingredients can soften the stratum corneum in a short period of time (Figure 5). In addition, when the hardness of the stratum corneum on the surface of the skin was measured 10 minutes after these ingredients were applied to the real skin, a softening change was observed (Figure 6). The effect disappears when the oil is washed away from the skin, but when it is used in combination with pure retinol, we expect that it will instantly soften and loosen the skin, while supporting the fundamental skin softening effect, thereby possibly maximizing the effect of pure retinol softening the stratum corneum.

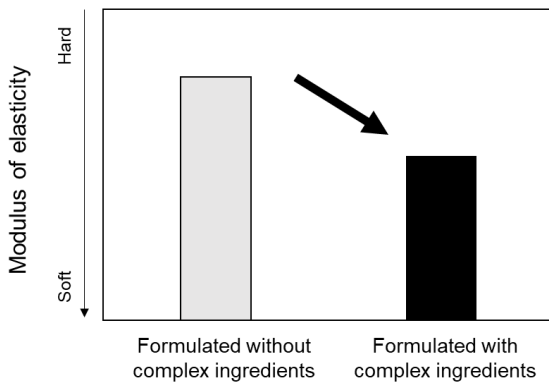


Figure 5. The stratum corneum showed a softening change immediately after applying complex ingredients

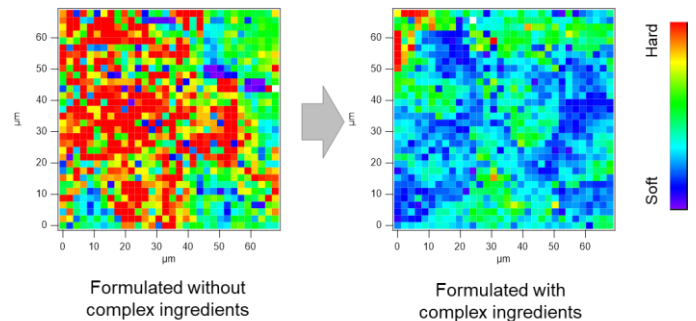


Figure 6. Stratum corneum softening effect observed 10 minutes after applying complex ingredients

Shiseido has developed “pure retinol,” an active ingredient that improves wrinkles, in a way that balances safety with functionality at a high level, receiving favorable reviews in the market. This reflects our continued effort to respond closely to the needs of our customers on a consistent basis. We have thus far clarified the effects of pure retinol on the epidermis and dermis, but apart from these effects, the present study clearly showed that it also has a softening effect on the stratum corneum on the surface of the skin. It demonstrated that wrinkles are improved by controlling the gap in hardness between the surface and inner layers of the skin, which Shiseido considers to be the “root cause of wrinkles,” and by preventing mechanical stress on the dermis that causes collagen degradation.

As the only manufacturer in Japan that can manufacture and sell products (quasi-drugs) containing pure retinol, an approved active ingredient capable of improving wrinkles, we will continue to pursue our studies that will help our customers live with positive feelings and lively, expressive faces.

### <Related Information>

“Shiseido Retinol TripleLock Technology”- Shiseido's unique technology to prevent the degradation of pure retinol

Retinol, or generally called vitamin A, is a fat-soluble vitamin essential for the growth of the body, maintaining vision, and keeping the skin and mucous membrane healthy. It has been recognized to exert a high skin improvement effect when applied to the skin, but it is also a difficult ingredient to handle, as it degrades easily when exposed to oxygen, heat, light, etc.

Applying the formulation technology cultivated through many years of research, and using the

company's original manufacturing methods, Shiseido succeeded in blending pure retinol in a stable manner while preventing it from degradation. In addition, a unique container specially developed for pure retinol formulations has BEEN adopted, which does not allow oxygen and light to pass through. Combining these technologies in formulation, manufacturing, and container design, "Shiseido Retinol TripleLock Technology" has led to the realization of delivery of the effects of pure retinol to the skin while ensuring its protection.

#### About Our R&D Strategy:

This study was conducted with the aim of elucidating the causes of "permanent skin concerns" that our customers have been expressing for many years, including dark spots/dullness, wrinkles, sagging, and pores, and developing solutions under "Skin Beauty INNOVATION," one of the three pillars of Shiseido's R&D strategy.

- Integrated Report 2022 (Beauty Innovation)

[https://corp.shiseido.com/report/en/2022/value\\_creation/innovation/](https://corp.shiseido.com/report/en/2022/value_creation/innovation/)

- Keywords

Skin Beauty INNOVATION, permanent skin concern, wrinkles

<Reference>

## Researchers' challenges

### ■ R&D Philosophy “DYNAMIC HARMONY” approach

Shiseido has been conducting research based on the Inside/Outside approach of the company's unique R&D philosophy, "DYNAMIC HARMONY." Focusing on the difference in hardness between the surface and inner layers of the skin, we aimed to elucidate the mechanism underlying wrinkle formation and develop solutions.

### ■ Challenge to wrinkles

The phenomenon of aging is something that will happen to everyone. Still, we want our customers to live a colorful life in the ways they like, without worrying too much about it. This is the motivation of Shiseido researchers. While the world is filled with information and products, we want to create truly reliable solutions for our customers. With this desire in mind, we have undertaken research to elucidate wrinkles from top to bottom.



Dr. Yuki Ogura, researcher

### ■ Development of measurement techniques to accurately capture the phenomenon of wrinkles, and elucidation of the root cause of wrinkles

Since the skin has a structure composed of overlapping layers having different properties—the stratum corneum, epidermis, and dermis—we came to the idea that wrinkles in the skin are not a simple phenomenon, but rather, they should be understood as a complex mechanical transformation involving changes in the shapes of multiple layers. However, we did not have the technology to measure the mechanical properties of each microlayer of the skin, and it was not possible to accurately measure the phenomenon of wrinkles in each customer's skin. Therefore, we conducted joint research with Honda Electronics, which had the ultrasonic measurement technology, and Toyohashi University of Technology, which was then working on the development of technologies to mechanically convert ultrasonic signals, and we were able to dramatically advance the development by introducing these new technologies. In 2017, we achieved our goal, completing the instrument that enabled the mechanical measurement of micro-regions inside the skin for each layer of the stratum corneum, epidermis, and dermis. This new instrument made it possible to collect precise data, and hence to understand the physiological mechanisms inside the skin. The obtained results became the material for the next study, and through a simulation study with Toyota Technological Institute, with their advanced technical prowess in the field of structural analysis, we were finally able to clarify the root cause of wrinkles, that is, "the collapse of balance in elasticity between the stratum corneum and the dermic layer."

### ■ Wrinkle improvement by pure retinol

Pure retinol that we have been working to develop realizes fundamental wrinkle improvement based on this mechanism, and we have demonstrated that it is a drug that can most effectively realize wrinkle improvement combined with its previously reported effects on the epidermis and dermis. We will continue to engage in our studies, aiming to contribute to the future where our customers can spend every day with smiles without worrying about wrinkles.

Shiseido's R&D Philosophy “DYNAMIC HARMONY”

Shiseido Formulates Its Unique R&D Philosophy “DYNAMIC HARMONY” (2021)

<https://corp.shiseido.com/en/news/detail.html?n=00000000003252>

DYNAMIC HARMONY website:

<https://corp.shiseido.com/en/rd/dynamicharmony/>