

Research and Development

Shiseido discovers that a decrease in female hormone induces the dysfunction of lymphatic vessels in the skin

The turmeric extract from the ginger family has an effect to restore the function of skin lymphatic vessels

Shiseido discovered that female hormone contributes to the integrity of lymphatic vessels^{*1} in the skin, which are important for maintaining the skin homeostasis. Using its unique 3D technology^{*2} to visualize the internal structure of the skin, the abnormal morphology of lymphatic capillaries in the skin associated with the dysfunction was confirmed in post-menopausal women, who start to experience a rapid decline in female hormone. In addition, with the cooperation of Dr. Nobuyuki Takakura, Professor at Osaka University, apelin^{*3} was identified as a factor that induces the stabilization of lymphatic vessels by working synergistically with the decreasing female hormone as age progresses. Moreover, an extract of turmeric, a plant in the ginger family (Zingiberaceae), was found to enhance the weakened function of lymphatic vessels by promoting the production of apelin (Figure 1). We will continue to conduct advanced research from a holistic perspective to investigate the relationship between the skin and its internal conditions, such as blood vessels, lymphatic vessels, immunity, and nerves, and open up a new world of dermatological research. The results of the present study have been submitted in part to the *Journal of Dermatological Science* and were presented at the ISID (International Societies for Investigative Dermatology) meeting (2023/5/10-5/13) and the 47th Meeting of the Japanese Society of Lymphology (2023/6/9-6/10).

*1 Lymphatic vessels are present in peripheral tissues including the skin and serve as a starting point for the collection of waste products and excess water

*2 Shiseido Establishes Lymphatic Vessel Visualization Technology (2020) <https://corp.shiseido.com/en/news/detail.html?n=0000000002997>

*3 Apelin, a known component in living organisms, is a peptide composed of 13 or 36 amino acids

Shiseido Becomes the First to Reveal the Relationship between Impaired Lymphatic Function and “Sagging” Skin (2015)

https://corp.shiseido.com/jp/newsimg/archive/0000000001834/1834_a4z87_jp.pdf(Japanese)

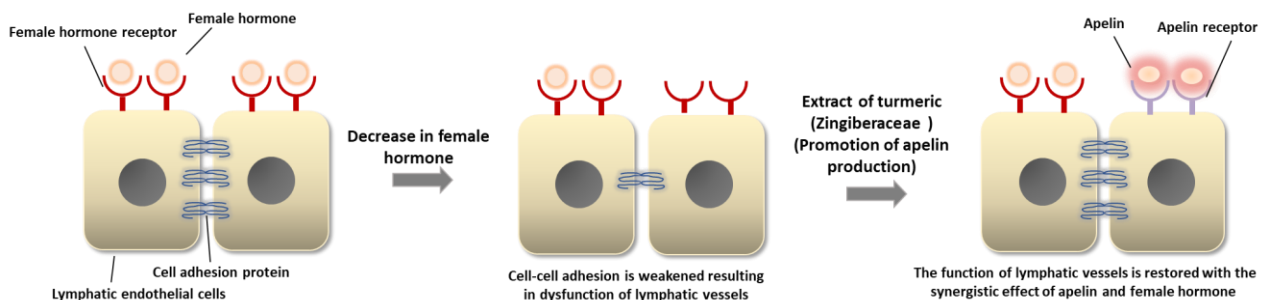


Figure 1. Dysfunction of lymphatic vessels due to decreased female hormone and the effect of turmeric extract from the ginger family to promote functional recovery (conceptual diagram)

Research background

Shiseido believes that the relationship with the inside of the body is important to bring out the natural beauty of the skin. We were among the first to tackle dermatological research from a holistic perspective based on the relationship with the whole body, including blood vessels, lymphatic vessel, immunity and nerves, and have applied this knowledge to our products.

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*4 Shiseido clarifies that impaired lymphatic vessel function is a cause of wrinkle formation

https://corp.shiseido.com/jp/newsimg/archive/0000000000905/905_a5c92_jp.pdf(Japanese)

*5 Shiseido Reaches World's First Elucidation of Aging Mechanism of Lymphatic Vessels in the Skin (2020)

<https://corp.shiseido.com/en/news/detail.html?n=00000000002998>

*6 Shiseido Succeeds in 3D Visualization of Morphological Changes in Dysfunctional Lymphatic Capillaries (2023)

<https://corp.shiseido.com/en/news/detail.html?n=00000000003620>

Morphological changes of lymphatic capillaries in the skin associated with menopause

It has previously been known that the lymphatic flow becomes restricted in post-menopausal women, when female hormone rapidly decreases, making women more prone to swelling. However, their mechanism has not been clarified. In the present study, the skin of women in each age group was analyzed using 3D visualization technology in order to assess the morphological changes of lymphatic capillaries in pre- and post-menopause. As a result, the volume of lymphatic capillaries was reduced in post-menopause, and that the vessels have become thin and fragile. These findings suggest that a decrease in female hormone may be one of the causes of functional impairment of lymphatic vessels in the skin, with the resulting morphological changes (Figure 2).

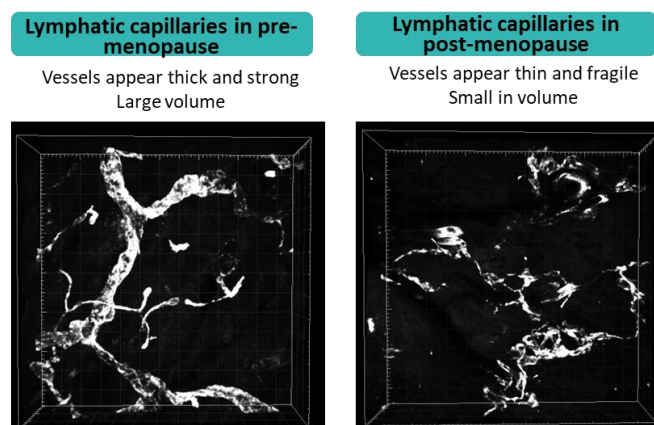


Figure 2. Lymphatic function is impaired due to decreased female hormone

Apelin works synergistically with female hormone to contribute to the stabilization of lymphatic vessels

Female hormone induce cell proliferation and stabilization through its receptor expressed in lymphatic endothelial cells (Figure 3). Thus, considering the age-related decrease in the secretion of female hormone that has a protective effect on the function of lymphatic vessels, we explored factors that work synergistically with low concentrations of female hormone and enhance their effect. With the cooperation of Dr. Takakura, we identified apelin, which is a well-known factor that stabilizes the vascular integrity, to possess this ability.

The function of apelin on lymphatic vessels has already been clarified in our previous study, and this time, we examined how apelin can assist in the actions of female hormone that are reduced in post-menopause. We found that the cell-cell adhesion was stronger when they were stimulated simultaneously with both apelin and female hormone than individual stimulation with each factor (Figure 4). These results revealed that apelin works synergistically with female hormone to induce stabilization of lymphatic vessels.

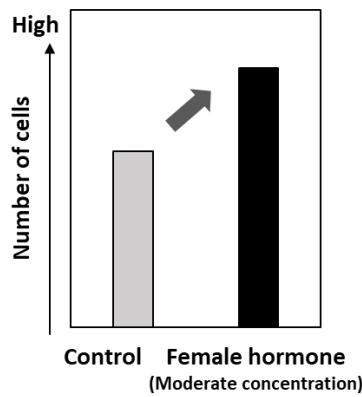


Figure 3. Female hormone promotes the proliferation of lymphatic endothelial cells

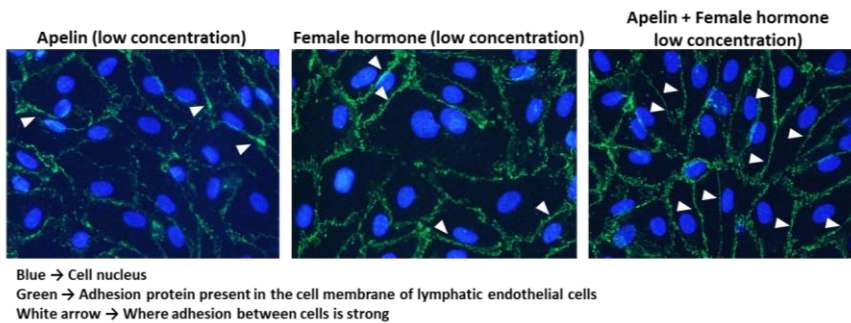


Figure 4. Co-stimulation of apelin and female hormone strengthen the cell-cell adhesion

The turmeric extract from the ginger family promotes the production of apelin and stabilizes lymphatic vessels

A search for active ingredients that can promote the production of apelin, which works synergistically with female hormone, led to the discovery of an "turmeric extract from the ginger family." We confirmed the effect of this extract to strengthen cell-cell adhesion in lymphatic vessels and thereby stabilize lymphatic vessels by promoting the production of apelin (Figure 5).

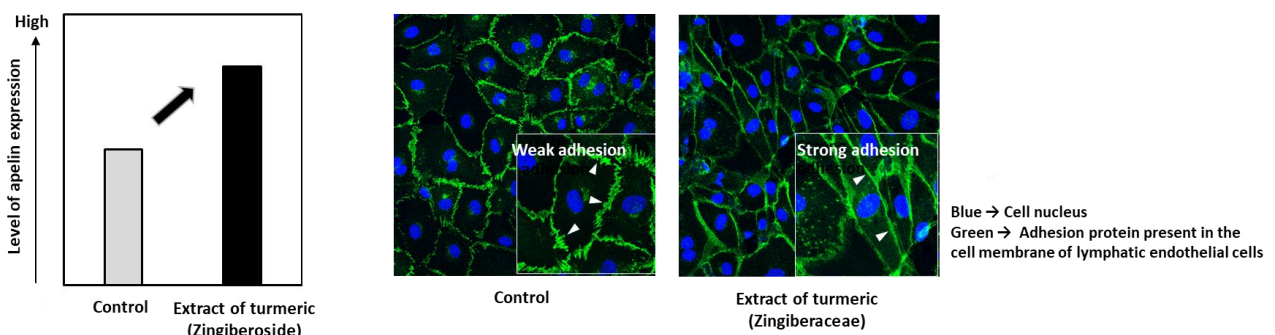


Figure 5: Turmeric extract from the ginger family stabilizes lymphatic vessels by increasing apelin gene expression

Future prospects

In the present study, we clarified that changes in female hormone, which are important for maintaining the homeostasis of the whole body, affect the function of lymphatic vessels in the skin, and found the possibility that the impaired function of lymphatic capillaries could lead to skin problems such as wrinkles and sagging that increasingly occur in post-menopause. Accordingly, by clarifying the relationship between the whole body and lymphatic vessels, which are responsible for the removal of waste products, we will demonstrate the importance of maintaining the function of lymphatic vessel in producing healthy skin. Shiseido aims to bring out the original beauty of each and every person by challenging beauty innovation that works not only on the surface of the skin but also inside and outside of the skin, moving toward the realization of the company's management strategy vision, "Personal Beauty Wellness Company."

About Our R&D Strategy:

Under "Skin Beauty INNOVATION," one of the three pillars of the company's R&D strategy, the present study was carried out in the field of "skin foundation," which aims to elucidate the relationships between the skin and the conditions inside the skin, such as blood vessels and lymphatic vessels, immunity, and nerves.

- Integrated Report 2022 (Beauty Innovation)

https://corp.shiseido.com/report/en/2022/value_creation/innovation/

- Keywords

Skin Beauty INNOVATION, skin foundation, lymphatic vessels

<Reference>

Researchers' challenges

■ R&D Philosophy "DYNAMIC HARMONY" approach

This research was carried out under the Inside/Outside approach of Shiseido's R&D philosophy, DYNAMIC HARMONY. It is our goal to create healthy and beautiful skin by focusing on the relationship between lymphatic vessels and hormone that are important for maintaining the homeostasis of the whole body.

■ Hypothesis that remained unaddressed for 10 years

About 10 years ago, we discovered a mechanism by which "swelling leads to sagging," or how weakened lymphatic vessels in the skin

lead to subcutaneous fat accumulation. At that time, we identified apelin to be a factor that works defensively against the impairment of lymphatic vessels, and researchers then came up with a hypothesis that there may be an involvement of female hormone, with a perception that "apelin may act differently depending on gender."

When women reach menopause, they tend to experience swelling more. Also, swelling is a problem that some women actually feel due to the menstrual cycle. Ten years ago, however, that hypothesis could not be verified and so was put aside for later consideration. Then, with the development of the visualization technology to analyze lymphatic vessels in the skin, our hypothesis blossomed all at once, leading to the finding that apelin can act to protect lymphatic vessels like female hormone do. We were able to propose an approach to hormonal balance, which is inseparable from a woman's life, and skin problems caused by its changes and disturbances.

■ Development of a new approach to skin aging by capturing small changes in lymphatic vessels and capillaries

Shiseido is energetically promoting research on lymphatic vessels and capillaries—organs that exist on the inside of the skin and are connected to the whole body. Going forward, we will further deepen our investigation of lymphatic vessels and blood vessels from the perspective of holistic beauty, and develop an approach to make the skin beautiful from the inside of the body by examining, for example, how changes in people's daily lives and lifestyles lead to aging of the skin focusing on the route that connects the inside and outside, i.e., lymph vessels and blood vessels.



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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=0000000003252>

DYNAMIC HARMONY website:

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