

**Shiseido Becomes the First to Reveal the Relationship
between Impaired Lymphatic Function and “Sagging” Skin**
Discovery of Lymphatic Function-Enhancing “Pine Cone Extra”

Shiseido Co., Ltd., through joint research with Professor Nobuyuki Takakura of the Research Institute for Microbial Diseases, Osaka University, has revealed for the first time that impaired function of dermal lymphatic vessels lead to accumulation of subcutaneous fat, which ultimately causes “sagging” of the skin. Moreover, this study was the first to discover that “pine cone extra” collected from *Pinus Sylvestris*, which is distributed throughout Europe and Asia, has the effect of strengthening and normalizing the lymphatic vessels.

The development is underway to apply these study findings to skin care cosmetics.

Shiseido’s approach to lymphatic and capillary vessel research

Shiseido has long focused on research pertaining to capillary and lymphatic vessels, since capillary vessels, which supply nutrients and oxygen, and lymphatic vessels, which are indispensable in collecting water and waste products, play important roles in the maintenance of healthy skin. Previous studies have found that impaired blood vessel and lymphatic function is a root cause of skin aging. For instance, the structures of capillary and lymphatic vessels become slimy due to the effect of ultraviolet rays or aging, and this prevents nutrients from spreading into every corner of skin. In addition, reduced lymphatic function causes prolonged inflammation, which results in wrinkles.

On the other hand, “sagging,” one of skin aging phenomena, has thus far been attributed to a decrease in collagen fibers or reduced elasticity, accumulation of subcutaneous fat, enlargement of adipocytes, and so on. In carrying out a joint research with Professor Takakura, the present study was initiated based on the idea that there might be an association between the state of lymphatic vessels and “sagging.”

From “swelling” to “sagging”

Impaired lymphatic function causes skin troubles, such as “swelling.” Professor Takakura has identified “apelin”^{*1} as a novel endogenous factor that enhances the function of lymphatic vessels, and furthermore, he discovered that apelin suppresses the accumulation of subcutaneous fat.

Based on these study results, we set out to examine in detail the relationship between lymphatic function and accumulation of subcutaneous fat. The results revealed that 1) fatty acids, which are present abundantly in lymph, cause the destabilization of lymphatic vessels, leaking from the vessels, and 2) leaked fatty acids directly promote the differentiation of adipocytes. Furthermore, it was found that apelin has a function to suppress the leakage of fatty acids from lymphatic vessels (Figure 1).

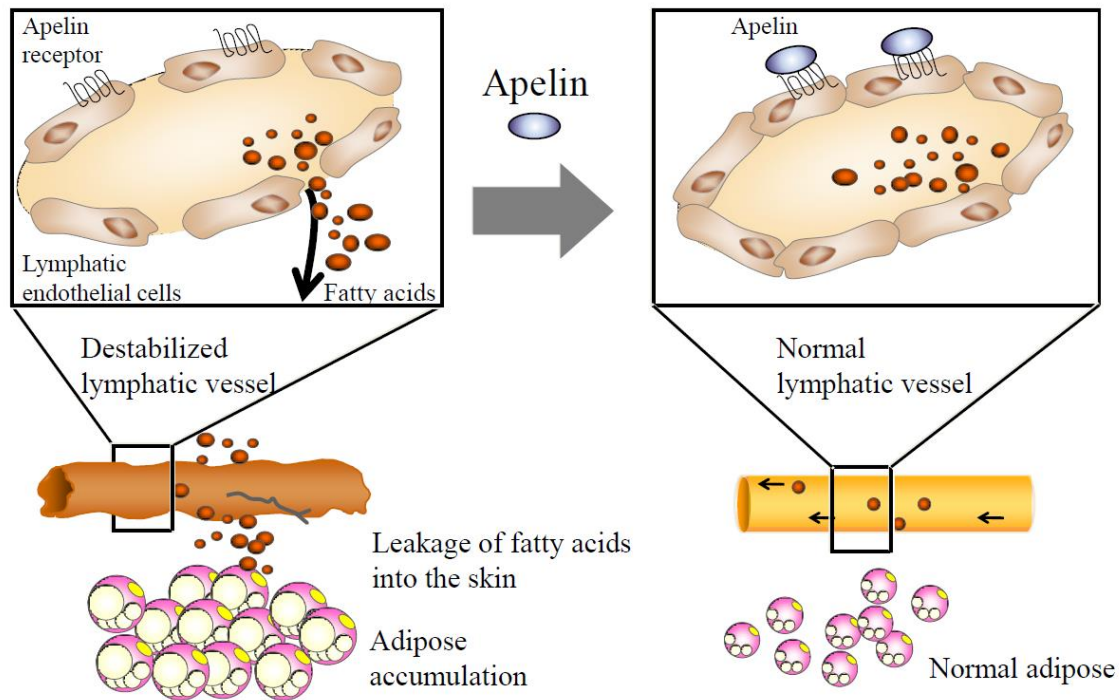


Figure 1: The mechanism leading to “sagging” from “swelling”

Our previous study has shown that in saggy parts, there is an accumulation of subcutaneous fat. The new study results signify a new discovery of the mechanism of how “swelling” due to impaired lymphatic function causes “sagging” via association with an increase and accumulation of subcutaneous fat.

*1 Apelin is a known biological component, the peptide comprising 13 or 36 amino acids. It has been known to stabilize vascular structure.

The discovery of “pine cone extra” having the same function as apelin, an endogenous factor

Shiseido, in collaboration with Osaka University, initiated the screening of herbal components with the same function as apelin, which increases lymphatic function and suppresses subcutaneous fat increase and accumulation. It is known that apelin binds to G protein-coupled receptor APJ, which is expressed in the cell membrane of lymphatic endothelial cells, and stabilizes lymphatic vessels. From among approximately 200 herbal components, “pine cone extra” was found to have the same high activity as apelin that binds to APJ. As with apelin, “pine cone extract” was shown to have a suppressing effect on fatty acid-induced destabilization of lymphatic vessels. In addition, when a trial product formulated with “pine cone extra” was used for two months (morning and night), effects were observed to improve the nasolabial line, the facial line, and sagging of the neck.

Shiseido will continue to conduct basic research on capillary and lymphatic vessels to develop new skincare cosmetics.

The study results were presented at the Society for Investigative Dermatology (SID) Annual Meeting*2 in Atlanta, Georgia.

*2 SID (Society for Investigative Dermatology) is the world's largest society in the area of dermatological science. SID annual meetings attract up-and-coming researchers who present advanced research findings. (Held annually (this year from May 6th through 9th), with approximately 1,000 participants from 25 countries and regions)

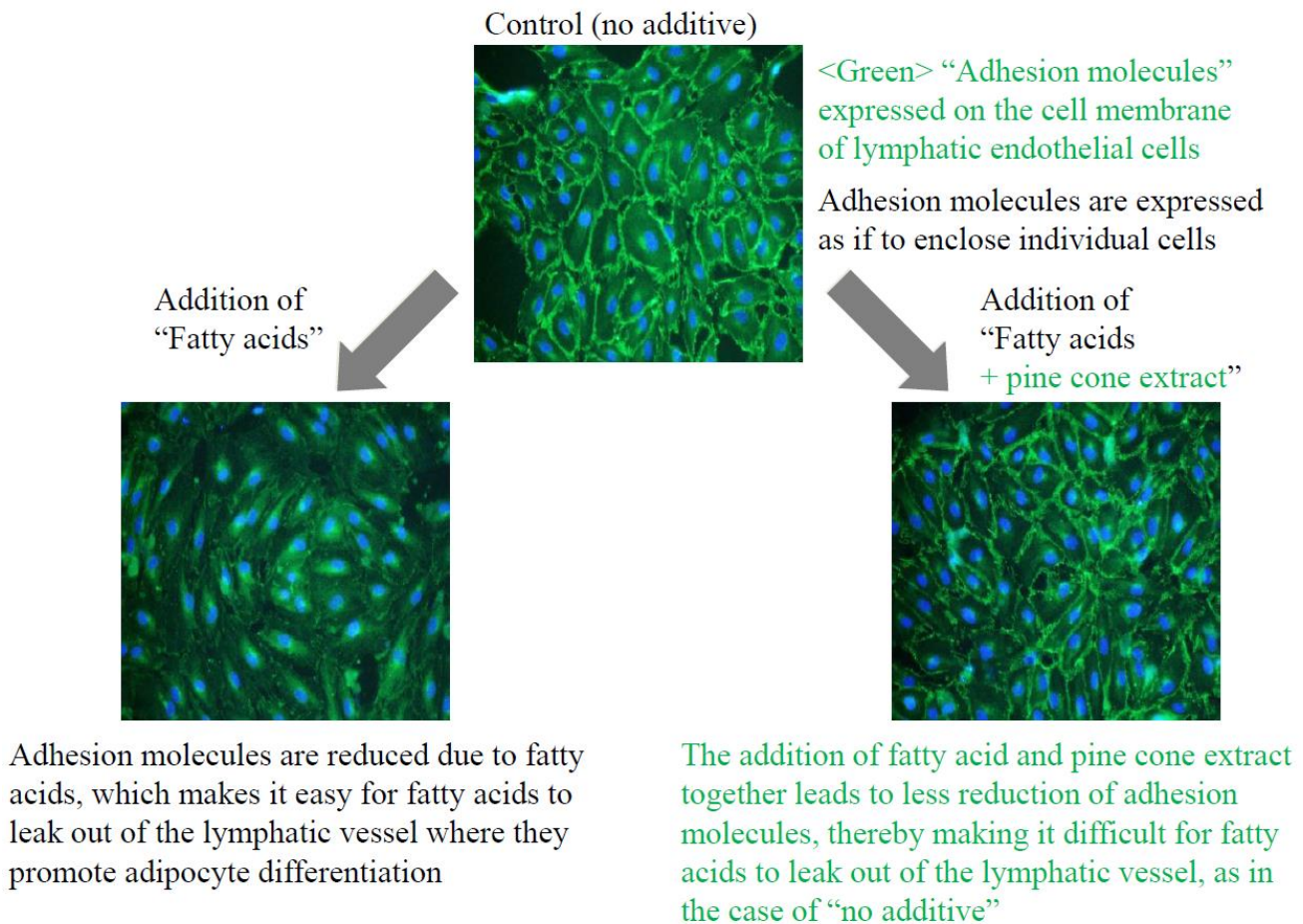


Figure 2: Lymphatic vessel stabilizing effect of pine cone extract

While adhesion molecules (green) expressed on the cell membrane of lymphatic endothelial cells are reduced by the addition of fatty acids, an improvement was found with the addition of pine cone extract.