

Research and development

Shiseido advances epidermal stem cell research, discovering the lemon ironwood leaf extract with potential to solve aging-related skin problems

Inhibiting the senescence of epidermal stem cells while also increasing the quantity of the cells and improving the ability to produce cells

Shiseido discovered that the extract of lemon ironwood^{*1} leaf extract has an effect to inhibit the senescence of epidermal stem cells (Figure 1). Moreover, this extract was found to increase the quantity of epidermal stem cells and improve the ability to produce cells. These findings suggest that the extract may help maintain healthy epidermal stem cells that serve as the source of turnover of the skin, leading to solutions for skin problems caused by aging.

This study applied the findings^{*2} from Shiseido's collaborative research with the Cutaneous Biology Research Center (CBRC)^{*3} at Massachusetts General Hospital, which led to a revelation that senescence of epidermal stem cells may be controllable. Moving forward, Shiseido will continue to advance epidermal stem cell research with the aim of addressing various skin problems caused by aging.

The results of this study were partly presented at the International Societies of Investigative Dermatology (ISID) meeting, held in Tokyo on May 10–13, 2023.

^{*1} A plant in the family Myrtaceae having aromatic leaves with a lemon-like scent, known for its use as a healing plant in its native Australia since ancient times. The various effects of lemon ironwood, including antibacterial and antioxidant activities, have also been studied in academic settings

^{*2} Shiseido reveals the possibility of controlling senescence of epidermal stem cells in collaborative research with CBRC (2023)

<https://corp.shiseido.com/en/news/detail.html?n=0000000003636>

^{*3} CBRC (Cutaneous Biology Research Center): CBRC is a general research institute for advanced research and development in the field of dermatology established by Harvard Medical School and Massachusetts General Hospital with support from Shiseido in 1989. Shiseido also dispatches its researchers to CBRC to conduct collaborative studies with world-class researchers

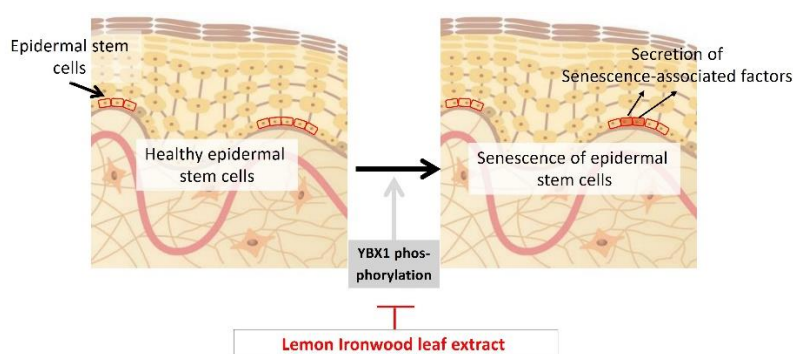


Figure 1. Phosphorylated YBX1, which causes the senescence of epidermal stem cells, is inhibited by the lemon ironwood leaf extract (conceptual diagram)

Research background

Skin turnover occurs as a result of cells in the epidermis constantly proliferating and differentiating, helping the skin to stay healthy. Epidermal stem cells that are present in the basal layer serve as the source of these cells. Based on the idea that maintaining healthy epidermal stem cells is crucial for achieving beautiful skin, Shiseido has discovered that supporting the maintenance of the quantity of epidermal stem cells through the basement membrane under the basal layer of the epidermis contributes to skin hydration, barrier function, and even collagen production in the dermis. Moreover, a joint study with the CBRC focusing not only on the quantity of epidermal stem cells but also on their quality revealed that phosphorylation^{*4} of YBX1^{*5}, the RNA^{*6} binding protein that inhibits

the senescence of epidermal stem cells, decreases the function of YBX1 and thereby causes cellular aging. The present study applied these findings and aimed to improve the quality of epidermal stem cells with cosmetic ingredients.

*4 Phosphorylation: One of post-translational modifications of proteins. The addition of phosphate groups changes the structure of proteins, causing changes in their activities

*5 YBX1: Y-box binding protein-1. YBX1 is known to bind to DNA and RNA, thereby controlling protein synthesis in the processes of transcription and translation, and regulate cellular function

*6 RNA: Ribonucleic acid. Genetic information carried by deoxyribonucleic acid (DNA) is transcribed into RNA, and proteins are synthesized based on that information

Lemon ironwood leaf extract not only inhibits the aging of epidermal stem cells but also promotes epidermal stem cell proliferation

The function of YBX1, which inhibits the senescence of epidermal stem cells, has been shown to decrease by phosphorylation. Among more than 100 cosmetic ingredients, we identified the leaf extract of lemon ironwood, a plant native to Australia, to have the effect to inhibit the phosphorylation of YBX1 and prevents the senescence of epidermal stem cells in cultured cells containing epidermal stem cells (Figure 2).

As for the mechanism to prevent epidermal stem cell senescence by YBX1, it has been known that YBX1 inhibits the production of SASP factors, which are secreted from aged cells and trigger the propagation of aging. In the present study, we observed that the production of IL-8^{*7}, a SASP factor^{*8}, is suppressed in cultured cells containing the lemon ironwood leaf extract. In addition, the lemon ironwood leaf extract increased the expression of MCSP^{*9}, a marker gene of epidermal stem cells, and also increased the proliferation of cells (Figure 3). These results suggested the effect of the lemon ironwood leaf extract to inhibit the senescence of epidermal stem cells while also increasing the quantity of epidermal stem cells and improving the ability to produce cells.

We will apply these findings as a solution to maintain healthy epidermal stem cells, which serve as the source of skin turnover, in solving the various skin problems that emerge with aging.

*7. IL-8: Interleukin-8

*8. SASP factors: Senescence-associated secretory phenotype factors

*9. In this study, cells expressing melanoma-associated chondroitin sulfate proteoglycan (MCSP) on the cell surface were considered epidermal stem cells

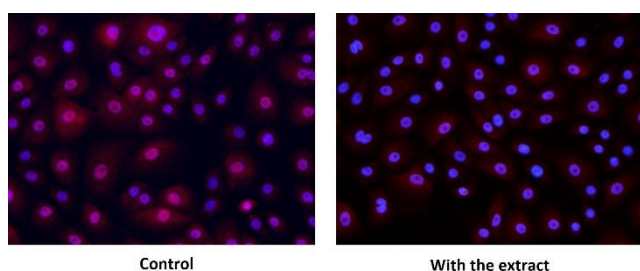


Figure 2. A decrease in phosphorylated YBX1 (red) is observed in cells cultured with the lemon ironwood leaf extract (blue: cell nucleus)

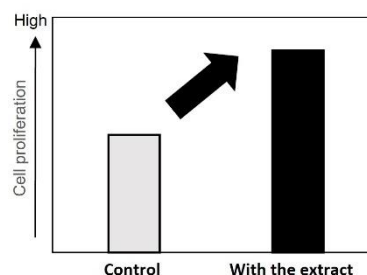


Figure 3. The addition of lemon ironwood leaf extract improved cell proliferation

About our R&D strategy:

Under "Skin Beauty INNOVATION," one of the three pillars of the company's R&D strategy, we applied the results of joint research with CBRC in The United States, one of the world's leading institutions in advanced medical research, to the present study.

- Integrated Report 2023 (Beauty Innovation)

<https://corp.shiseido.com/report/en/2023/message/cmio/>

- Keywords

Skin Beauty INNOVATION, stem cell

<Reference>

Researchers' challenges

■ Focusing on changes in the quality of epidermal stem cells

For many years, Shiseido has been conducting studies on the basement membrane of the epidermis. One of the results of these studies is the finding that aging-related changes in the epidermal basement membrane causes a decrease in epidermal stem cells. With this knowledge at hand, we continued to advance the research on epidermal stem cells, and through a joint study with the CBRC focusing on changes in the quality of epidermal stem cells, the mechanism of epidermal stem cell senescence by YBX1 phosphorylation was finally elucidated.

This time, we took on a challenge to develop cosmetic ingredients capable of inhibiting the senescence of epidermal stem cells. By setting up multiple screening steps based on the mechanism of senescence of epidermal stem cells, we searched among more than 100 candidates initially screened and were able to identify the effectiveness of lemon ironwood leaf extract.

■ Maintaining healthy epidermal stem cells is essential

Through this study, we aim to widely promote the understanding that maintaining healthy epidermal stem cells leads to preserving and enhancing the skin's inherent ability to rejuvenate. Furthermore, as the demand for reliable solutions based on science increases among consumers, we hope that our findings will meet these needs and solve each individual consumer's skin concerns due to aging.

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/>



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