UDC 613.49

Development of Functional Cosmetics "ASTALIFT WHITENING ESSENCE"

Fumi KUSUDA*, Toshiaki KUBO*, Yukio SUDO*, Tatsuo KAWABUCHI**,
Atsushi ORIKASA***, and Yoshisada NAKAMURA*

Abstract

Skin blemishes are big problems. We focused particular attention on "everlasting blemishes". We developed "ASTALIFT WHITENING ESSENCE", which contains Astaxanthin. Astaxanthin regulates cytokine levels during the production of melanin, and along with vitamin C, inhibits excessive melanin production. The "ASTALIFT WHITENING ESSENCE" combines substances that control formation of normal blemishes with other substances to act on "everlasting blemishes". We found this product moisturizes the skin and makes the skin more elastic. It also not only reduces the number and the size of blemishes, but inhibits the forming of wrinkles.

1. Introduction

FUJIFILM is seeking to be a total healthcare company covering "therapy" and "prophylaxis" in addition to our conventional expertise, "diagnosis," such as x-ray image diagnosis and hemodiagnosis. In the field of prophylaxis, we have launched functional food and functional cosmetics (skin care cosmetics) described below since 2006.

"Anti-aging" tops the list of cosmetic functions women look for, beating "moisturizing" and "whitening". Skin aging is largely attributed to UV radiation and resultant active oxygen, rather than genes considered to cause natural aging. The decline in the skin functions and changes in the skin structure by light are called photoaging. It is the main target of anti-aging care. Especially, age spot is the biggest skin complaint.

The ASTALIFT WHITENING ESSENCE (Fig. 1) launched in February 2009 has been designed to combat the age spot.

Fig. 1 ASTALIFT WHITENING ESSENCE.

2. What is Age Spot?

Production and Discharge of Melanin, Cause of Age Spot

Melanin pigment responsible for age spots is produced by the pigment cells (melanocyte) in the epidermis. The melanin pigment is transferred from the pigment cells to the surrounding epidermal keratinocytes and it protects DNA in the cells from harmful UV radiation.

Melanin pigment is normally discharged from the body as scurf with the metabolism (turnover) of keratinocytes. The rates of the production and the discharge are balanced to maintain the skin complexion[1].

When skin is exposed to UV radiation or other external stimulus or it suffers internal stimulus including stress, melanin pigment production is accelerated. The excessive production causes suntan and age spots. With the turnover, melanin pigment is gradually discharged and the skin restores its complexion. But, that is not always the case.

Age spots may result when melanin production does not stop or when some melanin pigments do not go with the turnover. We call the latter "everlasting blemish". The whitening essence in this report targets that type of age spot (Fig. 2).

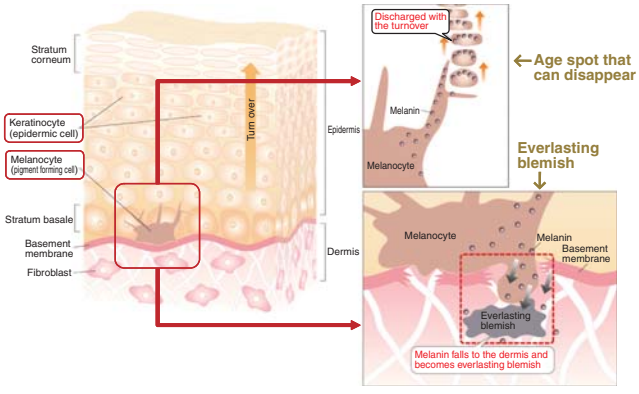

Fig. 2 Mechanism of blemish production.

Original paper (Received November 20, 2009)
* Life Science Research Laboratories
Research & Development Management Headquarters
FUJIFILM Corporation
Ushijima, Kaisei-machi, Ashigarakami-gun, Kanagawa 258-8577, Japan
** Life Science Products Division
Healthcare Business Headquarters
FUJIFILM Corporation
Nishiazabu, Minato-ku, Tokyo 106-8620, Japan
*** New Business Development Office
Life Science Products Division
Healthcare Business Headquarters
FUJIFILM Corporation
Akasaka, Minato-ku, Tokyo 107-0052, Japan

The "everlasting blemish" is caused when melanosomes containing melanin produced by melanocyte fall through a hole in the basement membrane into the dermis and they are not carried with the turnover.

Mechanism of Melanin Production

Melanin pigment that causes age spots is produced by the following mechanism of action (Fig. 3).

When stimulated by UV radiation or resultant singlet oxygen, keratinocytes produce a cytokine called IL-1α (interleukin-1α). And then, the keratinocytes also produce cytokines which give melanocytes a command to produce melanin, including ET-1 (endothelin-1) and SCF (stem cell factor), and proinflammatory cytokines such as PGE2 (prostaglandin E2). --- Fig. 3 (1)

The fibroblasts in the dermis produce cytokines including HGF (hepatocyte growth factor) and SCF. These cytokines stimulate melanocytes. --- Fig. 3 (1)

The stimulated melanocytes synthesize melanin pigment from tyrosine as the starting ingredient through oxidation polymerization inside melanosomes (a type of endoplasmic reticulum in a cell) provided with a substrate, e.g., tyrosine, and an enzyme, e.g., tyrosinase. --- Fig. 3 (2)

The melanosomes containing melanin pigment are normally carried through a dendritic projection of melanocytes and taken up by keratinocytes by their phagocytosis.

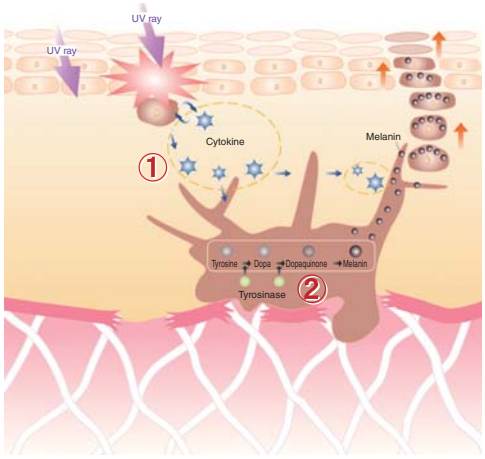

Fig. 3 Normal blemish generation mechanism.

2.1 Everlasting Blemish

Melanophage, the Culprit of Everlasting Blemish

Melanosomes that have not taken up by keratinocytes to fall into the dermis through a hole in the basement membrane are captured by macrophages in the dermis.

Macrophages provide cell immunity. They migrate and phagocytose foreign bodies. Macrophages in the dermis phagocytose melanosomes as foreign bodies. A macrophage that has phagocytosed a melanosome is called melanophage. Once turned into melanophage, the cell loses mobility, although it is unknown why. The melanin captured in a melanophage and remaining in the skin is the culprit of the everlasting blemish[2].

The left photo in Fig. 4 shows melanosomes containing melanin in a pigment cell on the basement membrane. The photo also shows a hole in the basement membrane near the cell. The right photo shows a melanophage that phagocytosed melanosomes.

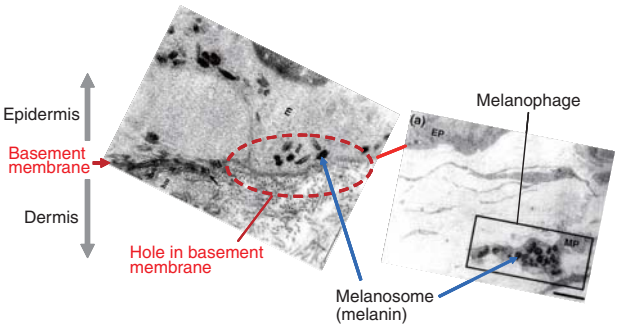

Fig. 4 Melanophage[2].

2.2 Breakage of Basement Membrane

What is Basement Membrane? Why is it Broken?

The basement membrane located between the epidermis and the dermis. It joins the relatively hard epidermis packed with cells and the relatively soft dermis mostly made of extracellular matrices. It also has something to do with keratinocyte division. This membrane is a sheet-like structure mainly made of type IV collagen.

Exposure to UV radiation increases production of MMP (matrix metalloproteinase) that degrades collagen as well as producing singlet oxygen in the keratinocytes in the epidermis and fibroblasts in the dermis. --- Fig. 5 (4)

When exposed to UV radiation, keratinocytes produce proinflammatory cytokines. They also increase production of MMP. --- Fig. 5 (3)

The MMP accelerates degradation of type IV collagen in the basement membrane and makes a hole in the basement membrane. --- Fig. 5 (5)

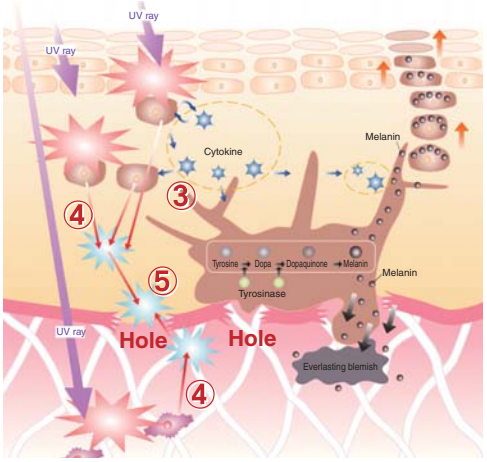

Fig. 5 Everlasting blemish generation mechanism.

3. Development of ASTALIFT WHITENING ESSENCE

Product Concept

The recently developed ASTALIFT WHITENING ESSENCE aims at combating the everlasting blemish. To achieve the aim, the essence is designed to control the melanin pigment production triggered by UV radiation and resultant singlet oxygen based on the above-described mechanism and to prevent the basement membrane from breakage and repair it.

3.1 Controlling Age Spot Formation

Protecting Against UV Radiation and Eliminating Singlet Oxygen

The first step to control production of melanin is protection against UV radiation. For this purpose, the ASTALIFT series has Day Protector containing UV inhibitor.

The next step is to eliminate singlet oxygen that is produced by UV radiation. We have focused on astaxanthin[3]. Astaxanthin eliminates singlet oxygen 1,000 times faster than CoQ10 the antioxidant effect of which is used for cosmetics (Fig. 6).

Astaxanthin

Astaxanthin is a type of carotenoid pigment derived from algae, such as Haematococcus pluvialis. Prawns, crabs, salmon and other water animals contain astaxanthin via food chain[4].

Astaxanthin inactivates singlet oxygen by taking its energy. Unlike inactivation by redox, repeated elimination counts performed by astaxanthin are 1,800 times more than those done by CoQ10.

Controlling Cytokine Production

We have found that astaxanthin has the effect of inhibiting production of cytokines that play an important role in the melanin production mechanism. Fig. 7 shows astaxanthin's effect of inhibiting IL-1α that is produced by UV radiation to human keratinocytes. Controlling IL-1a will help control melanin production. IL-1α is an upstream cytokine which commands melanin production.

We have also found that astaxanthin inhibits production of PGE-2 in keratinocytes, a proinflammatory cytokine that also commands transfer of melanosomes from melanocytes to keratinocytes (Fig. 10).

Controlling Melanin Production

We have confirmed that astaxanthin inhibits melanin production in melanocytes like APM does (Fig. 8). Fig. 9 shows effects of astaxanthin and APM, which inhibit melanocytes from producing melanin. It shows that astaxanthin has the similar effect to that of APM although they do not produce a synergetic effect.

Astaxanthin is thus effective for controlling age spots, inhibiting all the steps toward melanin production. To help

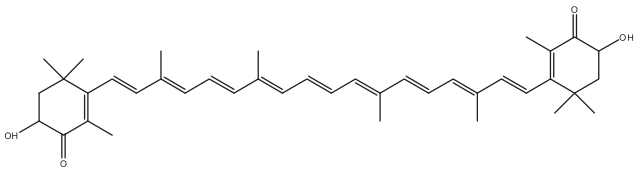

Fig. 6 Structure of Astaxanthin.

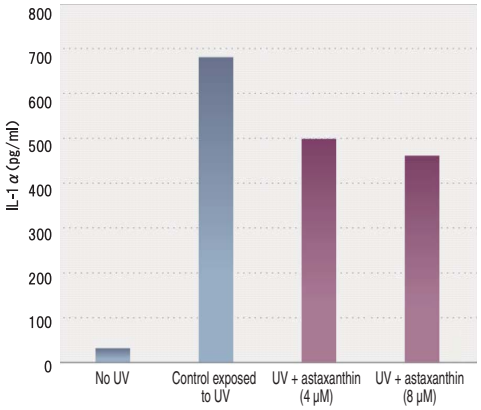

Fig. 7 Generation inhibition of IL-1α by Astaxanthin.

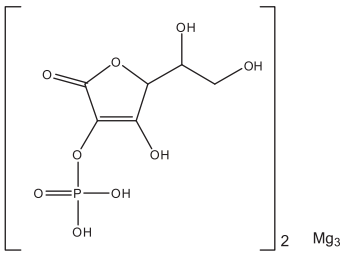

Fig. 8 Structure of the APM, "ascorbic acid manganese phosphate".

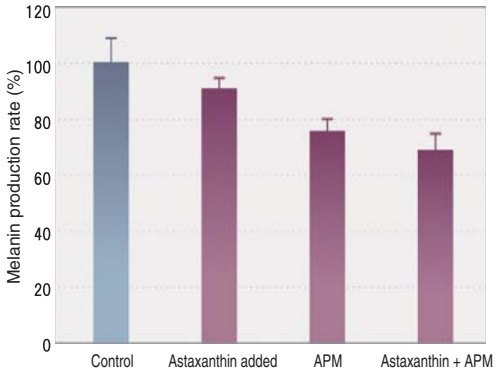

Fig. 9 Melanin production inhibition by Astaxanthin and APM.

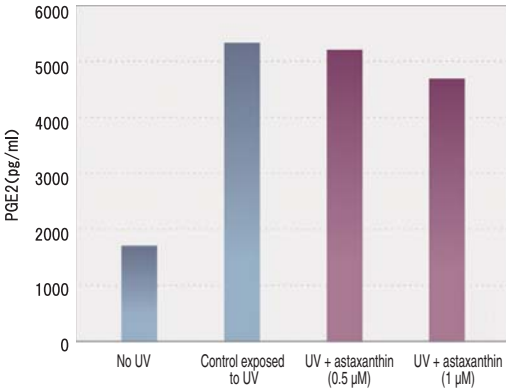

Fig. 10 Generation inhibition of PGE2 by Astaxanthin.

astaxanthin reach the depth of skin while keeping it effective, we have developed approximately 50-nm emulsion[5] making the most of our emulsifying and dispersion technology accumulated for photographic films.

3.2 Preventing Hole in Basement Membrane

The whitening essence contains an ingredient to prevent a hole in the basement membrane that is a cause of the everlasting blemish.

Preventing Breakage of Basement Membrane

MMP accelerates the creation of a hole in the basement membrane. Production of MMP is accelerated by singlet oxygen generated by UV radiation. As stated above, astaxanthin not only eliminates singlet oxygen but also inhibits cytokine production (Fig. 10) and thus it inhibits production of MMP.

Regeneration of Basement Membrane

The basement membrane is basically made of collagen. Pico-Collagen (acetyl hydroxyproline) and APM contained in the collagen whitening essence act on fibroblasts and accelerate production of collagen that forms the membrane structure.

Acetyl hydroxyproline is a derivative of hydroxyproline that specifically abounds in collagen protein. It becomes hydroxyproline in the skin. When hydroxyproline, a decomposed material of collagen protein, abounds, fibroblasts accelerate production of collagen.

3.3 Product Evidence

We have conducted four-week test for continued use of the whitening essence that contains an ingredient effective for all the steps of melanin production attributable to age spots and an ingredient preventing a hole in the basement membrane attributable to the everlasting blemishes.

We asked 49 women in their 40s to 60s to use the ASTALIFT WHITENING ESSENCE after their regular skin care in the morning and evening. We checked the skin condition before after the test. Fig. 11 shows a change in the number of age spots by continued use of the essence for four weeks. Fig. 12 shows a change in the average area of age spots of the 49 women. Both figures show a decrease.

Fig. 13 shows an example of a reduced age spot. The spot is reduced in area and lightened.

4. Conclusion

Development of Photographic Technology

We have developed the ASTALIFT WHITENING ESSENCE as a functional cosmetic with well-designed ingredients based on age spot mechanism, making the most of our accumulated technology developed for photographic films (Fig. 14). Specifically, the emulsifying and dispersion technology achieves highly functional fine particles (nanotechnology). The antioxidation technology helps utilize various antioxidants. Collagen material technology is common to skin and photographic film.

We will continue to study the science of skin care and put in our original technologies to develop functional cosmetics that provide new values for customers.

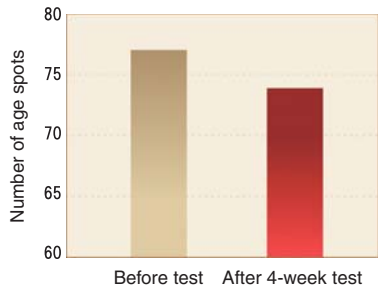

Fig. 11 Decrease in the number of blemishes after four weeks of continuous use.

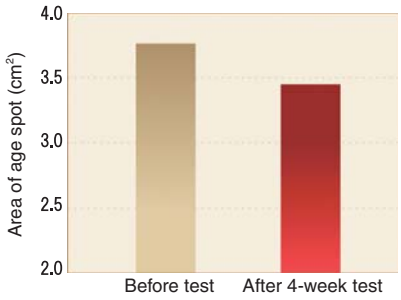

Fig. 12 Decrease in the size of blemishes after four weeks of continuous use.

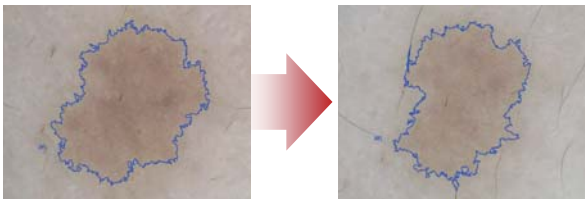

Fig. 13 Example of decrease in the color density of blemishes after four weeks of continuous use.

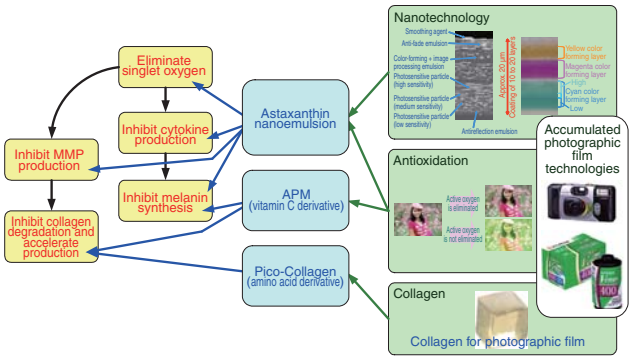

Fig. 14 Development of the photographic technology.

References

1) Advanced Cosmetic Dermatology. Imayama, Shuhei et al., eds., Tokyo, Nankodo (2008).
2) a) Bacharach-Buhles, M.; Lubowietzki, M.; Altmeyer, P. Dose-Dependent Shift of Apoptotic and Unaltered Melanocytes into the Dermis after Irradiation with UVA 1. Dermatology **198** (1), 5-10 (1999).
   b) Ünver, N.; Freyschmidt-Paul, P.; Hörster, S.; Wenck, H.; Stäb, F.; Blatt, T.; Elsässer, H-P. Alterations in the epidermal–dermal melanin axis and factor XIIIa melanophages in senile lentigo and ageing skin. British Journal of Dermatology **155** (1), 119-128 (2006).
3) Carotenoid –the Diversity and Bioactivity–. Takaichi, Shinichi ed., Tokyo, Shokabo Publishing, (2006).
4) Mori, Junichi et al. In-vivo Measurement of Antioxidant Ability of Astaxanthin. Japanese Society for Astaxanthin, reported on 2007-9-12.
5) Ogawa, Manabu; Sato, Masao; Suzuki, Keiichi. Development of Astaxanthin Nano Emulsion with Improved Shelf Life and Enhanced Absorbability. FUJIFILM RESEARCH & DEVELOPMENT. No.52, 26-29 (2007).