

Case Report

Effectiveness of 0.1% Retinol Serum and Astaxanthin Gel on Skin Photoaging

Efektivitas Serum Retinol 0,1% dan Gel Astaxanthin pada Photoaging Kulit

Boedhy Setyanto, Sinta Murlistyarini, Dea Florensia

Department of Dermatology dr. Saiful Anwar Hospital Malang

ABSTRACT

Skin photoaging is cumulative skin damage due to chronic environmental exposure, especially ultraviolet (UV) light, which interferes with the keratinocyte and fibroblast syntheses by matrix metalloproteinases (MMP). Retinol can improve wrinkles, pigmentation, elasticity, firmness, brightness, and various signs of photoaging on the skin. Astaxanthin is a powerful antioxidant that protects the skin from UV rays, inhibits MMP, and stimulates collagen production. This case report presents 2 cases of women complaining about deep skin wrinkles, dullness, and looseness. Physical examination in the facial region revealed wrinkles when resting in the first patient and wrinkles during motion in the second patient. The first patient was diagnosed Glogau III photoaging, while the second patient was diagnosed Glogau II photoaging. Both patients received astaxanthin gel therapy and SPF 33 sunscreen cream every morning, as well as 0.1% retinol serum every night. There was an improvement after six weeks. Astaxanthin and retinol 0.1% can be used as photoaging therapy. Adequate use of photoprotection is also necessary to prevent the worsening of photoaging.

Keywords: Astaxanthin, photoaging, retinol

ABSTRAK

Photoaging pada kulit merupakan kerusakan kulit kumulatif akibat paparan lingkungan kronis terutama sinar ultraviolet (UV) yang mengganggu sintesis keratinosit dan fibroblas oleh matriks metaloproteinase (MMP). Retinol dapat memperbaiki kerutan, pigmentasi, elastisitas, kekencangan, kecerahan, dan berbagai tanda photoaging pada kulit. Astaxanthin merupakan antioksidan kuat yang melindungi kulit dari sinar UV, menghambat MMP, dan merangsang produksi kolagen. Laporan kasus ini melaporkan 2 kasus perempuan dengan keluhan kerutan kulit dalam, kusam, dan terasa kendur. Pemeriksaan fisik pada regio fasialis didapatkan *wrinkle at rest* pada pasien pertama dan *wrinkles in motion* pada pasien kedua. Pasien pertama didiagnosis dengan photoaging Glogau III dan pasien kedua didiagnosis dengan photoaging Glogau II. Kedua pasien tersebut mendapatkan terapi gel astaxanthin dan krim tabir surya SPF 33 setiap pagi, serta serum retinol 0,1% setiap malam. Didapatkan perbaikan setelah 6 minggu. Astaxanthin dan retinol 0,1% dapat digunakan sebagai terapi photoaging. Pemakaian fotoproteksi yang adekuat juga diperlukan untuk mencegah perburukan photoaging.

Kata Kunci: Astaxanthin, photoaging, retinol

Correspondence: Dea Florensia. Department of Dermatology dr. Saiful Anwar Hospital Malang, Jl. Jaks Agung Suprpto No. 2 Malang
Tel. 081233520092 Email: drdeaflorensia@gmail.com

DOI: <http://dx.doi.org/10.21776/ub.jkb.2022.032.01.12>

INTRODUCTION

Extrinsic skin aging, or photoaging, results from cumulative damage due to chronic environmental damage, especially sun exposure, which exacerbates intrinsic aging. The effects of sun exposure may differ according to skin type and race (1). Ultraviolet (UV) radiation exposure indirectly interferes keratinocyte and fibroblast syntheses by matrix metalloproteinases (MMPs) without increased production of new collagen, resulting in loss of collagen amount and extracellular matrix fragmentation (ECM) (2). In addition, the performance of the endogenous antioxidant system also decreases and causes a number of Reactive Oxygen Species (ROS) that exceeds antioxidant defenses, called oxidative stress (3).

The best method to minimize the effects of photoaging is prevention. The key to prevention is the protection against the sun, such as clothing and other photoprotection like sunglasses and Sun Protection Factor (SPF) 30 sunscreen or higher.¹ Several other strategies can also be used for skin protection (4). Research and development of topical preparations that are clinically efficient, non-toxic, and provide continuous protection for complete physical, chemical, and biological photoprotection is still a big challenge for the pharmaceutical and cosmetic industries (5).

Retinol, a vitamin A derivative, is effective in slowing and preventing the aging process. Retinol has substantial evidence to support its efficacy in improving lines, wrinkles, pigmentation, elasticity, firmness, brightness, and overall photoaging (6). Several studies have also reported that, unlike retinoic acid, retinol causes less irritation (7). Researchers have recently used retinol combined with other anti-aging agents to obtain more significant results (8). Astaxanthin is a powerful antioxidant, anti-inflammatory agent, that prevents damage to Deoxyribonucleic Acid (DNA) and improves mitochondrial function. Besides, astaxanthin also provides UV protection, activates the Nuclear Factor Erythroid 2-Related Factor (Nrf2) pathway to stimulate the production of other antioxidants, inhibits MMP, and stimulates collagen production and wound healing (9). In this case report, two cases of photoaging with 0.1% retinol serum and astaxanthin gel therapy were reported.

CASE REPORT

The first case is a 57-year-old woman who came to the Dermatology and Venereology clinic of dr. Saiful Anwar Hospital Malang and complained about dull, loose skin and wrinkles on her face. She has felt this condition for eight years and has worsened since the last year. These conditions interfere patient's appearance and reduce her self-confidence. In the two previous months, the patient had undergone therapy using 8% glycolic acid cream, adapalene gel, moisturizer, and sunscreen at the Dermatology and Venereology clinic of dr. Saiful Anwar Hospital. The patient felt that the problem remained after the therapy. From the anamnesis results on the risk factors, the patient had never been to a beauty clinic before, had never done chemical peeling procedures, injection therapy procedures, or therapy using lasers. The patient admitted that she never applied sunscreen when she was young. The patient currently stays at home every

day, but the patient previously worked as a food seller but chose to stop selling for the last four months due to the pandemic. The patient never smokes, but she admitted that she was frequently exposed to pollution ten years ago while working in Jakarta.

The general examination revealed compos mentis, while the Dermatological examination showed Fitzpatrick skin type IV. The facial area had multiple, scattered, brownish macules varying in shape and size. Additionally, superficial wrinkle, deep wrinkle, crisscross wrinkle, decreased fat tissue, prominent nasolabial folds, eye bags, saggy skin were visible. Crow's feet were also noticeable in the periorbital area (Figure 1).

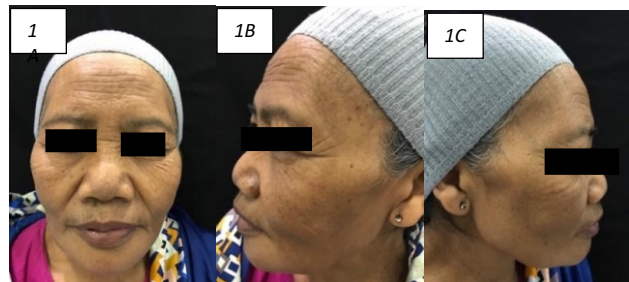


Figure 1. First dermatological examination

Note:

1A) The facial area had multiple, scattered, brownish macules varying in shape and size. Superficial wrinkle, deep wrinkle, crisscross wrinkle, decreased fat tissue, prominent nasolabial folds, eye bags, saggy skin were visible;

1B-C) Crow's feet were on the periorbital area

Based on history-taking and physical examination, the patient was diagnosed with Photoaging Glogau III. The patient was given SPF 30 sunscreen for morning and afternoon use, repeated every 4 hours, and astaxanthin gel. For the night, the patient was given 0.1% retinol serum therapy. The patient was then observed for six weeks and evaluated every two weeks. The treatment goals, side effects, and prognosis of therapy were explained; thus, the patient has realistic expectations of the outcome and the procedure.

The patient was evaluated three times, the end of the second week, the end of the fourth week, and the end of the sixth week. The patient felt a lessening pigmentation intensity on the second and third evaluations compared to the initial visit. In addition, the patient also felt that her skin was noticeably fairer. The patient did not complain about any side effects from the 0.1% retinol serum and astaxanthin gel. The evaluations were carried out by assessing the photos and the Global Subjective Skin Aging Assessment (GS2A2) scores by two evaluators.

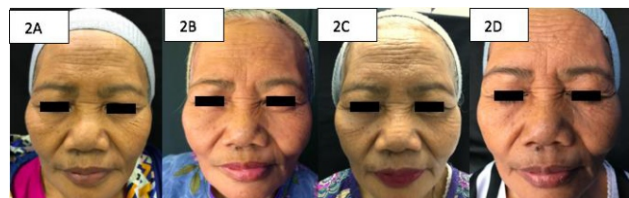




Figure 2. Patient photography evaluation

Note:

2A, 2E, and 2I) Facial area at the beginning of the evaluation;
 2B, 2F, and 2J) The first evaluation did not show any changes in wrinkle, but there was a decrease in brown color intensity compared to the initial visit;
 2C, 2G, and 2K) The second evaluation showed improvement in superficial wrinkles and decreasing intensity of brownish macules in the facial area compared to the first evaluation;
 2D, 2H, and 2L) The third evaluation showed improvement in superficial wrinkles, decreasing intensity of brownish macules in the facial area and brighter skin.

There was a decrease in the GS2A2 score from the beginning to the end of the evaluation (Figure 3).

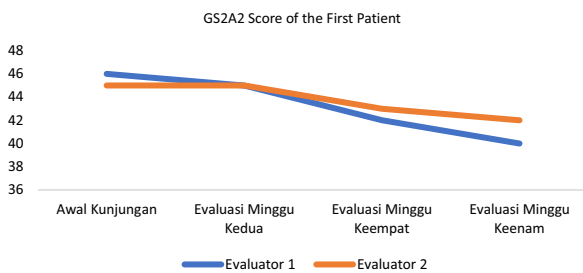


Figure 3. GS2A2 score of the first patient assessed by two evaluator

Note: There were decreasing GS2A2 scores from the initial visit until the sixth visit

The second case is a 47-year-old woman who came to the Dermatology and Venereology clinic of Saiful Anwar Hospital Malang and complained about saggy skin and wrinkles on her face. The complaint has remained for 3 years, but it has worsened since the last 6 months; thus, interfere her appearance and reduce her self-confidence. The patient admitted that she applied morning and night cream from a beauty clinic without knowing the substances. The patient admitted that she had never done chemical peels, injection therapy procedures, or therapy using lasers. Currently the patient works as a nurse in a hospital and mostly works indoor. However, when commuting to work, the patient rides a motorbike and never uses a mask or sunscreen. The patient denied any frequent exposure to pollution or smoking.

The general examination revealed a general condition of compos mentis, and the dermatological examination showed Fitzpatrick type III skin type. The facial area has

multiple, scattered, brownish macules varying in shape and size. Superficial wrinkles, nasolabial folds, eye bags, sagging skin were visible. Crow's feet in the periorbital area were obvious (Figure 4).



Figure 4. First dermatological examination

Note:

4A) The facial area had multiple, scattered, brownish macules varying in shape and size. Superficial wrinkle, nasolabial folds, eye bags, saggy skin were visible;
 4B-C) The periorbital area showed crow's feet

Based on history-taking and physical examination, the patient was diagnosed with Photoaging Glogau II. The patient was given SPF 30 sunscreen for morning and afternoon uses repeated every 4 hours and astaxanthin gel. For the night, the patient was given 0.1% retinol serum therapy. The patient was then monitored for six weeks and evaluated every two weeks. The patient was told about the treatment goals, side effects, and prognosis of therapy; thus, she had realistic expectations about the outcome and the procedure. The patient underwent three evaluations; the end of the second week, the end of the fourth week, and the end of the sixth week. The patient began to notice a reduction in the pigmentation intensity and wrinkles on the second evaluation compared to the initial visit. The patient did not complain about side effects of 0.1% retinol serum and astaxanthin gel. The evaluations carried out by evaluating the photos and the GS2A2 scores by two evaluators revealed a decrease since the first evaluation in the second week.

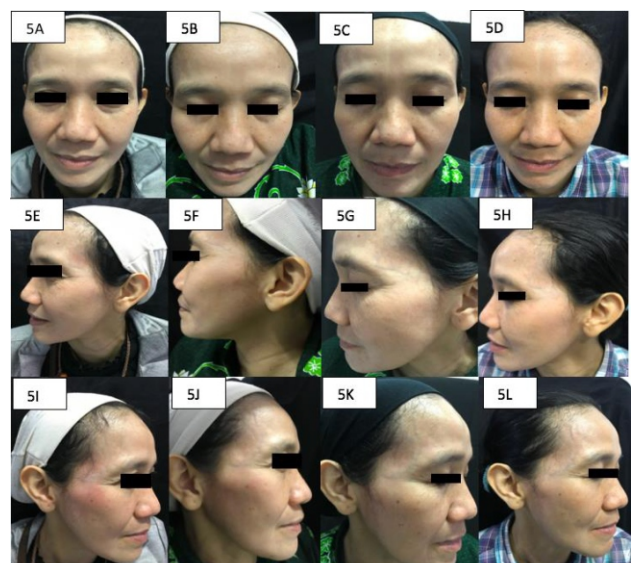


Figure 5. Patient Photography Evaluation

Note:

5A, 5E, and 5I) Facial area at first visit;

5B, 5F, and 5J) The first evaluation did not reveal any changes in either brownish macula, skin texture, superficial wrinkles and crow's feet;

5C, 5G, and 5K) The second evaluation showed a decreasing intensity of brownish macules in the facial area compared to the first evaluation;

5D, 5H, and 5L) The third evaluation showed a decreasing intensity of brownish macules in the facial area compared to the second evaluation. Periorbital repair of crow's feet was found.

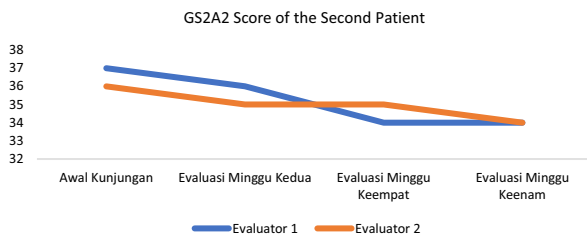


Figure 6. GS2A2 score assessed by two evaluators

Note: There were decreasing GS2A2 scores from the initial visit to the sixth week of visit.

Evaluation of the satisfaction level of the two patients was assessed by scoring ranging from 0 to 4 point using the following scale, 0 = no change, 1 = quite satisfied, 2 = satisfied, 3 = very satisfied, 4 = excellent. At the end of therapy, both patients were satisfied with the results of therapy.

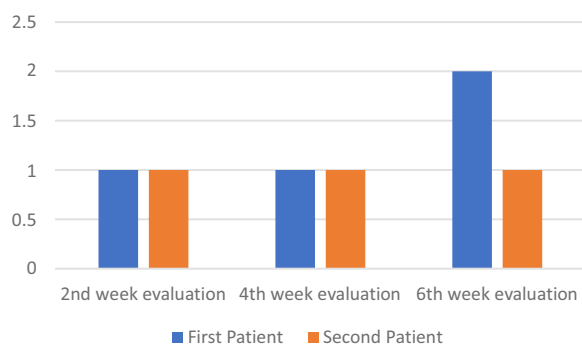


Figure 7. Comparison of patient satisfaction level

DISCUSSION

This case report describes two photoaging cases diagnosed from history-taking and physical examination. The first case is a Glogau III photoaging in a 57-year-old Asian female, and the second case with similar characteristics is Glogau II photoaging in a 47-year-old female. The complaints stated were saggy, dull skin and wrinkles on the face for a long time, namely eight years (first case) and three years (second case). The history-taking results showed the risk of continuous UV exposure, the absence of sunscreen usage, and exposure to pollution. Physical examination of both cases in the facial area found multiple, scattered, brownish macules varying in shape and size. Superficial wrinkle, deep wrinkle, crisscross wrinkle, decreased fat tissue, prominent nasolabial folds, eye bags, and saggy skin were visible. Crow's feet were also noticeable in the periorbital area, all of which are signs of photoaging. The therapy given was

sunscreen, astaxanthin gel, and 0.1% retinol serum, followed by GS2A2 evaluation. The evaluation results showed score improvement, and subjectively the patients showed satisfaction.

The aging process, including skin aging, is caused by many factors (multifactorial) (4). Based on the cause, skin aging is divided into two, extrinsic and intrinsic aging processes (10). The intrinsic aging process is a natural, biological, progressive, and irreversible phenomenon in the body (6). Extrinsic skin aging, known as photoaging, is premature skin aging mainly caused by solar radiation (1). It is difficult to separate intrinsic skin aging from various external factors that affect skin aging (4).

Intrinsic skin aging is a slow process that will change skin tissue structure, where the mechanism of change occurs simultaneously. There are skin morphology or structure changes in the epidermis, while in the dermis there are biochemical changes. Changes also appear in the adnexal organs of the skin, such as hair and sweat and oil glands (4). Intrinsic skin aging shows skin that is thinning due to the epidermis and dermis atrophy, looks paler, has fine wrinkles, looks thinner, transparent, fragile, and dry; and often causes itching (9). Intrinsic skin aging is also accompanied by thinning subcutaneous fat tissue, including facial fat, which will cause sunken, hollow cheeks and eye bags. In addition to age, other intrinsic factors related to intrinsic skin aging include race, variations in skin anatomy in certain areas, and hormonal changes.

The process occurring in intrinsic skin aging is a combination of three processes: a decrease in the skin cells' ability to proliferate, a decrease in the synthesis of the skin's extracellular matrix, and an increase in the enzymes' activity degrade collagen in the dermis layer. Skin cells, including keratinocytes, fibroblasts, and melanocytes, decrease in population parallel with age. The decrease in fibroblast cell population causes less collagen biosynthesis in the dermis layer. The slowed proliferation of skin fibroblast cells will also affect collagen production in the dermis layer, causing skin aging and wrinkles. In addition, MMP enzyme activity in fibroblast cells also increases with age that causes an increase in collagen degradation in the dermis layer. Intrinsic skin aging is also influenced by free radical production, especially ROS, the effectiveness of the free radical scavenging system, and body repair.

Some extrinsic factors simultaneously work with intrinsic factors and cause premature skin aging. The influencing external factors include heat, sleeping position, gravity, lifestyle such as smoking, pollution, and sunlight exposure, especially UV rays. Examples of gravity are the dropping tip of nostrils, lengthening ear lobes, dropping eyelids, disappearing upper lip, and a more visible lower lip. Besides, the main effects of UV radiation exposure, both acute and chronic, are DNA damage, inflammation, and immunosuppression. In this case report, UV exposure and the absence of sunscreen application were the two external factors found.

The clinical features of photoaging can be dry skin, varying skin pigmentation, pale yellowish skin, deep and rough wrinkles, atrophic skin, sagging skin, telangiectasia, solar elastosis, actinic purpura, or even the formation of pre-cancerous lesions (5,11). Dark skin is more resistant to skin damage caused by UV exposure, so the manifestations of skin aging are lighter and occur 10 to 20 years later than that in lighter skin. In skin with Fitzpatrick type III and IV,

dyspigmentation or changes in skin pigment is the main feature of photoaging.

In addition, a slower epidermal turnover rate, slower wound healing, and less effective desquamation add to aging severity. The clinical features of photoaging skin can be derived from the breakdown of various layers of the skin. In contrast, keratinocytes, melanocytes, endothelial cells, and fibroblasts play important roles as cellular mediators of the changes observed. Pigmentation changes and the appearance of fine and coarse wrinkles are some of the most important clinical features seen as a result of chronic UV exposure. They are significant constituents of various photoaging scales aimed at measuring a particular individual's photodamage level. Usually, in unexposed skin, there are no pigmentary and vascular changes, which are the characteristic of photoaging (12). In addition to changes in texture and pigment, photoaging also adversely affects the skin's function as a barrier, thermoregulation, immunity, and regenerative ability of the skin.¹ Each race also provides different features of photoaging. In Caucasian women, photoaging appears as noticeable deep wrinkles and dyspigmentation of the skin. Among Asian women, photoaging is mainly in the form of changes in skin pigmentation and wrinkles visible in the under-eye area but is not very significant compared to wrinkles in Caucasian women. Both cases in this report were Asian women complaining about wrinkles and sagging skin confirmed by objective wrinkle, decreased fat tissue, and crow's feet in the periorbital area.

In this case report, the diagnosis of aging and photoaging is based on a visual score of deep and fine wrinkles according to the Glogau reference scale (13). The first case is classified as Glogau III, which matches the patient's age (57 years); on the physical examination, the wrinkles appear during resting, and there is some discoloration. The second case is included in the Glogau II classification, which matches the patient's age (47 years); on the physical examination, wrinkles appear more when the patient moves. The available skin aging rating scales and their relative benefits are limited. Many of these scales currently require sophisticated and possibly invasive imaging equipment, so they are not generally applicable. Several skin aging rating scales have been developed over the last few decades. Skin aging is difficult to assess due to the large variety of parameters that limits the development of a common measurement system for determining severity (14).

Evaluation of the therapy in both cases was carried out using a GS2A2 score. The Global Subjective Skin Aging Assessment (GS2A2) is simplified into three factors based on empirical evidence from dermatologists and represents the pathophysiological changes during the skin aging process. Atrophy consists of the reduction of elastic fibers and changes in the components of collagen and subcutaneous tissue (fat, muscle, and bone), which causes signs of skin wrinkles, solar elastosis, reduced fat tissue, nasolabial folds, and others. Discoloration includes melanin, changes in vascular pigmentation, and keratinous cysts. All common malignancies in aging skin are included in those three factors. Skin aging is multidimensional, and one skin marker is not sufficient to state a general skin aging process (20). The GS2A2 score includes factors relevant to skin aging from the dermatologist perspective and is easily calculated as a 3-

factor score. Although each scoring item is assessed independently, the final summative score represents a person's overall skin aging as perceived by the dermatologist. This score is highly relevant for use on Asian skin (15). The World Health Organization (WHO) states that successful aging is not only getting physically old healthily but also mentally and socially healthy, including being happy and satisfied with own achievement, one of which is building individual self-confidence through prevention and treatment of skin aging.

As skin aging interventions are intrinsically difficult to carry out, prevention and therapy related to extrinsic aging for skin structure and appearance have received a lot of attention. Exposure to UV radiation plays a vital role in skin aging, so the prevention strategy is the most crucial step in preventing photoaging by avoiding sunlight, using sunscreen to block or reduce skin exposure to UV radiation, retinoids to inhibit collagenase synthesis and increase collagen production, and the use of antioxidants to reduce and neutralize free radicals (11). Effective strategies to protect the skin are available, including protection against UV rays using photoprotection and skin hydration to prevent dry skin. Skin protection should be started as early as possible to optimize skin health (4). Patient education is critical to minimize sun exposure from 10:00 to 16:00, depending on the season and geographical location, avoid using tanning beds and consistent use of protection against sun protection such as clothing with sun protection, sunglasses, SPF 30 sunscreen or higher (1).

Treatment in this case report was using 0.1% retinol serum. Retinoids, especially retinoid acid can reduce melanin, increase collagen deposition in the papillary dermis, and improve elastin fiber morphology. Retinoids include retinol (vitamin A) and natural ingredients such as retinaldehyde, retinyl esters, and tretinoin. Retinoid acid has commonly been used as a therapy for photoaging skin, but the drawback possessed is low tolerance. Retinol is known to have fewer erythema side effects and does not cause dry, flaky skin than retinoid acids. Since retinol is quickly degraded to its inactive biological form when exposed to light and air, it is essential to pay attention to the mode of delivery of retinol to the target area and its formulation. Retinol serums are safe and effective but have equivalent or better performance and tolerability than tretinoin cream (16).

Retinoids have shown beneficial effects in reducing skin photoaging. All-Trans Retinoic Acid (ATRA) has been widely proven to improve skin photoaging signs. ATRA, on collagen metabolism, affects the stimulation of collagen synthesis, which eventually accumulates in the upper papillary dermis. In addition, ATRA downregulates UV-induced MMP-1 and MMP-9 expression, thereby replenishing collagen levels. Although ATRA is recognized as an effective therapy for photoaging skin through its regulatory effects on collagen metabolism, it has been suggested that retinol (ROL), known as vitamin A, can reduce the main signs of photoaging with less irritating side effects (17). Scientific Committee on Consumer Safety sets standards regarding the use of retinol and its equivalent in cosmetic preparations applied in the European Union that the maximum retinol concentration on the hands and face is 0.3% (6).

Retinol has been used since the 1990s as an anti-aging agent.⁷ Topical retinoids can combat signs of aging through

collagen production, inhibition of collagen degradation, angiogenesis, and alterations in melanin synthesis (18). Study conducted by Pierard-Franchimont *et al.*, concluded that retinol at a concentration of 0.04% was superior to control. Tucker-Samaras *et al.*, evaluated the use of retinol at a concentration of 0.1% for eight weeks, randomized, double-blind, split-face, among women with moderate facial photodamage. Vehicle or 0.1% retinol was applied to half the face. Subjects were then evaluated using photoaging parameters on a scale of 0-9. The group given 0.1% retinol showed significant improvement in wrinkles, pigmentation, elasticity, and overall photodamage values compared to the control group with the vehicle (7).

The use of Vitamin A in cosmetics has a regulatory effect on skin regeneration, stimulates the formation of blood vessels, collagen I, III, and VII, inhibits the formation of MMP metalloproteinases, stimulates the production of inhibitors (TIMP), and stimulates the formation of fibrillin I, a component of elastin microfibrils. Retinol can exfoliate the stratum corneum, accelerate epidermal cell turnover, support cell renewal in the basal layer of the epidermis, reduce the number of atypical cells, inhibit the transport of melanin to epidermal cells, and affect the even distribution of melanin in the epidermis. Retinol renews the living layers of the epidermis, namely the ground and granular layers, and it reduces the thickness of the stratum corneum by stimulating exfoliation.

Topical application of 0.4% retinol on aging human skin changes the epidermis and dermis via epidermal keratinocytes, dermal endothelial cells, and fibroblasts. Topical retinoids also significantly increase epidermal thickness and stimulate epidermal keratinocyte proliferation, which involves the transcription factor c-Jun. In addition to changes in the epidermis, topical retinol also enhances the extracellular matrix by increasing the formation of dermal blood vessels by stimulating endothelial cell proliferation and ECM production by activating fibroblasts. In addition, topical retinol also stimulates the TGF- β pathway, a key regulator of ECM homeostasis, thereby enhances deposition of mature collagen in aging human skin *in vivo*. It is also reported that the anti-aging effects of retinol include inhibition of MMP induction and promoting collagen synthesis formation in photoaging skin. Clinical studies show that the use of topical retinol significantly improves fine wrinkles (9).

The study conducted by Zasada showed no significant difference between retinol serum concentrations of 0.15% and 0.3% during the two months of the study. The beneficial effects of retinol can be seen over a long period of time, up to three months of therapeutic use (6). Another study by Baran with a lower concentration of topical retinol (0.1%) on sun-exposed areas was conducted to examine its anti-aging effect at more tolerable doses on signs of photoaging. In the first blind-randomized study, topical 0.1% retinol and placebo were applied daily for 56 weeks. Clinical evaluation showed that under-eye wrinkles, fine lines in the crow's feet area, and even skin tone were significantly improved compared to placebo. Fine line improvement in the crow's feet area was also demonstrated by digital imaging and surface profilometry. Skin improvement signs due to photoaging began to completely appear after four weeks. Progressive improvement was seen between baseline and after 24 and 36 weeks of treatment. Improvement in fine lines was documented by surface profilometry, and gradual

disappearance of fine lines in the crow's feet area was also observed. In addition, retinol also stimulates the proliferation of epidermal cells. Low retinol concentrations (for example, 0.1%) can provide significant and rapid efficacy while maintaining a good tolerance profile (17). These clinical results were later confirmed by two other clinical studies conducted in middle-aged Japanese women. The study involved 57 volunteers and was performed with 0.075% and 0.04% retinol cream for 26 and 13 weeks, respectively. Both trials showed significant improvement, especially in fine wrinkles, with minimal irritation (19).

Retinol is generally assumed not as effective as retinoic acid due to the additional step required to convert retinol to retinoic acid. However, the study conducted by Kong *et al.* demonstrated that topical retinol induces similar changes in skin histology and expression of skin-related genes and proteins as seen in retinoic acid therapy (20). Researchers have recently tried using retinol in combination with other anti-aging agents to obtain more significant results (8). Since ROS production causes skin aging due to oxidative stress, antioxidant is one of the effective skin defense mechanisms. Enzymes and antioxidants react directly with ROS and prevent them from reaching their biological targets. The use of antioxidants in skincare products is significant. In this case report, astaxanthin gel has a better antioxidant effect than carotenoids and vitamin E (21). Astaxanthin is found as a red-orange pigment commonly found in many aquatic animals such as salmon, shrimp, and crayfish (9). Gel formulation was chosen because of its lower price, ease of use, ease of production, and improvement scalability (21).

Some effects of Astaxanthin on aging human skin can reduce wrinkles, fine lines, and age spots. It can also increase the skin's water content and reduce Trans Epidermal Water Loss (TEWL). Astaxanthin can also prevent skin damage caused by UV rays. As an antioxidant, Astaxanthin lowers Malondialdehyde (MDA) and activates Nrf2, which binds to the enzymatic elements responsible for the antioxidant response. Another study found that Astaxanthin regulates oxidative pathways by modulating Xanthine Oxidase (XO) and Nicotinamide Adenine Dinucleotide Phosphate (NADPH) Oxidase (Nox), which contribute to ROS generation. Pro-inflammatory mediators also have a role in skin damage caused by UV exposure. Astaxanthin reduces UV-induced skin damage by reducing Reactive Nitrogen Species (RNS) production and reducing the expression of inflammatory cytokines. UV-induced skin damage occurs due to DNA repair errors that cause mutations. The DNA products of UV-induced damage are altered structures leading to a chain of responses and leading to cell cycle arrest. Astaxanthin has a role in changing DNA repair kinetics and may limit UV-induced DNA damage. This DNA damage inhibition also leads to the stimulation of enzymes that are responsive to oxidative stress. The AKT pathway, also referred to as the Protein Kinase B pathway, plays a role in stabilizing the human genome as well as managing the response to DNA damage (22).

A topical formulation from algae extract containing Astaxanthin can be suggested as a topical anti-aging formulation. Comparative studies examining the photoprotective effects of carotenoids have shown that Astaxanthin is a superior antioxidant, having greater antioxidant capacity than canthaxanthin and β -carotene in human skin fibroblasts. Particularly, Astaxanthin inhibits

ROS formation and modulates the expression of oxidative stress-responsive enzymes such as Heme Oxygenase-1 (HO-1), which is a marker of oxidative stress and a regulatory mechanism involved in the adaptation of cells to oxidative damage (9). Research conducted by Sofiah et al. proved that topical Astaxanthin administered to shaved mice exposed to UVB for six weeks could decrease the expression of MMP-1, which is the leading cause of collagen degradation (23).

Overall strategies that need to be done to prevent photoaging include avoiding sunlight, sun protection using sunscreen to block or reduce skin exposure to UV radiation, retinoids to inhibit collagenase synthesis and increase collagen production, and antioxidants usage to reduce and reduce and neutralize free radicals (12).

Retinol can improve wrinkles, pigmentation, elasticity, firmness, brightness, and overall photoaging. Unlike retinoic acid, retinol causes minor irritation.⁷ The combination of retinol with antioxidants such as topical Astaxanthin is expected to provide a more significant appearance improvement (8). Astaxanthin works by inhibiting ROS formation and modulating the expression of enzymes responsive to oxidative stress (9).

Based on this case report, it is concluded that 0.1% retinol and Astaxanthin are effective as photoaging therapy. Combination therapy can provide a better appearance improvement. However, the therapeutic solution must be personalized to individual's aging, balancing the ratio of risks and benefits of each therapy to the patient's demands and expectations (17).

REFERENCES

- Huang AH and Chien AL. *Photoaging: A Review of Current Literature*. Current Dermatology Reports. 2020; 9(1): 22-29.
- Cole MA, Quan T, Voorhees JJ, and Fisher GJ. *Extracellular Matrix Regulation of Fibroblast Function: Redefining Our Perspective on Skin Aging*. Journal of Cell Communication and Signaling. 2018; 12(1): 35-43.
- Park MA, Sim MJ, and Kim YC. *Anti-Photoaging Effects of Angelica Acutiloba Root Ethanol Extract in Human Dermal Fibroblasts*. Toxicological Research. 2017; 33(2): 125-134.
- Zahrudin A and Damayanti D. *Penuaan Kulit: Patofisiologi dan Manifestasi Klinis*. Berkala Ilmu Kesehatan Kulit dan Kelamin. 2018; 30(3): 208-215.
- Kostyuk V, Potapovich A, Albuhaydar AR, Mayer W, De Luca C, and Korkina L. *Natural Substances for Prevention of Skin Photoaging: Screening Systems in the Development of Sunscreen And Rejuvenation Cosmetics*. Rejuvenation Research. 2018; 21(2): 91-101.
- Zasada M and Budzisz E. *Randomized Parallel Control Trial Checking the Efficacy and Impact of Two Concentrations of Retinol in the Original Formula on the Aging Skin Condition: Pilot Study*. Journal of Cosmetic Dermatology. 2020; 19(2): 437-443.
- Tetali BBS, Fahs FM, and Mehregan D. *Popular Over-The-Counter Cosmeceutical Ingredients and Their Clinical Efficacy*. International Journal of Dermatology. 2020; 59(4): 393-405.
- Mukherjee S, Date A, Patravale V, Korting HC, Roeder A, and Weindl G. *Retinoids in the Treatment of Skin Aging: an Overview of Clinical Efficacy and Safety*. Clinical Interventions in Aging. 2006; 1(4): 327-348.
- Mohiuddin AK. *Skin Lightening & Management of Hyperpigmentation*. American Journal of Dermatological Review and Research. 2019; 2(2): 1-66.
- Zhang S and Duan E. *Fighting Against Skin Aging: The Way from Bench to Bedside*. Cell Transplantation. 2018; 27(5): 729-738.
- Kang S, Amagai M, Brucner AL, et al. *Fitzpatrick's Dermatology*. 9th edition. New York: Mc Graw-Hill Education; 2019: p. 3623.
- Friedman BJ, Lim HW, and Wang SQ. *Photoprotection and Photoaging*. In: Wang SQ and Lim HW (Ed). Principles and Practice of Photoprotection 1st edition. Switzerland: Adis; 2016: p. 61-74.
- Sparavigna A, Tenconi B, Giori AM, Bellia G, and La Penna L. *Evaluation of the Efficacy of a New Hyaluronic Acid Gel on Dynamic and Static Wrinkles in Volunteers with Moderate Aging/Photoaging*. Clinical, Cosmetic and Investigational Dermatology. 2019; 12: 81-90.
- Yu SH and Baron ED. *Evaluation and Assessment of Photoaging*. Photonics & Lasers in Medicine. 2013; 2(4): 305-314.
- Buranasirin P, Pongpirul K, and Meehansan J. *Development of a Global Subjective Skin Aging Assessment Score from the Perspective of Dermatologists*. BMC Research Notes. 2019; 12(1): 1-6.
- Draelos ZD and Peterson RS. *A Double-Blind, Comparative Clinical Study of Newly Formulated Retinol Serums vs Tretinoin Cream in Escalating Doses: A Method for Rapid Retinization with Minimized Irritation*. Journal of Drugs in Dermatology. 2020; 19(6): 625-631.
- Glogau RGS. *Photo Aging and Aging Skin*. In: Rigel DS, Weiss RA, Linn HW, Dover JS (Eds). Photoaging 2nd edition. Canada: Maarced Decker Inc; 2003: p. 65-73.
- Dhaliwal S, Rybak I, Ellis SR, et al. *Prospective, Randomized, Double-Blind Assessment of Topical Bakuchiol and Retinol For Facial Photoageing*. The British Journal of Dermatology. 2019; 180(2): 289-296.
- Kikuchi K, Suetake T, Kumasaka N, and Tagami H. *Improvement of Photoaged Facial Skin in Middle-Aged Japanese Females by Topical Retinol (Vitamin A Alcohol): A Vehicle-Controlled, Double-Blind Study*. Journal of Dermatological Treatment. 2009; 20(5): 276-281.
- Kong R, Cui Y, Fisher GJ, et al. *A Comparative Study of the Effects of Retinol and Retinoic Acid on Histological, Molecular, and Clinical Properties of Human Skin*. Journal of Cosmetic Dermatology. 2016;

- 15(1):49-57.
21. Eren B, Tanrıverdi ST, Köse FA, and Özer Ö. *Antioxidant Properties Evaluation of Topical Astaxanthin Formulations as Anti-Aging Products*. Journal of Cosmetic Dermatology. 2019; 18(1): 242-250.
 22. Singh KN, Patil S, and Barkate H. *Protective Effects of Astaxanthin on Skin: Recent Scientific Evidence, Possible Mechanisms, and Potential Indications*. Journal of Cosmetic Dermatology. 2020; 19(1): 22-27.
 23. Sofiah AS and Lesmana R. *Astaxanthin Cream Alters Type I Procollagen and Matrix Metalloproteinase-1 (MMP-1) Gene Expression Induced by Ultraviolet B Irradiation In Rat Skin*. Journal of Biomedical and Clinical Sciences (JBACS). 2018; 3(1): 62-67.