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The Role of Hyaluronic Acid in Skin Treatment during COVID-19 Pandemic

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ABSTRACT
The COVID-19 global pandemic has now risen as a public concern. Sunbathing is believed can kill the coronavirus. Sun ray is important in the metabolism of vitamin D that plays a significant role in the immune system. In order to increase their immunity, people are risking themselves to sunbathing without any knowledge about skin damage as the consequence. The effects of sunlight on the skin are very influential and estimated to account for up to 90% of visible skin aging. Direct sunlight exposure for long period may lead to premature skin aging, the so called photoaging. The phenotypic signs seen in aging are caused by changes in the loss of hyaluronic acid (HA) and collagen, which are part of the extracellular matrix (ECM) of the skin. Losing HA will lead to ECM degradation with wrinkles as one of its manifestation. HA has been believed to be one of the solutions to improve skin aging, especially to treat wrinkles due to photoaging. HA can also increase skin hydration and has antioxidant effects. This review will discuss how to treat skin aging in the pandemic era by using HA as an alternative and efficient treatment. Furthermore, the correlation among skin aging, vitamin D, and COVID-19 phenomenon will be described.

Keywords: Covid-19, sun exposure, vitamin D metabolism, skin aging, photoaging, hyaluronic acid

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INTRODUCTION
Aging is a physiological process in all living creatures, the organism will progressively experience a decrease in biological function and the ability to adapt to metabolic stress. The skin is both the largest organ and the largest area of contact between the human body and the outside world. Since skin is always exposed to the environment, skin has a role as a barrier from external exposure, prevents water loss from the body, and also protects against the use of cosmetic products.[1] The skin shows a progressive physiological changes as signs of aging due to chronological age, due to ultraviolet (UV) exposure known as photo aging, as well as due to chemical pollution.[2] Wrinkles and sagging are examples of visible signs of aging. During aging, the skin loses its collagen and elastic fibers. The process is accelerated by the loss of fat under the skin and skin humidity, therefore, skin becomes wrinkled and appears to be sagging.[3]
Skin aging can occur internally and externally, the classification is seen from where things that induce aging appear, if aging arises from within the body it is called internal aging, if aging appears from outside the body such as skin exposed to sunlight or photo aging it is called with external aging. Chronological aging is caused by internal factors such as genetic factors, race, naturally occurring and difficult to alter hormonal factors. Interestingly, by changing external factors such as stress, cigarette smoking, unhealthy diet, cosmetic products and accumulated UV exposure, photo aging can be delayed.[2–4] Sun exposure plays a major role on skin aging, especially in countries located in the equator line.
The effects of sunlight on the skin are very noticeable and it can be estimated that up to 90% of ageing is evident on the skin. Direct sunlight exposure in the long time period will lead to premature skin aging.[4] An uncontrolled photo aging process will worsen the aging process that occurs naturally and also became an accelerating factor of skin aging. The phenotypic signs seen in aging are caused by changes in molecular and cellular level such as the loss of hyaluronic acid (HA) and collagen, both are extracellular matrix (ECM) of the skin. Losing HA is the sign of ECM skin degradation.[5] Just one gram of HA is able to attach and hold water vapor as much as six liters of water. It is very profitable to preserve the moisture of the skin. HA is present in large amounts of young skin, so the young skin appears moist.[6]
Recently, COVID-19 pandemic becomes a global health crisis of our time and the great challenge for every country. The impact of the pandemic has been seen on public health and changes in community behaviour. There are some misinformation and myths that have been spreading and the public can easily trust the information without analysing whether the information is reliable or not. The phenomenon of influencers, bloggers, and celebrities is currently rife. They create health content related to Covid-19 by inviting speakers who are not health experts. The news may create pros and cons to its content. Study has shown the behaviour of the community towards myths and facts related to COVID-19, showing that sunbathing above 25°C can kill the virus.[7] Other study reported a temperature of 56 °C.[8] It becomes, however, worrying news if those are not accompanied by knowledge about sun exposure itself. Sunlight damages across the skin through an electromagnetic spectrum. Due to photoaging, UV radiation is the main risk factor for skin aging. UV radiation, a carcinogen, can cause DNA mutations that occur as a result of accumulated UV exposure inflammation, thereby promoting cancer development.[4,9]
On the contrary, social restrictions and self-isolation by government regulation may trigger polemics in generating a risk of vitamin D deficiency, needed to support the immunity. Therefore, it is necessary to have a balance of knowledge about the sunbathing and vitamin D during COVID-19 pandemic.
As mentioned earlier, skin degradation has been described as a loss of hyaluronic acid (HA) and collagen, both are

extracellular matrix (ECM) of the skin. Various HA treatments have been studied to increase effectiveness and efficacy to maintain the skin, including the method of administering HA into skin such as topical and injection.[10] This review will explore whether hyaluronic acid could accepted as an alternative solutions to improve skin aging during the COVID-19 pandemic. Furthermore, the role of HA in affecting vitamin D and sun exposure on the skin will be reviewed.

METHODS

A literature search was carried out using several search engines: Embase, Cochrane, PubMed library, and Science Direct. The keywords used were "Skin Aging" AND "photoaging", "Hyaluronic acid" AND "Skin aging" OR "Anti-aging" OR "Dark spot", "Sun exposure" and "COVID-19", "COVID-19" and "Vitamin D" in any field. No time limits were set; the search contained articles published up until 2020. Only articles in Bahasa Indonesia and English were included. Bibliographic reference lists of articles found during the screening were searched manually to discover studies that were not identified in the search of the electronic literature databases.

RESULTS AND DISCUSSION

Skin Aging

Aging is a normal phenomenon occurring in many of the body's tissues, including the skin. Skin aging can also affect the social life of individuals because the skin is the most frequently exposed part of the body to external factors.[11] Aging is a phenomenon that happens extrinsically and intrinsically at the same time causing a gradual loss of structural integrity and physiological function. Naturally, intrinsic aging of the skin happens over time, it is unavoidable, and the rate of aging is genetically variable. Another intrinsic factor is race, which is related to skin variations in pigmentation, in addition to genetic factors. High levels of pigmentation can indicate a protective property against cumulative photoaging effects on the skin. Hormonal changes have been also considered as one of the factors contributing to skin aging, especially in women of whom oestrogen levels is associated with the skin.[4] However, extrinsic factors may be managed to varying degrees, including accumulated exposure to ultraviolet (UV), air pollution, nicotine, cosmetic products and various components of the lifestyle such as diet, sleep, smoking and others.[2,4]

Mechanisms of Skin Aging and the effect of photoaging

Accumulated damage to macromolecules in cells accompanied by impaired ability of stem cells results in loss of tissue regeneration function and loss of function to restore the physiological integrity of tissue structures, so that aging occurs. Changes in the integrity of the structure and function of the skin occur in extracellular matrix components including collagen, elastin, and fibroblasts. Skin collagen has naturally decreased by 1% every year. Decreased fibrin structure and decreased type VII collagen may cause weakness of the dermis and epidermis.[2,3,11]

Sun Exposure and Photoaging

Extrinsic aging such as photoaging causes premature skin damage due to radiation from the sun. The UV rays cause damage to the DNA structure Figure 1. Recent study has reported UV radiation as the causative factor in photoaging. It can cause oxidative and pro-inflammatory damage that can lead to structural changes in the skin.[9] Sunlight consists of different types of electromagnetic rays of varying wavelengths, ranging from short wavelengths to long wavelengths, high energy to low energy, ultraviolet to visible (VL) and infrared (IRR) rays. The spectrum of sunlight mostly reaches the skin. On the basis of wavelength, ultraviolet radiation is divided into three groups; the UVC (100–280 nm) is the shortest wavelength so that it cannot penetrate the skin because it has been filtered out by ambient ozone; the UVB (280–320 nm) and the UVA (320–400 nm) are the most contributing factors to photoaging.[9,12] Just 5% of the sun rays consist of UVB radiation, but it is very potent as this can penetrate the superficial skin layer and further down to the basal layer of the epidermis, primarily leading to sunburn and skin oncogenesis.[2,9] UVA, on the other hand, is present in a greater quantity, but compared to UVB, it has lower energetic photons, the longer UVA wavelength will penetrate deeper into the skin reaching the dermis. UVA is subdivided into UVA1 (340– 400 nm) and UVA2 (315–340 nm). UVA plays a significant role in chronic photoaging-related skin damage.[4] UV radiation gives rise to reactive oxygen species (ROS) which induces mutation of genes from mitochondria and influences nuclear transcription of these genes, causing clinical and histological changes in aging.[9,13]

The Changes in Skin Aging

Pale skin and fine wrinkles are clinical indicators of intrinsic skin ageing, among others. Furthermore, epidermis and dermis become atrophic, making the skin thinner, transparent, and look more fragile. The skin also becomes drier and itchier. Intrinsic skin aging is followed by thinning of subcutaneous fat tissue, including facial fat that result in sunken cheeks and eye bags.[11,14] On the other hand, extrinsic aging is also present in lighter phototypes with fine and coarse wrinkles, skin dullness, roughness, telangiectasias, and mottled pigmentation. [15] In the same way, the color of the skin due to photo aging shows less atrophy and fewer fine wrinkles, more noticeable features include dyschromia, leathery skin and deeper rhythms.[16,17] The changes in both intrinsic aging and photoaging are summarized in Table 1.

The mechanism that occurs in the intestinal aging of the skin is a mixture of three processes, including a decrease in the distribution of skin cells, a decrease in the synthesis of the extracellular matrix, and an increase in the enzyme activity that degrades collagen in the dermis layer. In addition, the development of skin cells, such as keratinocytes, fibroblasts and melanocytes, decreases with age, resulting in a decline in collagen biosynthesis in the dermis layer. Slow proliferation of fibroblast cells can influence the development of collagen in the dermis layer, causing aging of the skin and wrinkles.[18,19]

Individuals living in the area where geographically often exposed to sunlight have a higher risk of UV radiation and more susceptible to photoaging when they have brightly colored skin.[11,20] Compared with office employees, field workers such as farmers and fishermen have a greater chance of UV exposure. Open skin areas, such as the face, neck, upper chest, hands, and lower arms, are more sensitive to UV exposure, as these are favoured areas for photoaging to occur. In comparison, inherent predilection for skin aging is more readily seen in veiled areas of the skin, such as the gluteal zone.[11,14]

Wrinkle

Wrinkles are visible creases or folds in the skin which occur. Wrinkles appear as one of the clinical features most often encountered in the aging process. The wrinkles are classified into fine and rough wrinkles. Fine wrinkles are classified as wrinkles less than 1 mm deep, while wrinkles with a width and depth of 1 mm or more are defined as coarse wrinkles.[21] The clinical characteristics of photoaging in Asian skin are different from those of Caucasian skin, especially in wrinkle patterns and pigmentary changes. This difference is associated with melanocytic function. The higher pigment differences in Asian skin gave different responses acutely and chronically to UV exposure compared to white people. Collagen is known to be a main component that impacts the integrity of the skin tissue such that wrinkled skin causes alteration and collagen deficiency. Pigment-changing lesions on sun-exposed skin, including ephelids or freckles, melasma, lentigo, mottled pigmentation, and pigmented seborrheic keratoses are common.[22] Furthermore, according to Pierid Classification, [23] wrinkle is classified into (a) atrophic wrinkles, wrinkles can occur from either exposed skin or unexposed skin, these skin wrinkles can disappear if they are affected by skin traction or body posture orientation, it can also occur if there is extracellular matrix atrophy; (b) Elastotic wrinkles, wrinkles can occur on sun-exposed skin, they are permanent, progressive, and wrinkles cannot disappear by perpendicular traction; (c) Expressional wrinkles, wrinkles can occur due to repeated subdermal muscle contractions and can be permanent; (d) Gravitational wrinkles, wrinkles can occur due to sagging of the skin due to the effects of gravity and skin inelasticity.

Vitamin D status in Asian and its correlation with COVID-19 Pandemic Era

The Southeast Asia countries are mostly located in the equatorial zone. This area has abundant sun exposure, however, vitamin D deficiency is still found among its population.[24] The primary source of vitamin D that has played a part in the synthesis of vitamin D is sunlight. UVB photons induce the photolysis of7-dehydrocholesterol to previtamin D3 after exposure to UVB, which thermally isomerized vitamin D3 at 37 ° C via an enhanced membrane mechanism. In addition, vitamin D 3 is hydroxylated to become 25(OH)D3 in the liver and then 1-alpha-hydroxylated to become an active form in the kidneys; 1,25-dihydroxyvitaminD3[1,25(OH)2D3].[25]

Several studies have assessed the population status of vitamin D, such as a study of three countries in China, Singapore and Thailand, showing that Singaporeans have a significantly higher vitamin D deficiency prevalence rate than Thais. This may be partly due to the type of employment, as Singapore is a more developed nation, even though Singapore is closer to the equator. Women, young people, living in urban areas, and being physically inactive were common predictors of overall low vitamin D status in Southeast Asia.[24,26–28]

On the other hand, during this COVID-19 crisis, low vitamin D status could be worsened due to indoor living and self-isolation, which according to government guidelines, also decreases sun exposure.

Vitamin D and COVID-19 Fatality

Several studies have been performed to determine the link between low vitamin D levels, COVID-19 mortality rates, and possible COVID-19 deaths from pathophysiology. Vitamin D is believed to enhancing innate defense mechanisms against respiratory pathogens, inhibit pulmonary inflammatory responses.[29,30] Without adequate levels of vitamin D, the lungs are susceptible to immune dysregulation which can lead to cytokine storms, lack of protection from apoptosis of epithelial cells, and deficient epithelial cell repair.[31] United States research has shown that those with upper respiratory tract infections (URTI) have also been shown to be higher in people with low vitamin D status, the correlation has been greater in people with respiratory disorders such as asthma and chronic obstructive pulmonary disease.[29] There is evidence that acute respiratory tract infections (ARTI) are associated with reduced vitamin D status. A recent systematic review and meta-analysis found that supplementation with vitamin D decreased the risk of ARTI, with the greatest benefit for those who were baseline vitamin D deficient. [32,33]

Sun Exposure, Covid-19, and Its effect to Skin Aging

Misinformation related to the COVID-19 myth has spread rapidly among public, among others that sunbathing can kill the Coronavirus. This assertion is not completely false, as a study in Jakarta, Indonesia showed a link between exposure to sunlight and the recovery rate of COVID-19 (p-value =.025; r = 0.350).[34] When the skin is exposed to sunlight, UV radiation both from UVB and UVA will be absorbed into the skin, leading to reactive oxygen species (ROS) production harmful to the skin. Cellular components such as cell walls, lipid membranes, mitochondria and DNA are damaged by these compounds.[14] Moreover, UV irradiation induces AP-1 that increase MMP production, which further increases collagen breakdown. In addition, UV irradiation causes a decrease in TGF-β2 expression which functions to increase collagen formation. The decrease in procollagen synthesis is occured within 8 hours after UV exposure. Increased breakdown and decreased collagen production are the most important factors in photoaging. Other visible phenotypic signs in aging are caused by changes in molecular and cellular such as the loss of hyaluronic acid (HA) and collagen which are the composition of extracellular matrix (ECM) of the skin. As a consequence, unregulated exposure to UV light along with sun exposure myths can lead to the creation of noticeable "sun scars" that manifest as visible wrinkles and cause an increase in inherited hyperpigmentation associated with protection from sunlight damage.[14] It is obvious that COVID-19 pandemic will promote skin aging as an intrinsic factor that precipitates aging quickly.[4,19]

How to balance them?

According to Holick's rules we can exposing the face, legs, and arms for 25 minutes to sunlight every 9 p.m. and this is done 3 times a week would minimizing sun damage and still maintain adequate vitamin D.[35] Exhibiting arms and legs 5 to 30 minutes from 10 a.m. up to 3 p.m. depending on the weather, season, altitude, and skin pigment 2 times a week, vitamin D is also necessary.[36] This activity of exposing part of the body to sunlight can be considered as an alternative to overcome vitamin D deficiency, especially to enhancing innate defense mechanisms against respiratory pathogens to fight COVID-19 disease. Vitamin D supplements also can be used as an adjuvant treatment for treat COVID-19.[31] Another skin care product is needed to fight a wrinkle due to photoaging. Hyaluronic Acid (HA) has been accepted as one of the solutions to improve skin aging. Therefore, various treatments of HA have been tried to increase effectiveness and efficacy including the method of administering HA into skin such as topical and injection to preserve the moisture of the skin mainly due to sun exposure which damages the skin and causes dehydration of the skin. The use of sun protection products such as sunscreens is also recommended, particularly in areas of the skin that are frequently exposed to the sun, such as the face and neck

Hyaluronic Acid

Hyaluronic acid (HA) is one of the component of ECM that located between the epidermis and dermis with molecular weight up to 10^5-10^7 Dalton. Within the skin tissues, polysaccharide is the main building block of HA inside of

ECM.[37] The structure of HA is a carbohydrate which is synthesized as a large size of linear polymer of alternating repeating units of disaccharide composed of N-acetyl glucosamine and glucuronic acid Figure 2. These saccharides are connected by beta 1,3 and beta-1,4 glycosidic bonds. In addition to stimulating fibroblast, HA has a powerful ability to bind water, and it can enhance the skin humidity and elasticity.[38] HA is involved in the molecular synthesis of ECM and interaction of epidermal cells with the surrounding environment. HA is found in large quantities of young skin, therefore the young skin looks moist.[6] In the skin, HAS-1 and HAS-2 gene expression in the epidermis and dermis is regulated differently by TGF-β1 so that it has different functions between the epidermis and the dermis.[51]

Hyaluronic Acid and Skin Aging

Hyaluronic acid homeostasis has a distinct profile of intrinsic skin aging, which is entirely different from that of extrinsic skin aging. Study reported that the HA polymer in the skin gradually decreases with the aging process. Alter-related changes in the dermis layer are an increase in HA avidity in the surrounding tissue, followed by a concomitant loss of HA extractability. The dermis independently controls the synthesis of the dermal HA and influences the epidermal synthesis of HA. Thus, the epidermis loses the function of molecules that play a role in binding and retaining water molecules, causing skin moisture loss. This corresponds progressively between collagen and the loss of ability to extract collagen with age. Both age-related phenomena lead to the dehydration, atrophy and loss of elasticity that characterizes aging of the skin. Repeated long-term exposure to UV radiation causes premature aging of the skin. A wound healing responses scar-like collagen type I instead of the usual collagen mixtures between collagen types I and III, which provide skin resilience and pliability. The decreased HAS-2 expression occurs due to decreased HA synthesis in the dermal fibroblasts. This decrease occurs due to the activation of αvβ3-integrins, nuclear phosphor-ERK translocation, and Rho Kinase inhibiting signals. In one study reported a significant increase in HAS-1 reduction in photo-exposed skin compared to photo-protected skin. Skin exposed to sunlight or what we call extrinsic aging of the skin has been shown to increase the expression of HA at the lower molecular mass. This increase in degraded HA was accompanied by an increase in the expression of HYAL-1, -2, and -3. Photo-exposed skin also showed a decrease in the expression of HA receptors including CD44 and RHAM compared to photo-protected skin. The decrease in HA that occurs in skin aging is intrinsically observed in adult and juvenile photo-protected skin tissue showing a decrease in regulation that occurs in HAS-1 and HAS-2 expression, along with HA receptors, CD44 and RHAMM.[53]

Mechanism of Action Hyaluronic Acid and Its Benefit

Regulation of the HA mechanism is influenced by physical, chemical, environmental, and its receptors: 1) shape and size, properties, and molecular weight distribution; 2) chemical changes, binding molecules, crosslinking patterns, and macromolecular structures; 3) a microenvironment that affects the metabolism of HA synthesis and degradation; and 4) receptor and downstream signal interactions.[39] HA works as an anti-wrinkle by increasing soft tissue augmentation, increasing skin hydration levels, increasing fibroblast production, stimulating collagen formation, and stimulating facial rejuvenation. HA also provides a hydrating and antioxidant effect on the skin by stimulating cell regeneration and stimulating collagen production. HA also helps maintain skin elasticity, turgor, and moisture.[40] The benefits of HA are summarized in Table 2. The safety and tolerance of HA for various skin conditions have been proven from various studies. HA is non-toxic and non-sensitizing, making it safe for many skin types with low risk of allergies. The modified nano system of HA increases the penetration ability of biological membranes and increases the effectiveness of the drug on target cells.[40]

The forms of Hyaluronic Acid for skin treatment

There are various preparations of hyaluronic acid that are used as a treatment for skin aging, including injection (intra-dermal filler injection, dermal filler, face filler) and topical/transdermal (gel, cream, lotion, serum). A topical HA comes in various formulation such as hydrogel, nanoemulsion, microemulsion, prodrug, microneedles, and liposome/hyalurosome.[42] Several studies have been conducted to assess the efficacy of HA in various forms such as gels, creams, intra-dermal filler injections, dermal fillers, facial fillers, autologous fat gels, lotions, serums, and implants shows.[40] Those studies conclude that HA in any form shows good effectiveness in overcoming wrinkles due to aging.[40] The result of efficacy of HA in many forms such as reducing wrinkles (RW), increasing skin elasticity (ISE) and decreasing melanin content (DMC) areas as shown in table 2.

CONCLUSION

Hyaluronic acid is beneficial for skin treatment during COVID-19 pandemic. Since the need of sunbathing due to overcome vitamin D deficiency during this period social restrictions and self-isolation have been applied, sunlight becomes a dilemma for skin health as it is a major predictor to lead premature skin aging. Thus, hyaluronic acid applied to the skin for at least one month become a solution to treat wrinkle due to photoaging.

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TABLES

Table 1. The clinical appearance and skin changes in intrinsic aging and photoaging[42–44]

	Intrinsic Aging	**Photoaging**
Clinical Appearance	Fine wrinkles, decreased elasticity, Saggy skin	Coarse wrinkles, skin dullness, roughness, telangiectasias, and mottled pigmentation.
Epidermis	Thin and viable, keratinocyte minor abnormality, normal stratum corneum	Thick skin, acanthosis, cell atrophy, irregular basal keratinocytes
Elastic tissue	Increased or normal	Significantly increased, degeneration occurs to the amorphous period
Reticular dermis	Thinning of RD, decreased fibroblasts, no inflammation, has regular elastin fiber, decreasing of collagen	Thickening of RD, Elastosis, Increased fibroblasts, Increased elastin fiber production, Mast cell hyperactivity, and Collagen start to lose
Collagen	Thickened and irregular	Decreased dramatically
Glycosaminoglycans	Slightly decreased	Increase
Papillary dermis	There is no Grenz zone	Elastosis accompanied by the Grenz zone
Microvascular	Slightly decreased	Significant reduction, abnormality microvascular, telangiectasis

Table 2. The Benefit of Hyaluronic Acid in many forms

Study (first author, year)	**HA Formulation***	**Duration of Application**	**Results**
Cordero *et al.*, 2011[45]	**Topical** Cream (RAL 0.05% +HAFi 0.5%)(12W, Qn) - Concentrate (RAL 0.05% +HAFi 1%)(12W, Qn) - Both Cream and Concentrate (12W, Qn)	3 months	Reduce wrinkles and hyperpigmentation, Skin becomes moist
Ascer *et al.*, 2012[46]	**Topical** Cream: HA + Retinol + Adenosine (8W, Bid) applied on skin after botulinum toxin A was injectioned in the area of the glabellar lines (1 round, 4W interval)	2 months	Reducing wrinkles, and increasing skin elasticity
Nkengne *et al.*, 2012[47]	**Topical** Cream: HA + Retinol +dihydroxymethylchromon (DMC) (12W, Qd)	3 months	Reducing Wrinkles
Jegasothy *et al.*, 2014[6]	**Topical** Nano-*Hyaluronic Acid* (8W, Qd)	2 months	Increasing skin elasticity
Nobile *et al.*, 2014[48]	**Topical** Sodium hyaluronate + mix HA of different molecular weight (1 kDa, 5 kDa, 50 kDa, 200 kDa, 2000 kDa) as cosmetic active igredients (4W, Qd)	1 months	Reducing Wrinkles

Choi *et al.*, 2017[49]	**Microneedle patches** HA Micro-needle patches (8W, Biw) containing HA solution (18,4% (w/w), HA 16% (w/w) and Lactose	2 months	Reducing wrinkles, and increasing skin elasticity
Hong *et al.*, 2018[50]	**Microneedle patches** - Soluble HA Micro-needle patches (12W, Biw), - Soluble HA Micro-needle patches (12W, Biw) + adenosine wrinkle cream (12W, Bid), - adenosine wrinkle cream (12W, Bid)-	3 months	Reducing wrinkles, and increasing skin elasticity
Campiche *et al.*, 2020[51]	**Topical** 0.0005% tetradecyl-DabValDab +carnosine + sodium hyaluronate, + *Altermonas* ferment extract in a cosmetic formulation (4W,Bid)	1 months	Reducing wrinkles, and increasing skin elasticity

*HA: Hyaluronic Acid, Qd: once a day, Qn: once a night, Bid: twice a day, Tid: thrice a day, Qm: once a month, Qw: once a week, Biw: twice a week, Tiw: thrice a week, RAL: Retinaldehyde, HAFi: Intermediate-size hyaluronate fragment.

FIGURE

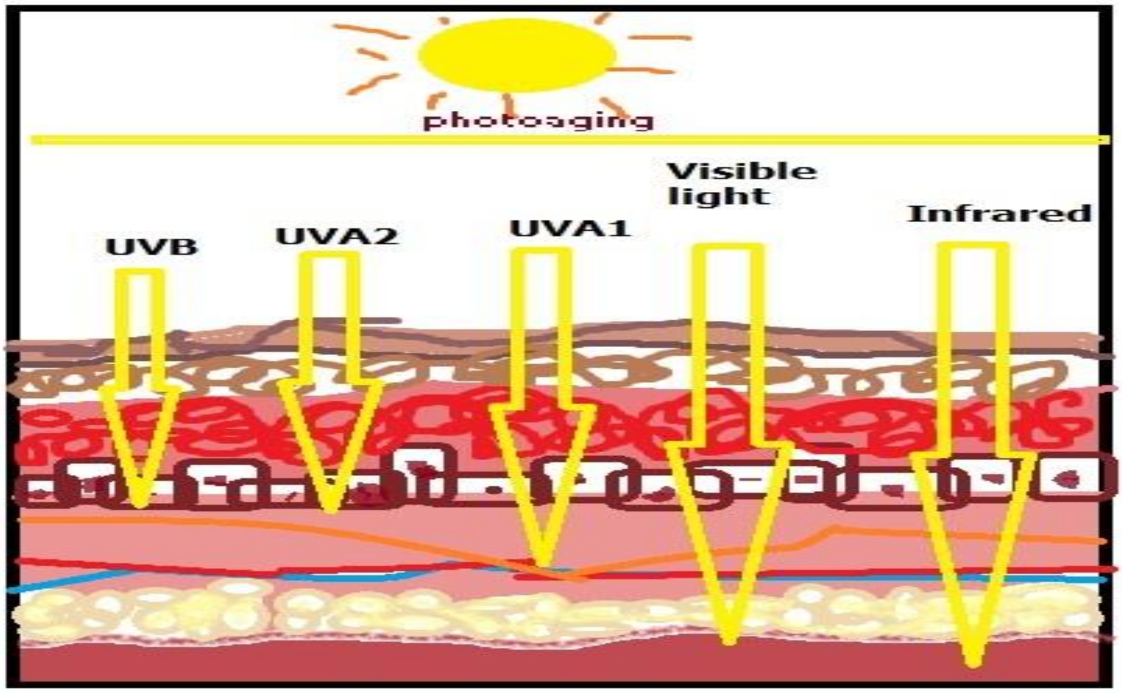

Figure 1. Exposing of UV rays causes damage to the DNA structure. It is influenced by the wavelength and type of radiation energy.

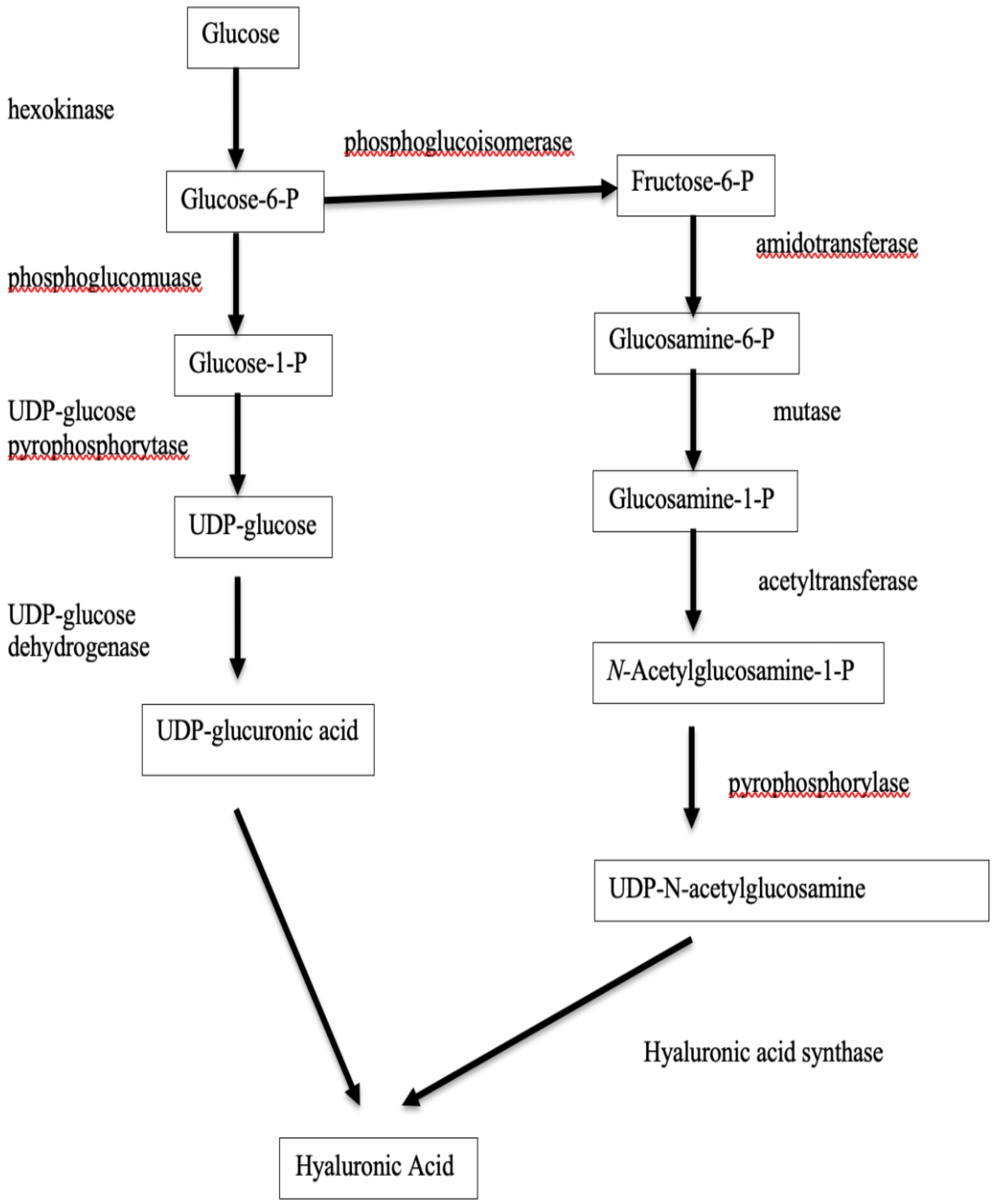

Figure 2. Biotechnological production of hyaluronic acid