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Review Article

Aging Skin and Anti-aging Strategies

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Abstract

The skin is a physical barrier that protects our body against various environmental, chemical and physical agents, and is the main organ that is easily visible as time progresses. Aging is a dynamic, progressive and undesirable biological process that unfortunately cannot be stopped, according to present knowledge. Intrinsic aging (chronological, spontaneous and biological aging) is a programmed natural process, while extrinsic aging (environmental aging and photoaging) is associated with sun exposure, smoking and malnutrition, which weakens the skin structure and functions. Over time, aging skin starts to lose elastin fibers, collagen and other proteins, which are the basic constituents that make skin healthy, bright, fit and elastic. There has been increasing interest in studies on various molecular and hormonal mechanisms, such as hormone dysfunction, changes in signaling pathways, the downregulation of mitochondrial function with cytokine increase, and mitochondrial DNA mutation. Antiaging treatment strategies can be divided into two parts: primary (basic) preventive antiaging approaches and secondary antiaging approaches after the phenotypic features of aging are revealed. The present study aims to review the literature information on the underlying causes of skin aging, healthy skin aging, and basic protective antiaging approaches. Understanding the extrinsic and intrinsic pathophysiological processes of aging would increase the effectiveness of future treatment-finding efforts.

Introduction

The skin is a multifunctional organ that is capable of vitamin D synthesis, thermoregulation and sweat-salt excretion, has a certain microbial flora, secretes antimicrobial peptides, and undergoes various inflammatory and immunological processes. Furthermore, it is a physical barrier that protects our body against various environmental, chemical and physical agents, and is the main organ that is easily visible as time progresses. Aging is a dynamic, progressive and undesirable biological process that unfortunately cannot be stopped, according to present knowledge. Intrinsic aging (chronological, spontaneous and biological aging) is a programmed natural process, while extrinsic aging (environmental aging and photoaging) is associated with sun exposure, smoking and malnutrition, which weaken skin structure and functions.[1]

The structure and properties of the epidermis, dermis, adipose tissue, muscle, ligaments and supporting bone tissue change with aging. Over time, aging skin starts to lose elastin fibers, collagen and other proteins, which are the basic constituents that make the skin healthy, bright, fit and elastic. The decrease in level of glycosaminoglycans, such as hyaluronic acid, which acts as a natural moisturizer by pulling water, causes loss of skin volume. Furthermore, senescent cells are usually observed to have insufficient proliferation capacity, be resistant to apoptosis, and have secretion factors that cause inflammation and tissue degradation. In addition to these changes, recently, there has been increasing interest in studies on various molecular and hormonal mechanisms, such as hormone dysfunction, changes in signaling pathways, the downregulation of mitochondrial function with cytokine increase, and mitochondrial DNA mutation. Understanding the extrinsic and intrinsic pathophysiological processes of aging would increase the effectiveness of future treatment-finding efforts.[1–7]

The present study aims to review the literature information on the underlying causes of skin aging, healthy skin aging, and basic protective antiaging approaches.

Underlying intrinsic (chronological, spontaneous and biological) causes of aging skin

Intrinsic aging in consequence of its dependence on the genetic program is affected by ethnicity, anatomical variations, hormonal

Keywords: Senescence; Skin aging; Intrinsic aging; Extrinsic aging; Antiaging; Antioxidants.

Abbreviations: AHAs, alpha hydroxy acids; AhR, aryl hydrocarbon receptors; ALA, alpha-lipoic acid; ATP, adenosine triphosphate; CoQ10, coenzyme Q10; GFs, growth factors; IR, infrared radiation; MAPK, mitogen-activated protein kinase; MMP, metalloproteinase; mtDNA, mitochondrial DNA; mTOR, the mammalian target of rapamycin; NF-κB, nuclear factor-kappa beta; NMF, natural moisturizing factor; NO2, nitrogen oxides; PL, polypodium leucotomos; PM, particulate matter; QC, quercetin; ROS, reactive oxygen species; RTA, resveratryl triacetate; RTG, resveratryl triglycolate; RV, resveratrol; SMAS, musculo-aponeurotic system; TEWL, transepidermal water loss; UVR, ultraviolet rays.

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Table 1. Effect of aging on skin components[1–10]

Category	Items
Epidermis	Decreased lipid ratio in the stratum corneum[1,2]
	The stratum corneum becomes more compact[1]
	Decreased ceramide levels[2]
	Decreased amount of filaggrin[2]
	Reduction of epidermal turnover and shaped become shorter of keratinocytes[1,2,5]
	Decreases of the amount of natural moisturizing factor (NMF)[2,6]
	Reduced epidermal stem cell number[1]
	Flattening of the dermoepidermal junction[2,5]
	Become of the basal layer more uniform[2]
	Decrease in the number of melanocytes and langerhans cells[1,2,7]
Dermis	Decrease in the number and size of dermal papillae[2,8,9]
	Decreases of the amount of type 1 and type 3 collagen[1,2]
	Reduced of hyaluronic acid[2,8]
	Reduction of the number and elastic fiber diameter[1,2]
	Decreased vascularity and cellularity[1,2,10]
Hypodermis	Reduction in fat volume and changes in distribution[8]
	Decreased function of sweat and sebaceous glands[2,8]

changes and individual differences.[8,9]

Altered epidermal features

With age, the skin shows both qualitative and quantitative changes in all layers of the epidermis.[5] Furthermore, the lipid ratio in the stratum corneum decreases, and ceramide levels are markedly reduced. Moreover, aged skin is more prone to irritation due to the reduced filaggrin and skin barrier.[2,7] As the skin ages, epidermal turnover decreases, and the shape of keratinocytes becomes shorter. Atrophy is particularly evident in the stratum spinosum layer, and cells in the basal layer become more uniform. Furthermore, the number of natural moisturizing factors (NMFs) of the skin is reduced, causing aged skin to be less hydrated. As the result of the flattening of the dermoepidermal junction and deletion of the dermal papilla, the epidermal rete lines cannot achieve the adequate communication and nutrient transfer between the epidermis and dermis.[1,2,9] The effect of aging on skin components is summarized in Table 1.[1–10]

Altered dermal features

Collagen is the major protein of the extracellular matrix, and provides tension to the skin. The decrease in the number and size of dermal papillae, the increase in coarse collagen and curled fibers, and the more selective decrease in amount of type 1 collagen, when compared to type 3 collagen, are the important changes in intrinsic aging. Glycosaminoglycans increase the water holding capacity of the skin, and provide its hydration.[1,5] The concentration of uronic sugar, which is the polysaccharide fraction of proteoglycans, decreases with aging.[10] Elastic fibers provide elasticity to the skin. As elastic fibers thicken, fragmentation would occur.[1,5]

Subcutaneous tissue (hypodermis)

The hypodermis is the layer below the dermis and above the muscles that protects the body from mechanical injury. The hypodermis consists of connective tissue septa and fat lobules. As people age, approximately 30% of the hypodermis fat pad on the face and hands are lost.[2,11] The sagging of superficial fat pads and atrophy of deep fat pads accentuate the aging of the face.[11] The subdermal plexus is located near the dermis-hypodermis border. With aging, the capillary density decreases, and the pericytes in the endothelium are lost. Since the functions of sweat and sebaceous glands are reduced, the skin becomes more prone to dryness.[2,12]

Altered facial muscles and facial ligaments

In the early stage of aging, the hypercontraction and hypertrophy of mimic muscles would lead to dynamic wrinkles, and sad and negative expressions. The mimic muscles of the face are located within the superficial fascia, and are known as the superficial musculo-aponeurotic system (SMAS). In the late stage of aging, the SMAS layer relaxes, and the tonicity of the mimic muscles decrease. Facial ligaments are dense fibrous structures that vertically connect the dermis and periosteum, supporting soft tissues. With aging, these ligaments weaken and lose its strength.[11,12]

Bone structure and hormonal changes

During the aging process, bone destruction would be observed in various areas, such as the orbit, middle maxilla and mandible body. These changes cause an increase in facial concavity.[11,12]

Estrogen affects skin thickness by stimulating the production of collagen from fibroblasts, and epidermal mitotic activity. Skin thickness and the amount of collagen decrease per year after menopause.[13,14]

Cellular changes and theories of aging

The most accepted theories on aging for a long time are telomere shortening, decreased number and function of molecular chaperones, increased free radical oxygen, and increased retinoic acid

Table 2. Cellular and molecular processes that affect skin aging

Category	Items
Cellular	Oxidative stress[1]
	Decrease in antioxidants[1]
	Increased inflammation[1,4,22]
	Loss of mitochondrial membrane potential[15–17]
	Accumulation of senescent cells in tissues and organs as a result of resistance to apoptosis[9]
	Decreased function of sirtuins[24]
	Decrease in coenzyme Q10 level[16,23]
Molecular	Advertent activation of oncogenes[9,24]
	Changes in chromatin structure and epigenetic stress[9]
	Persistent activation of DNA damage checkpoints[9,21]
	Mutations and deletions in mtDNA[15–17]

receptor-α (RAR-α).[1,9]

The skin is the largest organ of the body, with a high turnover rate. Epidermal cells need the adenosine triphosphate (ATP) produced by oxidative phosphorylation in the mitochondria to meet the energy needs. As cells age, the efficiency of the respiratory chain decreases, and electron leakage increases and causes a decrease in ATP production.[15,16]

Reactive oxygen species (ROS) are formed during oxidative phosphorylation. Free radicals generated by ROS contribute to DNA mutations, the oxidation of proteins and membranes, the induction of inflammation, and the activation of signaling pathways that affect gene transcription. Several studies have linked mitochondrial dysfunction, mtDNA deletion, high ROS levels, and oxidative stress to aging of the skin.[15,16] The accumulation of mtDNA mutations increase with aging, and damaged mitochondria is cleaned by mitophagy, which is called autophagy of mitochondria.[16–20] Aymard *et al.*[20] reported the critical relationship between keratinocyte differentiation and mitophagy.

Cellular processes, such as autophagy, mitochondrial respiration, mRNA translation, and ribosome biogenesis, that are regulated by the mammalian target of rapamycin (mTOR) signaling pathway suggest that mTOR plays an important role in the aging process. In the literature, it was suggested that mTOR inhibition can prolong the lifespan in various animal models.[19] Apart from the theories summarized in Table 2,[1,4,9,15–17,21–24] there are other cellular and molecular processes that affect aging, which have recently gained importance.[1,9,15,21]

Underlying extrinsic causes of aging skin

Extrinsic aging is the time-independent premature aging of the skin due to environmental factors, such as ultraviolet rays (UVR), blue light, infrared rays, cigarette smoke, air pollution, lack of sleep, stress, and insufficient and unbalanced nutrition.[1–19]

Ultraviolet (UV), infrared radiation (IR) and blue light

The most common cause of extrinsic aging is sun damage. Although the sun has beneficial effects, such as vitamin D synthesis, the sun also has undesirable effects, such as photoaging, nuclear and mitochondrial DNA damage, and skin cancer formation, as the result of repeated UV exposure.

UVB penetrates the epidermis due to its short wavelength, causing direct DNA damage and skin cancer development. UVA penetrates the deep dermis, and this is the wavelength responsible for free radical formation, photoaging and pigmentation.[1,15]

UVR-induced pyrimidine dimers lead to DNA changes and disruption in cell functions. Furthermore, UVR activates the growth factors and cytokine receptors located on the surface of keratinocytes and fibroblasts. The oxidative stress caused by UVR alters signal transduction pathways, such as mitogen-activated protein kinase (MAPK), nuclear factor-kappa beta (NF-κB), janus kinase (JAK), signal transduction and transcription activation (STAT), and nuclear factor erythroid 2-associated factor 2 (Nrf2). NF-κB and activator protein-1 (AP-1) trigger collagenase, gelatinase and stromelsin-1, causing the increase in matrix metalloproteinase (MMP) levels, and the breakdown of collagen.[1,25]

With age, the decrease in melanocyte activity would cause irregular pigmentation and an increase in the destructive effect of the sun.[16] Sun-exposed skin is thick and rough, and coarse wrinkles emerge and telangiectasia occurs. Furthermore, sun damage can make a person look older than they should look.[1,12] IR and blue light have been associated with photoaging of the skin.[1,26] The clinical and histological features of intrinsic and extrinsic aging of the skin are presented in Table 3.[1,2,8,15,27]

Smoking and air pollutants

Smoking is an independent risk factor for premature skin aging. Cigarette smoke changes the cellular repair, defense and extracellular matrix transformation functions by stimulating free radicals, impairing fibroblast growth and proliferation, and increasing dermal matrix MMP levels. Smokers experience significant deterioration in skin color and shine. Cigarette smoke significantly increases the melanogenesis-related transcription factor (MITF) expression in a dose-dependent manner, leading to greater melanin production in melanocytes *via* aryl hydrocarbon receptor (AhR)-mediated mechanisms. Skin aging due to smoking characteristically manifests as a "smoker's face" with wrinkles, skin atrophy, and a gray complexion.[28,29]

Air pollutants damage the skin by inducing oxidative stress. The major air pollutants that affect the skin are polycyclic aromatic hydrocarbons, nitrogen oxides (NO_2), ozon, and particulate matter (PM).

Atmospheric polycyclic aromatic hydrocarbon source is caused by the combustion of wood and organic materials, automobile ex-

Table 3. Features of intrinsic and extrinsic aging of the skin[1,2,8,15,27]

Category	Intrinsic aging	Extrinsic aging
Clinical Findings	Loss of elasticity[1,2]	Loss of elasticity[1,2]
	Fine wrinkles[1]	Fine and deep wrinkles[1]
	Pale[2]	Dyspigmentation[2]
		Telangiectasias[2]
Histological findings		
Epidermal thickness	Decreased[1]	Increased in the early period, decreased in the late period[1]
Dermis	Decrease in the amount of collagen and elastin, more moderate change[1,8]	Fragmented and disorganized collagen
		The accumulation of amorphous elastic fibers (solar elastosis)[1,8]
Melanocyte activity	Decreased[2,8]	Increased epidermal melanin[2,8]
Inflammatory cell	No signs of inflammation[1]	Perivascular lymphohistiocytic infiltration[1]
Sebaceous glands	Decreased in function and number[2,8]	Sebaceous hyperplasia[2,8]
Cellular and molecular findings	Less obvious mtDNA deletion[15,27]	Increase in the frequency of mtDNA deletions[15,27]

haust, diesel fumes, the industry, plastic production, pesticides, paints, and cigarette smoke. Polyaromatic hydrocarbons are associated with extrinsic skin aging, pigmentation and cancer.[30,31]

The PM in the air (including pollutants such as soot, exhaust and industry) consists of a mixture of different sizes and compositions. PM can be classified as fine (PM2.5 and PM10) and coarse particles. The most harmful components of PM are traffic-related nano-sized particles. These particles can act as carriers for organic chemicals and metals that can settle in the mitochondria, and form ROS. Pollutants may damage the skin by activating the MMP-1 expression and AhR. Furthermore, NO_2 and PM can cause pigmentation. There is increasing epidemiological evidence that prolonged or repeated exposure to high levels of pollutants can cause profound adverse effects on the skin, such as pigmentation and wrinkle formation.[30,31]

Stress, physicial activity and diet

The effect of stress on skin aging remains unclear. Repetitive cortisol exposure in chronic stress can lead to decreased immunity, impaired wound healing, and increased inflammation. Furthermore, stress can cause the accumulation of ROS and DNA damage.[22,32]

Exercise facilitates the supply of oxygen and nutrients that the skin needs for the formation of new cells by increasing blood flow. When sedentary older adults were included in a 3-month cycling program, the researchers found a significant reduction in stratum corneum thickness and an increase in collagen content of the reticular dermis, when compared to pre- and post-intervention skin samples.[33]

When excess sugar is consumed, sugar binds to proteins and lipids, and glycation occurs (Maillard reaction). High fat and carbohydrate intake has been associated with a higher likelihood of wrinkled appearance. The positive effects on health and aging of reducing red meat consumption and the adoption of mediterranean diet regimens rich in vegetables and fruits have been the subject of various studies.[32,34] In one cohort study, adults who consumed high antioxidant foods were followed up for 15 years, and it was found that these adults had 10% less photoaging, when compared to adults without high antioxidant consumption.[35] That is, a healthy diet can reduce the signs of skin aging.[32,34]

Clinical features of aging

In clinic, aging skin becomes thin and dry, leads to xerosis, rhytides and loss of elasticity occurs, becomes pale, dull and rough, and leads to atrophy. Temporal collapse, droopy eyelids, nasojugal grooves, reduction in malar fat pads, cheek depression, nasolabial grooves, and jowl deformity are the prominent clinical features of aging. Dyschromia associated with hyperpigmentation due to sun damage and hypopigmentation due to the reduction in melanocytes play an important role in the perception of old age (Fig. 1).[1,11]

Antiaging treatment strategies

Scientists have focused on studies that can prevent or delay skin aging at the cellular and molecular level in the past two decades.[15–20] In addition, rapidly evolving topical cosmeceuticals, and less invasive procedures than surgery have become the products and procedures that patients frequently demand from doctors and skin care practitioners.

Antiaging treatment strategies can be divided into two parts: primary (basic) preventive antiaging approaches before the phenotypic features of aging are revealed, and secondary antiaging approaches (this will not be discussed in detail in the present review) after the phenotypic features of aging are revealed. Below are the strategies that can enhance the youthful appearance of the skin and delay skin aging.

Primary (basic) preventive antiaging approaches

The term cosmeceutical was used by Kligman[36] to describe bioactive products that provide both cosmetic and therapeutic benefits. The regular daily use of cosmeceuticals produced with effective technology can prevent and treat various signs of skin aging. The

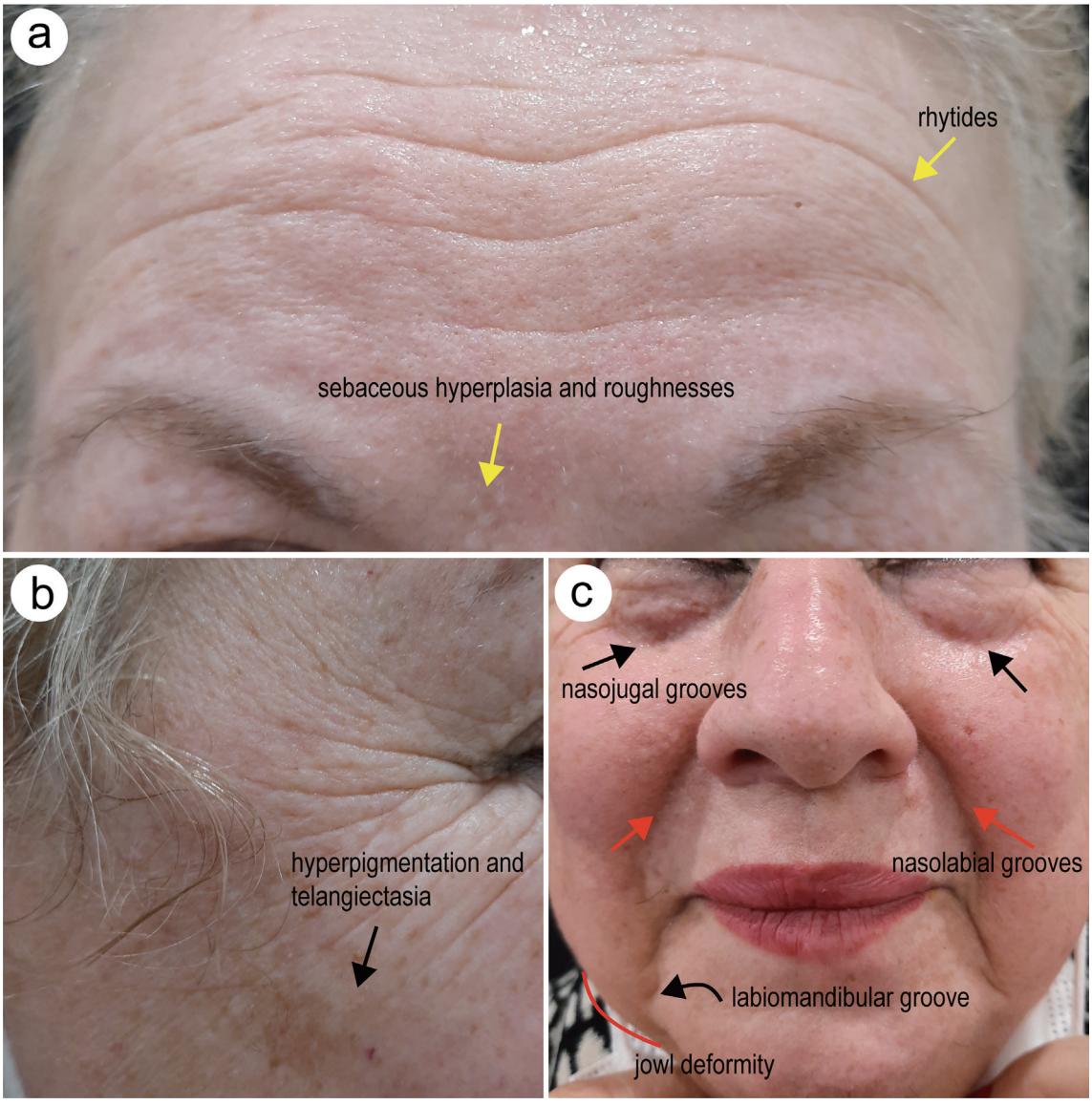

Fig. 1. Phenotypic changes of the face that occur with age. (a) Rhytides, sebaceous hyperplasia and roughnesses in the forehead. (b) Prominent rhytides, hyperpigmentation and telangiectasia around the eyes. (c) Nasojugal-nasolabial-labiomandibular grooves, jowl deformity, reduction in malar fat pads, and cheek depression.

"Topical Nutritional Pyramid", which provides cosmeceuticals that are easy to understand, was created by Kenner,[37] and this was recently revised by Draelos[35] as "The Skin Health and Beauty Pyramid." The cosmeceuticals and basic protective approach to the skin were explained and inspired by these pyramids (Fig. 2).[37,38]

General precautions and protection

Extrinsic aging includes causes that can be changed and prevented by taking precautions at an early age.

Protection from ultraviolet-infrared rays, visible and blue light, and air pollutants

Sunscreens are the most important step in protecting the skin from premature aging. Sunscreen products should have a sun protection factor (spf) value of at least 30, and protect against UVA-UVB radiation. Inorganic (physical) sunscreens with opaque filters, such as zinc oxide and titanium dioxide, are effective, reflecting UVA, UVB and visible light when used in non-nano forms. Nano forms that are in the transparent form are better tolerated by users.[38–40]

Chemical sunscreens that consist of organic chemicals, such as para-aminobenzoic acid and benzophenones, act by absorbing UV rays. Visible and blue light promotes photoaging through the production of ROS, and can cause pigment darkening, melasma and post-inflammatory hyperpigmentation in Fitzpatrick IV-VI skin types. For many years, it has been recommended that "sunscreens should be applied half an hour before going out in the sun, and should be renewed every 2–3 hours for continuous sun exposure."[1] In addition to this recommendation, it is important to use sunscreen at home and workplaces due to the intense exposure to blue light (digital light pollution) through the development of

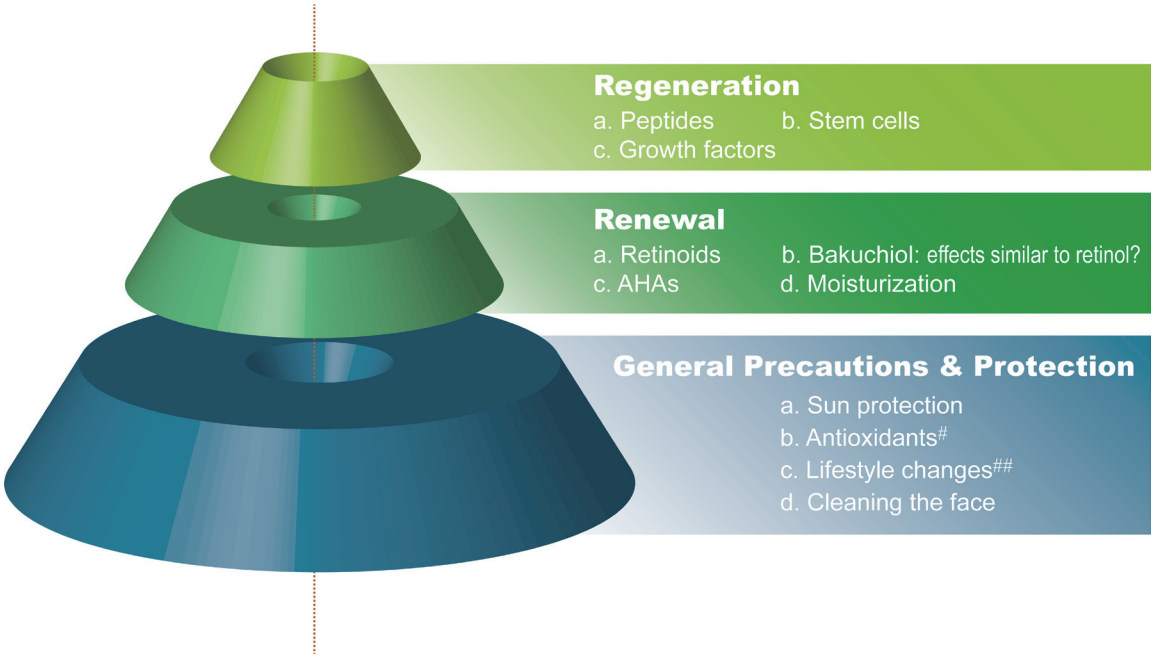

Fig. 2. The cosmeceuticals and basic preventive antiaging approach pyramid. General precautions and protection form the basis of the pyramid. The first step is to use sunscreens that protect against UVA-UVB rays and sunglasses-hats, and avoid tanning beds. Preferably, antioxidant creams can be applied under sunscreen in the morning to provide additional support in protecting against the harmful effects of UVR. Washing is performed to remove the oil, dirt and harmful particles that accumulate on the face throughout the day. The second step is started at the renewal stage. Retinoids (prescription [tretinoin, adapalene and tazarotene] and over-the-counter [retinol, retinol, retinyl esters, and retinoic acid]), bakuchiol, and alpha hydroxy acids (AHAs) should be applied at night, and preferably afterwards, the humidification phase should be started. The third step is the regeneration stage. Palmitoyl pentapeptide, acetyl hexapeptide, topical GFs derived from secretions of the snail, Cryptomphalus aspersa, and stem cell extracts derived from plants can be applied for 1–2 times a day to reduce wrinkles. #Topical vitamin C, vitamin E niacinamide, Coenzyme Q10, melatonin, polypodium leucotomos, and resveratrol; ##Cessation of smoking, drinking water, exercising, eating a healthy and balanced diet, and providing relaxation by reducing stress.

digital devices today. Furthermore, additional protection measures should be taken by using sunglasses, hats and clothing. It should be noted that UV damage continues even in cloudy weather, and that solarium should be avoided.[1,38,39,40]

The method of minimizing skin damage from air pollutants is to wash the face upon arriving home, and to prevent these particles from coming into contact with the skin by using moisturizers and sunscreen cream before leaving the house.[38]

Antioxidants

Antioxidants are substances that can prevent or slow the damage to cells caused by free radicals. With chronological aging and photoaging, the body's natural antioxidants decrease. Taking advantage of this information, it has been considered that the use of antioxidants can help delay skin aging. Various articles on the protective effects of polyphenolic antioxidant compounds, such as green tea, cocoa, soy, pomegranate, curcumin, resveratrol and polypodium leucotomos, have been published.[21,25,41–44]

Polyphenols are organic chemical compounds that exhibit antioxidant, anticancer, anti-inflammatory and antiapoptotic activities. Polyphenols can also regulate the mitochondrial activity and energy homeostasis.[21,45] It has been argued that these compounds may be effective through the inhibition of mTOR, which is associated with the prolongation of the lifespan, and the regulation of MAPK and NF-kB activity.[21,46,47] Furthermore, it has been reported that baicalin, quercetin, silymarin, flavangenol and raspberry extract induce the photoprotective activity against UVB radiation.[25]

Vitamin C (ascorbic acid) is a powerful antioxidant with antiaging, antipigmentary and photoprotective properties. This neutralizes the free radicals formed in cells by giving electrons. Furthermore, this stabilizes collagen fibers, reduces its destruction, and directly stimulates collagen synthesis by activating mRNA.[40–49]

Vitamin C is a hydrophilic molecule, and its most biologically active and unstable form is L-ascorbic acid. Its penetration into the skin is poor due to the hydrophobic character of the stratum corneum. Lowering the pH of L-ascorbic acid to below 3.5 improves its stability and permeability. Vitamin C is the replenisher of the oxidative form of vitamin E, and works synergistically with vitamin E to protect against oxidative damage.[40] That is the reason why products with vitamin C concentrations within 8–20%, combined with ferulic acid and vitamin E, have recently become popular.[50,51] Other commonly used stable lipophilic and esterified forms of vitamin C include ascorbyl-6-palmitate, magnesium ascorbyl phosphate, and tetraisopalmitoyl ascorbic acid. After these forms are absorbed through the skin, these must be converted to the active form, L-ascorbic acid, to be effective. However, it remains unknown exactly how many of these derivatives return to the active form in daily use.[48,50]

Vitamin E is a fat-soluble vitamin, and its effective form is α-tocopherol. This exhibits antioxidant properties by preventing lipid peroxidation. Furthermore, this is used as a moisturizer, because this reduces transepidermal water loss.[40] Moreover, this has been shown to protect against UV-induced inflammation and hyperpigmentation when applied topically. The electron microscopy analysis confirmed that the collagen and elastin fiber damage was corrected. Furthermore, creams on the market generally contain

0.5–5% of vitamin E.[51,52]

Niacinamide (nicotinamide) is the precursor of nicotinamide adenine dinucleotide (NAD) and its phosphate derivative (NADP) cofactors. The reduced forms of these cofactors (NADH and NADPH) play a role in antioxidation, DNA synthesis and repair. In a double-blind, placebo-controlled study, 50 women aged 40–60 years old were evaluated after using 5% nicotinamide gel formulation topically for 12 weeks. It was observed that the fine wrinkles, hyperpigmented spots, redness, yellowing and skin texture improved. Since oral forms of niacin are associated with flushing, these are recommended to be topically applied.[40,42,53]

Coenzyme Q10 (ubiquinone) is present in all cells as a ROS scavenger that acts as an electron shuttle in the electron transfer chain (ETC), and protects against membrane lipid oxidation. A decrease in coenzyme Q10 (CoQ10) level has been observed with age.[15] Prah *et al.*[46] reported that the addition of CoQ10 to keratinocytes isolated from aged skin can restore mitochondrial metabolism. CoQ10 is available in both oral and topical formulations. Several studies have revealed that the topical application of CoQ10 to photoaged skin improves the phenotypic signs of aging and restores mitochondrial function.[15,23,54] El-Leithy *et al.*[55] suggested that the nanoemulsion form of CoQ10 can be used to increase permeability, thereby providing anti-wrinkle efficacy. However Knott *et al.*[54] reported that the Q10 content does not increase in skin surface lipids after oral supplementation with Q10.[52]

Melatonin is a neurohormone that has regulating effects on the mitochondrial ETC, and regulates circadian rhythm. This can directly increase the electron flow through the respiratory chain.[17,18] Melatonin and its metabolites induce a photoprotective effect on cutaneous tissues by scavenging the free radicals caused by UV or X-rays. Melatonin plays an important role in pigmentation, inflammation and wound healing.[17] When melatonin is taken orally, this degrades as this passes through the liver, and its penetration into the skin is limited due to its low blood levels. Topical application may be more meaningful than oral application, since this can penetrate the stratum corneum due to its lipophilic structure. Pharmacological doses of melatonin protect keratinocytes and melanocytes from UVB-induced damage *in vitro*.[56] In one study conducted by Kim *et al.*[57] the topical application of melatonin has been shown to improve the barrier function of the epidermis by increasing keratinocyte proliferation.

Polypodium leucotomos (PL) is a powerful antioxidant due to its high phenolic content. PL functions in the inhibition of UV-induced ROS production and the prevention of mitochondrial DNA damage. Furthermore, this protects against damage induced by blue light and IR. In addition, this supports type I and V collagen synthesis in skin exposed to UVR by inhibiting the metalloprotease expression. Moreover, PL can be used in skin aging due to its photoprotective, antioxidant, anti-inflammatory and antiaging properties, orally and topically.[41,58] Studies often include oral forms. Nestor *et al.*[59] suggested that 240 mg of PL extract taken twice daily for 60 days is safe and effective for reducing the harmful effects of UVR.

Resveratrol (RV) is a compound with a very rich polyphenolic content. RV acts as an antioxidant by scavenging reactive oxygen radicals.[60,61] The antioxidant activity of resveratrol (95%) has been shown to be higher than that of vitamins E (65%) and C (37%).[62] Furthermore, this can modulate cell functions, signal transduction and gene expression.[61] The properties of RV as an anti-oxidant, anti-cancer and anti-inflammatory agent are most likely due to the changes in gene expression.[63] In an *in vitro* study conducted by Gopaul *et al.*[64] it was demonstrated that RV can stimulate collagen type I and III gene expression.

RV activates sirtuin-1, which has an important role in the aging process, reducing the expression of tumor necrosis factor (TNF)-α-induced inflammatory cytokines and MMPs.[24] The biological activity of RV depends on its concentration in the trans form. RV has poor bioavailability, low water solubility and unstable properties. Therefore, not all oral forms may be effective. Recently, new RV nano-delivery systems based on lipid nanoparticles have been studied to increase its physical stability and oral bioavailability.[65] More studies are needed to determine the effectiveness of oral intake due to its rapid metabolism.

In a prospective clinical study conducted by Janssens-Böcker *et al.*,[60] 2% RV emulsion was applied to 20 participants who presented with clinical signs of skin aging, once a day, for eight weeks. They reported that this increases the skin's elasticity, density, firmness, moisture, smoothness and glow. In addition, they observed a reduction in skin roughness and redness, and an improvement in the density of collagen fibers.

RV analogs, such as resveratryl triacetate (RTA) and resveratryl triglycolate (RTG), exhibit human skin lightening effects at concentrations of 0.4% RTA and 0.4% RTG. Furthermore, 0.8% RTA exhibits antiaging effects, such as improved facial skin wrinkles, sagging, elasticity, moisture and brightness.[61]

Alpha-lipoic acid (ALA) is a potential therapeutic agent for chronic diseases, which is associated with oxidative stress. In a study on healthy mice that were given ALA, fat accumulation was detected in the short term, and hepatic steatosis and liver damage were detected in the long term. Oral ALA intake for antiaging in healthy individuals should be carefully considered until adequate data becomes available.[66] In a single-blind, placebo-controlled, right-left comparative clinical study, 5% cubosomal ALA was used on the right half of the face, and at the end of six months, the increase in epidermis thickness and the greater improvement on the global aesthetic improvement scale were determined to be statistically significant on the right side.[67]

Curcumin is one of the polyphenolic bioactive components that are being attempted in clinical studies as an anticancer molecule. It has been considered that curcumin acts by affecting the cell cycle, apoptosis, proliferation, survival, formation of new blood vessels, inflammation, and various cell signaling pathways that play a role in these events.[68] Furthermore, curcumin suppresses the mTOR signaling pathway activity and delays cellular senescence.[69] Curcumin is known for its poor solubility, chemical instability and poor absorption. The study conducted by Ben Yehuda Greenwald *et al.*[70] revealed that the microemulsion form created using a nanotechnology-based delivery system can be used to restrain UV-induced cytotoxicity in epidermal cells.

Quercetin (QC) is a flavonoid with antioxidant and antiinflammatory activities. In cellular and animal-based models, QC has been shown to promote skin regeneration in wound healing and protect cells from UVR.[71] The study conducted by Vale DL *et al.*[72] revealed that topical formulations that contain QC-loaded microcapsules can inhibit the UVB-triggered depletion of antioxidants, and reduce the production of inflammatory cytokines, MMP-9 activity, skin edema, and collagen fibre damage.[71,72]

Antioxidants targeted to mitochondria: Oyowale *et al.*[26,73] reported that antioxidants targeted to mitochondria (MitoQ and thyron) can protect against mtDNA damage more than non-targeted antioxidants. MitoQ is a ubiquinone derivative. Ubiquinone prevents lipid peroxidation by acting as an electron carrier and antioxidant in ETC. Thyron is a mitochondrial-localized antioxidant that permeabilizes the mitochondrial membrane, acts as an iron

chelator, and protects against photoaging. Mitochondria-targeted vitamin E (MVE) is designed to reduce mitochondrial oxidative damage by accumulating within the mitochondria. MVE has been shown to increase collagen production and downregulate MMP, and decrease ROS production in animal models.[74]

More controlled studies are needed to demonstrate the effective concentrations, efficacy and safety of topical and oral antioxidants. New developments on targeted antiaging therapies may appear more frequently in the future.

Lifestyle changes

In antiaging treatment strategies, patient education is critically important to change a patient's lifestyle, and ensure compliance with treatment regimens. Cessation of smoking, drinking water, exercising, eating a healthy and balanced diet, and providing relaxation by reducing stress can help prevent skin damage.[36]

High glycemic index foods can cause the formation of glycation products, and can possibly play a role in the damage observed in collagen and elastin. Consuming foods with a low glycemic index, adopting the Mediterranean diet, and using metformin with the recommendation of a doctor (when necessary) are recommended to reduce glycation.[39,42] Exercise can improve circulation and mitochondrial functionality, and regular sleep can help the body regenerate.[39]

Skin renewal (moisturization and exfoliation)

Retinoid

Retinoids consist of vitamin A derivatives. The most active form of vitamin A is tretinoin. Other retinoid members are retinol, retinyl esters, retinoic acid, and retinyl palmitate. Retinyl palmitate is the most stable, but is not very biologically active.[1,38]

Retinoids regulate the gene expression by binding to the nuclear receptor. This inhibits the activation of collagenase and gelatinase through the inhibition of transcription factors AP-1 and NF-κB.[1] Furthermore, retinoids promote the growth, regulation and differentiation of epidermal cells.[1,38,75]

Retinoids increase the activity of procollagen genes, collagen synthesis and angiogenesis. This can improve skin tone, texture, pigmentation and pore size.[37] In previous studies, oral and topical retinoid use has been found to significantly reduce fine wrinkles and hyperpigmentation.[1]

Retinoids should be considered as the first choice to treat aging skin and prevent skin aging. Since this can cause redness, irritation, scaling and stinging in the first few weeks, the use time of retinoids should be gradually increased.[42] Furthermore, retinoids should be applied at night, and protected from sunlight using sunscreen.

Bakuchiol

Bakuchiol is a phenol that has anti-proliferative, anti-inflammatory, and antioxidant activity. It has been suggested that this can modulate retinoic acid receptor genes and upregulate collagen synthesis enzymes by acting like a retinoid, when applied topically.[76]

A clinical study revealed the statistically significant improvement in wrinkles and pigmentation after the topical application of bakuchiol twice daily.[77] In a prospective, randomized, double-blind study conducted by Dhaliwal *et al.*[76] the participants were instructed to apply 0.5% bakuchiol cream or 0.5% retinol cream twice daily. It was observed that both creams significantly reduced the wrinkle surface area and hyperpigmentation with no statistical difference. Participants who used retinol reported more facial skin flaking and stinging. Although bakuchiol appears to be a new alternative for sensitive skin and for those who cannot tolerate retinol, more scientific studies are needed.

Alpha hydroxy acids (AHAs)

The use of AHAs, including glycolic acid (GA), lactic acid (LA), malic acid (MA), tartaric acid (TA) and citric acid (CA), as peeling agents, is becoming increasingly popular. Structurally, these are organic weak acids. The effectiveness of AHAs is dependent on the pH, concentration, and exposure time. AHAs reduce corneocyte cohesion by detaching and desquamating the stratum corneum.[38,78]

LA is part of the skin's natural moisturizing complex, and may be important in boosting cell renewal function.[62] A study revealed that CA increases the proliferation of collagen I and procollagen II, the rate of skin renewal, the thickness of the epidermis, and the amount of glycosaminoglycans. Furthermore, GA improves the epidermis and dermis.[79]

AHAs are presently used to treat melasma, hyperpigmentation, roughness, age spots and seborrhea. Despite these benefits, such as improvement in skin firmness and elasticity, reduction of lines and wrinkles, and cell renewal, peelings can cause redness, burning and itching. Furthermore, these can make the skin sensitive to UV light.[78,79] In order to avoid this, it may be helpful to apply AHAs at night in appropriate concentrations, and protect oneself from UV by regularly applying sunscreen.

Moisturization (occlusives and humectants)

The water content of the skin is lost to the environment by evaporation. NMF is used to describe the combination of various chemicals, such as amino acids, organic acids, peptides, lactate, urea, ammonia, uric acid, glucosamine and sugar, which are naturally found in the stratum corneum, and keeps the skin moist. Moisturizers work to rehydrate the skin by reducing transepidermal water loss (TEWL), and through formulations created by mimicking NMF.[80]

Sphingolipids, free sterols and free fatty acids are required to maintain the skin barrier. When there is an increase in TEWL, barrier repair is provided by initiating lipid synthesis. Functionally, moisturizers are used for the initiation of barrier repair, the synthesis of intercellular lipids, and the improvement of dermal-epidermal moisture diffusion. Cosmetically, moisturizers are used to make the skin smooth and soft, increase skin moisture, reduce fine lines of dehydration, and improve appearance.[38,80]

Occlusives (petrolatum, paraffin, mineral oil, squalene, silicones, lanolin, shea butter, and vegetable oils), which can reduce TEWL, and humectants (hyaluronic acid, glycerin, sorbitol, urea, sodium lactate, and propylene glycol), which can draw water like a sponge, constitute the main types of moisturizers.[38,80]

Skin regeneration (peptides, growth factors and stem cells)

At present, peptides are used with the aim to increase the production of collagen, elastin, proteoglycan and glycosaminoglycan. In previous studies, it was observed that proteins and peptides can reduce the signs of skin aging, and increase skin elasticity and firmness. *In vitro* studies have revealed that palmitoyl pentapeptide, which is a procollagen I fragment, can stimulate the production of collagen I, III and IV. Furthermore, polypeptides can increase collagen synthesis and activate dermal metabolism.[38,81,82] In addition, it has been considered that for acetyl hexapeptide, the modulation of SNAP-25 can relax the muscles and reduce wrinkles with a botulinum toxin-like effect. Although the data on peptides remain

limited, its application 1–2 times a day can stimulate collagen and reduce wrinkles.[37,38]

In recent years, topical growth factors (GFs) have emerged as intriguing cosmeceuticals. Human GFs serve as cellular chemical messengers that direct cellular growth, migration, extracellular matrix activity, and inflammatory response. Various GFs and peptides have been found to enhance cellular growth, stimulate stem cells, reverse cell senescence, and facilitate cell renewal.[81–83] GFs can directly stimulate genes, but these must be presented to the correct receptor site to function.[42]

Recent studies support the use of topical GFs for skin rejuvenation, which are derived from sources, such as secretions or lysate of human dermal fibroblasts, and secretions of the snail, Cryptomphalus aspersa.[84]

Stem cells in animals and plants have properties that help regenerate after injury. Living stem cells cannot survive in cosmetic formulations. Therefore, skin care products often contain stem cell extracts.[38,85] A product with patented stem cell technology has been claimed to protect from aging damage, regenerate cells, and increase the level of filagrin.[86] However, the development of formulations that contain stem cells and further studies are needed.

Secondary rejuvenating anti-aging approaches

After the phenotypic features of aging emerged, secondary anti-aging approaches, such as botulinum toxin, mesotherapy, platelet rich plasma, filler, subcutaneous thread applications, autologous fat injections and laser treatments, have led to the increase in demand for aesthetic dermatology. The needs of every face and skin are different, and require different approaches.[11] This issue will not be discussed in detail in the present study.

Future directions

Understanding the pathophysiological processes of aging to optimally use of the skin's regenerative capacity would help in defining antiaging treatment strategies more clearly. As knowledge on molecular and cellular events that cause aging has increased in recent years, it is expected that bioactive cosmeceuticals produced with effective technology would enter the stage of daily use. However, there are problems that reduce the effectiveness, such as the unstable nature of antioxidant compounds, and the poor solubility of topical forms. It is necessary to clarify at what doses these oral forms would be effective, and what the systemic side effects are. In addition, there are limitations in the passage of large molecule substances, such as peptides, growth factors and stem cells, into a cell. It is expected that innovative pharmaceutical nanoformulations should be developed, in addition to standard emulsifying agents, in order to increase dermal and cellular penetration.

Conclusions

Clinicians frequently encounter aging skin, and the clinical conditions it brings in daily practice. Skin aging is a complex, insidious and progressive process that affects certain functions, based on the various reasons mentioned above. Dividing anti-aging treatment strategies into basic preventive and secondary anti-aging approaches can assist clinicians in treatment planning. A consistent and accurate skin care regimen that consists of at least 30 spf sunscreen (tinted when possible), cleansers, moisturizers, nighttime topical retinoid, and oral and topical antioxidants in the daily care routine, are the minimum requirements. Other products, such as hydroxy acids, growth factors, peptides and stem cells, are other options that can be recommended according to the patient's skin structure. Explaining a healthy lifestyle to patients and informing them on the treatment approaches would increase their compliance.

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Conflict of interest

The authors have no conflict of interest to declare.

Author contributions

The study concept and design (EYB); data collection and interpretation (EYB); writing of the manuscript or critical review of important intellectual content (EYB and İOT); final approval of the final version of the manuscript (EYB and İOT). All authors have made a significant contribution to the study, and approved the final manuscript.

Ethics statement

The authors have obtained a written informed consent from the patient for the publication of the images in the manuscript.

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