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ABBREVIATIONS

ACTH: Adrenocorticotropic.

ADSCs: Adipose derived stem cells.

AGE: Advanced glycation end product.

AHR: Aryl hydrocarbon receptor.

BFGF: Basic fibroblasts growth factors.

CGs: Glucocorticoids.

CRH: Cartictropin releasing hormone.

CRP: C. reactive protien.

DAO: Depressor anguli oris.

EFAs: Essential fatty acids.

HA: Hyaluronic acid.

HACAT: Human

HGF: Hepatocyte growth factors.

HPA: Hypothalamic pituitary adrenal.

HTERT: Human telomerase reverse transcriptase.

IL : Interleukine.

IRR : Infrared radiation rays.

KGF: Keratinocyte growth factors.

LA: Linoleic acid.

MMP: Matrix metalloproteinases.

MUPA: Monosaturated fatty acid.

NOX: Nitrogen oxides.

PAHS: Polycyclic aromatic hydrocarbons.

PDGF: Platelet derived growth factors.

PGF: Placental growth factors.

PM: Particulate maters.

PRP: Platelet rich plasma.

PUFA: Polyunsaturated fatty acid.

PVN: Paraventricular nucleus.

ROS: Reaction oxygen species.

SFA: Saturated fatty acid.

SMAS: Superficial Musculo aponeurotic system.

SOD: Superoxide dismutase.

SVF: Stromal vascular fraction.

TEWL: Trans epidermal water loss.

TGF: Transforming growth factor.

TGF: Transforming growth factors.

TIMP: Tissue inhibitor of matrix metalloproteinase.

TNF: Tumor necroisis factor.

UVR: Ultra violet radiation.

VEGF: Vascular endothelial growth factors.

VL: Visible light.

VOC: Volatile organic compounds.

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Introduction

Introduction

Most evolutionary biologists define aging as an age-dependent or age-progressive decline in intrinsic physiological function, leading to an increase in age-specific mortality rate (i.e., a decrease in survival rate) and a decrease in age-specific reproductive rate **(Flatt and Schmidt, 2009; Bronikowski and Flatt, 2010; Fabian and Flatt, 2011)**. Rose (1991), for example, in his seminal book on the evolution of aging defines aging as “a persistent decline in the age-specific fitness components of an organism due to internal physiological degeneration.” At level of the individual, the intrinsic physiological state at a specific age determines, among other things, whether an individual is dead or alive and how much it reproduces. At the level of the cohort, the underlying physiological states of the individuals trans- late into the age-specific rates of mortality and reproduction. We therefore diagnose demographic aging to occur if we observe an increase in age-specific mortality and a decrease in age-specific reproductive rate in the cohort **(Bronikowski and Flatt, 2010).**

In particular, the notion that aging is a de-tuning of adaptation is completely consistent with the standard definition of aging. Adaptation by natural selection is based on heritable variation in fitness among individuals, and survival and reproduction are the most important determinants or components of fitness **(Stearns, 1992).** Thus, in agreement with Rose's definition, the age-dependent decline of age-specific survival and reproductive rates represents an age-progressive loss or de-tuning of fitness or the state of adaptation. Moreover, it is well-accepted among evolutionary biologists that this decline is due to the declining forces of natural selection with increasing age.

Aging has been defined as a progressive and generalized impairment of function resulting in a loss of adaptive response to stress and in a growing risk of age-associated disease **(Kirkwood, 1963).** Charaka (2012) considers that old age starts at 60 years of age, while Sushruta demarcates old age starts at 70. It is important to distinguish normal aging that is universal biological changes that occur with advancing age and are unaffected by disease and environmental influences which is known as chronological aging and according to Ayurveda kalaja jara (natural aging). Some western bio-gerontologists also accept that aging is a disease **(Gorman, 1999).**

Aging does not take place simultaneously in all tissues. Ashthanga Samgraha (2012), was the first to mention how aging proceeds, whether it starts simultaneously in all tissues or from particular part of the body. According to this view, some qualities are being deteriorated in each decade of life beginning from, for in- stance at the end of first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, and tenth decade; the childhood, growth, complexion, intellect, skin luster, reproductive capacity, vision, hearing, mind, and functions of sense organs are lost, respectively, **(Gupta, 2005)** and the maximum life span is 100 years.

Premature aging is strongly influenced by the effects of environmental, lifestyle, and disease states that, in turn, are related to or change with aging but are not due to aging itself. This is an accelerated aging due to many reasons, in which biological aging is more intense irrespective of chronological age. Although, the rate of aging is genetically predetermined; lifestyle, dietary habits, addictions, mental makeup, social and family life, medication, and many other environmental factors may influence the aging process, and their unfavorable effects cause premature aging. Among hundreds of theories of aging, free radical theory has remained rational over time as it provides many realistic explanations for the process of aging. The changes induced by free radicals are believed to be the key cause of aging, disease, and death. Diet, active, and stress-free living play an unparallel role in neutralizing free radicals there by retarding aging and age-related disease as well.

Many mechanisms likely contribute to age-related inflammation. As with all other physiological systems, there are significant declines in immune function with aging that promote inflammation, but the chronic low grade inflammatory state in the elderly also is clearly a consequence of age-related chronic diseases **(Chung et al., 2009).** Among the dysregulated proinflammatory mediators, cytokines and chemokines are major culprits in the development of chronic inflammation and the immune senescence process, for instance, interleukin (IL)-6, tumor necrosis factor (TNF)-α, and their receptors, are upregulated in aged tissues and cells **(Bruunsgaard et al., 2003).** Elevated levels of chemokines and C-reactive protein (CRP) have been found to be involved in age-related pathogenesis **(Gordon et al., 2011).** So, for the topic, the following question will be answered through this study: what are the causes and factors that control aging? and how can fight aging?

Aging is an inevitable part of life, as we notice one person who appears to age more than another even though they are at the same age, as some seem younger than they really are and others live the opposite situation. The purpose of our study is therefore to explain how the aging process takes place and to search for the true way in which the skin ages, by studying the internal and external factors that control the appearance of signs of aging, and how our lifestyle, food, and where we live, and how we deal with our environment affects the human body from a scientific point of view.

Chapter one:

Factors that control aging

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Factors that influence aging can be categorized as external (extrinsic) and internal (intrinsic) factors.

1. External (extrinsic) for aging

Several external triggers the way you age. they may be environmental factors or your own lifestyle choices. these are few of them**. (Fig. 1).**

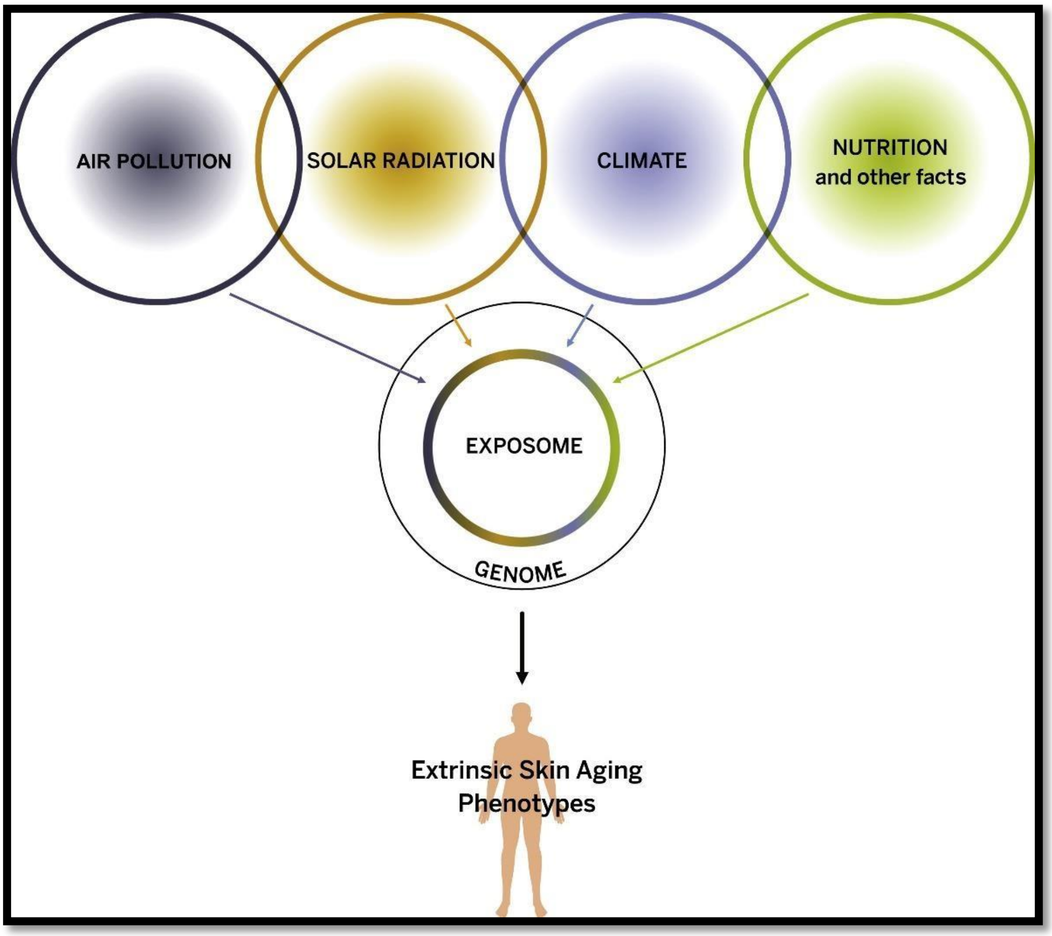

Fig. 1 Extrinsic skin aging phenotypes result from exposure to exposomal factors (Krutmann et al., 2021).

1.1 Sunlight

The effects of sunlight on the skin are profound, and are estimated to account for up to 90%of visible skin ageing **(Martini, 2004; Sudel et al., 2005),** particularly in those without the natural protection associated with higher levels of melanocytes in the skin **(Robinson, 1999).** Sunlight, or the solar spectrum is composed of electromagnetic rays of different wavelengths, ranging from short wavelength, high energy, ultraviolet radiation (UVR) rays to visible light (VL) and to long wavelength, low energy, infrared radiation (IRR) rays **(Fig. 2).** Most of the solar spectrum reaches the skin. Ultraviolet radiation accounts for 5% of the total solar spectrum and is divided into three groups, in order of shortest to longest wavelength; UVC (100–280nm) that does not reach the skin, as it is filtered by atmospheric ozone, UVB (280–315nm), UVA (315–400nm). The latter accounts for most of the UV radiation that penetrates the skin **(Krutmann et al., 2017).**

Sunlight damages skin across a spectrum of physiological processes. UV radiation in the dermis causes a molecular chain reaction which ultimately results in the upregulation, in both dermis and epidermis, of matrix metalloproteinases which stimulate the production of collagenase, gelatinase and stromelysin-1 in both fibroblasts and keratinocytes. The result is a deterioration of both collagen and elastin, as well as other components of the dermal extracellular matrix. Repeated exposure to solar radiation yields repeated, and increasingly faulty, attempts to repair the dermal matrix, with a cumulative effect on the structure and organization of its collagenous foundation. Invisible flaws in the repaired dermal matrix, with repeated cycles of exposure, eventually become visible to the naked eye in the form of sagging skin and wrinkles **(Kang et al., 2003).**

Accordingly, to UV irradiation, IRA irradiation causes an increase in MMP-1 in vitro **(Schieke et al., 2002)** and in vivo **(Schroeder et al., 2010)** with- out a concomitant upregulation of MMP-1 tissue inhibitor. Furthermore, IRA exposure also reduces collagen I expression **(Kim et al., 2006).** IRA irradiation of the skin is mainly absorbed by mitochondria and increases here the intramitochondrial production of ROS **(Schroeder et al., 2007; Darvin et al., 2010).** These ROS then leave the mitochondria, alter intracytoplasmic calcium levels, activate the

MAP kinases signaling pathway and lead to elevated MMP-1 expression **(Krutmann and Schroeder., 2009).** However, approximately 600 genes are IRA responsive **(Calles et al., 2010)** and thus IRA radiation might further induce the extrinsic skin aging process through various other pathways. Up to now it is shown that IRA is able to in- duce angiogenesis **(Chung and Eun, 2007)** and increases the number of mast cells in human skin in vivo, effects which are characteristic for photoaging **(Daniell, 1969).**

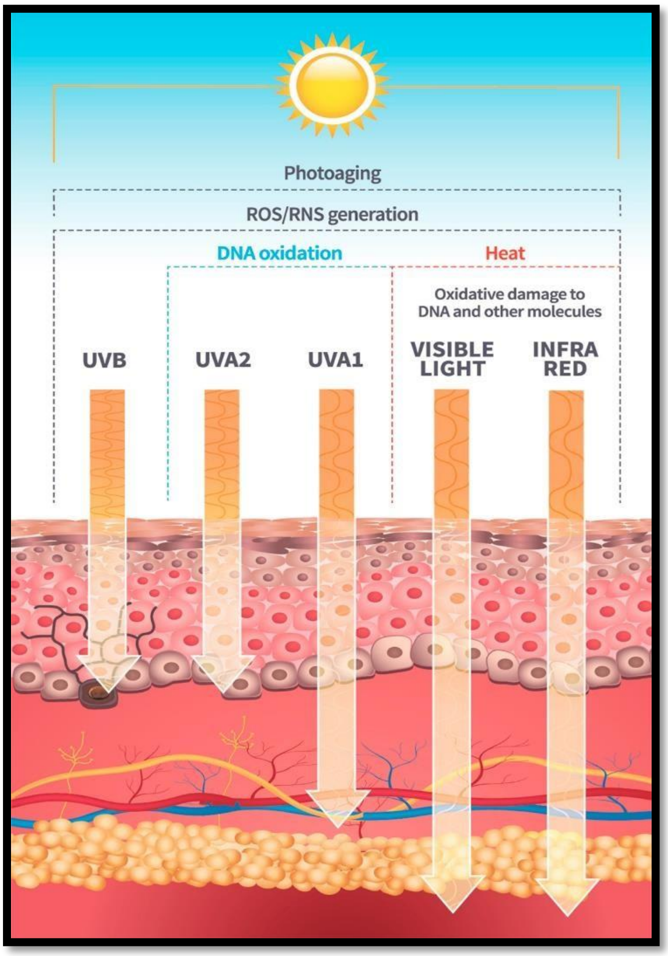

Fig. 2 The solar spectrum is composed of various wavelengths, which penetrate into skin at different levels (Dupont and Gomez, 2013).

Oxidative stress is the primary cause of extrinsic aging or photoaging caused mainly UVR. Other environ- mental extrinsic factors also cause skin aging **(Krutmann et al., 2017).** The principal effects of UVR in the skin are DNA damage, oxidative stress, deleterious impact on the ECM, inflammation, and

Immunosuppression **(Kochevar et al., 2012; Zamarróó et al., 2018).** Oxidative stress is the leading cause of photoaging, and it is involved in several diseases, including cancer **(Kammeyer and Luiten, 2015).** UVR, mostly UV-B radiation, alters DNA by the formation of pyrimidine–pyrimidine dimers (mainly thymine–thymine dimers). Those dimer creations are the basis of mutations in specific genes, including the tumor suppressor gene p53. UV-B radiation also damages DNA through ROS promoting the generation of 8-hydroxy-2′-deoxyguanosine (8-OH-dG), a marker of DNA oxidative damage **(Kochevar et al., 2012).** However, 8-OH-dG is the major UVA-induced DNA lesion **(Kammeyer and Luiten, 2015).**

Ultra violet radiation also initiates damage to the genetic material. UVB primarily acts to create pyrimidine dimers that eventually result in mutation through errors in DNA replication; UVA radiation primarily initiates genetic damage through the creation of reactive oxygen species or free radicals **(Goukassian and Gilchrest, 2004).** However, the excessive production of free radicals has detrimental effects on DNA, collagen, elastin and blood vessels **(Floyd and Carney, 1992).** Oxidative damage to different biomolecules, such as DNA, macromolecules and proteins, takes place over time **(Kumar et al., 2020).** It is considered a significant factor, but is not the only factor responsible for ageing **(Thanan et al., 2014).** Fundamentally, oxygen has a dual role in our body, i.e., it is necessary for life and is one of the chief components of harmful compounds like free radicals **(Sharma et al., 2014).** Free radicals are generated by the aerobic metabolism. They liberate different types of reactive oxygen species, such as singlet oxygen (1[O2]), superoxide anion radicals (O2–), hydroxyl radicals (OH–), hydroperoxyl radicals (HO2), peroxide radicals (R = lipid) (ROO–) and hydrogen peroxide (H2O2) **(Ozcan and Ogun, 2015).**

1.2 Excessive alcohol

Excessive alcohol consumption impacts the body in many ways (e.g., vitamin deficiency, tissue damage, disruption of inflammatory responses, and diminished ability of skin fibroblasts to produce type I collagen)**. (Darvin et al., 2013).**

Alcohol abuse has been reported to reduce fat mass **(Addolorato et al., 2000),** which might underlie the midface volume loss reported by heavy drinkers. The increased under-eye puffiness might have been due to the unveiling of the suborbital fat pad as the midface volume receded. Alcohol impairs the skin’s antioxidant defense system, leaving it more prone to sunburn and the aging effects of ultraviolet light**. (Li et al., 2013; Darvin et al., 2013).**

Chronic alcohol exposure can lead to impairment of a wide range of physiological functions Some of these pathological effects, such as alcohol-induced damage of liver and pancreas functions, appear to result directly from alcohol’s toxic effects on those organs. Other health problems associated with chronic alcohol use (e.g., cardiovascular disease, sleep disorders, gastrointestinal dysfunction, and increased susceptibility to infections), however, appear to be less specific in nature **(Colsher and Wallace, 1990; Brower et al., 1994).** In fact, theseeffects, which vary from person to person, may represent an accelerated or exaggerated aging process.

1.3 Stress

Psychological stress arises when people are under mental, physical, or emotional pressure. It arises when the individual perceives that the pressure exceeds his adaptive power. It is perceived by the brain and stress hormones such as corticotropin-releasing hormone (CRH), glucocorticoids, and epinephrine are released. This triggers a wide range of physiological and changes and responses that try to adapt the body to the stress **(Papadimitriou and Priftis, 2009)**.

The stressor also triggers the activation of the hypothalamic- pituitary-adrenal (HPA) axis, which begins with the activation of the parvocellular neurons in the paraventricular nucleus of the hypothalamus (PVN). The release of corticotrophin releasing hormone (CRH) from the PVN leads in turn to the release of adrenocorticotropic hormone (ACTH) from the hypothalamus. ACTH will be delivered into the blood- stream, reaching the adrenal cortex and promoting the release of glucocorticoids (GCs) into the blood **(Fig.3) (Armario, 2006)**.

Chronic psychological stress stimulates the autonomic nervous system, renin-angiotensin system, and the hypothalamic-pituitary-adrenal axis. This prolonged activation can result in chronic immune dysfunction, increased ROS production, and DNA damage, which are known contributors to skin aging, although the underlying mechanisms have not yet been clearly define **(Dunn and Koo, 2013).** Feedback mechanisms and crosstalk between the brain and the skin, have also been found and pro-inflammatory cytokines and neurogenic inflammatory pathways participate in mediating these responses **(Chen and Lyga, 2014)** The by-products of these systems (like cortisol, catecholamines and neuropeptides) can have an impact on the immune system **(Chen and Lyga, 2014).**

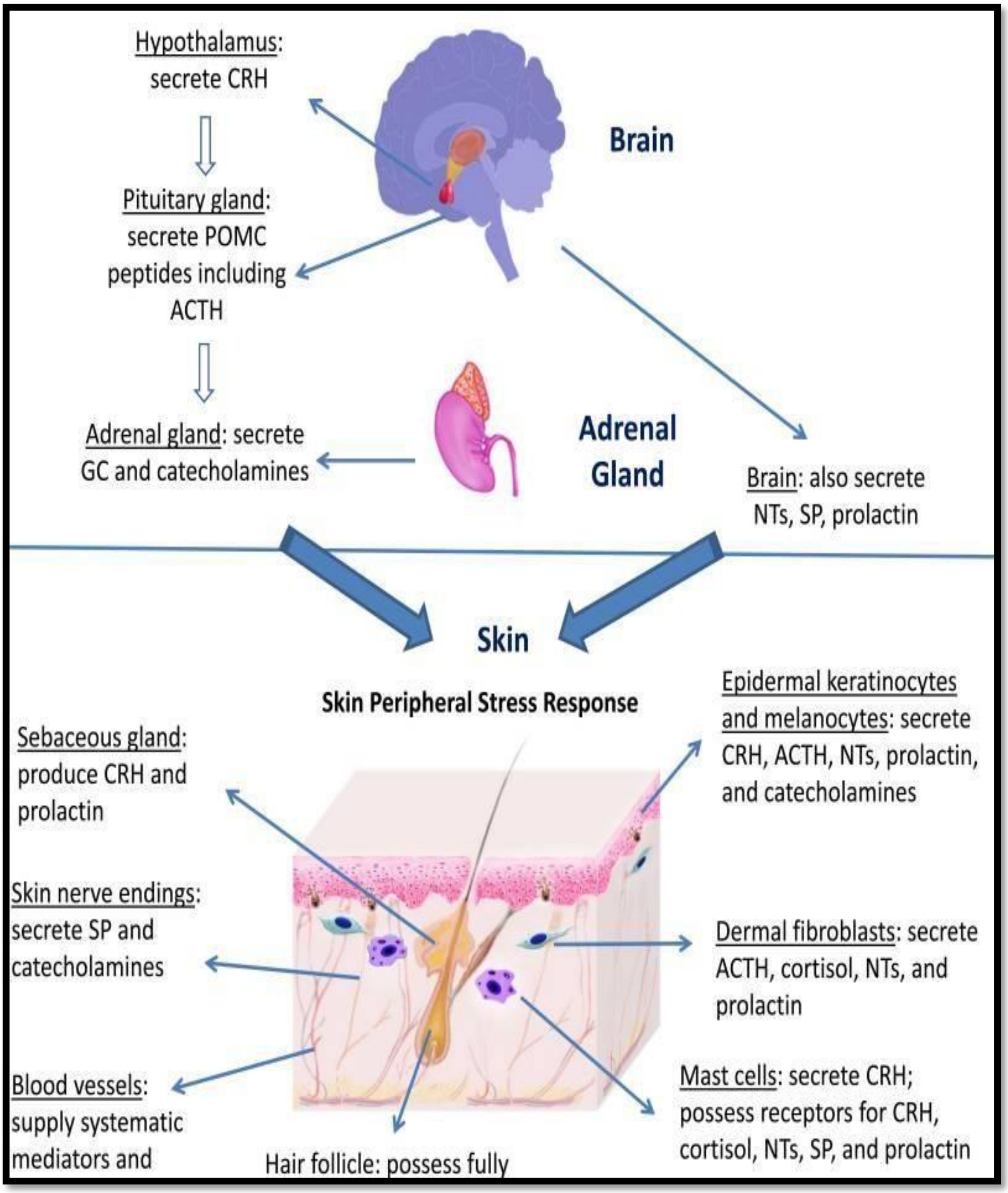

Fig.3 Central stress response and skin peripheral stress response (Chen and lyga, 2014).

1.4 Facial exercises

many regions of the face, the facial vasculature demonstrates an intimate relationship with the SMAS, particularly in the jawline, perioral, nasolabial fold, infrabrow, and temple regions **(Surek, 2019).** The mimetic muscles connect the dermis to the deep facial structure and function to create facial expressions by contraction. The masticatory muscles connect bone to bone and influence the mandible movement **(Ezure et al, 2009).**

Dynamic (expression) lines of the skin are the result of muscle contraction in the SMAS layer. The skin, superficial fat, and muscle layers are tightly bound to each other, and muscle contraction gives rise to wrinkles in the skin, perpendicular to muscle fibers' direction. These are transient in youth but become permanent due to skin atrophy, superficial fat loss in some areas, and muscle hyperactivity. Wrinkles due to muscle actions are predictably observed in the glabella, forehead, periocular, and perioral regions, the chin, and depressor anguli oris (DAO) territories. The clinical effect of these changes is due to a general tightening of the facial muscles, with a limited amplitude of facial expression. These permanent contractures result in a potential shifting of fat, an accentuation of skin creases, and permanent skin wrinkling. The dynamic facial lines eventually evolve into lines of a static nature **(Cotofana et al, 2016).** It is essential to know a muscles' location and depth to understand the dynamic movements of the face that displace the filler and make it visible with the action of the muscles **(Tamura, 2010).**

1.5 Unhealthy diet

Dietary habits refer to the preference for food or drink, are an important part of the dietary culture and influenced by regional, historical, cultural, product, and other factors. Although the incidence of vitamin, trace elements, and protein deficiencies in developed western countries are very low, imbalanced or incomplete diet can also lead to diseases and aging, thereby affecting skin health. Data from epidemiological and experimental studies suggest an important role of diet and dietary patterns in the pathogenesis of many age-related diseases (**Hanjani and Vafa, 2018**).

A high-fat diet is closely related to various diseases such as obesity, diabetes, fatty liver, and skin aging. Raman spectroscopy studies have shown that dietary fat intake is closely related to the body's adipose tissue and the lipid composition of the skin **(Meksiarun et al., 2015).** High-fat diets delay healing of the skin by promoting skin oxidative stress and inflammatory responses, reducing protein synthesis, and may also cause morphological changes in skin and damage to matrix remodeling (**Rosa et al., 2017).**

Seafood (fish + shellfish) is a nutrient-rich lean protein food and is a component of many healthy eating patterns **(Bach-Faig et al., 2011; Lloyd et al., 2010; Sacks et al., 1995).** Consumption of seafood, particularly fish, is associated with reduced risk of cardiovascular disease **(Kris-Etherton et al., 2002; Raatz et al., 2013).** While benefits are often ascribed to the long chain n -3 fatty acids found in fatty fish, Omega-3s, used both orally and topically, can improve the skin's ability to repair itself from damage as well as protect against UV damage and hence had a potent anti-aging effect. People who are deficient in omega-3s will experience the loss of moisture content in the skin as well as a higher incidence of eczema, psoriasis, and dermatitis.

Dietary restriction in humans causes changes that protect against many age-related pathologies **(Fontana et al., 2010).** In contrast, obesity increases the risk of chronic age-related diseases, such as type 2 diabetes, heart disease, osteoarthritis, and certain types of cancer, and thus constitutes a major and rising global health problem **(Haslam and James, 2005).** It is a plausible hypothesis that obesity increases the risk of at least some of these diseases through accelerated tissue aging **(Fig. 4).**

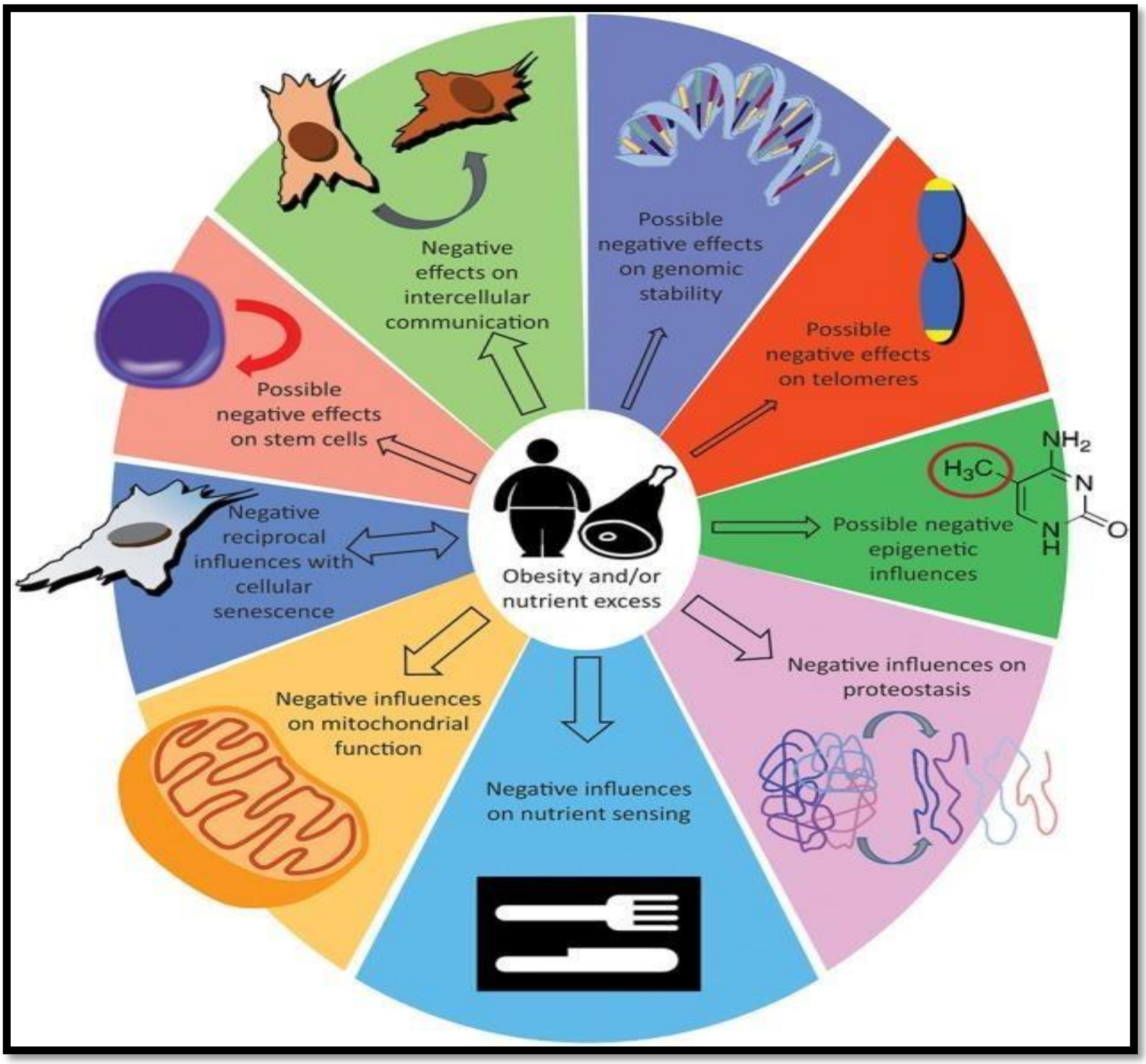

Fig. 4 Effect of obesity or nutrient excess on the hallmarks of aging (Salvestrini et al., 2019).

Some studies have also shown a close association between sugar and some food processing methods (such as grilling, frying, baking, etc.) with skin aging, and their mechanisms are related to skin advanced glycation end products. A high-sugar diet, ultraviolet irradiation, and eating barbecued fried foods, lead to the accumulation of AGEs and acceleration of skin aging. However, strict control of blood sugar for four months can reduce the production of glycosylated collagen by 25%, and low-sugar food prepared by boiling can also reduce the production of AGEs **(Nguyen and Katta, 2015; Draelos, 2013; Danby, 2010).** Further, high-salt, spicy, and extremely vegetarian diets are also considered to be detrimental to skin health. Therefore, scientific, rea- sonable, healthy, and diverse eating habits and eating some antioxidant-rich foods are essential to maintaining skin health.

Vitamin deficiency affects skin health. The lack of vitamins in the body can cause skin disorders. For example, lack of vitamin C causes the symptoms of scurvy such as fragile skin and impaired wound healing. Vitamins, as skin antioxidant defense ingredients, are mostly taken from food, so the content of vitamins in the diet is closely related to skin antioxidant capacity and physiological functions. **(Alqanatish et al, 2015., Ellinger and Stehle, 2009., Evans and Lawrenson, 2017).**

1.6 Pollution

The human skin, and mainly the upper layer of the epidermis, plays the role of a barrier, but is also one of the first and major targets of air pollutants. Air pollutants include those of environmental origin, as well as those of anthropic origin **(Valacchi et al., 2012).** Major air pollutants with effects on the skin include the solar ultraviolet radiation (UVR), polycyclic aromatic hydrocarbons (PAHs), volatile organic compounds (VOCs), nitrogen oxides (NOx), particulate matter (PM), and cigarette smoke. The actions of various air pollutants may be amplified in the presence of other air pollutants and with the interaction of UVR, and form major active components of the pro-oxidant smog **(Baudouin et al., 2002; Katsouyanni, 2003; Kampa and Castanas, 2008).**

Three mechanisms seem to be involved in the adverse effects of ambient air pollutants on skin health: a) the generation of free radicals; b) the induction of an inflammatory cascade; and c) the impairment of the skin barrier **(Fig .5).** Thus, chronic exposure to O produces oxidative damage in the stratum corneum, which generates free-radical species. Also, O depletes the reserves of both enzymatic and non-enzymatic antioxidants in the skin and decreases vitamin C and E levels. In the mitochondria, O decreases ATP and sirtuin 3, a protein related to the elimination of free radicals. Also, the other air pollutants promote oxidative stress and a proinflammatory environment in the skin. The inflammatory mediators activate the chemotaxis of granulocytes and phagocytosis. The response to environmental stressors also activates cutaneous and central neuroendocrine responses. Epidermal keratinocytes, Langerhans cells, melanocytes, and dermal cells such as fibroblasts, macrophages, mast cells, and lymphocytes may be involved in skin cutaneous neuroendocrine responses. On the other hand, extrinsic factors can alter skin immunity and the immune system of skin interacts with the neuroendocrine responses **(Slominski et al., 2012; Slominski et al., 2018).**

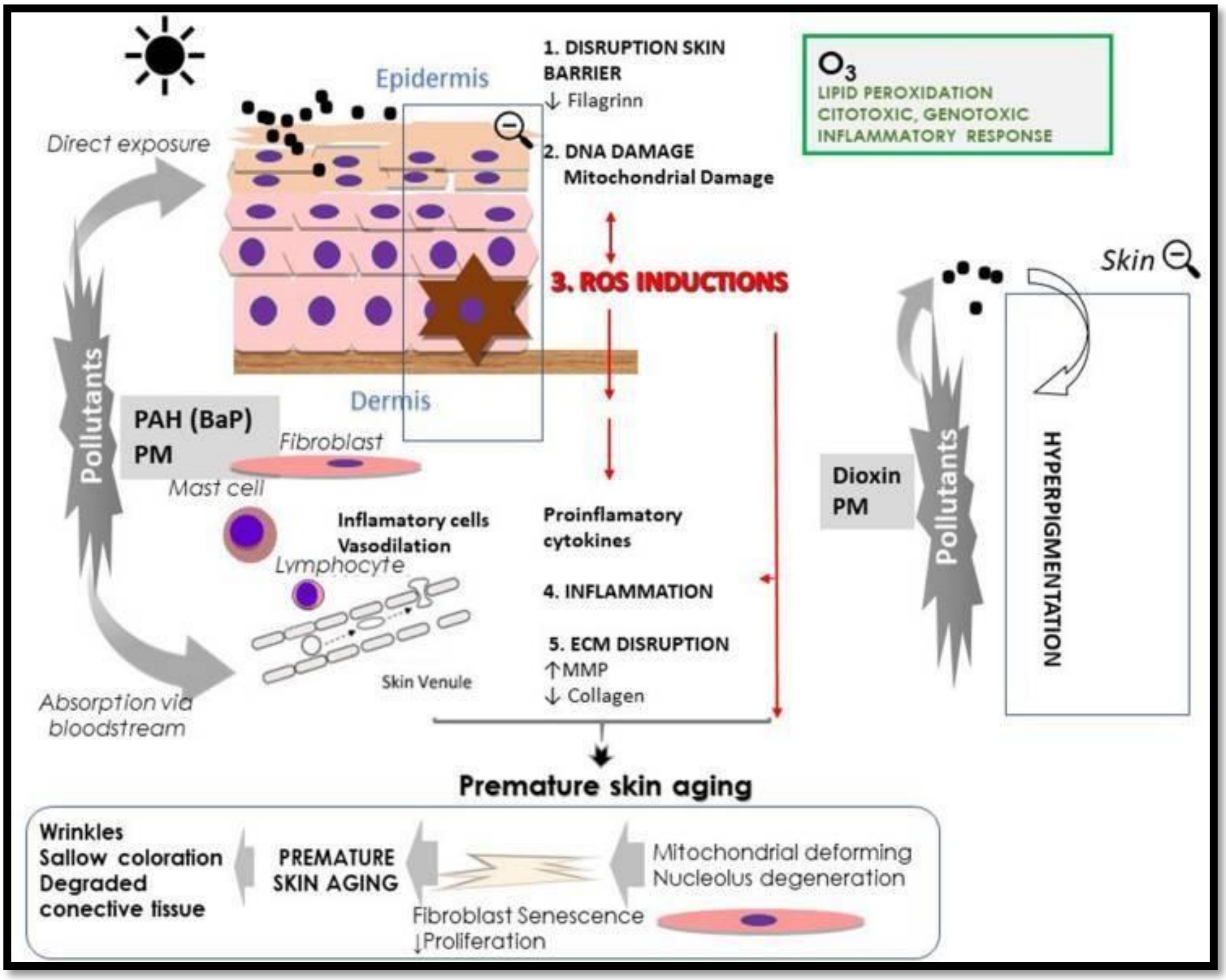

Fig .5 Skin responses to air pollutions (particulate matter, PM; polycyclic aromatic hydrocarbons PAH; and ozone, O) and ultra-violet radiation (parrado et al, 2019).

1.7 Cigarette smoking

Cigarette smoke is another exposomal factor that contributes to extrinsic skin aging **(Krutmann et al., 2017).** The major skin-aging effect of cigarette smoke is skin wrinkling, particularly around the mouth, the upper lid, and eyes **(Fig 6) (Aizen and Gilhar, 2001; Doshi et al., 2007; Koh et al., 2002),** and MMP-1 mRNA expression, as a surrogate marker of increased collagen breakdown, is increased in smoker's skin compared with that in nonsmoker's skin **(Lahmann et al., 2001).** Mechanistic studies indicate a role for AHR signaling and disturbed TGFβ signaling in cigarette smoke–induced collagen breakdown **(Ono et al., 2013; Yin et al., 2003).**

Fig. 6 Effects of smoking on facial skin (Used by permission from Lippincott, Williams and Wilkins, 2008).

Cigarette smoking, is well-known to generate not only systemic health complications but also cause premature aging of the skin. Smoking increases oxidative DNA modifications, inter- feres with the dynamic of telomeres and with the activity of human telomerase reverse transcriptase(hTERT) **(Lotfi et al,**

2014), where he described a higher percentage of negative hTERT in the skin of smokers, but a higher percentage of positive hTERT expression was observed among non-smokers, despite non-significant levels. Thus, the potential effects on telomerase activity of smoking could possibly contribute to skin aging processes. Other studies have shown long-term smoking association to cutaneous microvascular dysfunctions **(Rossi et al., 2014)** and marked changes in the skin temperature and oxygen content on the face **(Fan et al., 2012).**

1.8 Climate

Climate When discussing climate impact on skin health, it is important to define a dermatological impact of season variations and global climate change, often in a connection to geographical zone. Seasonal variations have a big impact on skin appearance and texture. Especially during the winter in northern countries, the risk of skin concerns, such as dermatitis, is increasing due to low temperature and humidity **(Engebretsen et al., 2016).**

Seasonal variations various skin parameters have been reported in several cities in Asia. Generally, pigmentation and wrinkles were reduced in the winter compared to the summer, while other features such as skin barrier and moisture, for instance, worsened **(Galzote et al., 2014).**

The skin is the barrier between the rest of the body and its environment; thus, it is expected that cutaneous alterations may occur in a response to climate change. Drier environmental conditions in- crease the permeability of the epidermis **(Denda et al., 1998),** with lower humidity that stimulates the production of epidermal inflammatory mediators and promotes hyperproliferative response **(Ashida et al., 2001; Singh and Maibach, 2013).** Moreover, cold temperatures and dry conditions have been linked to a higher rate of irritations **(Engebretsen et al., 2016).** Daily skin exposure to a low-humidity environment induces a lower watercontent in the stratum corneum and accentuates fine wrinkles related to skin dryness **(Egawa et al., 2002).**

2. Internal (intrinsic) factors for aging

2.1 Genetics and origin

Ethnic Skin Physical and biological phenotypes of the skin aging processes manifest differently between diverse ethnic populations **(Del Bino et al., 2018).** Chinese women exhibit notably lower pore size and density across all the age groups compared to other ethnicities **(Sugiyama-Nakagiri et al., 2009).** Highly pigmented skin individuals have aberrant epidermal architecture, with stalagmite-like structures at the dermo-epidermal junctions, correlating with an enlarged pore size compared to individuals from other ethnicities **(Lee et al., 2016).**

Research shows that wrinkles appear at early stages in Caucasian, compared to other ethnic groups. In fact, Chinese women exhibit a prevalence of pigmented spot and a delayed appearance of wrinkles by 10 years, when compared with French women **(Fig 7) (Nouveau-Richard et al., 2005).** Highly pigmented skin individuals have smaller collagen fiber bundles but larger nucleated fibroblasts compared to Caucasian skin individuals **(Montagna and Carlisle, 1991).** Compared to Caucasian skin, Asian and dark skin tone have much thicker and structurally more compact dermis. This could be one of the reasons why Asians and dark skin tone individuals have lower incidence of facial rhytids **(Vashi et al., 2016).** Furthermore, stratum corneum of darker skin types exhibits a higher lipid content and more cornified cell layers compared to the lighter skin **(Berardesca et al.,1991)**. Studies have also highlighted ethnic differences in the elastin fiber networkand in TGF-β signaling in African American and Caucasian skin. African Americans have less UV dependent damage in elastin than Caucasian subjects **(Fantasia et al., 2013).** have studied Asian populations and found declined skin elasticity, epidermal cell turnover, and an increase in collagen cross-links with progress in age, which, in turn, increased the collagen cross-links and are widely associated with advanced glycation end products (AGE), one of the major factorsinhibiting skin repair and cell turnover **(Galzote et al., 2014; Couturaud et al., 1995).**

The most striking dissimilarities when comparing Caucasian's skin to darker skin color are both the quantities of melanin and proportions **(Alaluf et al., 2001).** Higher skin melanin content provides a stronger advantage against UV rays, photo aging, and cancer. At the same time, darker skin is more prone to be sensitive to hypopigmentation, making uneven skin a typical sign of photoaging on dark skin tone people **(Kaidbey, 1979).** Uneven pigmentation is more frequent and appears earlier in Japanese women than in Frenchwomen **(Hillebrand and Miyamoto, 2001).** Autophagy is another key contributor to the ethnic skin color diversity. It has been documented that keratinocyte derived from Caucasian skin exhibit higher autophagic activity than those de- rived from African American skin **(Murase et al., 2013).** With age, both Caucasian and Asian skin becomes darker, but Caucasian skin tone tends be redder while the Asian one tends to be more yellow. Skin redness is due to changes in the microvasculature of the dermis, mostly at the cheekbone area **(Halder and Richards, 2016).** One interesting study was conducted between different ethnic groups to define skin barrier properties. By measuring the trans epidermal water loss (TEWL), it has been demonstrated that Caucasian skin had strong barrier proper- ties, followed by African, Chinese, andfinally Indians **(Voegeli et al., 2015).** studied the differences in conditions of ethnic skin to characterize its susceptibility to oxidative stress. The findings show variations of susceptibility to oxidation (melanin content and catalase activity in the skin) contributed to better skin conditions in Japanese subjects compared to French subjects **(Yamashita et al., 2012).**

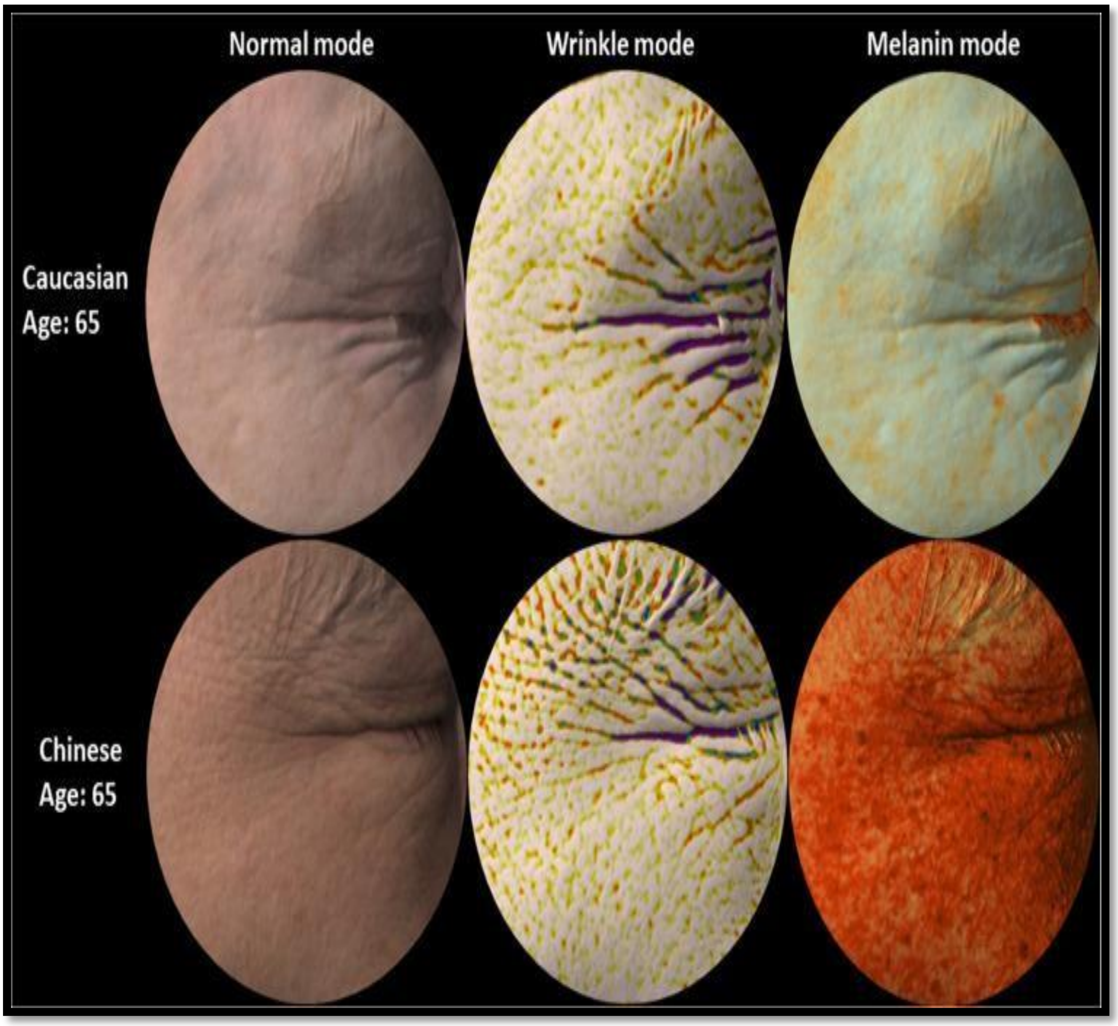

Fig. 7 Representative images of Caucasian and Chinese skin (Khmaladze et al., 2020).

2.2 Gender and life stages

Hormones and gender specific factors may also play an important role in skin morphology and aging process, respectively. Hand male skin has a thicker dermis than females but has a thinner hypodermis, thus suggesting the influence of gender-related hormones **(Makrantonaki et al., 2012).** One interesting study in- volving whole genome screening of sun-protected skin areas show an overlap of just 39 genes, thus pointing out how the process of aging may differ between males and females **(Makrantonaki et al., 2012).**

Androgens may play a substantial role in skin morphology. This fact has been described in several animal and human studies, which have documented gender-specific characteristics of the skin structure. A comparison between male and female mouse dorsal skin revealed that the dermis in the male is much thicker than in the female (+190%, $p < 0.01$). In contrast, epidermis and subcutaneous tissue are thicker in the female (+40%, $p < 0.01$ and 11-fold, $p < 0.01$, accordingly), thus resulting in total skin that is 40% thicker in the male. In addition, significant larger sebaceous glands were observed in males (+45%, $p < 0.01$) **(Azzi et al., 2005).** In females, gonadectomy resulted in a decrease of epidermalthickness (-40%, $p < 0.01$), an increase of the dermal thickness (+22%, $p < 0.05$)and of the thickness of the hair shaft. Our own data **(Makrantonaki et al., 2012).** correspond to previous studies showing that in humans, male skin is thicker than female skin, while females have thicker subcutaneous tissue and provide evidencethat androgens and their decline with age may play a significant role in the regulation of the dermis and the hair shaft thickness. A comparison between male and female sun-protected skin derived from the inner side of the upper arm revealed that the male der- mis is much thicker than the female one (1.8-fold, $p <0.05$). In contrast, epidermis and subcutaneous tis- sue is thicker in the female (3.5-fold, $p < 0.05$ and 10-fold, respectively) **(Fig.8) (Seidenari et al., 1994).**

Some researchers shed light on gene mutation–caused progeroid syndromes, such as Hutchinson-Gilford progeria syndrome (HGPS), Werner syndrome, Rothmund Thomson syndrome, Cockayne syndrome, ataxia-telangiectasia, and Down syndrome **(Makrantonaki et al., 2012).** Gene mutation is inherited and causes progeria, a type of premature aging, often showing accelerated skin aging phenotype, including skin atrophy and sclerosis, poikiloderma, alopecia, thinning, and graying of the hair **(Makrantonaki et al., 2012),** for example, HGPS is caused by the mutation of gene LMNA **(Gonzalo et al., 2017),** which produces progerin, a mutant protein that impairs many important cellular processes **(Vidak and Foisner, 2016)**. More work is being done to try to gain insight into genetic variation during the aging process. In2014 and 2017, different groups identified single-nucleotide polymorphisms associated with skin aging in Caucasians and the Chinese Han population, respectively **(Naval et al., 2014; Gao et al.,2017).**

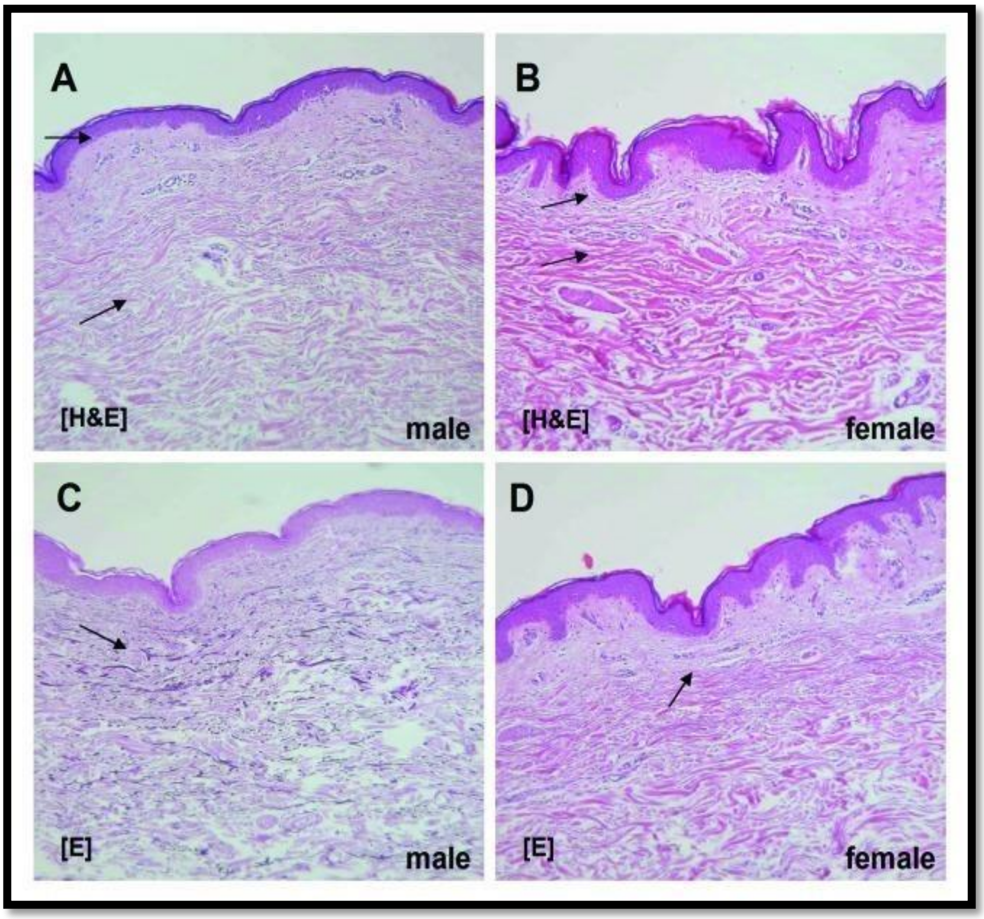

Fig. 8 A comparison between male (A and C) and female (B and D) endogenous aged skin (Makrantonaki et al., 2012).

Life stages habits have cumulative effects on skin aging and cause diseases, so we will talk about how they affect skin aging.

Lack of physical activity, that is, inactivity, accelerates the physiological changes that occur with the aging process, increases the frequency of many chronic diseases, enables these diseases to be seen at an earlier age, in short, it accelerates old age and shortens the life span. Regular physical activity has positive effects on the function of many systems and organs. It has been shown that regular exercise increases the life expectancy and quality of life even in people who did not do regular physical activity until old age. It has been scientifically proven that physical activity has many positive effects **(Ferhan, 2021).**

Consistent lack of sleep is another factor that leads to damaging inflammation and premature aging. Not only does poor sleep negatively impact your skin, making you look older than you actually are, it's one of the worst offenders for accelerated aging — especially where your brain is concerned **(Ferozan, 2021).**

If you're not applying a facial moisturizer daily, you're overlooking an effective first responder to the most visible signs of aging. "Moisturizer traps water in our skin, giving it a more youthful appearance," says the American Academy of Dermatology. For maximum anti-aging effect, choose a moisturizer with sunscreen, which can protect your face from photoaging caused by the sun. You'll want one that's at least 30 SPF and blocks both UV-A and UV-B light **(Michael, 2021).**

Chapter two:

Prevention of aging

Chapter two: Prevention of aging

Skin aging is a complex biological process influenced by a combination of endogenous or intrinsic and exogenous or extrinsic factors. and diet is the main way for the body to obtain the required substances for growth and maintenance. as we have previously agreed, wrong eating habits are the primary responsible for the occurrence of early aging, whether for the external appearance of the body or its internal functions. and diet is the main way for the body to obtain the required substances for growth and maintenance, and there are some foods that are very effective in treating premature aging, as the nutrients in these foods help in slowing down the signs of aging.

After we touched on one of the ways to fight aging, which is fighting aging with nutrition, we must now refer to some other ways that contribute significantly to fighting aging and preventing it. Because of the fact that skin health and beauty is considered one of the principal factors representing overall “well-being” and the perception of “health” in humans, several anti-aging strategies have been developed during the last years. So, we will talk about the most important anti-aging strategies that dermatologists have nowadays in hand, including preventive measurements, cosmetological strategies, topical and systemic therapeutic agents and invasive procedures. **(Ganceviciene et al., 2012).**

1. Skin care

Healthy and functioning skin barrier is important protector against dehydration, penetration of various microorganisms, allergens, irritants, reactive oxygen species and radiation. The skin barrier may be specifically adjusted to allow penetration. For this reason, daily skin care may increase skin regeneration, elasticity, smoothness, and thus temporarily change the skin condition **(Tabata et al., 2000; Lüübbe, 2000).** However, it is necessary to stop the degradation of the skin primary structural constituents, such as collagen, elastin, to prevent the formation of wrinkles. Although the technology required to suitably deliver these compounds into the skin has not yet been developed, some products do promote the natural synthesis of these substances except elastin enhancing **(Varani et al., 2000; Margelin et al., 1996).** Another integral approach preventing wrinkle formation is the reduction of inflammation by topical or systemic antioxidants which should be used in combination with sunscreens and retinoids to enhance their protective effects **(Baumann, 2007).**

1.1 Cosmetological care

Cosmeceuticals are topical cosmetic—pharmaceutical hybrids intended to enhance health and beauty through ingredients that influence the skin's biological function **(Grace, 2002).** The various topical application products that delay and/or reverse visible signs of aging are termed anti-aging cosmeceuticals. Research trends in anti-aging skin care products are moving towards developing new plant extracts and botanical ingredients based on their traditional medicinal uses **(Roehl, 2000).** These antiaging products are not classified as prescription drugs or regulated by the Food and Drug Administration, but produce changes in skin structure or function. Examples include the alpha and beta hydroxy acids, which are generally found in over-the-counter preparations at relatively low concentrations (3–15%) and may be used to exfoliate the skin, increase cell turnover, and reduce fine wrinkles and mottled hyperpigmentation **(Stiller et al., 1996).**

In recent times, skin health and beauty have been perceived as an indicator of one’s health, which has resulted in an increasing demand for more and more advanced skincare products. UV protectants are amongst the most efficacious products to prevent photo-aging, hyperpigmentation, and skin cancer **(Shanbhag et al., 2019).** Even though not being recognized as a term, cosmeceuticals refer to cosmetics that deliver a physiological skin benefit through either pure chemicals or natural active ingredients **(Lorencini et al., 2014; Cherubim et al., 2020)**. These are being used in anti-aging, barrier function improvement, anti-inflammatories, UV/pollution protection, and moisturization.

1.2. Treatments for Skin Aging

As age progresses, the skin tends to become dry and scaly, especially in the elderly. So, it becomes important to use a barrier to preserve this vital layer. Protection against dehydration, preventing the penetration of irritants, microorganisms, allergens, radiation, and protection against the reactive oxygen species requires a healthy and functioning skin barrier. Penetration via the skin can be regulated to allow selective penetration of substances which helps in skin regeneration, maintaining smoothness and elasticity **(Ganceviciene et al., 2012).** Some of the practices that can improve the skin conditions are drinking more water, eating healthier foods, reducing stress, using sunblock and exercising more. Another approach is the use of topical or systemic antioxidants which helps in the prevention of wrinkles by reducing inflammation. Some of the skin care approaches are discussed below **(Shreya et al., 2019).**

1.1.1 Stem Cell Therapy

Stem cell transplantation is a promising therapy for the treatment of skin aging. Adipose tissue transplantation could improve skin quality at the recipient site in addition to increasing skin volume **(Mojallal et al., 2009)**. Further experiments demonstrate that adipose-derived stem cells (ADSCs) contribute to the regeneration of skin during aging **(Kim et al., 2008; Zhang et al., 2014).** In recent clinical tests, autologous fat grafting rejuvenates aging skin and enhances the volume of periocular and perioral skin in recipients with an average age of 50 al.; years **(Bernardini et al., 2015; Gennai et al., 2017).** Data show that ADSCs produce a series of growth factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), transforming growth factor (TGF)-β1, TGF-β2, hepatocyte growth factor (HGF), keratinocyte growth factor (KGF), platelet-derived growth factor AA (PDGF-AA), and placental growth factor (PGF) **(Park et al., 2008)**, reminding us that ADSCs may influence surrounding cutaneous cells through these secretions. It seemed that ADSC may also transdifferentiate into epithelial stem cells that express epithelial stem cell marker p63 after fat grafting **(Derby et al., 2014).**

The most widely used technique for the extraction of stromal vascular fraction (SVF), from which adipose-derived stem cells (ADSCs) can be subsequently isolated, is enzymatic and involves the following steps: fat harvesting by liposuction ,washing with phosphate-buffered saline, enzymatic digestion with collagenases at 37 °C to release the cell mixture embedded in the extracellular matrix between adipocytes, and centrifugation to separate the SVF (lower cellular pellet) from the floating mature adipocyte fraction. Both SVF and Invitro -expanded ADSCs can be injected for the local treatment of facial and hand cutaneous lesions of systemic sclerosis patients **(Fig.9) (Rosa et al., 2021).**

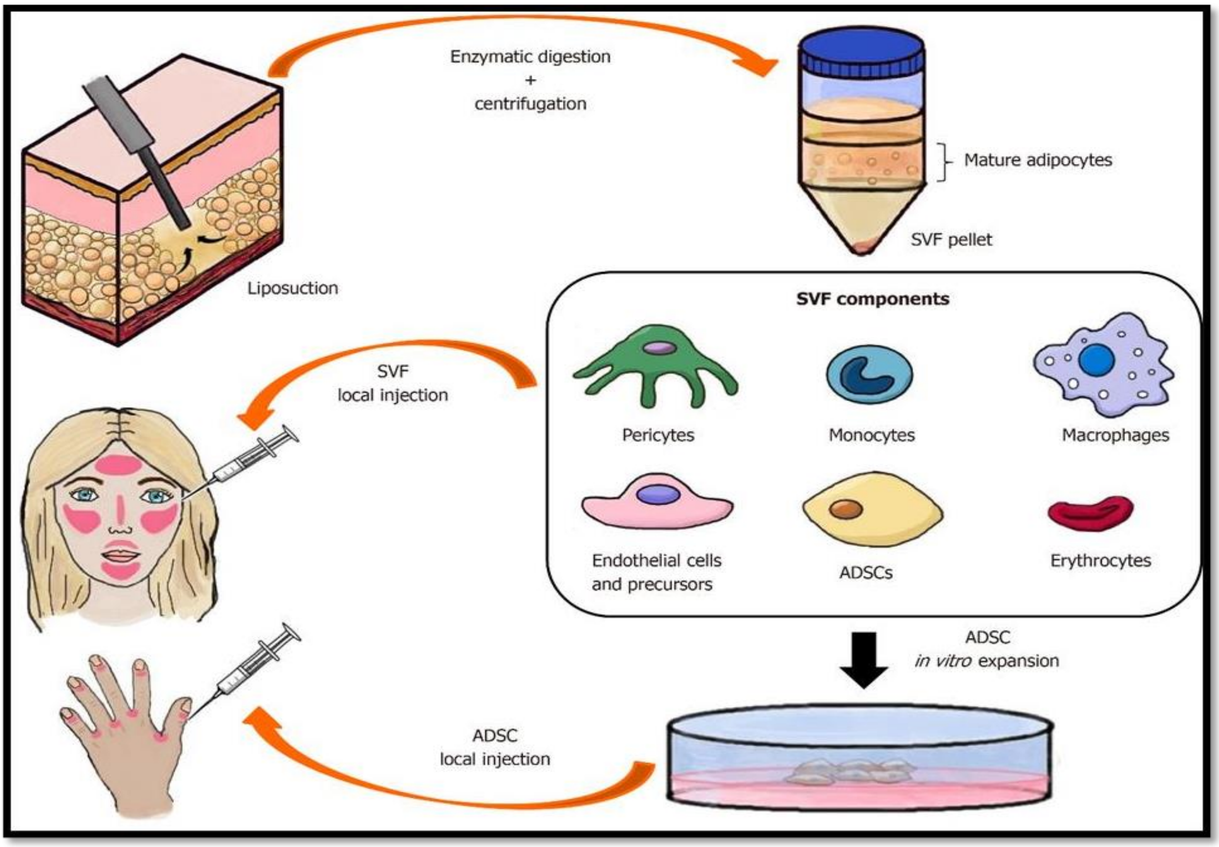

Fig. 9 Technique for the extraction of the stromal vascular fraction from white adipose tissue and subsequent adipose-derived stem cell isolation (Rosa et al., 2021).

1.1.2 Retinoids

Retinoids are chemically similar to vitamin A, and tretinoin is the first retinoid approved for clinical use **(Fisher et al., 1996).**

Further studies on retinol activity in various cosmetic formulas are required in order to select the one that is best tolerated by the skin and to determine whether the concentration significantly influences the effect it exerts on the skin. Natural retinoids have a positive effect on the skin parameters. They are characterized by good absorbability (they are fat-soluble) which improves the skin function. Retinoids boost production of epidermal proteins and accelerate the process of keratinization, forming a layer of keratin which is more developed. Retinol penetrates into the basal layer of the epidermis (composed of living (nucleated) cells that are constantly producing new cells) as well as to a small extent, into the dermis and marginally to the subcutaneous tissue. In the case of retinol applied topically, there is an interaction with specific nuclear receptors. Retinol makes the connections between epidermal cells mor loose and facilitates keratosis. What is more, it enhances epidermis turn-over and accelerates proliferation of the basal layer of epidermal cells and the stratum corneum. In keratinocytes, proliferation AP-1 transcription factor, exposed to various stimulants, growth factors and cytokines, plays a major role. In retinol-treated aged human skin, AP-1 complex is comprised of c-Jun/c-fo s and c-Jun transcription factor was increased **(Shao et al., 2017).**

1.1.3 Chemical Peels

Chemical peels are methods to cause a chemical ablation of defined skin layers to induce an even and tight skin as a result of the regeneration and repair mechanisms after the inflammation of the epidermis and dermis. Chemical peels are classified into three categories **(Monheit and Chastain, 2001; Fischer et al.,**

2009). Superficial peels [α-β-, lipo-hydroxy acids (HA), trichloroacetic acid (TCA) 10–30%] exfoliate epidermal layers without going beyond the basal layer; medium-depth peels (TCA above 30 to 50%) reach the upper reticular dermis; deep peels (TCA >50%, phenol) penetrate the lower reticular dermis. The depth of peeling depends not on the substance used only, but on its concentration, pH of the solution and time of application **(Fischer et al., 2009).** A number of skin modifications have been reported after several weeks: epidermal architecture returns to normal; melanocytes are present and distributed uniformly, basal cells contain small melanin grains distributed homogeneously, the thickness of the basal membrane is homogeneous, in the dermis, a new subepidermal band of collagen appears, elastic fibers form a new network, often parallel to those of collagen **(Brown et al., 1960).** If superficial peelings target the corneosomes, cause desquamation, increase epidermal activity of enzymes, lead to epidermolysis and exfoliation **(Fartasch et al., 1997; Deprez, 2007).**

Dermatologists frequently use chemical peels to treat an array of cutaneous conditions, including acne vulgaris, actinic or solar keratoses, melasma and scarring. This technique has also been used to rejuvenate the skin of the face, neck, trunk and hand. Peeling agents may be divided into superficial, medium-depth and deep subtypes based on the depth of their penetration **(Fig.10).** They may be used alone or in combination with other cosmetic procedures for cutaneous aesthetic enhancement **(Connor et al., 2017).**

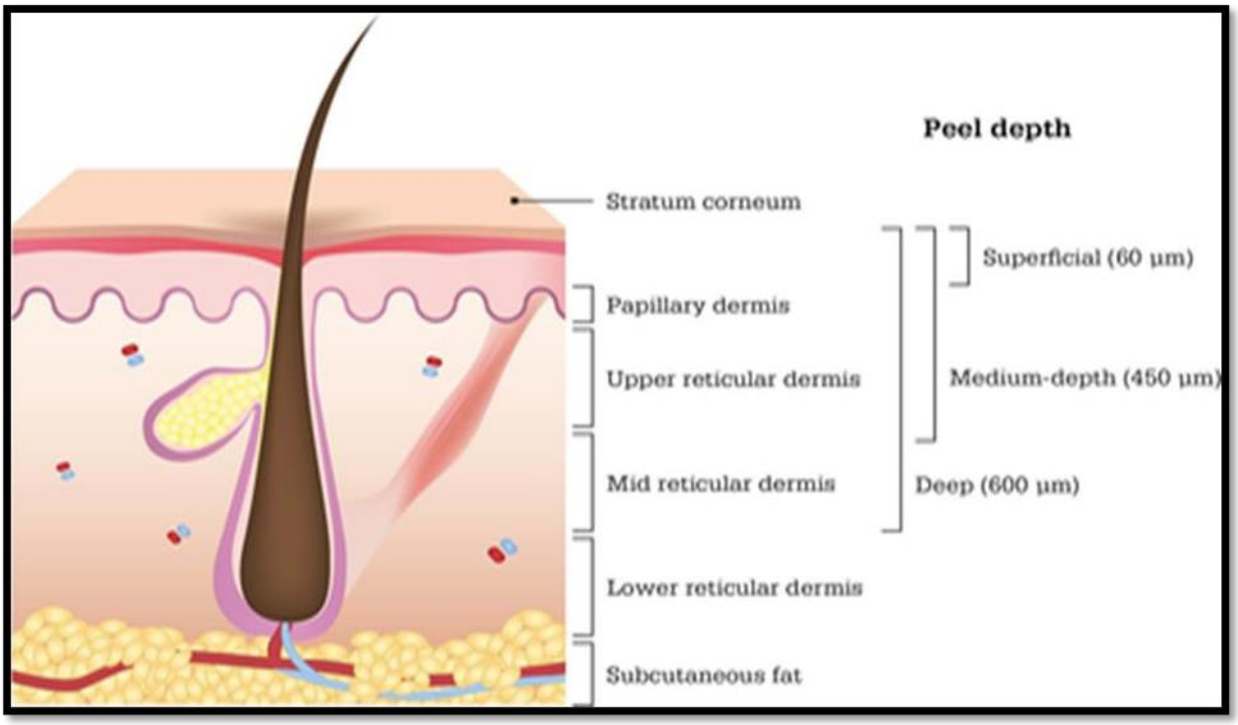

Fig. 10 Depth of chemical peel penetration (Connor et al., 2017).

1.1.4 Injectable Skin Rejuvenation and Dermal Fillers

The goal of skin bio rejuvenation is to increase the biosynthetic capacity of fibroblasts, inducing the reconstruction of an optimal physiologic environment, the enhancement of cell activity, hydration, and the synthesis of collagen, elastin and HA (hyaluronic acid) **(Iorizzo et al., 2008).** Products injected within or beneath the skin to improve its physical features by soft tissue augmentation are known as fillers **(Eppley and Dadvand, 2006; Klein, 2006).** There are autologous (fat, cultured human fibroblasts), collagen (bovine-derived, human-derived from tissue culture), HA (nonanimal stabilized or viscoelastic HA from bacterial fermentation), synthetic or pseudo-synthetic implants (silicone, polymethacrylate microspheres, poly-L-lactic acid, calcium hydroxyl apatite microspheres suspended in aqueous polysaccharide gel, alkyl-imide gel polymer). These may be grouped into temporary, semipermanent (lasting between 1–2 y), or permanent materials (lasting longer than 2 y) **(Ganceviciene et al., 2012).**

Injection of HA is thought to promote skin rejuvenation by increasing both hydration and fibroblast activation **(Tammi et al., 2002; Yoneda et al., 1988)**. HA injected into the skin can stimulate fibroblasts to express Col-1, MMP-1 and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) **(Jager et al., 2011; Gao et al., 2010)** ,as well as is participating in wound healing, modulation of inflammatory cells, interaction with proteoglycans of the extracellular matrix **(Jiang et al, 2007)** , All these features of HA have made it to be useful as an ideal structural compound and have raised injections of HA products to the most acceptable and scientifically investigated “gold standard” procedures for skin rejuvenation and augmentation .

1.1.5 Autologous Platelet-Rich Plasma (PRP)

Platelet-rich plasma (PRP) is a highly concentrated platelet plasma obtained from whole blood. In total,>1100 different proteins have been found in PRP, including immune system messengers, various enzymes and growth factors **(Fig.11) (Pavlovic et al., 2016; Wang and Avila, 2007).** These proteins have been demonstrated to participate in biological processes, such as cellular proliferation and differentiation, matrix remodeling and angiogenesis **(Pavlovic et al., 2016; Wang and Avila, 2007**). PRP proteins enhance wound healing and tissue regeneration. Among all the proteins in PRP, growth factors are the most important components **(Andia et al., 2012; Frautschi et al., 2017).** Platelet-derived growth factor, transformation growth factor, insulin-like growth factor, epidermal growth factor, fibroblast growth factor and vascular endothelial growth factor have well established roles in angiogenesis, cell migration, cell proliferation and collagen deposition **(Pavlovic et al., 2016; Bielecki et al., 2012; Yu et al., 2011).**

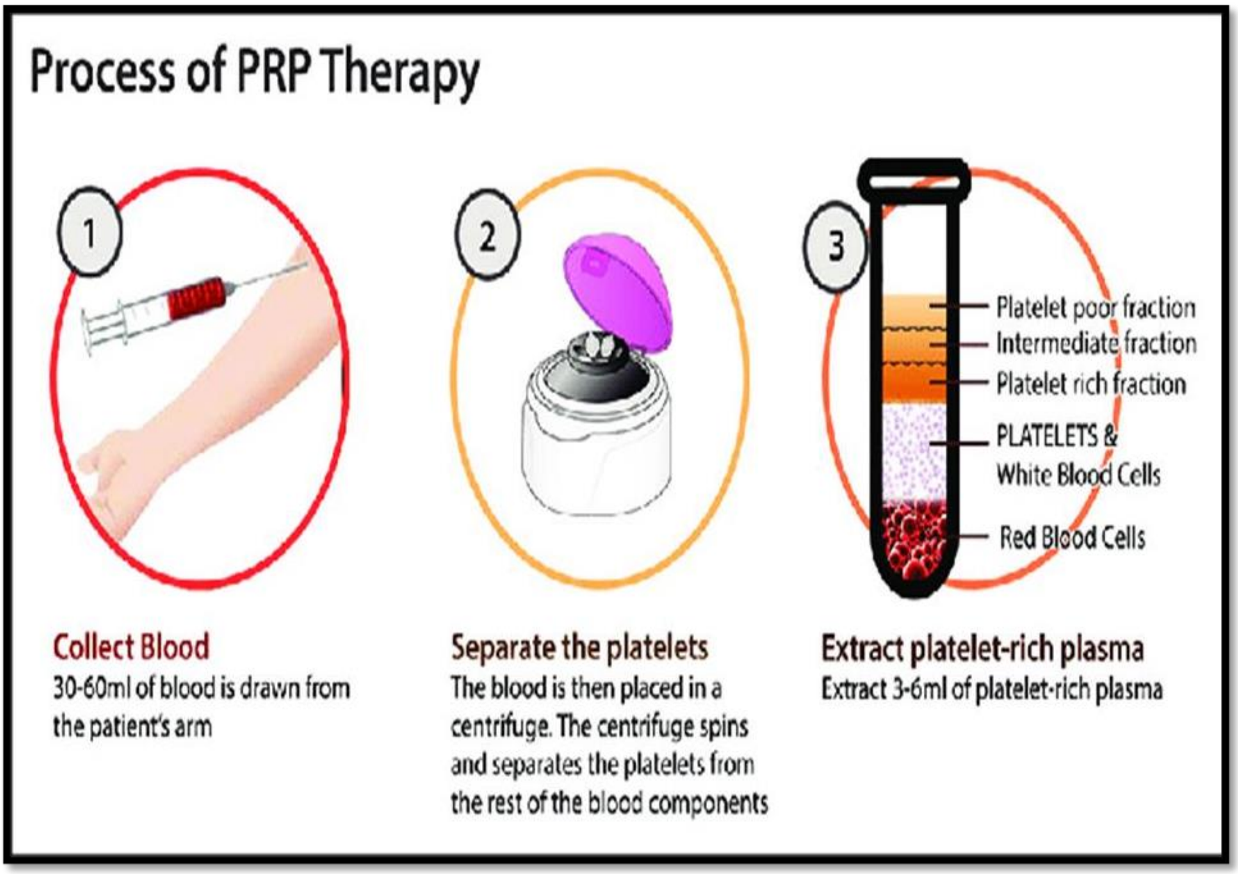

Fig. 11 The procedure of separation of platelet-rich plasma from the venous blood (Shwetha et al., 2018).

PRP has been widely applied for tissue repair in the fields of plastic surgery, oral and maxillofacial surgery, orthopedics and neurosurgery **(Pavlovic et al., 2016; Frautschi et al., 2017; Yu et al., 2011; Kamakura et al., 2015)**. As part of the diverse functional factors contained in PRP, autologous PRP has the best ratio of growth factors. The growth factor content in PRP is consistent with that in the patient's body, and compensates for the deficiencies of poor activity and low repair capacity of a single growth factor **(Pavlovic et al., 2016).** In addition, there are no immunological problems and no risk of spreading diseases in allogeneic transplantation **(Marques et al., 2015).** Furthermore, PRP forms a gel, which protects platelets from damage and loss during injection, and allows platelets to secrete growth factors for an ex- tended period to maintain a high concentration of growth factors **(Del Fabbro et al., 2019; Ali et al., 2018).** The benefits of PRP treatment in skin anti-aging repair come not only from the variety of high-concentration growth factors, but also from its gelatin state, which has plasticity and good support for skin wrinkles, cavities and skin relaxation **(Fabbro et al., 2019; Ali et al., 2018)**. In addition, PRP also contains a large number of cell adhesion proteins, such as cellulose, fibronectin and vitronectin, that may keep skin smooth and tight **(Qian et al., 2017).** Physiologically, the growth factors in PRP have important roles in reducing the rate of aging by restoring the declining DNA synthesis that occurs with aging, resisting cell death and enhancing gene expression for tissue repair **(Ramaswamy et al., 2018; Maisel-Campbell et al., 2019).** A positive correlation between PRP and skin anti-aging has also been reported in both pre-clinical and clinical practice **(Ramaswamy et al., 2018; Caruana et al., 2019).**

2. The role of diet in anti-aging

Since the ageing phenotype results from the accumulation of damage to the cell's macromolecules, nutritional interventions that reduce ageing must do so because they reduce the amount of damage sustained by the cell and/or because they enhance the capacity of the cell, tissue or organism to repair, or to cope with, that damage **(John and Mathers, 2014).**

2.1 Water

Water is a vital constituent of the body and facilitates maintenance of balance and tissue function in the body. Water in the body and cells mainly serves the role of nutrient, solvent, transportation carrier, maintains body volume, and regulates body temperature **(Popkin et al., 2010; Jéquier and Constant, 2010; Arnaud and Noakes, 2011).** Water within the skin helps keep it elastic, flexible, supple-looking and protected from external stressors. Most of the water in our skin lives in the deeper dermis layers and progressively decreases as you move to the surface **(Fig 12) (Bonté, 2011).**

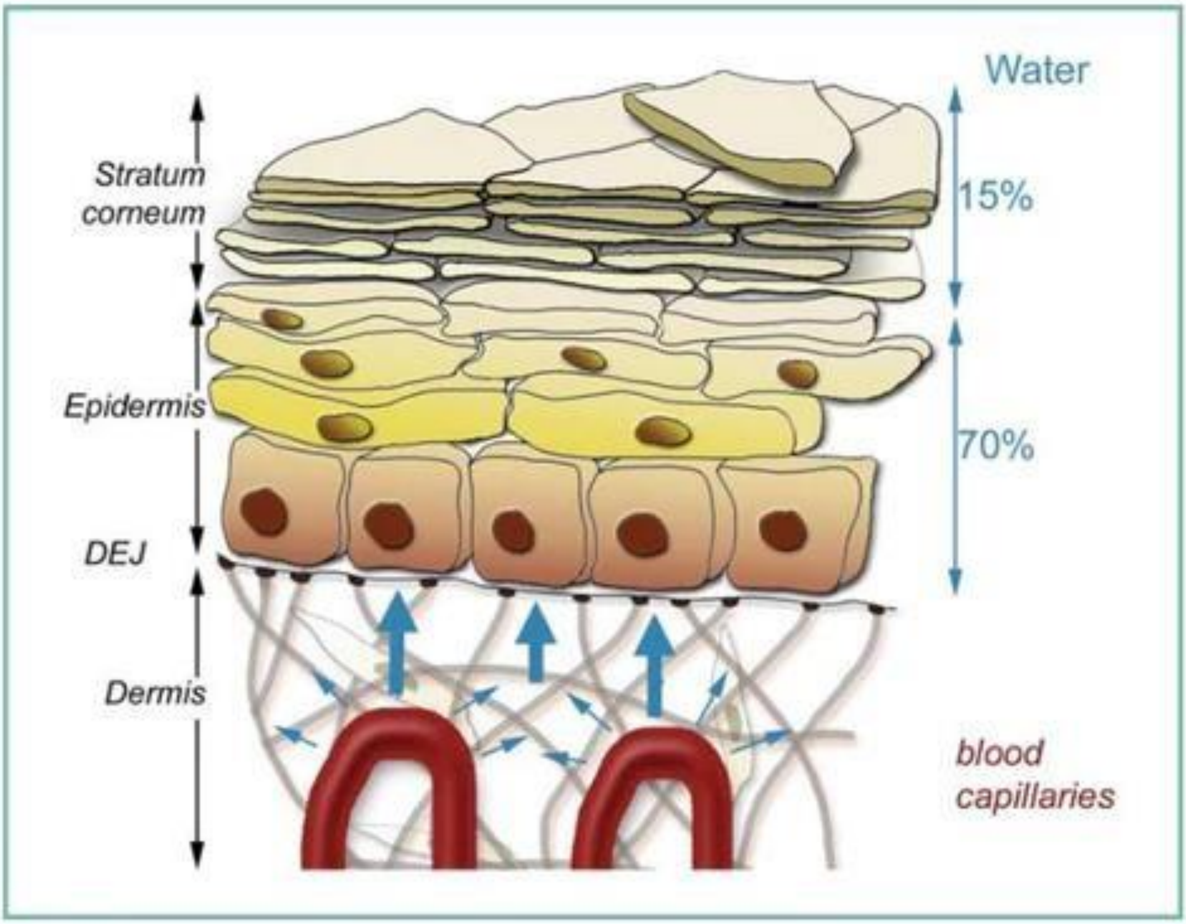

Fig. 12 Water Content of Skin (Bonté, 2011).

2.2 Carotenoids

Carotenoids are vitamin A derivates, such as lycopene and -carotene, which are known to possess high antioxidant potential as well as photoprotective characteristics. B-carotene and lycopene can moderately improve skin texture **(Stahl and Sies, 2012).**

B-Carotene is obtained from various plant sources, such as carrots, mangoes, papaya and pumpkins, among others **(Pritwani and Mathur, 2017).** It has emerged as a significant carotenoid owing to its characteristics, such as pro-vitamin-A activity,lipid radical scavenging activity and single oxygen quenching properties **(Jaswir et al,2011).** B-Carotene has been reported to avert erythema induced by UV rays and possess excellent photoprotection properties **(Fig.13) (Parrado et al., 2018).**

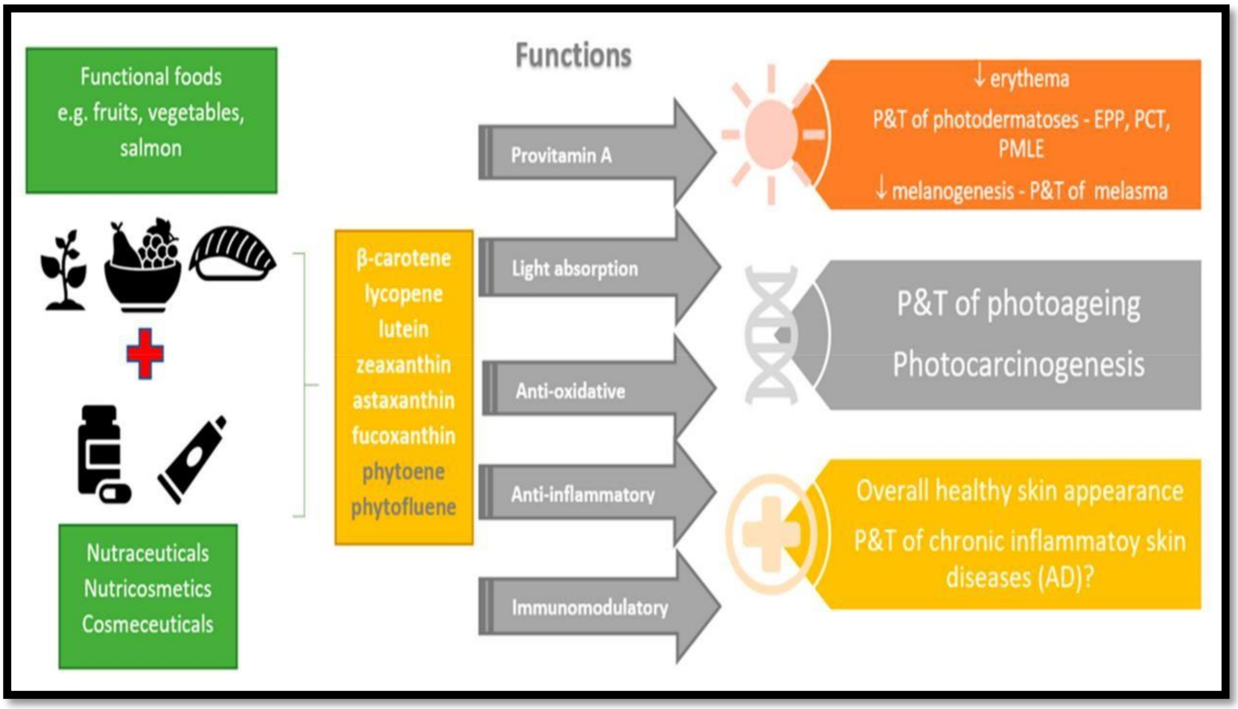

Fig. 13 Diverse skin health-promoting effects of food rich in carotenoids or their supplementation through nutraceuticals or cosmeceuticals (Balić and Mocos, 2019).

Lycopene is a red carotene, carotenoid and phytochemical present in numerous fruits and vegetables such as papayas, watermelons, tomatoes, carrots and others **(Schagen et al., 2012).** It possesses a high single oxygen quenching potential, but lacks vitamin A activity **(Evans and Johnson, 2010).** Moreover, a study confirmed the role of lycopene in attenuating oxidative damage in tissues. Upon exposure to UV light, it was observed that more skin lycopene was destroyed in contrast to B -carotene **(Ascenso et al, 2016).** Products of lycopene have also been reported to be effective against cancerous cells, in addition to their potential to significantly reduce MMP-1 activity, which is known to degrade collagen **(Przybylska, 2020).** Both lycopene and B-carotene, dominant carotenoids found in human tissues and blood, are known to regulate skin properties **(Darvin et al, 2011).**

2.3 Polyphenols and isoflavone

Polyphenols are secondary metabolites of plants and exist widely in vegetables, fruits, tea, and other plants. Due to their obvious antioxidant properties, polyphenols have become one of the most important compounds to be used in cosmetics and nutritional cosmetology to combat skin aging. In recent years, tea polyphenols, curcumin, flavonoids, silymarin, and grape resveratrol have been the most studied polyphenols with anti-aging properties. Polyphenols reduce oxidative damage and inflammation in the skin through their antioxidant and anti-inflammatory effects, mainly by inhibiting collagen degradation, increased collagen synthesis, and inhibiting inflammation, which involves the regulation of matrix metalloproteinases, cytokines, and signaling pathways (e.g., Nrf2, NF-κB, MAPK, etc.) **(Davinelli et al, 2018; Chuang et al, 2017).** Some polyphenolswith therapeutic properties have been described below**. (Fig 14).**

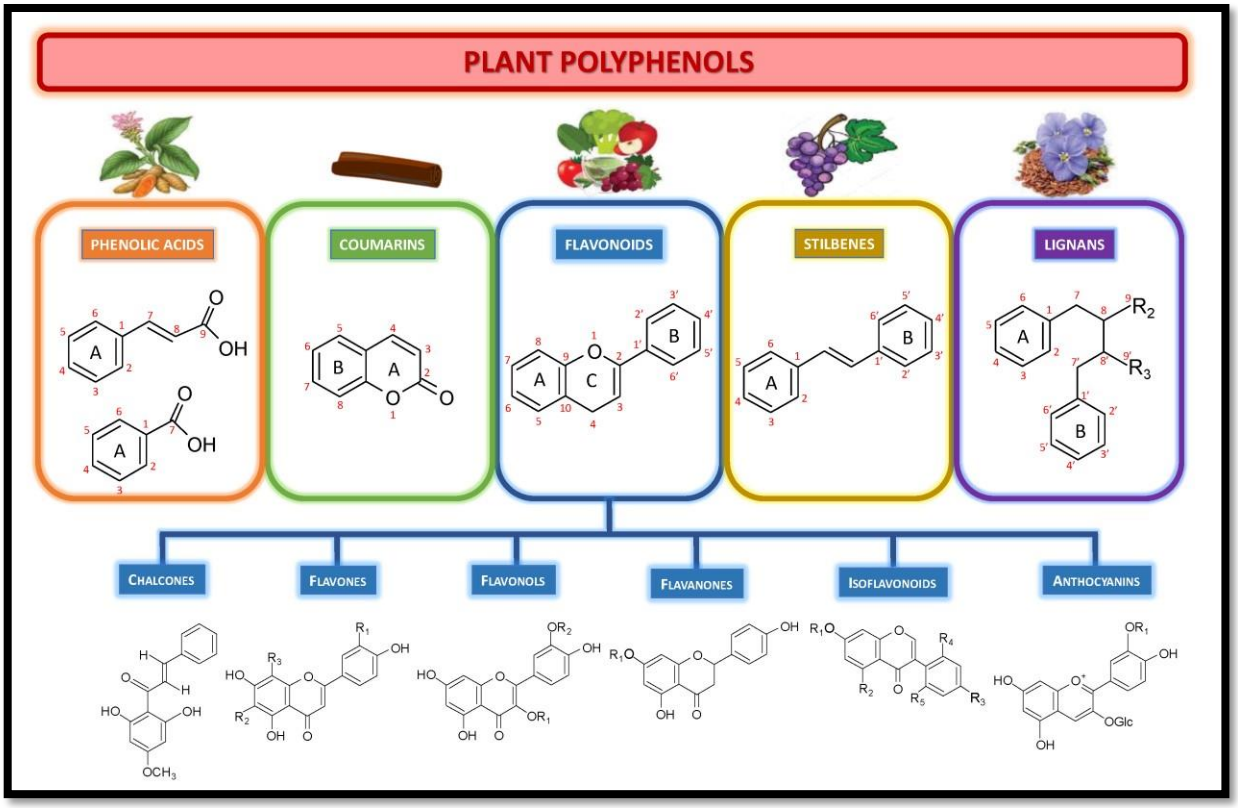

Fig.14 polyphenol classification including phenolic acids, coumarins, flavonoids, stilbenes and lignans (Hano, 2020).

Resveratrol (Stilbenes), for example, is a natural polyphenolic compound with antioxidant potential, and is present in the skin of peanuts and grapes **(Adhikari et al., 2019).** In the last two decades, it has been a prime area of extensiveresearch owing to its application as an anti-ageing ingredient **(Camins et al., 2009).** Additionally, it exhibits anti-inflammatory action and radical scavenging properties, and can act as a chelating agent **(Salehi et al., 2018).** Although it has been claimed that resveratrol has the potential to combat ageing at the cellular level and could be a breakthrough in anti-ageing and geriatric medicine, data supporting this claim in the human context are quite limited **(Demidenko and Blagosklonny, 2009; Giovannelli et al., 2011).** It has been well comprehended that resveratrol modulates mitochondrial biogenesis via stimulating Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1), which further slows down the process of ageing and circumvents the chronic diseases. **(Fig 15) (Lagouge et al., 2006; López-Lluch et al., 2008).**

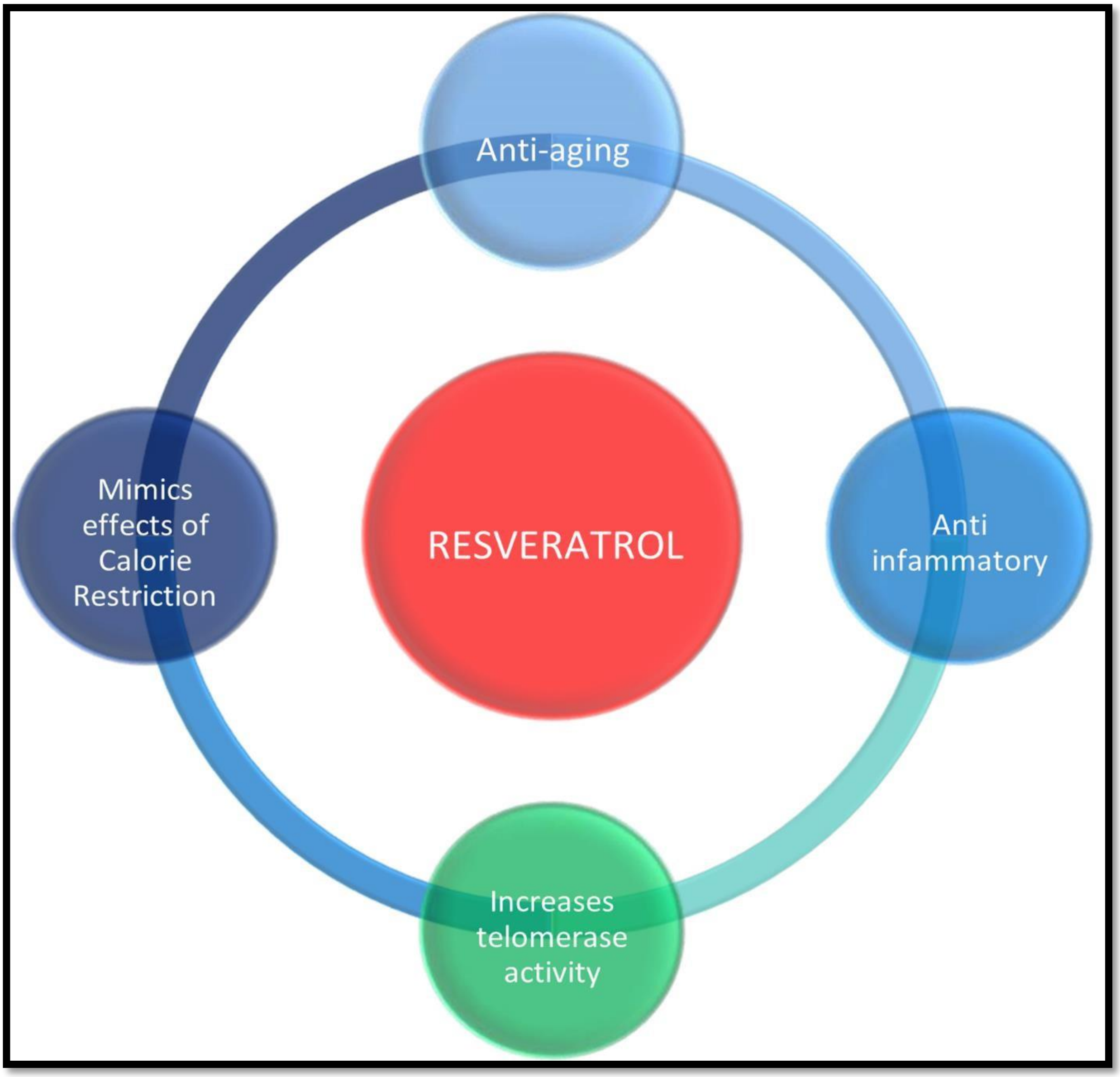

Fig. 15 Effects of resveratrol (Gutlapalli et al., 2020).

Soybean isoflavone, a well-known anti-aging agent, is also referred to as a phytoestrogen because it has a chemical structure similar to estrogen **(Basaria et al., 2009).** soy isoflavones are considered to have beneficial effects on the skin via mechanism such as prevention of lipide oxidation of the skin tissue **(Brand Garnys et al., 2001).** stimulation of fibroblast proliferation **(Kim et al; 1997).** reduction of collagen degradation **(Schmid et al., 2002).** and have been widely used as ingredients of cosmetics **(Schmid and Zulli, 2003).**

2.4 Fatty acids

Lipids are an important part of the skin and are closely related to skin epidermal barrier function, membrane structure, internal environment balance, and damage repair. Skin aging is accompanied by a decrease in fat content, mainly due to a decrease in the ability of cells within the skin to synthesize and secrete fat **(Pappas et al., 2013).** Besides, the amount of dietary fat intake is closely related to the lipid composition of the body and skin tissues, and insufficient intake of essential fatty acids or abnormal fat metabolism leads to serious skin diseases **(Meksiarun et al., 2015; Horrobin, 1989)**. Fatty acids are classified as saturated fatty acid (SFA), monounsaturated fatty acid (MUPA), and polyunsaturated fatty acid (PUFA) **(Siddiqui et al., 2008).**

EFAs are a type of polyunsaturated fatty acid (PUFA) that cannot be synthesized in our bodies and must therefore be obtained from the diet. EFAs have documented roles in both the dermal and epidermal layers of the skin, and the appearance of skin is linked to its functional health. There are two classes of EFAs: omega-6 (n-6) and omega-3 (n-3) fatty acids. Linoleic Acid (LA) is the parent compound of the n-6 PUFAs; α-linolenic acid (ALA) is the parent compound of n-3PUFAs. From these two parent compounds, the body synthesizes longer chain derivatives that also have important functions in healthy skin. Omega-3 and omega-6 polyunsaturated fatty acids play an important role as human skin barriers, and also have certain effects in the prevention and treatment of skin inflammation **(Fig.16) (Balićć et al., 2020).**

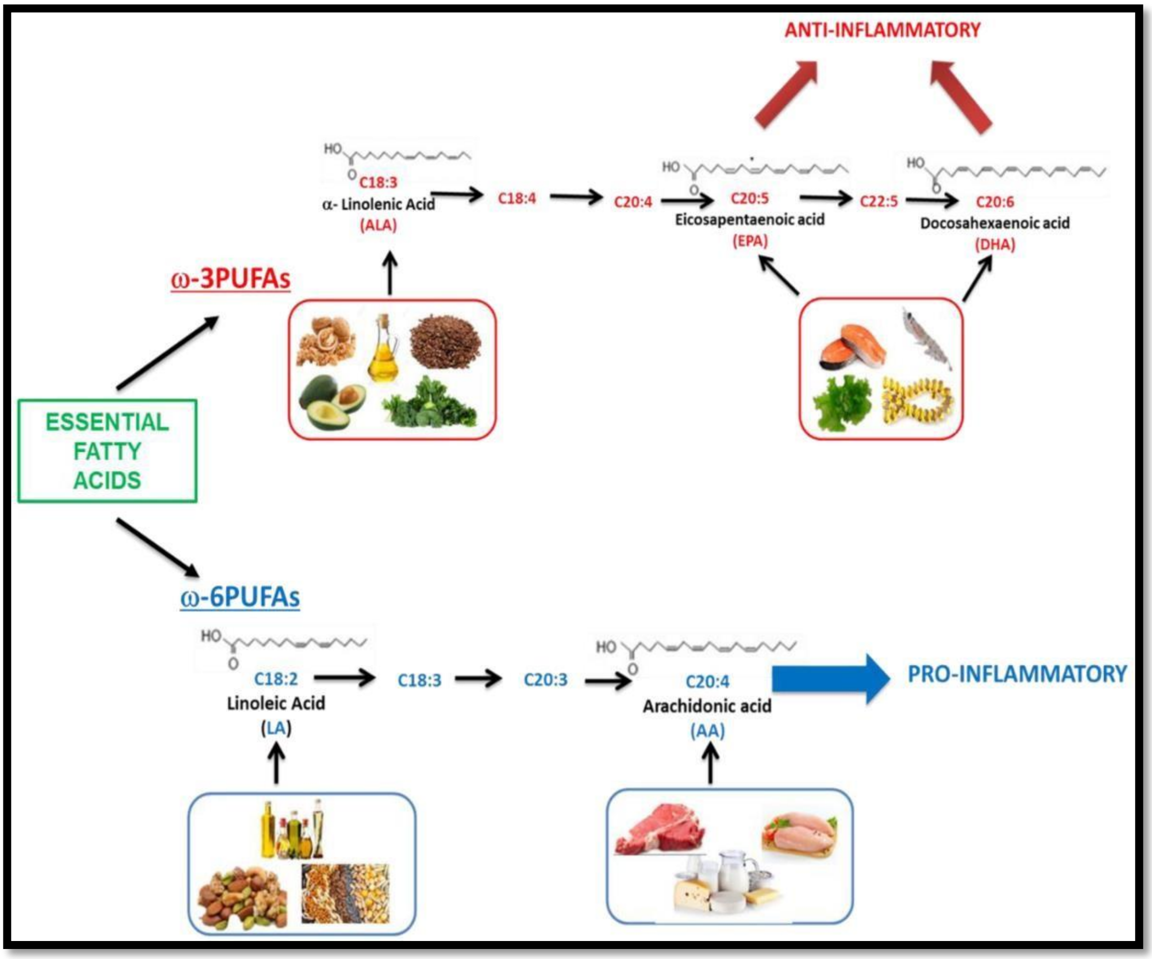

Fig. 16 Essential fatty acids and dietary source (D'Angelo et al., 2020).

2.5 Collagen peptides

Collagen is one of the most widely distributed and abundant proteins in mammals. Generally used collagen types include I, II, III, IV, and other various collagen types. As a structural protein, it plays an important role in organizational structures, for example, the structural integrity and strength of tissues. Additionally, collagen protein can also support connective tissues such as tendons, skin, teeth and stabilize cell structures in body tissues and strengthen them **(Sliva et al., 2014; Gelse et al., 2003).** Previous studies have shown that collagen can release bioactive peptides with a variety of physiological functions after enzymatic hydrolysis. These collagen hydrolysates and collagen-derived peptides obtained have positive effects in improving skin conditions **(Kim et al., 2018; Song and Li, 2017).**

In other words, collagen peptide intake has a potential effect on avoiding skin moisture loss induced by ultraviolet (UVB) **(Asserin et al., 2015).** Animal tissue from livestock and poultry is the main way for people to obtain natural collagen and collagen peptides **(Ahmed et al., 2020) (Fig. 17).** In recent years, aquatic animals have the further in-depth developed and utilized due to their special advantages, such as low resistance and hypoallergenic.

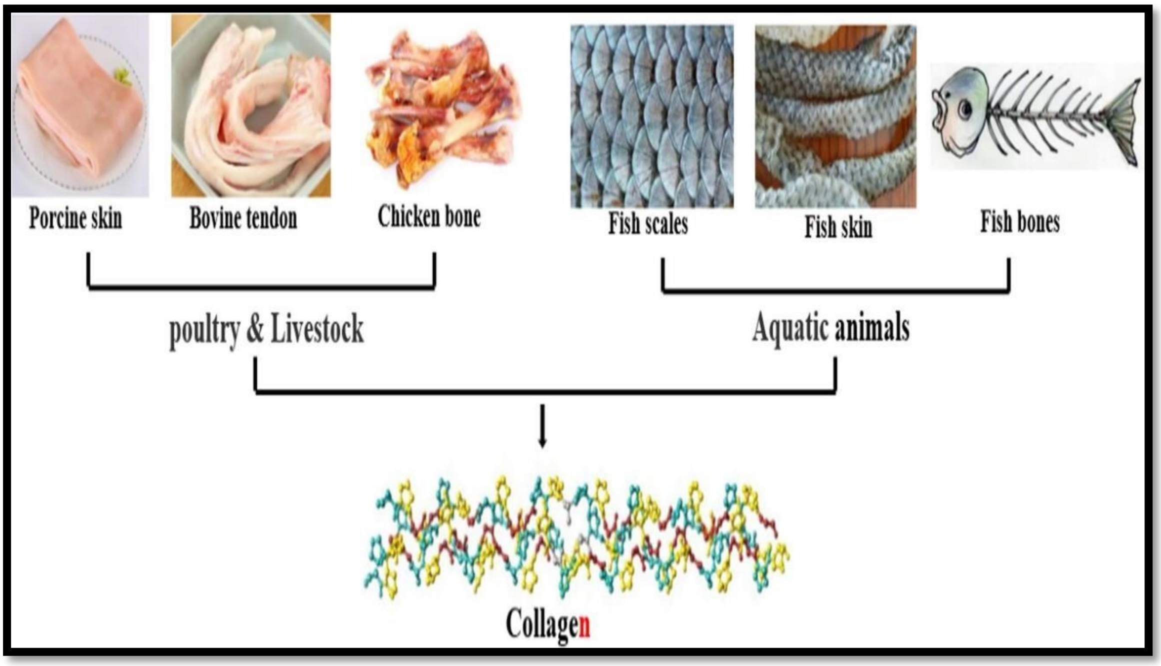

Fig. 17 Different sources of the collagen (Zhao et al., 2021).

Different sources of collagen peptides have different effects on anti-skin aging. Proksch et al. found that type I collagen-derived collagen peptide can stimulate the synthesis of procollagen I elastin, and fibrin in the skin, increase the synthesis of dermal matrix and reduce the generation of eye wrinkles by ingesting collagen peptide derived from pig collagen I for 4–8 weeks **(Proksch et al., 2014).** the chicken-derived collagen peptide has significant effects on inflammatory changes, oxidative stress, collagen I synthesis, and cell proliferation through studying the effect of chicken-derived collagen peptide on human skin fibroblasts **(Offengenden et al., 2018).** Additionally, the extraction of collagen peptides from aquatic animals has also been developed and used to improve skin problems

(Fig.18). Some researchers had extracted collagen peptide whose sequence was YGDEY (Tyr-Gly-Asp-Glu-Tyr) from tilapia collagen hydrolysate. They found that it had various advantages such as increase the expression of antioxidation factor [superoxide dismutase (SOD) and glutathione (GSH)], maintain the balance between reduced glutathione and oxidized glutathione, enhance the generation of type I procollagen, reduce the level of reactive oxygen species (ROS) significantly in human keratinocytes (HaCaT), prevent DNA oxidative damage, and inhibit the expression of MMP-1 (collagenase) and MMP-9 (gelatinase), etc. In a word, YGDEY had the function of preventing ultraviolet (UVB)-induced damage to cells and inhibiting UVB-mediated photoaging of skin **(Xiao et al., 2019).**

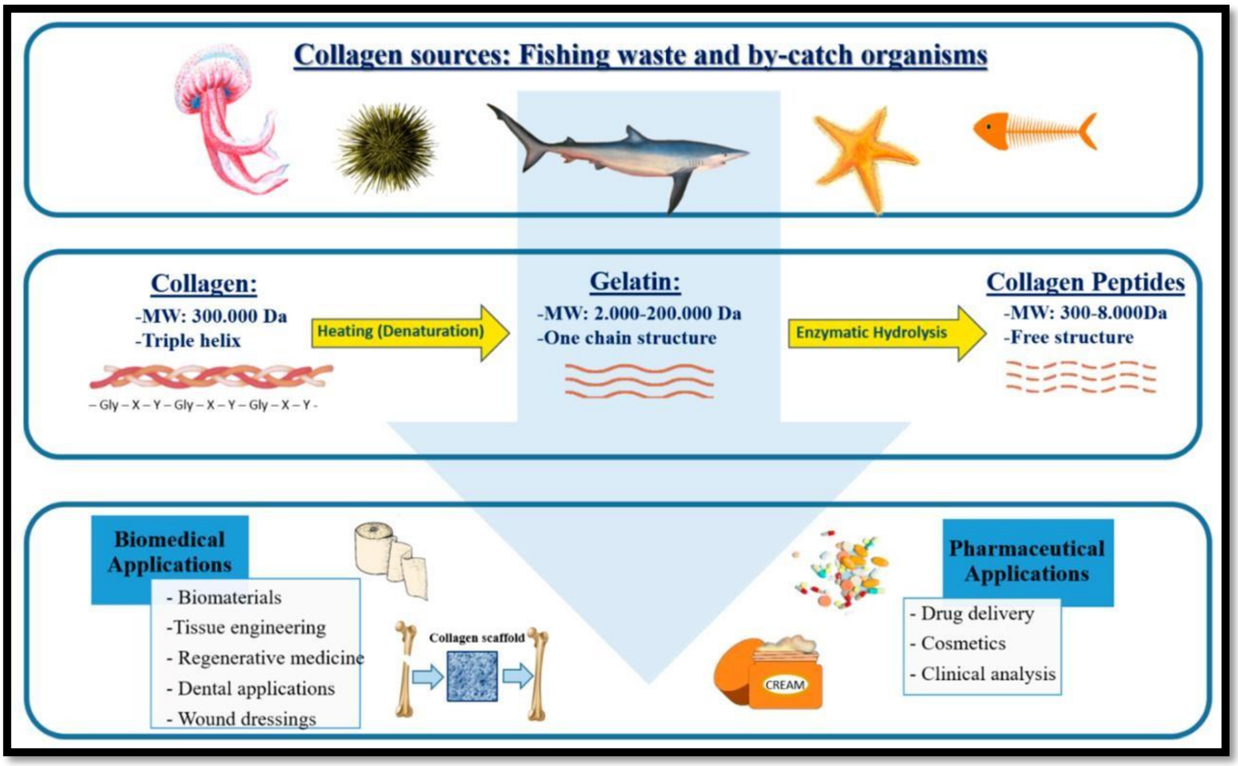

Fig. 18 the classical structure and applications of marine collagen, gelatin, and collagen peptides extracts from sustainable marine sources (Coppola et al., 2020).

Mechanistically, collagen peptides and other protein peptides may relieve skin aging through either of the three pathways. First, the protein or peptide enters the blood circulation after digestion and absorption, and then participates in the skin fibroblasts as a precursor of collagen synthesis, thereby protecting the aging skin. Second, collagen peptides that enter skin cells incur anti-aging effects by removing ROS from cells, protecting the cell's endogenous antioxidant defense system, and reducing oxidative damage and inflammatory responses in cells. In the third pathway, protein peptides entering skin cells promote collagen and hyaluronic acid synthesis and inhibit the production of inflammation by regulating cytokines and activating TGF– mad or other signaling pathways, while, these peptides concurrently also prevent skin collagen degradation by inhibiting the expression of proteases such as nuclear transcription factor activating protein–1 (AP–1), MMP–1 and MMP–3.

2.6 Polysaccharides

Polysaccharides are polymer carbohydrates formed by the dehydration and condensation of multiple monosaccharides. Due to their pharmacological effects, such as improving immune function, anti-tumor, anti-virus, anti-glucose, anti-oxidative, lowering blood lipids, and low cytotoxicity, polysaccharides are an ideal functional food and drug active ingredient **(He et al., 2012).** Dietary polysaccharides are mainly extracted from natural resources such as medicinal plants, fruits, vegetables, grains, algae, fungi, and mushrooms **(Ganesan et al., 2019)**, Some examples and their source are given in **Table 1.**

Table 1. Some polysaccharides and their sources. (Singh et al., 2021).

Sr. No.	Polysaccharides		Sources
1	Monosaccharides	Glucose	Cereal grains (wheat, oats, barley, corn, rice,

			etc) and their products (bread, pasta, pastries, cookies, etc), potatoes, jam
		Fructose	Fruit juice (grape juice), vegetables including sugar cane, honey, sugary soft drink like coke
		Galactose	Milk, yogurt, cream, cheese, honey, celery, cherries, dried figs,

			plums, soy sauce, kiwi fruit, ice cream, grains, fresh meat, and eggs
2	Disaccharides	Lactose	Milk
		Sucrose	Dairy products, beverages, soda, artificially flavored juices, drinks, sweetened coffee, tea, fruits, and vegetables
		Maltose	Grains, cereals, wheat, corn, barley, and rye

3	Oligosaccharides	Raffinose	Beans, asparagus, cotton seeds, sugar beet molasses, cabbage, broccoli, Brussels sprouts, sweet potatoes, and whole grains
		Stachyose	Green beans, soybeans, and other beans
4	Polysaccharides	Starch	Potatoes, bread, cereals, rice, and grains
		Glycogen	Oatmeals, juice, whole potato, and yogurt

Polysaccharides found in seaweeds are used to make skin moisturizers that form a thin/transparent layer on the skin that acts as a UV protectant, anti-wrinkle, and anti-aging molecule **(Fig.19) (Lin et al., 2019).** there are numerous large-sized polysaccharides found in microorganisms or fungi that are used in anti-aging skin formulations that provide moist, smooth, wrinkle-free, and even skin tone. Large-sized polysaccharides, proteins, and fatty acids are primarily used in the manufacture of skin care products such as facial cleaning products, baby care, facial care, and body care products that provide skin smoothness and suppleness **(Corinaldesi et al., 2017).**

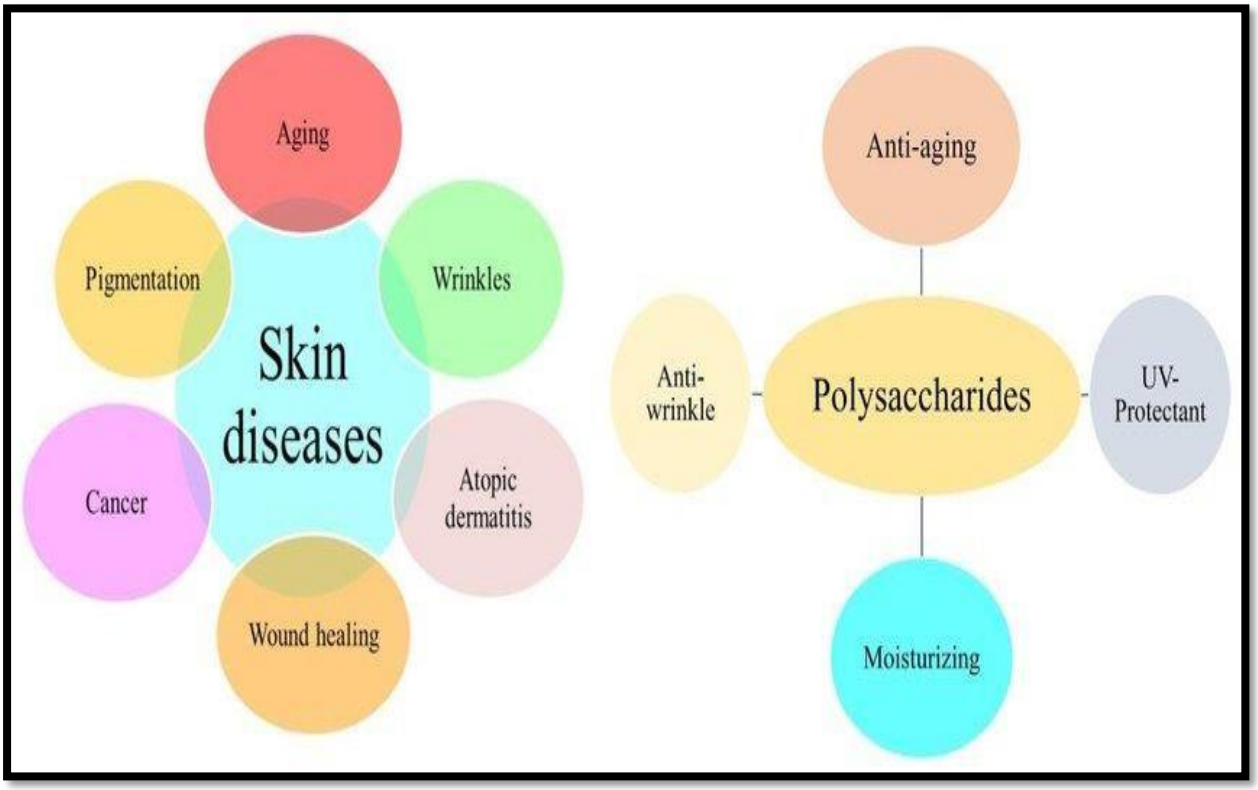

Fig. 19 Different types of Skin ailments and major potent properties of Polysaccharides (Davinder Singh et al., 2021).

2.7 Micronutrients

Micronutrients play an essential role in our wellness. Vitamins, antioxidants, and other food derived chemicals protect our bodies against infection, slow the aging process, and help the human body function at an optimum level.

Micronutrients have a special role in general wellbeing, and a lack thereof can seriously affect your health (**Hardy, 2018).** Micronutrients include the different vitamins and minerals. The dietary sources of vitamins and minerals are fruits, vegetables, animal source foods, grains, seeds, nuts and so on **(Fig. 20)(Teferra, 2015).**

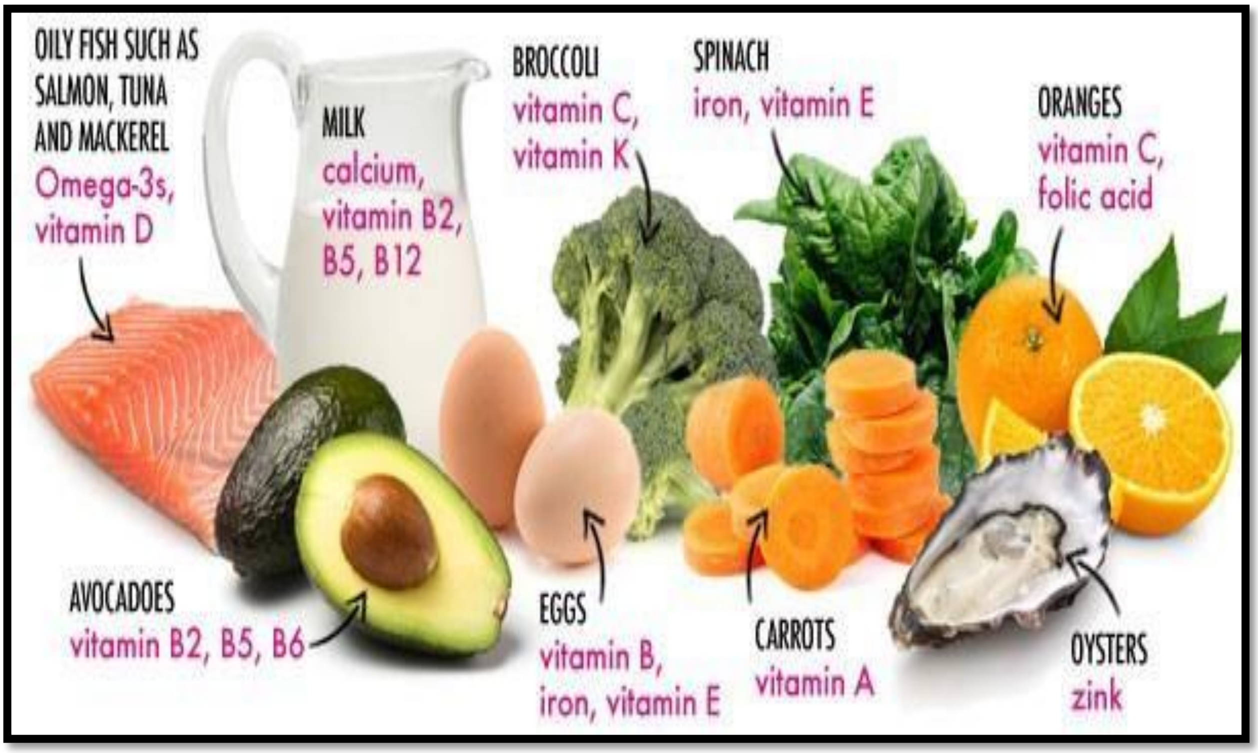

Fig. 20 Foods considered to be rich sources of micronutrients (Teferra, 2015).

2.7.1 Vitamins

Many vitamins have been tested for their antioxidant properties. They can reduce ROS in aging skin cells to low-activity molecules and reduce oxidative damage to key components of skin cells. Most research has focused on vitamins A, B (B3, B12), E, D, C, coenzyme Q10, and lipoic acid. Retinoids are the most common anti-aging drugs that have been used (such as retinoic acid prevents skin aging by regulating genes and MMPs) to treat and prevent photo-aging of the skin **(Fuchs et al., 1981; Fisher et al., 1999).** the sources and functions of some vitamins are shown in **(table 2).**

Table 2 Summary of the functions and dietary sources of some vitamins (Teferra, 2015).

Vitamins	Functions	Food Sources
Vitamin A	Night vision, healing epithelial cells, normal development of teeth & bones	Breast milk, Tomatoes, Cabbage, lettuce, Pumpkins, mangoes, papaya, Carrots, liver, kidney, egg yolk, milk, butter, cheese, cream
Vitamin B complexes	Metabolism of carbohydrates, proteins and fats	Milk, egg yolk, liver, kidney and heart, whole grain cereals, meat, whole bread, fish, banana
Vitamin C	Prevention of scurvy, aiding wound healing, assisting absorption of iron	Fresh fruits (orange, banana, mango, grapefruits, lemons, potatoes) and vegetables (cabbage, carrots, pepper, tomatoes), breast milk
Vitamin D	Needed for absorption of	Ultra violet light from the sun, egg,

	calcium from small intestine calsification of the skeleton	butter, fish, fortified oils, fats
Vitamin K	For blood clotting	Green leafy vegetables, Fruits, Cereals, meat, dairy products

Vitamin C is a powerful antioxidant, its concentration in the skin is closely related to skin biological functions, and it is often used as a positive control for skin aging tests. It acts as an enzymatic factor and antioxidant to promote collagen synthesis and eliminate cellular ROS to relieve skin aging **(Pullar et al., 2017).** This crystalline compound is not synthesized in humans; therefore, it has to be taken in the regular diet **(Souyoul et al., 2018)**. Diets should be supplemented with vitamin C-rich sources, such as oranges, broccoli, brussels sprouts, green peppers, strawberries, kiwifruit and grapefruit, to avoid the vitamin C deficiency associated health problems like cardiovascular diseases, scurvy, and others **(Brickley et al., 2008).**

Vitamin E is a fat-soluble membrane-bound compound which has high free radical-scavenging as well as antioxidant potential **(Galliet et al., 2017).** This nonenzymatic antioxidant is found in wheat germ oil, safflower oil, sunflower oil, vegetables, peanuts, corn, almonds, soy and meat **(Sivakanesan, 2018).** Vitamin E consumption helps in combating skin ageing symptoms due to its efficacy in preventing the peroxidation of lipids and the cross-connection of collagen fibers **(Schagen, 2012).** Vitamin E has been proven to relieve sunburn and UV-associated skin damage **(Keen and Hassan, 2016**).

A combination of vitamin E and C can help activate vitamins E, which protects skin against chemical stimuli and UV-induced irritation and damage by inhibiting lipid peroxidation in the skin **(Wu et al, 2013; Schempp, 2012).**

2.7.2 Minerals

Minerals have numerous functions in human’s body. Sodium, potassium and chlorine are present as salts in body fluids, where they have a physiological role in maintaining osmotic pressure. Minerals form part of many tissues. For instance, calcium and phosphorus in bones combine to give rigidity to the whole body. They are also essential constituents of certain hormones. Iodine for example is important part of the thyroxine produced by the thyroid gland. The principal minerals in the human body are calcium, phosphorus, potassium, sodium, chlorine, Sulphur, copper, magnesium, manganese, iron, iodine, fluorine, zinc, cobalt and selenium. Minerals that are of most importance in human nutrition are calcium, iron, iodine, fluorine and zinc (**Teferra, 2015).**

Conclusion and Perspectives

Conclusion and perspectives

Aging is a continuous process that is expressed in different ways. aging is defined by the appearance of some physical symptoms such as the appearance of wrinkles and white hair. Aging is often accompanied by some health problems. as the skin ages, the processes that occur in it begin to slow down and weaken. as the materials that maintain the cohesion and smoothness of the skin begin to diminish due to a group of factors, internal factors and temporal aging, as a result of the passage of time that affects the entire body and depends on genetic, physiological factors, and external factors it is represented in lifestyle, exposure to sunlight, as well as smoking, stress.

The effect of nutrition on skin aging is an interesting field of research because nutrition is closely related to skin health. So, when you adopt a balanced and healthy diet, it leads to flawless skin, getting rid of early signs of aging, and maintaining a healthy weight. while unhealthy eating affects the health of the skin and accelerates the aging process and causes diseases. Sunscreen, the biggest reason behind using sunscreen is that it protects us from harmful UV rays, prevents premature aging, tanning and sunburn, reduces facial stains, improves skin health and reduces the incidence of skin cancer. In additions to different food like, arginine has anti-aging properties and assists in minimizing the appearance of fine lines and wrinkles hydrates and nourishes dry skin. Also, many nuts (particularly almonds) are an excellent source of vitamin E, which can help repair skin tissues, retain skin hydration and protect the skin from harmful UV rays. Nuts even contain anti-inflammatory omega-3 fats that can help for give skin a beautiful glow by preserving its natural oil barrier.

In view of all these facts, it is of importance to search for new substances as anti-aging factors. The aim of my future research project is to study the effect of new natural substances on aging such as sidra leaf (Ziziphus spina Christi) and food containing vasodilators.

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Abstract

Abstract

aging is an inevitable biological phenomenon for human life, and the skin is the first defensive barrier of our body being in contact with the environment reflecting the general health conditions and aging in humans, where some changes in the skin that are affected by certain external and internal factors are considered changes in the skin are signs of aging which are represented in wrinkles, sagging skin, dryness, and fat loss, as the skin loses its natural smoothness.

Nutrition plays an important role in human health and in maintaining its youth, as there are eating habits that contribute to accelerating aging, for example, poor quality foods that contain unsaturated fats, also consuming a lot of carbohydrates and processed sugars in the diet can lead to a number of diseases (such as diabetes, heart) and also lead to weight gain. but aging can be fought with nutrition, as there are many theories about good foods rich in antioxidants that slow down the aging process, so a balanced diet maintains the freshness and youth of the skin from the inside and outside.

There are various other ways that contribute to fighting and preventing aging. with age, the body produces less collagen and elastin which makes the skin lose its elasticity, so by using anti-aging products or treatments, collagen production can be boosted or slowed down. emphasizing different strategies to delay the aging process, these treatments are essential to reduce fine lines and wrinkles and help make the skin firm.

Keywords: anti-aging, skin, nutrition, antioxidant, aging.

Résumé

Le vieillissement est un phénomène biologique inévitable de la vie humaine, et la peau est la première barrière défensive de notre corps en contact avec l'environnement qui reflète les conditions de santé générale et de vieillissement chez les humains. Lorsque certains changements de la peau sont affectés par certains facteurs externes et internes sont considérés comme des changement de la peau sont des signes de vieillissement qui sont représentés par les rides, le relâchement de la peau, la sécheresse et la perte de graisse, ainsi la peau perd sa douceur naturelle.

La nutrition joue un rôle important dans la santé humaine et dans le maintien de la jeunesse, en effet il existe des habitudes alimentaires qui contribuent à accélérer le vieillissement, notamment des aliments qui contiennent des acides gras insaturés. En outre, la consommation excessive de glucides et de sucres transformés dans l'alimentation peut conduire à un certain nombre de maladies (comme le diabète, les maladies cardiaques) et l'obésité. Mais le vieillissement peut être combattue avec la nutrition, car il été mentionné que les aliments riches en antioxydants peuvent ralentir le processus de vieillissement, donc une alimentation équilibrée maintient la fraîcheur et la jeunesse de la peau de l'intérieur et de l'extérieur.

Il y a diverses autres façons de lutter contre le vieillissement et de le prévenir. Avec l'âge, le corps produit moins de collagène et d'élastine, ce qui fait perdre à la peau son élasticité. Mettant l'accent sur différentes stratégies pour retarder le processus de vieillissement, ces traitements sont essentiels pour réduire les ridules et les rides et aider à raffermir la peau.

Mots-clés : anti-âge, peau, nutrition, antioxydant, vieillissement.

ملخص

الشيخوخة ظاهرة بيولوجية حتمية لحياة الإنسان، والجلد هو أول حاجز دفاعي لأجسامنا على اتصال بالبيئة يعكس الظروف الصحية العامة والشيخوخة لدى البشر، حيث تعتبر بعض التغيرات في الجلد التي تتأثر بعوامل خارجية وداخلية معينة تغيرات في الجلد من علامات الشيخوخة الممثلة في التجاعيد، ترهل الجلد والجفاف وفقدان الدهون، حيث يفقد الجلد نعومته الطبيعية.

وللتغذية دور هام في صحة الإنسان وفي الحفاظ على شبابه، نظرًا لوجود عادات غذائية تساهم في تسريع الشيخوخة، على سبيل المثال، الأطعمة رديئة الجودة التي تحتوي على دهون غير مشبعة، وتستهلك أيضًا الكثير من الكربوهيدرات والسكريات المصنعة في النظام الغذائي يمكن أن تؤدي إلى عدد من الأمراض (مثل السكري والقلب) وتؤدي أيضًا إلى زيادة الوزن. ولكن يمكن محاربة الشيخوخة بالتغذية، حيث توجد العديد من النظريات حول الأطعمة الجيدة الغنية بمضادات الأكسدة التي تبطئ عملية الشيخوخة، لذلك يحافظ النظام الغذائي المتوازن على نضارة البشرة وشبابها من الداخل والخارج.

وهناك طرق أخرى مختلفة تسهم في مكافحة الشيخوخة ومنعها. مع تقدم العمر، ينتج الجسم كمية أقل من الكولاجين والإيلاستين مما يفقد الجلد مرونته، لذلك باستخدام المنتجات أو العلاجات المضادة للشيخوخة، يمكن تعزيز إنتاج الكولاجين أو إبطائه. مع التأكيد على استراتيجيات مختلفة لتأخير عملية الشيخوخة، فإن هذه العلاجات ضرورية لتقليل الخطوط الدقيقة والتجاعيد والمساعدة في جعل البشرة متينة.

الكلمات الرئيسية: مكافحة الشيخوخة، الجلد، التغذية، مضادات الأكسدة، الشيخوخة.

Academic year: 2021-2022	**Done by:** GUERRAICHE Rayene

Study of Antiaging Factors

Dissertation to get a diploma of masters in biochemistry

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