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Paul C. Guest *Editor*

Reviews on Biomarker Studies in Aging and Anti-Aging Research

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Preface

The lifespan of every organism is limited by the aging process, which involves physical decline, an increase in chronic diseases, and ultimately death. It has been an ongoing quest of mankind to understand the aging process and use this information to develop ways of extending both the health and lifespan of individuals. Through these efforts, researchers have gained new insights into the physiological and molecular aspects of aging using both epidemiological and model organism approaches, and this has led to significant advancements in potential antiaging strategies. This is important as most chronic diseases in the world are intertwined with the aging process and occur more frequently in the aged population. According to the World Health Organization, non-communicable diseases affect mainly adults and elderly individuals, and this imposes the greatest burden on global health with staggering costs to the healthcare services. This book presents a series of reviews in various aspects of aging and age-related disease research along with several methods which have shown progress as potential antiaging approaches.

Chapter 1 covers studies which have focused on long-lived mutant and naturally occurring animal species. Chapter 2 describes the association of glycolytic dysfunction with the accelerated aging of neuronal cells in schizophrenia patients. Chapter 3 covers studies on the screening of antiaging drugs and gives clues into further research of aging biomarkers and antiaging targets. Chapter 4 describes the effects of sex differences in the aging process and the role of sex hormones in this process. Chapter 5 covers the efficacy of the ketogenic diet in a variety of neurodegenerative, neurodevelopmental, and metabolic conditions throughout different stages of life. Chapter 6 reviews the potential role of CoQ10 supplementation in the treatment of tissue fibrosis, implicated in the age-related loss of function of various organs including the heart. Chapter 7 reviews the evidence that associates dietary restriction, cardiovascular aging, and age-related cardiovascular diseases, and related strategies to prevent or retard age-related cardiovascular diseases in the elderly. Chapter 8 focuses on the possible use of fecal microbiota-related parameters and microbiota-derived metabolites as biomarkers of cognitive performance and dementia, with a spotlight on the most promising areas of future research. Chapter 9 looks at the potential impact of herbal products on the prevention, regeneration, and delayed

aging of skin. Chapter 10 explores the influence of epigenetics on aging and the potential of restoring age-related changes to a "younger" state. Chapter 11 describes the basics of adipose tissue biology, growth hormone secretion, and action, and how the interactions of these may play a critical role in determining lifespan and healthspan. Chapter 12 provides a brief overview of cytoskeletal structure and function, and discusses the evidence which links cytoskeletal function and dynamics with aging and neurodegeneration. Finally, Chapter 13 details how the most promising avenues to halt the aging process have come from studies of the molecular pathways involved with caloric restriction, insulin/insulin-like growth factor signaling, and mitochondrial ROS production, in nematode, fly, and rodent models.

As a way of highlighting the growing interest in this topic throughout the world, the authors in this series come from all six of the world's habitable continents. This includes the countries Australia, Brazil, China, Indonesia, Iran, Italy, Greece, Russia, the United Kingdom, and the United States of America. As each review describes the cutting edge of research in this important field in a functional blend of scientific and layperson's language, this volume will be of interest to scientists, medical practitioners, members of health organizations, and pharmaceutical company employees, as well as those without professional or specialized knowledge.

Campinas, Brazil Paul C. Guest

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Chapter 9
The Impact of Herbal Products in the Prevention, Regeneration and Delay of Skin Aging

Mega Ferdina Warsito and Idha Kusumawati

1 Introduction

The skin is the outermost and the largest organ of the human body, representing one sixth of the total body weight [1]. Skin has a role as a physical barrier against harmful microorganisms, toxic substances and ultraviolet radiation, and it regulates water loss and body temperature [2, 3]. Changes in the skin will affect an individual not only physiologically but also psychologically, which are both significant for quality of life. Along with aging, the skin like all human organs changes progressively. This natural change is called chronological aging. However, as the outermost organ and as a body barrier, the skin will also be subject to exposure to stressors and dangers from the environment outside the body. Changes in the skin due to external factors are referred to as premature aging, and because they are often caused by Ultra Violet radiation (UVR), this is also called photoaging [4–6].

Skin reflects the intrinsic and extrinsic aging process in the human body, which further causes changes in its function and structure [7]. The dermatological concern correlated with skin aging has grown as the aging population in the world has increased. Skin aging not only affects appearance but it can also influence an individual's social behavior and reproductive status [2]. Thus, some people pay a considerable amount of expense for cosmetics and pharmaceuticals that could prevent, regenerate and delay skin aging [8].

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Aging phenomena are known but the aging process is not clearly understood. Aging is associated with a decrease in function and character of physiological, physical and appearance of the body [9–11]. In 1956, Harman developed the theory of free radicals (reactive oxygen species; ROS) as a cause of aging. An imbalance in the amount of exposure and elimination of ROS by antioxidants will affect many physiological processes in the body. Environmental insults to the skin such as those caused by UVR and pollutants can cause the formation of ROS [5, 6]. ROS are unstable molecules that can react easily with electron acceptors, such as oxygen, and turn into free radicals. The accumulation of ROS that are not eliminated by the antioxidant system in cells produces what is called oxidative stress. Clinical manifestations of oxidative stress on the skin due to accumulation of ROS include increased skin weakness, xerosis, wrinkles, pigmentation irregularities, benign growths (such as seborrheic keratosis) and/or malignant neoplasms such as basal or squamous cell carcinoma. At the cellular level, there can be a decrease in keratinocyte proliferation, reduced generation of the stratum corneum, lower regeneration of the protective layer caused by reduced lipid synthesis, and thermoregulation damage due to changes in responsive blood vessels and the autonomic nervous system.

The rate of skin aging is affected by intrinsic and extrinsic factors and almost every aspect of biological function [3]. Intrinsic skin aging factors can be affected by ethnicity, anatomical variation and hormonal changes in cutaneous tissues. Some of the extrinsic factors in skin aging include poor nutrition, smoking, nicotine, pollution, and UVR exposure.

Herbal extracts are complex mixtures of natural compounds with various structures and origins. These have been used in skin care and cosmetic products since ancient times. The strategies of herbal product for the treatment and prevention of aging skin are variously based on their potential activities as antioxidants [1], anti-photo-aging agents [12, 13], anti-inflammation activity [14, 15], as skin cell proliferation promotors [16], modulators of collagen and elastin synthesis [17], or as inhibitors of melanin production [18].

The increasing concerns regarding quality of life and appearance have led to an increase in the market of natural compounds with anti-aging and photoprotective properties [19]. Plant extracts and natural compounds are able to protect or ameliorate the deleterious effects on aged skin, and many of them are used as either oral dietary supplements or topical cosmetic formulations. The importance of cosmetical preparation is not only related to improving the overall appearance of the skin during aging but it also offers a better quality of life through prevention and treatment of skin disorders related to the aging process [20].

This review will summarize the skin aging characteristics in each layer, the usage of herbal products in the prevention, regeneration and delay of the skin aging process, and herbal formulations to increase the effectivity of cosmeceutical products.

2 Characteristic of Aging Skin

Aged skin has the characteristics of being thinner and pigmented, with increased laxity, coarseness, wrinkling, sallow coloration, telangiectasia (apparent widened venules), dryness, fragility, ease of bruising, and cutaneous malignancies. Intrinsic skin aging is a normal physiological process that occurs due to genetic or metabolic factors [3]. The most noticeable histological changes occur in the basal cell layer as the epidermis becomes thinner, the dermal-epidermal junction (DEJ) area decreases, and basal cell proliferative capacity weakens [21].

The skin consists of different cell types and compartments with different functions [22–25]. The salient features of aged skin occur throughout the epidermis, dermis and subcutaneous tissue, which in turn manifest in the alteration of skin topography. The basal layer contains pigment-producing melanocytes, which determine skin color and possess photo-protecting properties. The DEJ connects the epidermis to the underlying dermis, which contains dermal fibroblasts and appendages such as hair follicles, sebaceous glands and sweat glands. As shown schematically in Fig. 9.1, the aged skin dermis is relatively avascular and acellular compared with younger skin. It also has lower production and disorganization of collagen, fragmented elastic fibers, as well as lower glycosaminoglycans and melanocytes.

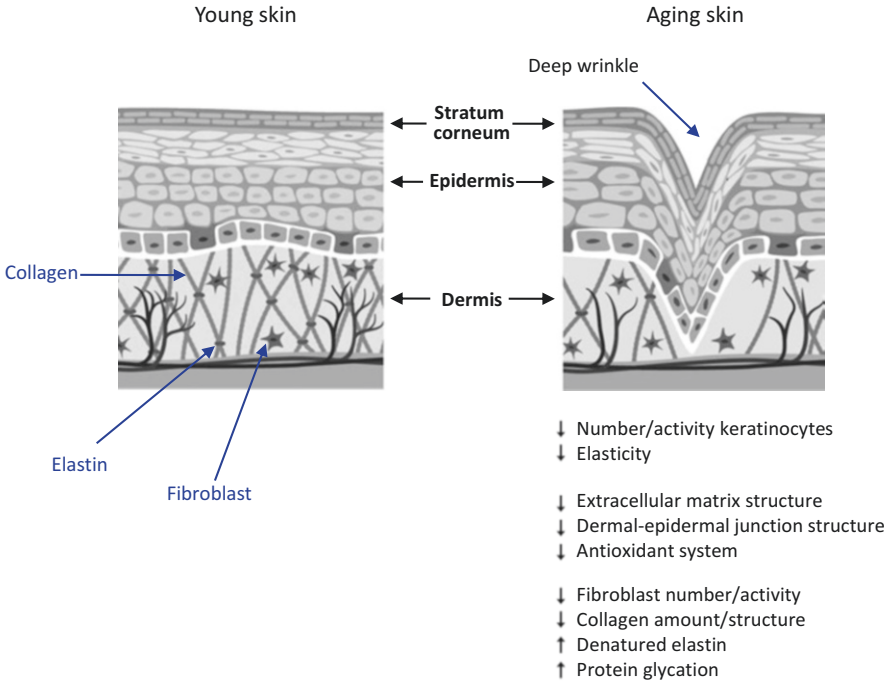

Fig. 9.1 Clinical manifestation of aged skin

Signs of skin aging include thin and dry skin, coarse wrinkles, decreased elasticity, laxity, aberrant pigmentation and a rough-textured appearance. Decreased proliferation and renewal capacity of basal keratinocytes and reduced epidermal stem cell number are also several factors that can cause epidermal, DEJ and dermal thinning [3]. The extracellular membrane (ECM) generates fibroblasts, which are responsible for maintaining skin integrity and elasticity in the dermis area. Therefore, alterations and degradation of the ECM during dermal thinning can cause increased numbers of wrinkles and decreased skin elasticity [26].

2.1 Epidermis

The epidermis is the outermost part of the skin, composed of four strata known as the basal, spinous, granular and cornified layers [4, 5, 27]. The dominant cell types in the epidermis are keratinocytes and melanocytes. It has a function to prevent water loss, protect the body from toxic chemicals and pathogenic microorganism, abrasions and UVR.

Regeneration of the epidermal cells occurs continuously in young skin. This regeneration begins with multiplication of proliferative cells in the deepest layer, and these are pushed out by differentiation and cell division [4, 5, 21, 28]. Differentiation causes molecular, structural and functional changes of keratinocytes so that these will occupy different layers. The peak of differentiation will produce corneocytes which are dead cells. Corneocytes, which are rich in proteins, are embedded in the matrix, which is composed of ceramides, cholesterol and fatty acids [23, 29].

In the cornification process, calcium has an important role. The lowest calcium level is found in the basal stratum and increases up to the stratum corneum. In young skin, the stratum granulosum has high calcium levels. In old skin, the distribution of calcium in each layer is so irregular that the composition of the protective proteins of corneocytes changes. This is also thought to be a mechanism of protection against aging [4, 5]. The speed and regeneration ability of epidermal cells is influenced by age. Aging leads to decreased numbers of cells that proliferate in each layer and dead cells accumulate so that the regenerative capacity of the tissue is lower. The structure and shape of cells change to become more porous and the functions of structural organizations become less effective [28].

The normal aging process does not affect dermis thickness, but there are noticeable changes in skin structure. For example, the skin becomes more susceptible to irritation and has lower permeability, which results in reduced trans-epidermal water flux [23, 29]. In some cases, the whole epidermal layer will gradually decrease in thickness with age at a rate of approximately 6.4% per decade. In photoaged conditions, this reduction in thickness will occur faster. The form of keratinocytes also becomes shorter and fatter, while the corneocytes become larger as a result of decreased epidermal turnover. In aged skin, there is a decreased water binding capacity due to changes in amino acid composition and lipid levels so that the

capacity of natural skin moisturizing factors are reduced. Disorders due to the aging process can also affect the barrier function of the skin, due to the global reduction of lipids in the stratum corneum, which will affect corneocyte binding in the matrix. In addition, the DEJ can be flattened, causing reduced interdigitation between the epidermis and dermis which results in reduced supply of nutrients and oxygen.

Melanin has a role as sun protector in the skin [23]. In photoaging, the production of melanin decreases due to a decrease in the functional amount of melanocytes in the basal layer of the epidermis (stratum basale). Therefore, older people are more susceptible to UVR exposure which can cause sun-induced cancer [23]. Aging of the skin causes uneven pigmentation with a tendency towards hyperpigmentation, even though there is a decrease in the number of melanocytes. In addition, there is also loss of melanocytes in certain areas and changes in interactions between melanocytes and keratinocytes [27].

2.2 Dermis

The dermis contains nerves, blood vessels, lymphatics and secretory organs [27]. Fibroblasts are the main cell type found in the dermis and these function to synthesize and degrade the ECM. The ECM structure consists of highly organized, elastic and reticular collagen fibers. The three primary structural components of the dermis are collagen, elastin and glycosaminoglican (GAG). Collagen functions to give skin its strength and maintain tissue integrity, whereas elastin provides elasticity and resilience. The extrafibrillar matrix consists of a complex mixture of proteoglycans, glycoproteins, glycosaminoglycans, water and hyaluronic acid.

Many of the components and characteristics of the dermis decrease with age, such as thickness, vascularization and cellularity, number of mast cells and fibroblasts, as well as the levels of glycosaminoglycans, hyaluronic acid produced by fibroblasts and the number of interfibrillary ground substances [22, 25, 27, 29]. Decreased elastin and collagen turnover caused by a decrease in fibroblasts and collagen synthesis also occurs due to aging. Photoaged skin shows disorganized collagen fibrils, fragmented elastic fiber and accumulation of abnormal elastin-containing material. The clinical manifestations of dermal aging include increased skin stiffness because the molecular integrity of the dermis is lost, decreased extensibility of torsion, reduced elasticity, and increased susceptibility to tearing-type injuries [29].

2.2.1 Collagen

Collagen is the most abundant protein in skin, constituting about 70% of dry skin mass, and it is responsible for conferring strength and gives support to human skin. Normal aging is characterized by atrophy of epidermis and dermis and also flattened rete ridges [23]. Aged skin has thickened fibrils in rope-like bundles and

it has a decreased collagen synthesis level [23, 30, 31]. The ratio of collagen types in human skin is also an indicator of the skin age, because this ratio is altered in aged skin. In young skin, 80% of collagen is type I and 15% is type III. In contrast, old skin contains more type III collagen due to decreased levels of type I collagen. In photoaged skin, studies have shown that there is 59% reduction of type I collagen. Collagen IV also plays an important role as the framework for other molecules and it is also responsible for maintaining the mechanical stability of DEJ, which is assumed to be correlated with wrinkle formation. However, there are no significant differences in collagen type IV levels in sun-exposed and uv-exposed skin. Collagen VII functions by anchoring the fibrils that attach the basement membrane to the underlying pappilary dermis. Sun-exposed skin also shows significantly lower numbers of anchoring fibrils compared to normal skin. Therefore, it is assumed that wrinkles may form as a result of a weakened bond between the dermis and epidermis, due to degradation of anchoring fibrils. Loss of collagen type IV and VII marks the base region of the wrinkle. Overall, the collagen abundance in the skin decreases at a rate of approximately 1% per year.

Skin aging, either caused by extrinsic or intrinsic factors, is marked by an elevation of activator protein-1(AP-1) activity, matrix metalloproteinase (MMP) gene expression, inhibition of transforming growth factor (TGF)-β signalling, reduction of collagen synthesis and increased collagen degradation [32]. UVR exposure has been found to up-regulate the synthesis of MMPs through increased amounts of transcription factors such as c-jun and c-fos. MMPs are increased even without UVR exposure and this leads to the formation of AP-1. AP-1 then activates the MMP genes and stimulates the production of collagenase, gelatinase and stromelysin. Thus, AP-1 activation and (TGF)-β signaling inhibition mediates collagen degradation via increased proteolysis. MMPs, especially collagenase and gelatinase, are known to be produced within hours of UVB exposure. Long term elevation of MMPs likely leads to disorganized and clumped collagen, and it is assumed that this causes the lower collagen I levels in photoaged skin [23, 30, 31].

2.2.2 Elastin

Photo-aged skin causes the accumulation of amorphous elastin material, called elastosis [23, 30, 31]. UV exposure induces elastin fibre thickening and coiling in the pappilary dermis and reticular dermis, reduction of microfibril numbers, increases in the interfibrillar area, complexed shaped and arrangement of the fibres and increased numbers of electron-dense inclusions. Aged skin also has small amounts of sugar and lipids and abnormally high levels of polar amino acids. MMP-2 is thought to be the protease responsible for degradation of elastin.

Sun exposure level affects the magnitude of the hyperplastic response or an increased amount of elastic tissue. Photo-aged skin has been found to have lower

elasticity and resiliency [31]. This skin is characterized by changes in the normal pattern of oxytalan fibers in the papillary dermis by the formation of the fibrous network in young skin that ascends perpendicullary from the uppermost section of the papillary dermis to just beneath the basement membrane. The loss of elasticity manifests as sagging skin in the elderly person [23, 30, 31].

2.2.3 Glucosaminoglycans

Glucosaminoglycans (GAGs) are polysaccharide chains with repeating disaccharide units attached to a core protein, which are responsible for conferring the outward appearance of the skin by its capability to bind water uo to 1000 times their volume [31, 33]. Hyaluronic acid (HA), dermatan sulphate, and chondroitin sulphate are types of GAGs, which give skin its plump, soft, and hydrated appearance. They also help to maintain the salt and water balance. There are conflicting reports regarding the effect of UVR exposure on GAG concentrations in the skin, especially regarding HA. Some studies have reported that the GAG concentration in the skin decreased following UVR exposure, but others have suggested that there are no UVR-induced changes in GAG levels. It is assumed that this discrepancy may have occurred because GAGs are produced in both the epidermal and dermal areas. In intrinsically aged skin, the HA level in the dermis remains stable but the epidermal HA diminishes almost completely. Reduced levels of HA can be observed in the photoaged skin and scars. HA can be found in young skin at the periphery of collagen and elastin fibers and also at the intercept of these fibers in the both dermal and epidermal area, but not in the stratum corneum or stratum granulosum [34]. Wrinkle formation, sagging skin, reduced turgidity and capacity to support microvasculature in the skin correlate with decreased HA levels.

2.3 Vasculature

Blood flow to the skin is decreased in aged skin, with the reduction reported to be around 40% between the ages of 20 to 70 years [31]. This results in lower nutrient exchange, inhibition of thermoregulation, decreased temperature in the skin surface and skin pallor. The anatomical and physiological changes in the microcirculation that have been reported include impaired microvascular reactivity, increased vascular stiffness, decreased vascular density and impaired vascular organization [35]. Acute and chronic UV radiation stimulates skin angiogenesis through upregulation of vascular endothelial growth factors and inhibition of thrombospondin-1, a potent angiogenesis inhibitor. In particular, a decreased vascular network appears in the papillary dermis, as shown by the disappearance of the vertical capillary loops which is the cause of the effects described above [36].

2.4 Subcutaneous Tissue

The subcutaneous layer maintains the structural integrity and function of blood vessels needed by the dermal and epidermal layers [30, 31, 36]. Subcutaneous fat is higher in females compared to males. In females, it represents 85–90% of the total body fat [36]. Subcutaneous fat is highly partitioned in distinct, independent compartments separated by septal barriers [37]. Fat redistribution in the aged skin results in a reduced subcutaneous:visceral fat ratio [38], which has been found to be correlated with physiological alteration of adipocyte metabolism and adipokine synthesis [39–41]. Skin aging also caused diminished subcutaneous fat in the face, as well as in the dorsal area of the hands and shins.

3 Herbal Products for Skin Anti-aging Strategies

The use of oral and topical exogenous antioxidants is one means of preventing and repairing oxidatively-damaged skin. Various plant species have been widely used as sources of oral and topical antiaging agents. In addition, a number of plant secondary metabolites have activities that may lessen the effects of aging on the skin, such as antioxidants, photoprotective agents, anti-inflammatory molecules, modulators of collagen/elastin synthesis and inhibitors of melanin synthesis.

3.1 Antioxidants

The secondary metabolites in plants include antioxidant compounds (especially phenolic compounds; catechins, isoflavones, proanthocyanidins, and anthocyanins), phenolic acids (benzoic, gallic, and cinnamic acids) and stilbenes [42–44]. These are derived from plants such as tea, grape, bergamot, fernblock, rooibos, grapefruit, and red orange, and are currently widely used in cosmetic formulations. Based on their structure, polyphenol compounds can act as antioxidants through radical scavenging or as oxidized prooxidants via phenoxyl reactive radicals or intermediate quinone or quinone metides. The antioxidant activities of polyphenols appear to be more effective than vitamin E and vitamin C. Their use in topical formulas has been shown to be effective as antiaging agents through antioxidant activities [42]. Flavonoids and phenolic acids have the activity of capturing free radicals and acting as chelating metal ions such as iron and copper, which can initiate the formation of reaction free radicals. In addition, flavonoids can inhibit the activity of some redox enzymes so they can inhibit cell damage caused by free radicals [45, 46].

Genistein and daidzein are effective antioxidant compounds. Both of these compounds are isoflavonoids, estrogen-like molecules, which are found in soybeans [45]. The glycoside group is not estrogenically active and can be used for topical

applications. Also, the epigallocatechin-3-galate (EGCC) contained in tea leaves is a polyphenol with strong antioxidant activity and topical preparations of tea leaf extract containing this compound can inhibit the effects of UVR exposure, including protecting the body from UVR-induced immunosuppressant activity. Various plant species from the coffee family also contain polyphenols such as proanthrocyanidins, quinic acid, caffeic acid, caffeine and chlorogenic acid, which are also powerful antioxidants [31, 45]. Ferulic acid is another antioxidant found in whole grains, spinach, parsley, grapes, rhubarb, and cereal grains (especially wheat) [47]. Topical use of grape seeds has been proven to prevent or modrate UVR-related damages, such as the thickening of the epidermal layer, erythema, pigmentation, inflammatory neutrophil infiltration and collagen degradation, as well as the increased expression of genes associated with skin aging such as those for cyclooxygenase 2 (*COX-2*), nuclear factor erythroid 2–related factor 2 (*NRF-2*) and heme oxygenase 1 (*HO-1*). The main content of grape seed is resveratrol which is a natural stilbene compound. There are also other antioxidant compounds which may have use as skin anti-aging products, such as quercetin, catechin, epi-catechin, gallic acid and oligomeric proanthocyanidins [43].

3.2 Anti-photo-aging Agents

It is well established that UVR can cause skin disorders such as sunburn and non-melanoma skin cancer. A photoprotective agent can be used to minimize the harmfull effects of UVR exposure to the bare skin. Sun protection factor (SPF) describes the effectiveness level of bioactive compounds that act as UV protectants. It is defined as the minimal erythema dose ratio between sunscreen-protected and unprotected skin [48]. Sunscreens slow the progression of photo-aging and prevent aging effects on the skin such as wrinkles, actinis keratosis reduction, solar elastosis and squamous skin carcinoma. Sunscreen preparations contain organic UV filters that block either UV-A and/or UV-B radiation by absorbing the radiation [49, 50].

Organic sunscreens that have been commonly used are aminobenzoate (e.g., p-aminobenzoic acid esters), cinnamate (e.g., octinoxate), salicylate, actocrylene and benzophenone (e.g., oxybenzone), avobenzone and mexoryl SX [48]. Many plant polyphenols have been evaluated as potential sun protection agents, since they are able to absorb UV-B radiation [12–14]. For example, the phenolic compounds of Schinus terebinthifolius crude extract, such as ethyl gallate, gallic acid and several flavonoid compounds, may be useful as natural sunscreen products [12]. In addition to their antioxidant activities, EGCG and resveratrol also have activities that can reduce the size of erythema caused by UVR exposure. High dosages of flavanol compounds from cocoapowder have a similar capability. Finally, carotenoids such as β-carotene, lycopene, canthaxan-thin, and lutein derived from tomatoes, carrots and algae, are antioxidants that exhibit photoprotective activity and are capable of reducing the size of erythema cause by UVR exposure [43].

3.3 Anti-inflammatory Agents

As noted above, UVR induces oxidative stress in epidermal cells which causes lipid peroxidation and cell damage. In this scenario, the complement system recognizes the oxidation-specific epitopes and causes inflammation, which leads to macrophage infiltration and activation that removes the damaged cells and oxidized lipids [51, 52]. Macrophage activation leads to MMP release that degrades the ECM. Thus, long term exposure to UVR can lead to overactivation of the complement system, which causes DEJ damage and overburdens macrophages with oxidized lipids, which further causes chronic inflammation and long-term damage to the dermis due to proinfammatory cytokines and ROS release [51, 53]. In cases of inflammation caused by photoinduced oxidative stress, phenolic compounds can help by attenuating the activity of inflammatory mediators such as interleukin 6 (IL-6) and prostaglandin-E2 (PGE2). In addition, the natural compounds such as veratric acid [15], dihydrochalcone phloretin, afzelin [14] and luteolin [54] can decrease expression of the inflammation-related molecules.

3.4 Promotion of Skin Cell Proliferation

Epidermal skin cells possess the ability for self-renewal and dead cell replacement with turnover times of 40–56 days, but aging makes the capacity decline [55]. Bioactive agents from herbal products can be used to restore this regenerative capacity to some extent. Several plants that had been proven to have skin cell renewal capacity include Populus nigra buds, oak woodm mate leaf, and benjoin resin [16]. Nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) analysis of Populus nigra buds extracts revealed the presence of 6 phenolic acids (caffeic, -coumaric, isoferrulic, di-O-methylcaffeic, cinnamic), three flavonoids (pinocembrin, pinobanksin, and its derivate) and salicin [16], which all have potent antioxidant, antiinflammatory and skin regeneration activity. This extract modulates transcription of genes, such as those for Kruppel-like factor 10 (*KLF10*), E2F-4 transcription factor (*E2F4*), and epidermal growth factor (EGF) response factor 1(*ZFP36L1*), which are involved in skin regeneration through effects on proliferation, differentiation, survival, and DNA synthesis. Expression of the catalase (*CAT*) gene was also found to be up-regulated, which is responsible for antioxidative effects, and the chemokine ligand 5 (*CCL5*) gene down-regulated, which is linked to inflammatory processes. The ellagitannin compounds of oak wood, caffeoyl derivatives from mate leaf and phenolic acids in benjoin resin have also been identified as compounds capable of modulating skin-aging related genes. All of these compounds have a demonstrated ability to down-regulate the proinflammatory *CCL5* gene and up-regulate proliferation marker genes (*KLF10*, *E2F4* and *ZFP36L1*) [16].

3.5 Modulation of Collagen and Elastin Synthesis

The ECM proteins such as collagen and elastin are increasingly proteolyzed with aging by the MMPs. MMPs in normal cells have been found to be regulated at the transcriptional level by specific protein inhibitors. The homeostatic imbalance of synthesis and degradation of the ECM causes loss of skin integrity, and may result in wrinkle formation. However, inhibition of MMP activity facilitates maintenance of skin structure and the phenolic compounds are known to preserve skin structure through this mechanism [56].

Crude grape pomace from white wine contains phenolic compounds such as cathecin, epicatechin, procyanidins B1 and B2, gallic acid, caftaric acid, quercetin glycosides and stilbene trans-resveratrol which all act as inhibitors of MMPs. The strongest activity was found in a fraction containing gallic acid, and this was followed by procyanidins and catechin which had proteolytic inhibitory activity, especially to collagenase [56]. Unfortunately, the use of these compounds is limited due to their high molecular weights and low permeabilities.

Gallic acid and elaeocarousin in an Emblica officinalis Gaertn ethanolic extract has been reported to enhance proliferation and collagen production in fibroblasts [17]. The extract was capable of minimalizing wrinkle formation through collagen synthesis, MMP inhibition and revival of damaged collagen fibers. Tannins such as emblicanin, pedunculagin and punigluconin are assumed to have similar activity as green tea tannin (EGCG), which modulates the expression and production of MMPs via AP-1 and nuclear factor kappa B (NF-κB) activation [57].

Depletion of collagen production in the aged skin can also be treated with collagen synthesis enhancers, such as vitamin C and glycolic acid, which are claimed to have anti-wrinkle capacities, although this has not been proven.

3.6 Melanin Production Inhibitors

Melanin is capable of absorbing 50–75% of the UVR exposure to the skin [58, 59]. Therefore, it can play a significant role as a skin protector. However, the hyperpigmentation caused by melanin overexpression can also lead to dermal disorders. Melanin is natural pigment produced by melanosomes in melanocytes and it is transferred to keratinocytes through dendrites. Melanin is a tyrosine derivative that forms during oxidative stress reactions through the activity of the tyrosinase enzyme. Melanin synthesis is also regulated by tyrosine-related protein 1 and 2 (TRP-1, TRP-2) and cellular signaling.

Melanin inhibitors work through inhibition of tyrosinase [60, 61]. Phenolic and flavonoids which have a structure similar to tyrosine, with regards to the presence of aromatic purine rings, and these can act as substrate analog inhibitors in melanogenesis [62, 63]. The compounds Brazilin and isoflavonoiud-4-O-methylsappanol were identified in a Sappanwood methanolic extract as having the ability to inhibit melanogenesis [64] in faskulin-treated HMV-II human melanoma cells. Resveratrol

and oxyresveratrol are also tyrosinase inhibitors [65, 66]. Other herbal products that have melanogenesis inhibitor activity include Morus alba leaf extract [67], Arthrophytum scoparium [18], and Trifolium nigrescens Subsp. The petrisavi [68] and Morus alba leaf extract inhibitory effects are due to the presence of 20 phenolic compounds (8 benzofurans, 10 flavonoids, one stilbenoid and one chalcone) [67]. Catechol and tetrahydro-isoquinoline in Arthrophytum scoparium are responsible for the inhibition of tyrosinase and TRP-1 as well as down-regualtion of the tyrosinase microphthalmia-associated transcription factor (*MITF*) and melanocortin 1 receptor (*MC1R*) genes [18]. In addition, trifolium nigrescens phenolic compounds showed inhibitory effects on mushroom tyrosinase, and one of these containing a glucoside residue was found to have the highest activity [68].

4 Herbal Skin Care Product with Anti-aging Properties

The increasing proportion of the aging population globally correlates with the increasing demand of anti-aging products. The need for a beautiful, healthy and youthful appearance has become a trend and the cosmeceutical industry has become an ever-growing market in order to meet these demands. In line with this, new technologies and innovations have been brought into play to increase quality and effectivity of these products, and to attract more customers.

Presently, there are many topical and oral skin care products that function by improving or maintaining skin health [69–72]. Topical products are known as "cosmeceuticals", while oral products are known as "nutricosmeceuticals". Both of these are backed by scientific evidence of effectiveness and safety although these do not follow such strict rules as those demanded in the traditional drug discovery industry (Fig. 9.2).

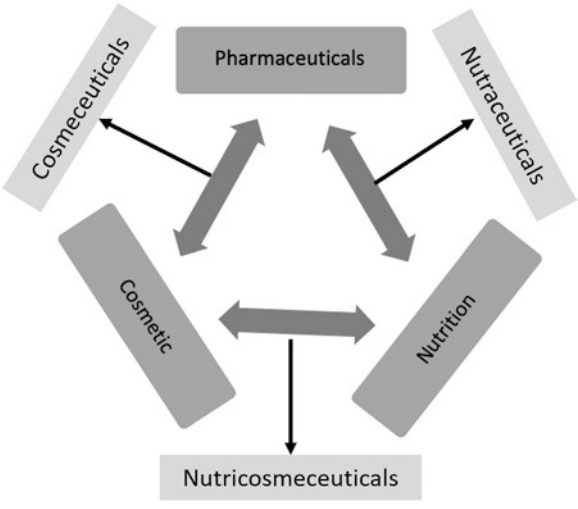

Fig. 9.2 Intersept between pharmaceuticals, cosmetics and nutrition

4.1 Cosmeceutical Products

Cosmeceutical is a portmanteau of the words cosmetic and pharmaceutical, which means that it is a cosmetic preparation that also has a pharmaceutical function (Fig. 9.2) [69–74]. Cosmeceuticals are intended to improve and reduce skin imperfections, compared to cosmetics that only hide or mask such imperfections. Similar to cosmetic products, cosmeceutical products are applied topically and intended for daily use. Such products are used to resolve facial aging problems, in particular wrinkles, mottled pigmentation, roughness of skin, rhytides, erythema, skin tone loss, dryness, sallowness, furrows, solar elastosis and black spots. The bioactive ingredients can comprise sunscreens and antioxidants to enhance the protection level of the skin against ROS and thus prevent photodamage and improve skin malignancies [74–77].

There are various forms of cosmeceutical products for antiaging treatments including lotions, creams, gels and liquids. These products usually function as moisturizers, antioxidants, anti-wrinkle agents, whitening agents, skin supplements (vitamins) or growth factors (Fig. 9.3). These products are often intended for daily use and thus the efficacy and safety aspects must be guaranteed. Apart from this requirement, there are several things about the quality that must also be fulfilled, such as it should not be irritative, it should be suitable for various or selected skin types [74, 76, 77].

Aged skin is more vulnarable to dryness. This is due to decreased production and increased degradation of GAG which reduces the ability of the skin to bind water. To improve this condition, regular use of a moisturizer could protect and strengthen the skin. It has been shown that this hydration ability of cosmeceutical products makes the skin softer and smoother [1, 76, 78, 79].

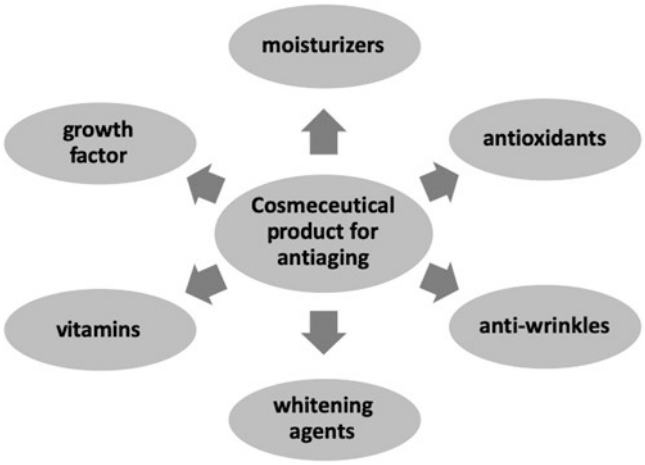

Fig. 9.3 Cosmeceutical product activity

In order to meet these consumer demands, the cosmeceutical is aiming for product specifications with higher efficacy, immediate effects and guaranteed levels of safety. Firstly, the material should have complete function in the form of natural product extracts, active compound isolates or synthesized or semi-synthesized compounds [25, 77]. Secondly, there is the need for development of new technologies for transdermal delivery systems so that the active ingredients can easily and quickly traverse the skin. Finally, the development of technologies that can objectively measure the penetration and effectiveness of the material should be developed in parallel as a means of quality and efficiency monitoring [74, 77, 79].

In the development of product cosmeceuticals, the mechanism of penetration into the skin layer is the basis for developing a drug delivery system. In general, the drug enters the target site through damaged skin However, the active ingredients must be able to penetrate into normal skin in the same manner as cosmetic products. Of the three main skin layers described earlier, the stratum corneum acts as a barrier layer against penetration. The choice of the drug delivery system technology applied to the material must be enable the active ingredient to traverse this barrier [11, 77].

Besides the skin penetration properties, the purpose of a drug delivery system is to increase the duration of action and stability, prevent incompatibility with other ingredients in the formulation and prevent the occurrence of undesirable effects either locally or systemic [73, 79, 80]. Various forms of drug delivery systems that are widely used include vesicles (liposomes, niozomes, nanosomes, phytosomes, herbosomes, marinosom, oleosom, aquasom, ultrasom, photozom, ethosome, transferosome, sphingosome, colloidosomes), emulsions (microemulsions, nanoemulsions, liquid crystals) and particulates (microparticles, nanoparticles, solid lipid nanoparticles, structured nano lipid carriers, microcapsules, nanocapsules, microspheres, nanocrystalline and cyclodextrin). The development of a drug delivery system for cosmeceutical products has been shown to increase its usefulness, but because the product is used daily for a long time, attention should be paid regarding the possibility of unwanted side effects. Therefore, product development must also take in to account the safety aspects [79, 80].

4.2 Nutricosmeceutical Products

The desire to have a youthful appearance may be met with good nutrition in line with the pharase, “beauty from inside”. This has led to new innovations regarded as “nutricosmeceuticals”, which are nutritional products that have both cosmetic and antiaging effects (Fig. 9.2) [70, 81–83]. As physical beauty is reflection of skin health status, the nutricosmeceutical industry aims to develop food products that have been proven to maintain healthy bodies and also have good effects on the skin. Recently, a number of skin food products have been developed, containing carotenoids, polyphenols, vitamins, essential fatty acids and pre-and probiotic substances, which have been used previously via topical applications to improve skin conditions (Fig. 9.4) [1, 82].

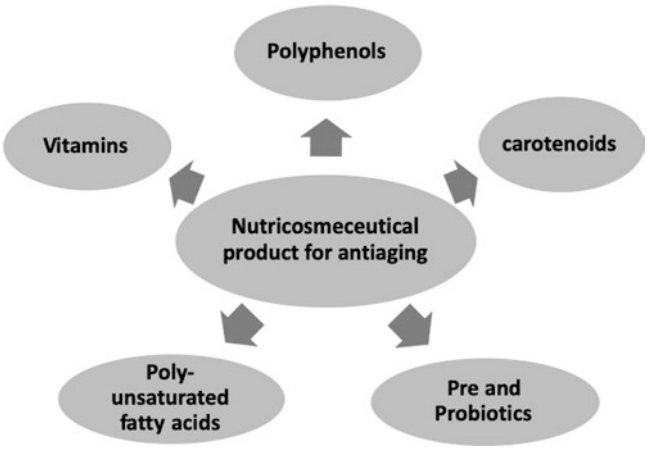

Fig. 9.4 Ingredients in nutricosmeceutical products

Since free radical formation appears to be linked to aging, antioxidant intake may help to restore homeostasis. Foods that are rich in antioxidants have also been shown to have a role in maintaining health and in delaying the aging process [75, 78, 81, 82]. These were shown to have a protective effect against free radicals found in the skin, through activation of endogenous antioxidants including enzymatic (reduced glutathione, superoxide dismutase and catalase) and non-enzymatic (vitamin E isoform, vitamin C and ubiquinol) ones. Thus both exogenous and endogenous antioxidants may have an important role in counteracting oxidative stress. In line with this, several endogenous antioxidants are known to be stimulated by a number of nutritional factors derived from fruits and vegetables.

Some carotenoid derivatives of vitamin A, such as β-carotene, astaxanthin, lycopene and retinol, are known to be effective anti-oxidants [1, 75, 78, 81, 82]. Tomatoes, watermelons, guavas, rosehips, and pink grapefruits can reduce oxidative damage because these all contain lycopene which acts as a singlet oxygen quencher. In addition, carrots, pumpkins, yams, mangoes and papayas, which are sources of β-carotene, can protect the skin from erythema caused by UV induction. The structure of polyphenols also shows strong anti-oxidant properties. Other molecules that have the basic structure of polyphenols include phenolic acids, flavonoids, stilbenes and lignans. Polyphenol compounds are found in fruits, vegetables, cereals, chocolate, dried beans and vegetables, as well as in drinks such as fruit juice, tea, coffee and red wine. Food sources containing linolenic acid and linoleic acid include fish and shellfish, flaxseed, flax oil, soybean oil, canola oil, chia seeds, pumpkin seeds, sunflower seeds, leafy vegetables, walnuts, sesame seeds, avocado seeds, avocados, salmon and albacore tuna. These foods can act as anti-inflammatory agents and thereby provide significant protection against UV radiation-induced erythema, for example. Probiotics and prebiotics can be consumed in various forms of food and beverage products, and studies have shown that these products can accelerate the recovery of human skin immune homeostasis after UV-induced immunosuppression.

The association between nutrition and skin conditions has led to the use of nutricosmeceutical products to maintain and regain body homeostasis through nutrients that enter the body, so that these can improve skin health and beauty. A complete and balanced nutrition can also positively affect the condition and appearance of the skin. Therefore, nutritional supplements in the form of nutricosmeceutical products can be used to help optimize diets and improve quality of life.

5 Conclusions

Chronological aging naturally affects and causes changes in the body, especially in the appearance and characteristics of the skin. Exposure to external factors will worsen this change. Considerable efforts have been made to improve, maintain and delay the effects of aging due to both intrinsic and external factors through invasive and non-invasive methods. In line with this, antiaging products have developed rapidly. The consumers demand products that can show the effects of rapid change, but they also realize that the results will not be as fast as surgery. Nevertheless, they prefer antiaging products that can "improve", "maintain" and "delay" the effects of aging on their appearance. Products that can meet these demands are nutricosmeceuticals and cosmeceuticals, which offer a complementary means of acquiring skin health from inside and outside.

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References

1. Pérez-Sánchez A, Barrajón-Catalán E, Herranz-López M, Micol V (2018) Nutraceuticals for skin care: a comprehensive review of human clinical studies. Nutrients 10(4). pii: E403. https://doi.org/10.3390/nu10040403
2. Blanpain C, Fuchs E (2006) Epidermal stem cells of the skin. Annu Rev Cell Dev Biol 22:339–373
3. Zhang S, Duan E (2018) Fighting against skin aging: the way from bench to bedside. Cell Transplant 27(5):729–738
4. Rinnerthaler M, Bischof J, Streubel MK, Trost A, Richter K (2015) Oxidative stress in aging human skin. Biomol Ther 5(2):545–589
5. Ahsanuddin S, Lam M, Baron ED (2016) Skin aging and oxidative stress. AIMS Mol Sci 3(2):187–195
6. Tu Y, Quan T (2016) Oxidative stress and human skin connective tissue aging. Cosmetics 3(3):28. https://doi.org/10.3390/cosmetics3030028
7. Helfrich YR, Sachs DL, Voorhees JJ (2008) Overview of skin aging and photoaging. Dermatol Nurs 20(3):177–183; quiz 184

8. Kazanci A, Kurus M, Atasever A (2017) Analyses of changes on skin by aging. Skin Res Technol 23(1):48–60
9. Oliveira BF, Nogueira-Machado JA, Chaves MM (2010) The role of oxidative stress in the aging process. ScientificWorldJournal 10:1121–1128
10. Avantaggiato A, Bertuzzi G, Pascali M, Candotto V, Carinci F (2015) The theories of aging: reactive oxygen species and what else? J Biol Regul Homeost Agents 29(3 Suppl 1):156–163
11. Jadoon S, Karim S, Bin Asad MH, Akram MR, Khan AK, Malik A et al (2015) Anti-aging potential of phytoextract loaded-pharmaceutical creams for human skin cell longetivity. Oxidative Med Cell Longev 2015:709628. https://doi.org/10.1155/2015/709628
12. Bulla MK, Hernandes L, Baesso ML, Nogueira AC, Bento AC, Bortoluzzi BB et al (2015) Evaluation of photoprotective potential and percutaneous penetration by photoacoustic spectroscopy of the Schinus terebinthifolius raddi extract. Photochem Photobiol 91(3):558–566
13. Almeida IF, Pinto AS, Monteiro C, Monteiro H, Belo L, Fernandes J et al (2015) Protective effect of C. sativa leaf extract against UV mediated-DNA damage in a human keratinocyte cell line. J Photochem Photobiol B 144:28–34
14. Shin SW, Jung E, Kim S, Kim JH, Kim EG, Lee J et al (2013) Antagonizing effects and mechanisms of afzelin against UVB-induced cell damage. PLoS One 8(4):e61971. https://doi.org/10.1371/journal.pone.0061971
15. Shin SW, Jung E, Kim S, Lee KE, Youm JK, Park D (2013) Antagonist effects of veratric acid against UVB-induced cell damages. Molecules 18(5):5405–5419
16. Dudonné S, Poupard P, Coutière P, Woillez M, Richard T, Mérillon JM et al (2011) Phenolic composition and antioxidant properties of poplar bud (Populus nigra) extract: individual antioxidant contribution of phenolics and transcriptional effect on skin aging. J Agric Food Chem 59(9):4527–4536
17. Fujii T, Wakaizumi M, Ikami T, Saito M (2008) Amla (Emblica officinalis Gaertn.) extract promotes procollagen production and inhibits matrix metalloproteinase-1 in human skin fibroblasts. J Ethnopharmacol 119(1):53–57
18. Chao HC, Najjaa H, Villareal MO, Ksouri R, Han J, Neffati M et al (2013) Arthrophytum scoparium inhibits melanogenesis through the down-regulation of tyrosinase and melanogenic gene expressions in B16 melanoma cells. Exp Dermatol 22(2):131–136
19. Allemann IB, Baumann L (2009) Botanicals in skin care products. Int J Dermatol 48(9):923–934
20. Kraft JN, Lynde CW (2005) Moisturizers: what they are and a practical approach to product selection. Skin Therapy Lett 10(5):1–8
21. Makrantonaki E, Zouboulis CC (2007) Molecular mechanisms of skin aging: state of the art. Ann N Y Acad Sci 1119:40–50
22. El-Domyati M, Attia S, Saleh F, Brown D, Birk DE, Gasparro F et al (2002) Intrinsic aging vs. photoaging: a comparative histopathological, immunohistochemical, and ultrastructural study of skin. Exp Dermatol 11(5):398–405
23. Tobin DJ (2017) Introduction to skin aging. J Tissue Viability 26(1):37–46
24. Baumann L (2018) How to use oral and topical cosmeceuticals to prevent and treat skin aging. Facial Plast Surg Clin North Am 26(4):407–413
25. Kusumawati I, Kurniawan KO, Rullyansyah S, Prijo TA, Widyowati R, Ekowati J et al (2018) Anti-aging properties of Curcuma heyneana Valeton & Zipj: a scientific approach to its use in Javanese tradition. J Ethnopharmacol 225:64–70
26. Stearns HC, Sneeden VD (1966) Observations on the clinical and pathologic aspects of the pelvic congestion syndrome. Am J Obstet Gynecol 94(5):718–732
27. Costin GE, Hearing VJ (2007) Human skin pigmentation: melanocytes modulate skin color in response to stress. FASEB J 21(4):976–994
28. Lorencini M, Brohem CA, Dieamant GC, Zanchin NI, Maibach HI (2014) Active ingredients against human epidermal aging. Ageing Res Rev 15:100–115
29. Farage MA, Miller KW, Elsner P, Maibach HI (2013) Characteristics of the aging skin. Adv Wound Care (New Rochelle) 2(1):5–10
30. Calleja-Agius J, Muscat-Baron Y, Brincat MP (2007) Skin ageing. Menopause Int 13(2):60–64

31. Baumann L (2007) Skin ageing and its treatment. J Pathol 211(2):241–251
32. Rittié L, Fisher GJ (2002) UV-light-induced signal cascades and skin aging. Ageing Res Rev 1(4):705–720
33. Elsner P, Maibach HI (2005) Cosmeceuticals and active cosmetics: drugs versus cosmetics. Taylor & Francis, Boca Raton. ASIN: B01K0U81P0
34. Sakai S, Yasuda R, Sayo T, Ishikawa O, Inoue S (2000) Hyaluronan exists in the normal stratum corneum. J Invest Dermatol 114(6):1184–1187
35. Bentov I, Reed MJ (2015) The effect of aging on the cutaneous microvasculature. Microvasc Res 100:25–31
36. Rittié L, Fisher GJ (2015) Natural and sun-induced aging of human skin. Cold Spring Harb Perspect Med 5(1):a015370. https://doi.org/10.1101/cshperspect.a015370
37. Rohrich RJ, Pessa JE (2008) The retaining system of the face: histologic evaluation of the septal boundaries of the subcutaneous fat compartments. Plast Reconstr Surg 121(5):1804–1809
38. Hughes MC, Williams GM, Baker P, Green AC (2013) Sunscreen and prevention of skin aging: a randomized trial. Ann Intern Med 158(11):781–790
39. Guo WJ, Datta S, Band V, Dimri GP (2007) Mel-18, a polycomb group protein, regulates cell proliferation and senescence via transcriptional repression of Bmi-1 and c-Myc oncoproteins. Mol Biol Cell 18(2):536–546
40. Kim EJ, Kim YK, Kim JE, Kim S, Kim MK, Park CH et al (2011) UV modulation of subcutaneous fat metabolism. J Invest Dermatol 131(8):1720–1726
41. Sepe A, Tchkonia T, Thomou T, Zamboni M, Kirkland JL (2011) Aging and regional differences in fat cell progenitors - a mini-review. Gerontology 57(1):66–75
42. Stojiljković D, Pavlović D, Arsić I (2014) Oxidative stress, skin aging and antioxidant therapy. Acta Fac Medicae Naissensis 31(4):207–217
43. Petruk G, Del Giudice R, Rigano MM, Monti DM (2018) Antioxidants from plants protect against skin photoaging. Oxidative Med Cell Longev 2018:1454936–1454911. https://doi.org/10.1155/2018/1454936
44. Kusumawati I, Indrayanto G (2013) Natural antioxidants in cosmetics. In: Atta-ur-Rahman (ed) Studies in natural products chemistry, vol 40, 40th ed, pp 485–505. Elsevier; Amsterdam, Netherlands. ISBN-10: 0444596038
45. Simo A, Kawal N, Paliyath G, Bakovic M (2014) Botanical antioxidants for skin health in the world of cosmeceuticals. Int J Adv Nutr Health Sci 2(1):67–88
46. Kasote DM, Katyare SS, Hegde MV, Bae H (2015) Significance of antioxidant potential of plants and its relevance to therapeutic applications. Int J Biol Sci 11(8):982–991
47. Zduńska K, Dana A, Kolodziejczak A, Rotsztejn H (2018) Antioxidant properties of ferulic acid and its possible application. Skin Pharmacol Physiol 31(6):332–336
48. Gilaberte Y, González S (2007) Update on photoprotection. Actas Dermosifiliogr 101(8):659–672
49. Liang Y, Wu M, Chen Y (2019) Selected medicinal herbs and functional peptides for protection against photoaging of the skin. J Cosmet Dermatological Sci Appl 9(1):1–18
50. Kullavanijaya P, Lim HW (2005) Photoprotection. J Am Acad Dermatol 52(6):937–958
51. DeBuys HV, Levy SB, Murray JC, Madey DL, Pinnell SR (2000) Modern approaches to photoprotection. Dermatol Clin 18(4):577–590
52. Nash JF (2006) Human safety and efficacy of ultraviolet filters and sunscreen products. Dermatol Clin 24(1):35–51
53. Fourtanier A, Moyal D, Seité S (2008) Sunscreens containing the broad-spectrum UVA absorber, Mexoryl SX, prevent the cutaneous detrimental effects of UV exposure: a review of clinical study results. Photodermatol Photoimmunol Photomed 24(4):164–174
54. Wölfle U, Esser PR, Simon-Haarhaus B, Martin SF, Lademann J, Schempp CM (2011) UVB-induced DNA damage, generation of reactive oxygen species, and inflammation are effectively attenuated by the flavonoid luteolin in vitro and in vivo. Free Radic Biol Med 50(9):1081–1093
55. Koster MI (2009) Making an epidermis. Ann N Y Acad Sci 1170:7–10

56. Wittenauer J, Mäckle S, Sußmann D, Schweiggert-Weisz U, Carle R (2015) Inhibitory effects of polyphenols from grape pomace extract on collagenase and elastase activity. Fitoterapia 101:179–187
57. Chowdhury A, Sarkar J, Chakraborti T, Chakraborti S (2015) Role of Spm-Cer-S1P signalling pathway in MMP-2 mediated U46619-induced proliferation of pulmonary artery smooth muscle cells: protective role of epigallocatechin-3-gallate. Cell Biochem Funct 33(7):463–477
58. Hah YS, Cho HY, Lim TY, Park DH, Kim HM, Yoon J et al (2012) Induction of melanogenesis by rapamycin in human MNT-1 melanoma cells. Ann Dermatol 24(2):151–157
59. Liu WS, Kuan YD, Chiu KH, Wang WK, Chang FH, Liu CH et al (2013) The extract of Rhodobacter sphaeroides inhibits melanogenesis through the MEK/ERK signaling pathway. Mar Drugs 11(6):1899–1908
60. Zucca P, Pintus M, Manzo G, Nieddu M, Steri D, Rinaldi AC (2015) Antimicrobial, antioxidant and anti-tyrosinase properties of extracts of the Mediterranean parasitic plant Cytinus hypocistis. BMC Res Notes 8:562. https://doi.org/10.1186/s13104-015-1546-5
61. Roh HJ, Noh HJ, Na CS, Kim CS, Kim KH, Hong CY et al (2015) Phenolic compounds from the leaves of Stewartia pseudocamellia maxim. And their whitening activities. Biomol Ther 23(3):283–289
62. Sugumaran M (2002) Comparative biochemistry of eumelanogenesis and the protective roles of phenoloxidase and melanin in insects. Pigment Cell Res 15(1):2–9
63. Boissy RE, Manga P (2004) On the etiology of contact/occupational vitiligo. Pigment Cell Res 17(3):208–214
64. Mitani K, Takano F, Kawabata T, Allam AE, Ota M, Takahashi T et al (2013) Suppression of melanin synthesis by the phenolic constituents of sappanwood (Caesalpinia sappan). Planta Med 79(1):37–44
65. Park J, Park JH, Suh HJ, Lee IC, Koh J, Boo YC (2014) Effects of resveratrol, oxyresveratrol, and their acetylated derivatives on cellular melanogenesis. Arch Dermatol Res 306(5):475–487
66. Kim BH (2010) Safety evaluation and anti-wrinkle effects of retinoids on skin. Toxicol Res 26(1):61–66
67. Jeong JY, Liu Q, Kim SB, Jo YH, Mo EJ, Yang HH et al (2015) Characterization of melanogenesis inhibitory constituents of Morus alba leaves and optimization of extraction conditions using response surface methodology. Molecules 20(5):8730–8741
68. Demirkiran O, Sabudak T, Ozturk M, Topcu G (2013) Antioxidant and tyrosinase inhibitory activities of flavonoids from Trifolium nigrescens Subsp. petrisavi. J Agric Food Chem 61(51):12598–12603
69. Oricha BS (2010) Cosmeceuticals: a review. Afr J Pharm Pharmacol 4(4):127–129
70. Anunciato TP, da Rocha Filho PA (2012) Carotenoids and polyphenols in nutricosmetics, nutraceuticals, and cosmeceuticals. J Cosmet Dermatol 11(1):51–54
71. Kadam Vaishali S, Chintale Ashwini G, Deshmukh Kshitija P, Nalwad Digambar N (2013) Cosmeceuticals an emerging concept: a comprehensive review. Int J Res Pharm Chem 3(2):308–316
72. Wanjari N, Waghmare J (2015) A review on latest trend of cosmetics-cosmeceuticals. Int J Pharma Res Rev 4(5):45–51
73. Millikan LE (2001) Cosmetology, cosmetics, cosmeceuticals: definitions and regulations. Clin Dermatol 19(4):371–374
74. Bellad KA, Nanjwade BK, Kamble MS, Srichana T, Idris NF (2017) Development of cosmeceuticals. World J Pharm Pharm Sci 6(4):643–691
75. Pandel R, Poljšak B, Godic A, Dahmane R (2013) Skin photoaging and the role of antioxidants in its prevention. ISRN Dermatol 2013:930164. https://doi.org/10.1155/2013/930164
76. McCook JP (2016) Topical products for the aging face. Clin Plast Surg 43(3):597–604
77. Shin KO, Park HS (2019) Antiaging cosmeceuticals in Korea and open innovation in the era of the 4th industrial revolution: from research to business. Sustain 11(3):898. https://doi.org/10.3390/su11030898
78. Hodges AL, Walker DK (2017) Skin care for women. Nurs Womens Health 20(6):609–613

79. Kaul S, Gulati N, Verma D, Mukherjee S, Nagaich U (2018) Role of nanotechnology in cosmeceuticals: a review of recent advances. J Pharm (Cairo) 2018:3420204. https://doi.org/10.1155/2018/3420204
80. Alğin Yapar E (2017) Herbal cosmetics and novel drug delivery systems. Indian J Pharm Educ Res 51(3):S152–S158
81. Vranesić-Bender D (2010) The role of nutraceuticals in anti-aging medicine. Acta Clin Croat 49(4):537–544
82. Marini A, Krutmann J (2015) Beauty from the inside. In: Neves D (ed) Anti-ageing nutrients: Evidence-Based of Age-Associated Disease, 1st ed, pp 299–314. John Wiley & Sons Ltd; Chicago, USA. ISBN:9781118733271
83. Ramasubramania Raja R (2016) Nutraceuticals and cosmeceuticals for human beings – an overview. Am J Food Sci Health 2(2):7–17

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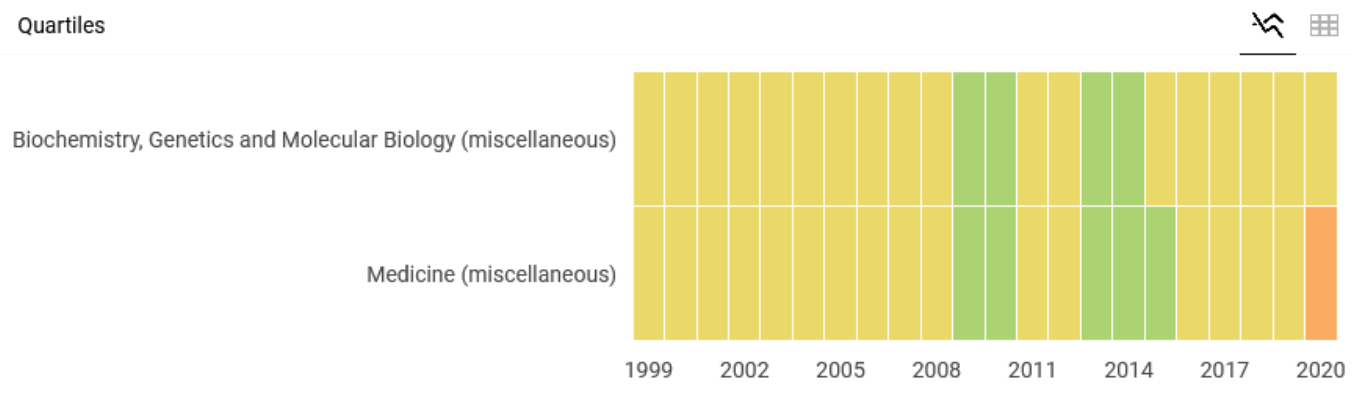

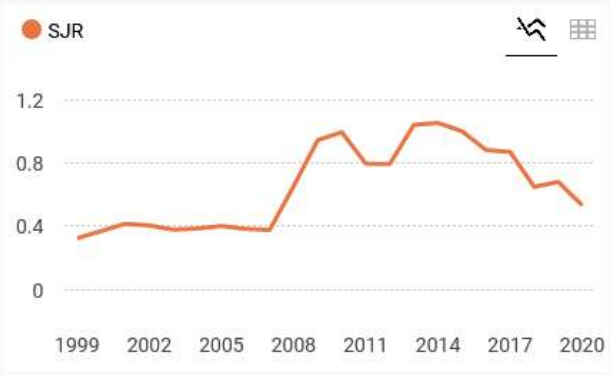

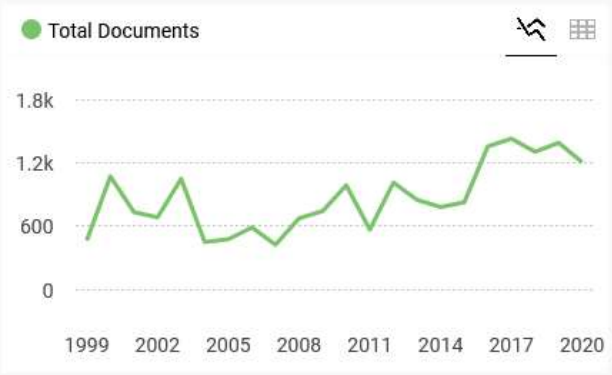

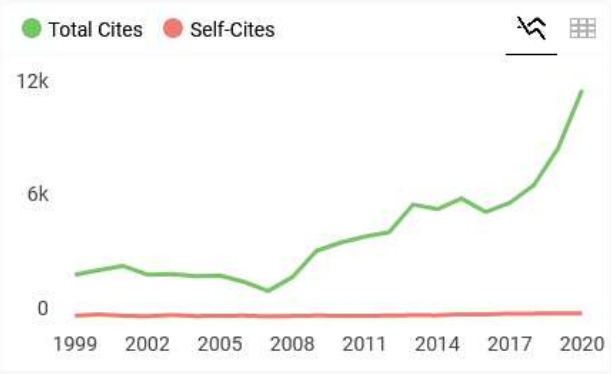

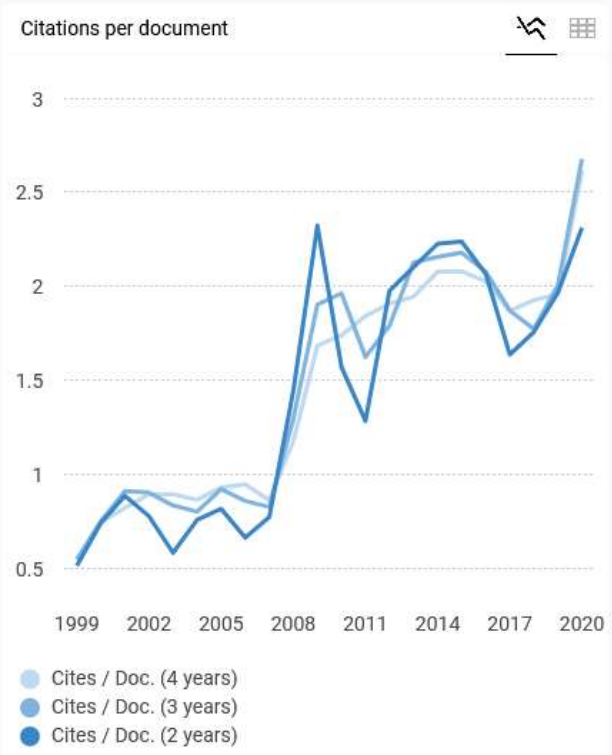

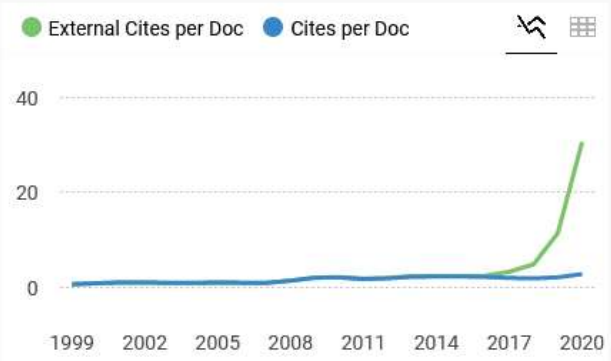

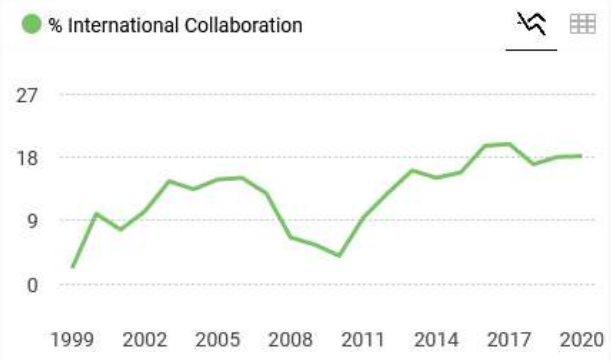

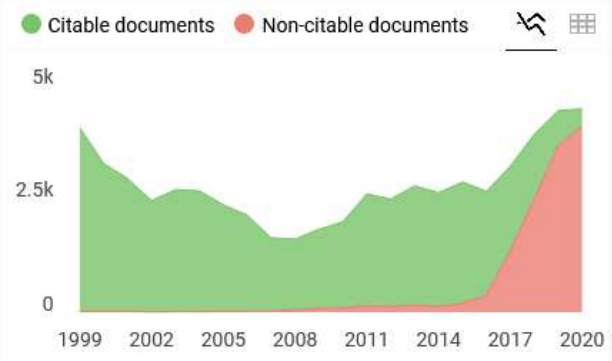

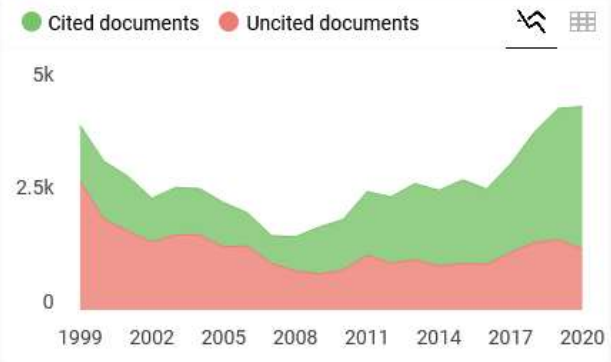

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