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REVIEW ARTICLE

Natural anti-aging skincare: role and potential

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Abstract The deterioration of the skin morphology and physiology is the first and earliest obvious harbinger of the aging process which is progressively manifested with increasing age. Such deterioration affects the vital functions of the skin such as homeodynamic regulation of body temperature, fluid balance, loss of electrolytes and proteins, production of vitamin D, waste removal, immune surveillance, sensory perception, and protection of other organs against deleterious environmental factors. There are, however, harmful *chemicals* and toxins found in everyday *cosmetics that consumers are now aware of*. Thus, the *natural* beauty industry is on the rise with innovative technology and high-performance ingredients as more consumers demand healthier options. *Therefore, the aims of this review are to give some critical insights to the effects of* both intrinsic and extrinsic factors on excessive or premature skin aging and to elaborate on the relevance of *natural beauty and natural anti-aging skincare approaches that will help consumers, scientists and entrepreneurs make the switch. Our recent investigations have shown the potential and relevance of identifying more resources from our rich natural heritage from various plant sources such as leaves, fruits, pomace, seeds, flowers, twigs and so on which can be explored for natural anti-aging skincare product formulations. These trending narratives have started to gain traction among researchers and consumers owing to the sustainability concern and impact of synthetic ingredients on human health and the environment. The natural anti-aging ingredients, which basically follow hormetic pathways, are potentially useful as* moisturizing agents; barrier repair agents; antioxidants, vitamins, hydroxy acids, skin lightening agents, anti-inflammatory ingredients, and sunblock ingredients.

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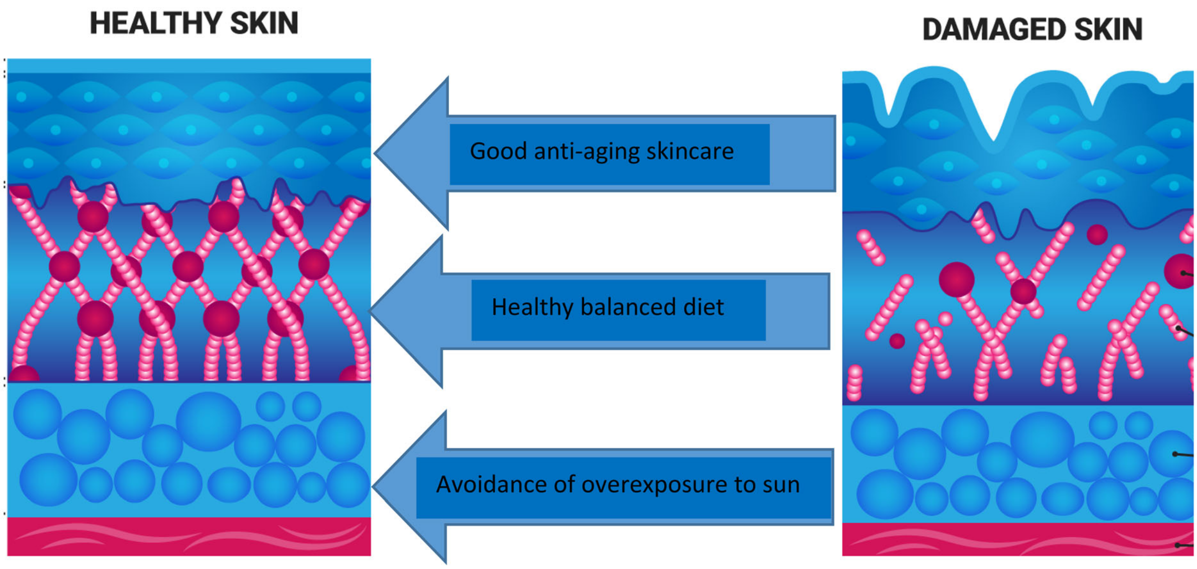
Graphic abstract



Keywords Aging · Anti-aging · Homeodynamic · Hormesis · Hormetins · Skincare · Natural beauty

Abbreviations

MMP	Matrix metalloproteinases
Cav-1	Caveolin-1
NLCS	Nanostructured lipid carriers
UVB	Ultraviolet B
SPF	Sun protecting factor

Introduction

Aging is a time-dependent event that is governed by two separate clocks, a mechanical clock and a biologic clock which determine our chronologic age and our biologic age, respectively (Malik and Hoenig 2019). The first and earliest obvious harbingers of the aging process are progressively manifested in the deterioration of the skin morphology and physiology with increasing age (Zouboulis et al. 2019a, b). It is also a basic concept that the skin is a barrier to the transcutaneous penetration of external harmful agents. The skin barrier mainly resides in the stratum corneum, comprising the corneocytes, surrounded by the intercellular lipid lamellae and attached by the corneodesmosome. Other components of the skin barrier are the tight junctions attaching to the lateral walls of the keratinocytes in the upper part of the stratum granulosum as well as the intercellular lipids, such as cholesterol, ceramides and free fatty acids which prevent transepidermal water loss (Choi 2019). Thus, the skin is not only vital for the homedynamic regulation of body temperature, fluid balance, loss of electrolytes and proteins, production of vitamin D, waste removal, immune surveillance, and sensory perception but also a protecting organ against deleterious environmental factors (Wang and Wu 2019; Zouboulis et al. 2019a, b).

The skin is the human body's largest and fastest-growing organ. The skin is considered an organ because it assumes and regulates *several important* physiological processes such as environmental and mechanical protection, sensing stimuli, thermoregulation, vitamin D synthesis immune surveillance and moisture *regulation* (Anderson et al. 2015). The skin also represents a social interface between an individual and other members of society (Yagi and Yonei 2017). *In view of the fact that the skin is the key personal identity, many are now* searching for remedies *against* the *aging* process of the skin, and thus opens the door for a new exploration of the so-called "*anti-aging products*". *The anti-aging cosmetic*

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industry is booming. The possibility of finding *anti-aging* treatments is at the forefront of the dermatological research and cosmetic industry. Individual's sense of self-identity and physical appearance are inseparable. Thus, self-esteem and self-consistency are the two basic self-concept motives that define consumers' attitudes towards cosmetics as well as other personal care products and services (Dai and Pelton 2018).

On the other hand, consumers nowadays are increasingly concerned about their health, thus demanding and advocating for the incorporation of natural bioactive or functional ingredients into cosmetics and other formulations to enhance their health status (Aguiar et al. 2016; Wen et al. 2017). Though the modern skincare products development requires relevant and extensive knowledge of the ingredients, natural products chemistry and skin biology (Anderson et al. 2015), there is also a continuous and significant increase in the research involving the use of biodegradable materials mainly due to the increasing environmental concerns and the ecological impacts of the use of synthetic counterparts (Mir et al. 2018). For instance, besides the Mediterranean diet and Indian Ayurvedic system, both the therapeutic effects and minimal side effects of traditional Chinese medicines have been known for thousands of years as a valuable resource for the development of several novel compounds used for the treatment of many skin diseases (Xu et al. 2018). As of 2018, it has been estimated that the global demand for natural and organic skincare products alone would have reached $13.2 billion with the general market demand keep growing at a fast rate. Similarly, the largest category in the beauty business has always been the personal care product category with global value sales over $630 billion (Emerald et al. 2016). Therefore, the aim of this review is to critically review the effect of skin aging, biochemical and morphological changes in connective tissues in aging skin, intrinsic and extrinsic aging factors as well as hormesis in skin aging. Better approaches to prevent excessive dermal aging and the relevance of natural skincare products are also presented.

Biochemical changes in aging skin

Aging disrupts the sensitive balance between those enzymes that regulate remodeling and repair of the dermal matrix, contributing to the loss of collagen production and other connective tissues (Farage et al. 2013). Though an aged dermis is obviously vulnerable, there are, however, other invisible risks associated with aging. One of the highly-studied risks is cellular senescence which occurs in culture as well as in the organism as a response to both excessive extracellular or intracellular stress. Senescent cells are known to accumulate during the lifetime in various animals including humans. In most cases, the senescence program only drives the cells into a cell-cycle arrest without eliminating them from the tissues, thus, leaving them viable and functional. Senescence may also lead to extensive changes in gene expression of affected cells otherwise known as senescence-associated secretory phenotypes involving several families of soluble and insoluble factors such as growth factors, interleukins, and chemokines (Strnadova et al. 2019).

On the other hand, the largest component of normal skin is the extracellular matrix, a complex meshwork of proteins and carbohydrates, composed of collagens, proteoglycans/glycosaminoglycans, elastin, fibronectin, laminins, and several other glycoproteins (Calleja-Agius et al. 2013; Lee et al. 2016). Collagen, elastin and hyaluronic acid are the major components of the dermis that contribute to supple, smooth and elastic skin. The skin's strength and *firmness* depend on *collagen*. The elasticity of the *skin* is maintained by *elastin*. *Hyaluronic acid* plays a role in maintaining the moisture of the *skin* by filling the free space of the *skin* matrix with water and giving it a fuller, firmer and youthful appearance (Calejja-Agius et al. 2007). As human ages, both natural (intrinsic) and environmental (extrinsic) factors cause *decreases in the* production of these important elements and *skin* becomes prone to damage, wrinkles and sagging (Farage et al. 2008). The weakening of the bond between the epidermis and dermis of extrinsically age skin also contributes to wrinkling formation due to the reduction in collagen type VII content and a marked loss of fibrillin-positive structures. The role of MMP, serine, and other proteases in the increased degradation of collagen is also responsible for the sparse distribution as well as a decrease in collagen content in photoaged skin. A continuous loss of collagen I in older skin does not only make collagen looks disorganized and irregular but also causes an increase in the ratio of collagen III to collagen I (Lee et al. 2016; Zouboulis et al. 2019a, b).

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In addition, adult dermis contains more decorin which mainly regulates collagen fibrillogenesis while various models of skin aging also suggest a progressive accumulation of senescent fibrocytes in an aged dermis as well as a dramatic reduction in the production of collagen I, loss of its volume, and local overproduction of matrix metalloproteinases [MMP] (Strnadova et al. 2019). A continuous increase and an upregulation of caveolin-1(Cav-1) expression levels have also been demonstrated by human corneal epithelial in aged subjects as a result of oxidative stress. This has also been linked to the development of premature cellular senescence. In addition, skin fibroblasts, both in chronological and UV-induced aging, demonstrate an up-regulation of Cav-1 expression, in vitro as well as in vivo (Kruglikov et al. 2019). Furthermore, the pH range for normal healthy skin is 5.4–5.9 for normal bacterial flora. The use of soap with high pH, however, can cause an increase in the skin pH, thus, leading to an alteration in the skin bacterial flora, irritability, and an increase in dehydration (Tarun et al. 2014). According to Lambers et al. (2006), skin with pH values less than 5.0 is in a better condition compared to skin with pH values more than 5.0 using the biophysical parameters such as barrier function, scaling, and moisturization. The authors also suggest that acidic skin pH (4–4.5) supports the firm attachment of resident skin bacterial flora while an alkaline skin pH (8–9) promotes their dispersal from the skin. The stratum corneum has a normal acidic pH which greatly contributes to the skin protective functions such as permeability barrier homeostasis, the integrity, and cohesion of the stratum corneum, primary cytokine activation, and epidermal antimicrobial defense. The three endogenous pathways and exogenous insults which contribute to the acidic environment of the stratum corneum are the free fatty acids generated from phospholipids by secretory phospholipase A2, the sodium ion/hydrogen ion (Na^+/H^+) antiporter-1 (NHE1), and the urocanic acid degraded by histidase from histidine. The deterioration of any of these pathways is mainly responsible for the increase in stratum corneum pH and thus an alteration in the skin protective functions. Generally, those with black skin, women, and younger people tend to have lower skin pH compared with those with white skin, men, and older individuals (Choi 2019). Therefore, cosmetic formulators and consumers should give due consideration to the pH factor especially when dealing with sensitive skin and acne-prone skin. Excellent and effective skincare products should be more skin and hair-friendly (Tarun et al. 2014).

Morphological changes in aging skin

Aging is undoubtedly a natural process of biochemical events responsible for the gradual damage accumulation which eventually leads to disease and ultimately death. The skin, however, appears to be the first bearer of the marks of time passage as well as an easily accessible model for the determination and assessment of the molecular mechanism involved in the aging process (Zouboulis et al. 2019a, b). As we get older, the skin starts to become drier, paler, clear (translucent) and more fragile (Poljšak et al. 2012). The epidermis and dermis become naturally thinner and flatter. As the skin ages, it doesn't stay as plump and smooth as it once was. *Easy bruising* is a common issue for all old skins. Fine lines, pigmented spots, sagging, telangiectasia, and wrinkles are an inevitable consequence of aging (Tobin 2017; Liu et al. 2019a, b). The complex physiology and biochemistry as well as structural integrity of the dermis, in aged skin, are dramatically altered due to the cumulative and combined effects of both intrinsic and extrinsic aging (Choi 2019). The genetic predisposition, qualitative and quantitative hormonal alterations, and cellular metabolic pathways are the main factors of the complex biologic intrinsic factors (Zouboulis et al. 2019a, b).

Though evidence of dermal aging is sometimes highly prevalent in routine histology, the principal environmental factor responsible for skin damage is ultraviolet (UV) radiation that is accumulated by the tissues over the years of life from both natural and artificial sources. This photodamage is linked to a structural complexity known as solar elastosis (or actinic elastosis, dermal elastosis) which clinically manifests as thickened, yellowish and coarsely wrinkled skin. This visual aspect has a substantial impact on tissue esthetics and health. Other ionizing radiation types (such as microwaves, and X-rays), chemical pollution, reactive oxygen radicals, smoking, lifestyle and diet, poor nutrition, and overeating are also known to accelerate or intensify signs of aging with clinical and subclinical manifestations such as deep wrinkles, reduced elasticity, uneven pigmentation, benign

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neoplasms, and xerosis, (Godoy et al. 2019; Kruglikov et al. 2019; Safdar et al. 2019; Strnadova et al. 2019).

Similarly, an aged epidermis is characterized by a significant increase in the number of stratum corneum layers in addition to other remarkable structural changes such as epidermal thinning, orthokeratosis flattening of the rete ridges, uneven distribution of melanocytes in the basal layer, and a significant decrease in Langerhans cells, as well as various changes and impairment of the skin barrier impairment such as a decrease in the tight junction components (such as claudin-1 and occluding), increased sensitivity to irritants, increased transdermal drug delivery, development of pruritus, and aggravation of xerosis (Choi 2019). The degenerative changes that occur in aging skin have always been increasingly studied. In older adults, about 20–80% of dermal thickness disappears.

Intrinsic and extrinsic skin aging factors

The skin and hair aging is caused by intrinsic (inevitable, genetically determined process or internal physiological factors) and extrinsic (declination process caused by external factors) mechanisms (Vierkötter et al. 2016; Cavinato et al. 2017). Intrinsic (chronologic) aging is the natural skin declining process that is generally controlled by genetics (Assaf et al. 2016). Extrinsic or photoaging (environmentally -induced) aging is caused by external factors. The common characteristics of intrinsic aging through advancing age include, but not limited to, fine wrinkles and a thinned epidermis while photoaging which is mainly caused by chronic sun exposure is characterized by skin laxity, the appearance of lentigines, deep wrinkles, and telangiectasias (Lee et al. 2016). Nevertheless, aging is known to be a continuous process which is very difficult to measure precisely owing to the complexity of the frequently subtle, structural and physiologic changes occurring over time. Though intrinsic and extrinsic aging types follow different pathways and mechanisms their effects are synergistic for every individual and both the internal and external factors influence the onset of age-related changes including the skin (Strnadova et al. 2019). The chief culprit of skin weakening, however, is extrinsic aging. A few of the key factors that cause extrinsic aging include UV radiation, diet, cigarette smoking, air pollution, lack of sleep, topical applications, alcohol consumption, lifestyle, repetitive muscle movements, among others. Scientifically, only 10% of aging is intrinsic. Some studies suggest that as little as 3% of the skin-aging processes are caused by genetic factors while the rest is all lifestyle-based. Extrinsic aging is what you do to your skin (Tsatsou et al. 2012).

Aging, hormesis, and homeodynamics

The concept of aging, senescence, as well as the origin of the various age-related disorders and death, have been directly linked to the progressive shrinking of human buffering capacity otherwise referred to as homeodynamic space which ultimately determines individual's survival chance and capability to maintain a healthy state. The homeodynamic space, in turn, is a product of interactions between several genes and various other cellular, molecular and physiological processes such as detoxification mechanisms, free radical counteracting mechanisms, nuclear and mitochondrial DNA repair pathways, protein turnover and repair, as well as immune and stress responses (Rattan 2008).

Hormesis is the new paradigm being employed to characterize and understand the concept of homeodynamic space and the beneficial nonlinear biphasic dose–response effects of numerous foods and food components. Hormesis basically refers to life-supporting beneficial effects from the cellular responses to mild stress (Rattan 2008; Demirovic and Rattan 2013; Agathokleous and Calabrese 2019; Kadlecová et al. 2019). Generally, in hormesis, a low dose causes stimulation while a high dose leads to inhibition. And usually, hormetic dose responses occur either through a direct stimulation or as an overcompensation (Calabrese 2020). In other words, the consequences of stress can either be beneficial or harmful depending on the duration, frequency, and intensity of the stress as well as the responses to stress such as metabolic disturbances and energy utilization. The homeodynamics disruption, modest overcompensation, as well as the eventual reestablishment of homeodynamics are the key conceptual features of hormesis. The stressors which strengthen the homeodynamic space, otherwise referred to as hormetins, on the other hand, are generally categorized as physical, psychological, biological, metabolic, and nutritional hormetins. Nutritional hormetins (such as dark chocolate, ferulic acid, flavonoids, geranylgeranyl, kinetin, phenolic

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acids, polyphenols, rosmarinic acid, saffron, spinach, tea extracts, and zinc), particular of plant origin, have myriads of beneficial health effects (Demirovic and Rattan 2013).

Both hormesis and its quantitative features describing biological plasticity are highly generalizable and applicable to all life kingdoms and all biological organization levels, depending neither on the stressor, or endpoint nor the cell type or the underpinning biological mechanisms. It has also challenged both the proportionality rule (the linear non-threshold) and the threshold models (Agathokleous et al. 2019; Calabrese et al. 2019).

Prevention of age-related changes in skin

Factors or mild stresses such as acetaldehydes, alcohol, exercise, food restriction, heavy metals, hypergravity, irradiation, pro-oxidants, temperature shock, have been reportedly studied and proved to be capable of prolonging longevity, delaying aging in cells and animals, extending replicative lifespan, maintaining youthful morphology, improving angiogenesis, wound healing and differentiation as well as enhancing stress tolerance and reducing the levels of glycoxidatively- and oxidatively-damaged proteins (Demirovic and Rattan 2013). There are many natural and sustainable ways or approaches which are being successfully adopted for the prevention of excessive and premature dermal aging. The most relevant three approaches are illustrated in Fig. 1.

Avoidance of overexposure to the sun

Several varieties of both acute and chronic responses are known to be induced by human skin exposure to terrestrial solar radiation. Sunlight, principally, UV is the major skin aging extrinsic factor responsible for the generation of free radical generation through homolytic cleavage, which, in turn, initiates DNA strand break, lipid peroxidation, and other inflammatory responses such as premature aging and cancer (Cavinato et al. 2017; Lan et al. 2019). UV also induces skin aging through the activation of MMP, which is known to digest the various components of the extracellular matrix such as collagens, fibronectin, and elastin (Lee et al. 2016; Kruglikov et al. 2019). Specifically, an increase in the synthesis of MMP 1, 2, 3 and 9 as well as other cell activities linked to a decrease in type I procollagen synthesis are triggered by the activation of a key transcription factor in cells upon acute exposure to UV (Limbert et al. 2019). There are several epidemiologic studies implicating the role of chronic sun exposure in the increasing incidence of both melanoma and nonmelanoma skin cancer. UV radiation induces DNA damage, thus, causing the development of mutations and the consecutive skin carcinogenesis. The UV radiation is not only a potent inducer of stress in the epidermis tissue but also and penetrates deep and reaches the dermis (Cavinato et al. 2017). The cumulative exposure to UV light has, thus, been linked with basal cell carcinoma, malignant melanoma, and squamous cell carcinoma (Strnadova et al. 2019).

Premature photoaging is directly linked to pigmentary changes such as uneven pigmentation and wrinkling due to DNA damage. Thus, the best strategies to prevent photo-aging are by avoiding exposure to sun, especially during peak sun hours of 10 am to 4 pm, wearing of clothing, hats, and sunglasses that are able to block UV radiation, in addition to the use of antioxidants, use of retinoids to promote collagen production and inhibit collagenase synthesis, avoidance of indoor tanning beds as well as the use of sunscreens to reduce or block skin exposure to UV radiation (Trojahn et al. 2015; Malik and Hoenig 2019; Zouboulis et al. 2019a, b).

Healthy balanced diet and lifestyle habits

A significant reduction in the cell proliferative capacity is known to be the most prominent physiological change underlying aging because it inevitably results in cellular senescence, thus, altering the biosynthetic activity of the various skin-derived cells and components. Though intrinsic factors such as genetics determine the skin aging rate through the ultimate control of the essential factors, the roles of other triggers such as chromosomes' telomere shortening and DNA damage are indisputable in the aging process. This shows the importance of other external factors such as environmental, mechanical (e.g. repetitive muscle actions such as squinting and frowning) and lifestyle [e.g. sleep patterns and diets such as poor nutrition and overeating] (Limbert et al. 2019). A healthy balanced diet and good lifestyle habits are, therefore, essential not only to delay skin

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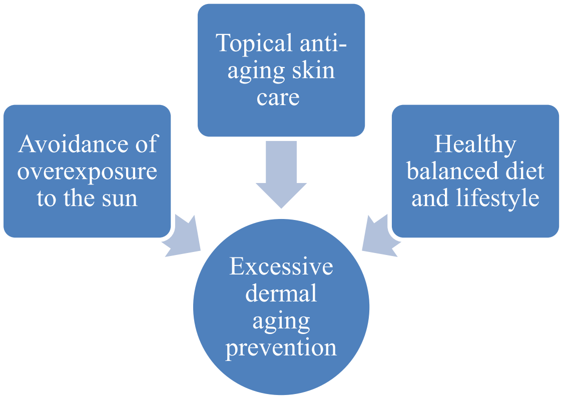

Fig. 1 Natural and sustainable ways to prevent excessive dermal aging

aging but also to improve skin conditions (Schagen et al. 2012).

Nutritional antioxidants are mainly free radical scavengers that act in different body compartments through different mechanisms (Mikail et al. 2016; Ahmed et al. 2017, 2019; Zouboulis et al. 2019a, b). Nutritional antioxidants, on the other hand, fall under nutritional hormetins with remarkable health beneficial effects (Demirovic and Rattan 2013). Thus, the prevention of skin damage responsible for premature aging can be achieved through healthy eating, well-balanced diet such as Mediterranean diet in combination with antioxidant supplements (such as vitamin C and vitamin E, exercise, proper sleep, avoidance of foods with high glycemic index, and avoidance of alcohol consumption (Ahmed et al. 2019; Malik and Hoenig 2019).

Topical anti-aging skin care

Both the intrinsic and extrinsic factors are majorly responsible for the structural rearrangement of elastin and collagen as well as the decrease in their contents, reduction in skin moisture content, increase in transepidermal water loss, vessel walls thinning, diminished production of sebum, arteriosclerosis of both small and large vessels, reduction in mast cells, Langerhans's cells, melanocytes, Merkel cells, Meissner cells, and Pacinian corpuscles as well as an increase in the skin surface pH (Limbert et al 2019). An effective topical anti-aging skincare product, however, helps one age well, naturally (Ganceviciene et al. 2012).

Role of topical anti-aging skin care

A good topical anti-aging skincare regimen is the panacea for natural graceful aging. The major roles and functions of good topical anti-aging skincare products are, thus, illustrated in Fig. 2.

Strengthen the skin's barrier function

The role and importance of a functioning and healthy skin barrier are to protect the body against dehydration as well as the penetration of various microorganisms, irritants, allergens, radiation, and reactive oxygen species. Daily skincare is thus essential not only to enhance and strengthen skin, elasticity, regeneration, and smoothness but also to prevent the formation of wrinkles through the prevention of the degradation of collagen and elastin (Zouboulis et al. 2019a, b).

The lipids in the skin's barrier that provide a thicker *layer* are the best defense against damaging factors. The *strength* and integrity of this *barrier* not only provide softness and bind skin cells together but also help in making our *skin* look healthy and moisturized by keeping water molecules and natural moisturizer factors locked inside the stratum corneum, ensuring firmness and plumpness. The agents that strengthen the skin's barrier function are generally categorized into (1) Emollients, which soften and smoothen the skin, such as, avocado oil (Lodén 2003). (2) Occlusives, which provide a barrier that sits on the surface of the skin and prevent transepidermal water loss, such as, beeswax and jojoba oil (Stamatas et al. 2008). (3) Humectants, such as glycerin, draw water from the dermis (deep down skin layer) up to the epidermis (outer layer) that can be dry, itchy and perhaps dull looking, too (Sethi et al. 2016).

Provide antioxidant properties

Human skin is naked and *constantly directly exposed to the* UV rays, *radiation*, air, cigarette smoke, automobile exhaust, pesticides, other environmental pollutants, or other mechanical and chemical insults, which stimulate *free-radical* production (Howard 2018). *Free radicals* are unstable atoms, to become more stable, they take electrons from other atoms. *Free radicals* thus adversely cause damages to lipids, proteins, cell membranes, and DNA (Ahmed et al. 2015; Mikail et al. 2016; Ibrahim et al. 2018). When

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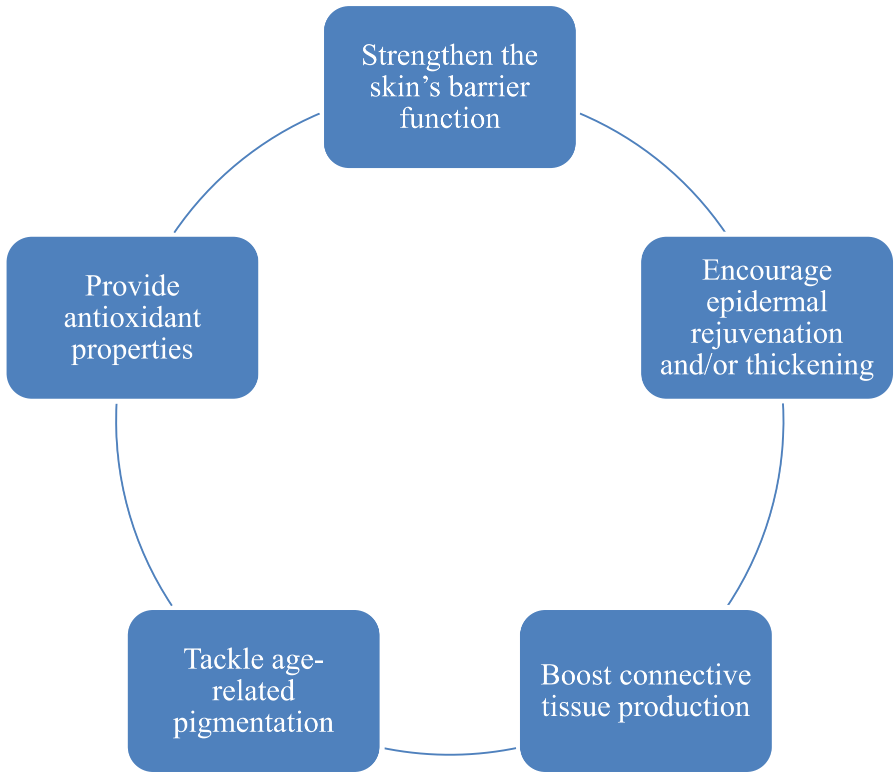

Fig. 2 Functions of good anti-aging skincare products

atoms are taken away from molecules in the skin, it causes damage to our skin's DNA which results in wrinkles, lines, dehydration, and loss of youthful volume. It is estimated that among all these environmental factors, UV rays contribute up to 80%.

The use of antioxidants in skincare products is a great approach to attenuate the damaging *effects of* free radicals and to help maintain healthy skin (Rajagopalan et al. 2018). Topical and systemic antioxidants can thus be employed whether alone or in combination with retinoids and sunscreens to prevent wrinkle formation through the reduction of inflammation (Zouboulis et al. 2019a, b). Antioxidants help to delay or prevent lipid oxidation, a major cause of spoilage in foods, cosmetics, and other lipids-containing formulations. The effects of lipid oxidation include off-flavors and rancidity development, loss of nutritional quality due to degradation of polyunsaturated fatty acid and formation of toxic aldehydes. Antioxidants are also being recently applied in active packaging (Ganiari et al. 2017).

Encourage epidermal rejuvenation and/or thickening

Common skin processes such as regeneration, fibrosis and scarless wound healing depend on many factors which include the phylogenetic scale of the organism, the inflammatory response, the organism's sex, age, as well as the interaction with the environment (Abarca-Buis et al. 2018). However, as we age, the slowing of the epidermal *turnover* rate, reduction in lipid production on the *skin's* surface and *cell* cycle lengthening are certain. For this reason, the use of alpha hydroxy acid (such as glycolic, lactic, and citric acids) and beta hydroxy acid (such as salicylic acid) is often *recommended,* although these would need to be used with care. Hydroxy acids are a group of plant and animal-derived chemical compounds used as skin rejuvenating ingredients, in many *skincare* products. They are often used in cosmetics to increase skin cellular renewal, slough off rough and dead *skin cells* and enhance the skin's *moisture*-retaining ability (Farris 2018). Lactic acid, in particular, has

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antimicrobial, rejuvenating, and moisturizing effects on the skin (Martinez et al. 2013). Hyaluronan, a linear glycosaminoglycan and a major extracellular matrix component, is also responsible for water balance regulation in the skin, keratinocyte differentiation and proliferation in the epidermis as well as the maintenance of the cell structure in the dermis (Kawada et al. 2015; Lee et al. 2016).

Tackle age-related pigmentation

Skin pigmentation is a remarkable and one of the most strongly selected phenotypes and strikingly variables among human populations. Our variable exposure to UV radiation is mainly responsible for the creation of opposing selective forces for folate protection and vitamin D production. This undoubtedly results in global pigmentation differentiation and variable melanin production such that lighter pigmentation is observed at high latitudes while darker skin is observed closer to the equator (Martin et al. 2017). Melanin is *the pigment* that determines skin color. *Modification of* skin pigmentation is also seen in aging skin (Casadevall 2018). Hyper*pigmentation* is one of the common conditions associated *with aging*. *Hyperpigmentation* is a condition in which melanin is overproduced in certain spots on the skin, causing that area to become darker in color than other normal surrounding parts (Goodman et al. 2018). *Sun* exposure definitely triggers melanin production, so it is best to avoid excessive sun exposure or use sunscreen. Premature photoaging causes uneven pigmentation and wrinkling due to DNA damage. The wearing of clothing and sunglasses to block UV radiation, use of antioxidants, use of retinoids to promote collagen production and inhibit collagenase synthesis, use of sunscreens are some of the recommended strategies in addition to reduced exposure to sun (Trojahn et al. 2015; Malik and Hoenig 2019; Zouboulis et al. 2019a, b). Furthermore, a number of results-driven - glow-boosters that fade dark spots by reducing melanin production have also emerged in recent years.

Boost connective tissue production

The top layer of the skin is a strong protector that *prevents* the absorption of many agents into the bloodstream and binds in *moisture* when necessary. Many skincare products do not have the *capacity* to *penetrate deeply enough into* the lower *layers* of the *skin to combat wrinkles and other flaws.* No products are known to replenish the components of dermis, *such as collagen, that are responsible for warding off wrinkles and treating stretch marks. Anti-aging or stretchmark products should, however, contain* some ingredients, such as vitamin C or retinoids that are known to stimulate collagen synthesis (D'Aniello et al. 2017; Li et al. 2017).

Collagen is an *essential* building block for the entire body including the skin. Skincare products that stimulate collagen synthesis will not only revive but also completely renew skin complexion and fend off signs of aging (Humbert et al. 2018). Both vitamin C and retinoids are capable of penetrating the *skin* and efficiently target skincare concerns such as hyperpigmentation or signs of aging. Numerous other agents, that have been found useful for facial skin rejuvenation, are too large a molecule to fit through the stratum corneum. A skin is a fascinatingly complicated system. Fortunately, current research is designing new delivery *systems* and natural nanocompounds which carry high-performance ingredients past the epidermis into the dermis in order to have an effect on the skin's connective tissue network (Hameed et al. 2018).

Role of nanotechnology and encapsulation

Phenolic compounds from natural products are susceptible to various environmental factors such as heat, light, oxidant, and metal ions during processing and storage, thus, reducing their biological efficiency and stability. These problems can be promisingly solved through nanoencapsulation technology (Liu et al. 2019a, b). Nanotechnology is the science of manipulating atoms and molecules in the nanoscale—80,000 times smaller than the width of a human hair. Encapsulation, on the other hand, is a process of entrapping biochemical compounds within an immiscible solid or liquid substance. In general, nanoencapsulation yields nanocapsules with less than 1000 nm (Assadpour and Jafari 2018; Rehman et al. 2019).

Furthermore, *many* ingredients in skincare are biologically active macromolecules that *cannot penetrate through the skin.* Despite the potential therapeutic effect of natural products and their purified compounds, their skin impenetrability,

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Table 1 List of bioactive compounds enhanced by delivery systems

S. no	Compounds	Delivery system	Findings	References
1	Astaxanthin	Liposome	Encapsulation leads to enhanced antioxidant activity	Pan et al. (2018)
2	Lycopene	Encapsulation using dextran, whey protein concentrate and chitosan	Significant protection against moisture and thermal degradation	Pérez-Masiá et al. (2015)
3	Curcumin	Nanostructures lipid carriers (NLC)	Acceptable NLC and curcumin stability ($\geq$ 95%) in SGM	Behbahani et al. (2019)
4	Glutathione	Liposome	Increased therapeutic efficiency and decreased systemic side-effects	Kadry (2019)
5	Phyllanthus urinaria phenolic compounds	Nanoparticles	Enhanced antioxidant activity and pH-dependent compounds release	Liu et al. (2019a, b)
6	Alpha-tocopherol	Encapsulation with different hydrocolloid matrices	Matrices protected the bioactive compound from degradation	Fabra et al. (2016)
7	Vitamins A and E	Gelatin nanofibers	Better wound healing performance and less degradation during the release process	Li et al. (2016)
8	Fish oil (Omega-3 polyunsaturated fatty acids (PUFA))	Encapsulation using coaxial electrospinning	Improved oxidative stability and shelf life	Yang and Ciftci (2017)
9	Curcumin, diclofenac and vitamin B12	Encapsulation using chitosan/phospholipid nanofibers	Sustained-release behavior without significant burst effect	Mendes et al. (2016)
10	Ferulic acid	Encapsulation using modified coaxial electrospinning	Useful for the development of the targeted delivery system	Wang et al. (2015)
11	Rosehip seed oil	Encapsulation using coaxial electrospinning	Significant and prolonged shelf-life	Yao et al. (2016)
12	Cinnamon essential oil	Encapsulation using polyvinyl alcohol and β-cyclodextrin matrix	Prolonged shelf-life and better antimicrobial activity	Wen et al. (2016)

environmental-instability, gastric-degradation, poor solubility, poor bioavailability, uncontrolled-release, rapid metabolism, systemic elimination issues as well as unspecific delivery seriously limit and hinder their biological activities (Patra et al. 2018). A potential tool popularly used to overcome these limitations is the use of different delivery systems using food-grade materials from proteins, polysaccharides, and lipids owing to their safety and biodegradability. Protein-based include whey proteins, caseins, gelatins, soy proteins, cereal proteins, and pulse proteins while carbohydrate-based include, starch, cellulose, pectins, chitosan, alginate, and gums. Lipid-based nano-encapsulation systems, however, are extensively applied due to their excellent functionality on encapsulation, stability, controlled release as well as sustained release profile. Liposomes, for instance, are commonly used for the protection and encapsulation of both lipophilic and hydrophilic compounds and thus have a wide range of potential applications in cosmetics, food formulations, and drug delivery. A liposome is simply a self-assembling and cell-resembling spherical bilayer vesicles lipid-based colloidal delivery system (Pan et al. 2018; Shishir et al. 2018, 2019). The hydrophilic head and hydrophobic tail of liposomes confer on them both hydrophilic and lipophilic characteristics and thus make possible for them to encapsulate a wide range of bioactive compounds (Zhao et al. 2019).

Therefore, liposomes and niosomes are used in the cosmetic industry to encapsulate active ingredients and act as delivery vehicles for various drugs and *cosmetic* formulations. Nevertheless, factors such as the core material, wall material, microencapsulation

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technique, release mechanism, and microparticles application should be given adequate consideration when adopting microencapsulation (Aguiar et al. 2016). Different encapsulation systems are suitable and thus applicable to different active compounds (Shishir et al. 2018). Pomegranate bioactive compounds, for instance, have been used in the development of several nanostructures such as nanoemulsion, nanoparticles, phytosomes, nanoliposomes, nanovesicles and niosomes (Karimi et al. 2017). Some examples of bioactive compounds that have been successfully encapsulated using liposomes are presented in Table 1.

Solid lipid nanoparticles and nanostructured lipid carriers (NLCs) that are of higher drug loading capacity have now been found to be better performers than liposomes (Ray and Gupta 2018). Nanostructured lipid carriers, in particular, *have* gained much *interest in* scientific research and commercial industries during the last few decades. Likewise, NLCs have been identified as a potentially attractive and marketable next-generation cosmetic delivery agent that can provide enhanced skin hydration, better therapeutic prospects, bioavailability, the stability of bioactives and occlusive effects (Mahant et al. 2018).

Why going natural?

Natural products have been traditionally used in the pursuit of health and well-being and thus offer potential promising nutritional and medicinal value with little or no side effect (Ahmed et al. 2017; Shishir et al. 2019). Natural products do not only serve complementary medicine purposes but also create a potential resource platform for both drug discovery and development (Moeini et al. 2019). On the other hand, conventional personal care products that are used on a regular basis are loaded with potentially toxic chemicals that do not only harm human health but also the environment (Ramalhete et al. 2018). Natural products are basically chemical compounds which are derived from living organisms found in nature, such as microbes, algae, plants, and animals. These compounds include, but not limited to proteins, carbohydrates, essential fatty acids, crude fibers, vitamins, minerals, squalene and antioxidants such as tocochromanols, polyphenols, terpenoids, organosulfur, and phytosterols (Kowalska et al. 2017).

Essentially, natural skincare uses topical creams, lotions, and serums made of ingredients found in nature. Thus, natural skincare products use plant-derived ingredients, which may include, fruits, flowers, vegetables, cereals, legumes, nuts, roots, oils, pulses, herbs, and spices as well as animal-derived products such as beeswax in their formulations (Ibrahim et al. 2017; Hughes 2018). Organic skincare, however, contains these ingredients grown without the use of pesticides, herbicides, synthetic fertilizers, genetically modified organisms, and so on and often come with an organic certification. *Organic* skincare products tend to offer the added benefits of decreased risk of skin irritation, allergies, and diseases (Ibrahim et al. 2018). There are abundant and sustainable several plant sources that could be explored and harnessed by the cosmetics industry to create a different innovative combination of ingredients. Natural products, particularly plant, have several specific pharmacological actions which include but not limited to anti-aging, antioxidants, anti-inflammatory, anti-carcinogenic, anti-allergy, as well as moisturizing, anti-hyperpigmentation, pro-collagen, and UV protective (Charles Dorni et al. 2017). According to the World Health Organization, there are more than 20,000 different medicinal plants available across the globe in 91 different countries, including the global 12 mega-biodiversity countries (Patra et al. 2018).

Natural anti-aging ingredients groups

Natural anti-aging ingredients are basically biological and nutritional hormetins with many potential and beneficial health effects (Demirovic and Rattan 2013). The various categories of natural anti-aging ingredients include moisturizing agents; barrier repair agents; antioxidants, vitamins, hydroxy acids, skin lightening agents, anti-inflammatory ingredients, and sunblock ingredients.

Moisturizing agents

There are three main types of skin moisturizing agents- occlusives, emollients and humectants. Occlusives work through providing a physical *epidermal barrier* to prevent trans-epidermal water loss. Organic ingredients with occlusive properties include waxes

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and oils such as beeswax, candelilla wax, jojoba oil, olive or coconut oil (Stamatas et al. 2008). Emollients are substances that make skin soft, smooth and supple which help reduce rough, flaky skin. Emollients may be fluid or thick in texture. Examples include shea butter, cocoa butter, mango butter, cupuacu butter, Kombo butter, murumuru butter, almond oil, argan oil, avocado oil, babassu oil, borage oil, broccoli oil, castor bean oil, chia seed oil, coconut oil, evening primrose oil, palm oil, olive oil, passion fruit oil, pomegranate oil, rapeseed oil, raspberry oil, safflower oil, sunflower oil, and many more. Some emollients such as coconut oil or castor oil can also function as occlusives. Humectants work by pulling *water* from the *dermis* toward the stratum corneum (outer layer of the epidermis) as well as *binding water vapour* from the atmosphere (Sethi et al. 2016). Examples of humectants include hydration-boosting superstars hyaluronic acid, glycerine, glycerol, honey, and sorbitol. The antimicrobial, rejuvenating, and moisturizing effects of lactic acid on the skin has also made it a sought after ingredient in the cosmetic industry for the manufacture of hygiene and esthetic products. Some derivatives of lactic acid such as lactate esters are also commonly used owing to their emulsifying and hygroscopic properties (Martinez et al. 2013).

Barrier repair agents

Natural oils contain fatty acids that play key roles in maintaining the skin barrier as well as having anti-inflammatory and anti-irritancy activities. The two main essential fatty acids are omega-3s (such as flaxseed (linseed) oil, walnut oil, and chia oil) and omega-6s (such as grapeseed oil, safflower oil, sunflower oil, blackcurrant seed oil, evening primrose oil, and borage oil). They are the building blocks of healthy cell membranes. Barrier repair agents are fantastic ingredients in the *skin*care regimen for strengthening skin *barrier function* and overall health of the skin. Barrier repair agents also include ceramide and cholesterol (Vaughn et al. 2018). Ceramide is one of the best *skin* barrier-boosting ingredients that hold the skin together and keep its appearance firm and plump. Topical application of a ceramide-containing skincare ointment reduced IL-31 induced impairments of the physical skin barrier and skin barrier function in an in vitro model of the disrupted skin barrier (Huth et al. 2018).

Antioxidants

When it comes to anti-aging ingredients, antioxidants are excellent additions. A*ntioxidants* nurture the *skin* and shield it from the damaging effects of free radicals by acting as a substitute for the skin molecules that free radicals usually destroy (Mikail et al. 2016; Petruk et al. 2018). *There* are so *many* different *antioxidants,* which can be categorized as water-soluble and oil-soluble antioxidants. Water-soluble antioxidants include vitamin C (ascorbic acid), glutathione, coffeeberry, resveratrol, and green tea. Oil-soluble ones include vitamin A, vitamin E and coenzyme Q10 (Brewer 2011). In a study, treatment with vitamin E restored expression of cornifin A, antileukoproteinase and suprabasin that were altered after exposure of primary skin keratinocytes to diesel particulate extract and its vapor (Rajagopalan et al. 2018).

The consumption of tree nuts have also been reported to potentially mitigate the effects of pro-inflammatory Western diets, diminish the inflammation process by decreasing the levels of inflammatory molecules and reactive oxygen/nitrogen species, present cytoprotection, stimulate detox enzyme and antioxidant systems, promote mitochondrial biogenesis and energy homeostasis, and prevent mitochondrial dysfunctions (Rusu et al. 2019). Plant extracts contain other numerous amounts of compounds which have been classified into primary and secondary metabolites. Some of these metabolites have high biological activities such as anticancer, anti-microbial as well as anti-aging. In the last decade, scientists have researched plant extracts containing several compounds with the ability to scavenge free radicals and anti-aging properties. Resveratrol found in red wine showed a good anti-aging property and had been used in antioxidant skincare formulations (Farris et al. 2013). Furthermore, resveratrol-based skincare formulation had 17 times greater antioxidant activity than idebenone, a synthetic analog of ubiquinone (Baxter 2008). Besides resveratrol, biochanin A, an O-methylated isoflavanoid found in peanuts and alfalfa sprouts, can be used for the treatment and prevention of aging and wrinkles (Gorbach et al. 2000).

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Vitamins

Vitamins play a crucial role in good *skincare*. *Vitamins are natural miraculous nutrients tha* a more radiant, healthy and youthful glow. The most commonly found vitamins in skincare include vitamin C (Ascorbic Acid—water-soluble), vitamin E (Tocopherol—oil-soluble), vitamin A (Retinol—oil-soluble) and vitamin B3 (Niacinamide—water-soluble) (Pullar et al. 2017). Vitamin C (ascorbic acid) *helps the* body synthesize *collagen* to *firm* up and plump *skin* and diminish *fine lines*, wrinkles or scars. *Vitamin E* (tocopherol) is a powerful antioxidant and a conditioning active that may be effective at neutralizing free radicals as well as softening the *skin* (Thiele and Ekanayake-Mudiyanselage 2007). Vitamin A (retinol) stimulates the production of new skin cells. Vitamin A is important to healthy skin cell production and growth. *Vitamin* A increases collagen production; therefore, improves the *wrinkles* associated with natural *aging,* minimize scars, burns and stretch marks (Shapiro and Saliou 2001). Vitamin B3 (niacinamide) is an anti-*aging* ingredient which is very crucial in carrying out *skin* functions like maintaining oil balance, reducing fine lines or *wrinkle,* treating and preventing solar keratoses (“sun spots”), retaining moisture and lot more (Watson et al. 2018). An anti-aging skincare system, containing alpha-hydroxy acids and vitamins, significantly improves wrinkles, skin texture and elasticity in fifty-two volunteers (Tran et al. 2015).

Hydroxy acids

Hydroxy acids also are known as fruit *acids*, are topical exfoliants that have been used for years as *skin* rejuvenating ingredients that reverse some of the effects of aging such as fine *wrinkles*, discolored *skin,* dryness, and spots. The best-known compound in this group is Alpha-Hydroxy Acid which includes citric acid (from citrus fruits), glycolic acid (from sugar cane), lactic acid (from fermented fruits), malic acid (from fruits) and tartaric acid (from grapes) (Ditre et al. 1996). *Beta-Hydroxy Acid* refers to the ingredient of salicylic *acid.* Alpha-hydroxy acids are water-soluble, while Beta-hydroxy acid is lipid (oil) soluble. Alpha-hydroxy *acids* are best for dry *skin* and aging *skin.* Beta-hydroxy acid is better used on oily skin and acne (Farris 2018; Khuphe et al. 2018). Lactic acid has been reported to have repaired artificially UV damaged human dermal fibroblast cell lines by enhancing the amount and integrity of elastin fibers while some derivatives of lactic acid have also been widely used due to their hygroscopic and emulsifying properties (Martinez et al. 2013; Jarrar 2018).

Skin lightening agents

Skin lightening agents work by reducing the concentration of *skin’s* pigment called melanin. Less melanin means lighter and more even skin tone. Tyrosinase, a copper-containing enzyme, is one of the key enzymes required in the biosynthesis of melanin. The action of the skin whitening agents occurs at various levels of melanin production where they act as competitive inhibitors to tyrosinase, the key enzyme in melanogenesis. Other whitening agents, however, inhibit either tyrosinase maturation or pigment granules (melanosomes) the transportation from melanocytes to the surrounding *keratinocytes* (Smit et al. 2009). *Voluntary* depigmentation through the use of preparations to lighten skin tone has become a common practice, particularly in African countries. In most cases, the procedure is achieved by the use of illegal cosmetics or preparations which are not regulated by any cosmetics laws or drug laws. The commonly used active ingredients include steroids, kojic acid, hydroquinone, and its derivatives, as well as mercury derivatives. These ingredients are harmful and cause many undesirable effects such as diabetes, hypercorticism, arterial hypertension skin atrophy, osteoporosis, and family member such as children may also become poisoned by proxy (Couteau and Coiffard 2016).

Furthermore, most lightening agents make it all the way down to the hypodermis and act as tyrosinase inhibitors. Lightening agents are usually used to combat skin problems like melasma, Dark Age spots, hyperpigmentation, and dullness (Jin et al. 2018; Pillaiyar et al. 2017; Shin et al. 2018). Many organic agents, however, have been shown to be safe and effective in skin lightening include citrus extracts, licorice extract, kojic acid, bearberry extract, white mulberry extract, vitamin C (ascorbic acid), vitamin B3 (niacinamide), Indian gooseberry, hydroquinone and its derivatives such as retinoids, alpha- and beta-hydroxy acids, ascorbic acid, divalent ion chelators,

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azelaic acid, as well as diverse herbal extracts (Couteau and Coiffard 2016).

Anti-inflammatory ingredients

Inflammation has long been recognized as one of the most significant factors in the pathogenesis of acne. An anti-inflammatory ingredient curbs pain, swelling and redness in the skin. Several different *plant species* have demonstrated *anti-inflammatory* activity. These plants include turmeric, licorice root, oats, feverfew, willow bark, lavender, calendula, chamomile, witch hazel, yarrow and oak bark (Maione et al. 2016). Tree nuts also have the potential to diminish the inflammation process by decreasing the levels of inflammatory molecules and free radicals, stimulate detox enzyme and antioxidant systems, and prevent mitochondrial dysfunctions (Rusu et al. 2019).

Sunblock ingredients

Dermatologists now say that nothing is as important for your *skin,* in slowing the signs of aging, as being sun smart. Ultraviolet B (UVB) is the shorter wave UV ray that causes sunburn, discolorations and dark spots, skin reddening, sagging or leathery *skin*, wrinkles and even skin cancer (Nguyen et al. 2018). Sun Protection Factor (SPF rating, introduced in 1974) is a relative measure of a sunscreen's protection against UVB rays. *Most sunscreens* with an SPF of 15 or higher *do* an exceptional job in preventing photoaging and skin cancer. Many sunscreen products contain the powdered mineral called titanium dioxide or zinc oxide which sits on top of the skin to reflect and absorb the *sun's* harmful rays (Joshi and Fedders 2018). Suncare products require extensive SPF testing as many do not provide adequate protection as claimed. There are many natural and organic ingredients that have been shown to offer a small number of photoprotective properties for anti-aging skincare products. These plants include Aloe Vera, caffeic acid, calendula, coconut oil, ginger, green tea resveratrol, shea butter, tamanu oil and tocopherol (vitamin E).

Future perspectives and conclusion

Graceful, positive and healthy aging is the goal of almost everyone, everywhere thus, providing a catalyst for the ever-blooming and continuously growing *anti-aging market*. Graceful aging can be achieved through several means such as avoidance of overexposure to the sun, healthy balanced diet and lifestyle habits as well as good topical anti-aging skincare practices. Therefore, skincare formulation stakeholders should not only harness the versatile potential of *natural anti-aging skincare ingredients but adopt them holistically to appease the growing awareness and concerns of consumers.* Natural products are characteristically safe and effective for various pharmacological activities such as anti-aging, antioxidants, anti-inflammatory, anti-carcinogenic, anti-allergy, as well as moisturizing, anti-hyperpigmentation, pro-collagen, and UV protective. Natural products are also abundant as well as sustainable in nature.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abarca-Buis RF, Martínez-Jiménez A, Vera-Gómez E, Contreras-Figueroa ME, Garciadiego-Cázares D, Paus R, Robles-Tenorio A, Krötzsch E (2018) Mechanisms of epithelial thickening due to IL-1 signalling blockade and TNF-α administration differ during wound repair and regeneration. Differentiation 99(2018):10–20

Agathokleous E, Calabrese EJ (2019) Hormesis: The dose response for the 21st century: the future has arrived. Toxicology 425(2019):152249

Agathokleous E, Kitao M, Calabrese EJ (2019) Hormesis: a compelling platform for sophisticated plant science. Trends Plant Sci 24(4):318–327

Aguiar J, Estevinho BN, Santos L (2016) Microencapsulation of natural antioxidants for food application: the specific case

Journal : Medium 10522 | Dispatch : 4-3-2020 | Pages : 18
Article No. : 9865 | LE | TYPESET
MS Code : BGEN-D-20-00003R1 | CP | DISK

of coffee antioxidants: a review. Trends Food Sci Technol 58(2016):21–39

Ahmed IA, Mikail MA, Ibrahim M (2017) *Baccaurea angulata* fruit juice ameliorates altered hematological and biochemical biomarkers in diet-induced hypercholesterolemic rabbits. Nutr Res 42(2017):31–42

Ahmed IA, Mikail MA, Bin Ibrahim M, Bin Hazali N, Rasad MS, Ghani RA, Wahab RA, Arief SJ, Yahya MN (2015) Antioxidant activity and phenolic profile of various morphological parts of underutilized Baccaurea angulata fruit. Food Chem 172:778–787

Ahmed IA, Mikail MA, Mustafa MR, Ibrahim M, Othman R (2019) Lifestyle Interventions for nonalcoholic fatty liver disease. Saudi J Biol Sci 2019:1–6

Anderson J, Anderson Y, Diyabalanage T (2015) Paving the way with actives for skincare. Planta Med 81:IL23

Assadpour E, Jafari SM (2018) A systematic review on nanoencapsulation of food bioactive ingredients and nutraceuticals by various nanocarriers. Crit Rev Food Sci Nutr 2018:1–23

Assaf H, Adly MA, Hussein MR (2016) Aging and intrinsic aging: pathogenesis and Manifestations. In: Farage MA, Miller KW, Maibach HI (eds) Textbook of aging skin. Springer, Berlin, Heidelberg, pp 1–12

Baxter RA (2008) Anti-aging properties of resveratrol: review and report of a potent new antioxidant skin care formulation. J Cosmet Dermatol 7(1):2–7

Behbahani ES, Ghaedi M, Abbaspour M, Rostamizadeh K, Dashtian K (2019) Curcumin loaded nanostructured lipid carriers: in vitro digestion and release studies. Polyhedron 164(2019):113–122

Brewer M (2011) Natural antioxidants: sources, compounds, mechanisms of action, and potential applications. Compr Rev Food Sci Food Saf 10(4):221–247

Calabrese EJ (2020) Stimulating hair growth via hormesis: Experimental foundations and clinical implications. Pharmacol Res 152(2020):104599

Calabrese EJ, Dhawan G, Kapoor R, Mattson MP, Rattan SIS (2019) Curcumin and hormesis with particular emphasis on neural cells. Food Chem Toxicol 129(2019):399–404

Calejja-Agius J, Muscat-Baron Y, Brincat MP (2007) Skin ageing. Menopause Int 13(2):60–64

Calleja-Agius J, Brincat M, Borg M (2013) Skin connective tissue and aging. Best Pract Res Clin Obstet Gynaecol 27(5):727–740

Casadevall A (2018) Melanin triggers antifungal defences. Nature 555:319–320

Cavinato M, Waltenberger B, Baraldo G, Grade CVC, Stuppner H, Jansen-Dürr P (2017) Plant extracts and natural compounds used against UVB-induced photoaging. Biogerontology 18(2017):499–516

Charles Dorni AI, Amalraj A, Gopi S, Varma K, Anjana SN (2017) Novel cosmeceuticals from plants: an industry guided review. J Appl Res Med Aromat Plants 7(2017):1–26

Choi EH (2019) Aging of the skin barrier. Clin Dermatol 37(4):336–345

Couteau C, Coiffard L (2016) Overview of skin whitening agents: drugs and cosmetic products. Cosmetics 3(3):27

Dai B, Pelton LE (2018) Exploring consumers' skincare retail patronage. J Retail Consum Serv 43(2018):269–277

D'Aniello C, Cermola F, Patriarca EJ, Minchiotti G (2017) Vitamin C in stem cell biology: impact on extracellular matrix homeostasis and epigenetics. Stem Cells Int. https://doi.org/10.1155/2017/8936156

Demirovic D, Rattan SIS (2013) Establishing cellular stress response profiles as biomarkers of homeodynamics, health and hormesis. Exp Gerontol 48(1):94–98

Ditre CM, Griffin TD, Murphy GF, Sueki H, Telegan B, Johnson WC, Yu RJ, Van Scott EJ (1996) Effects of α-hydroxy acids on photoaged skin: a pilot clinical, histologic, and ultrastructural study. J Am Acad Dermatol 34(2):187–195

Emerald M, Emerald A, Emerald L, Kumar V (2016) Perspective of natural products in skincare. Pharm Pharm Int J 4(3):00072

Fabra MJ, López-Rubio A, Lagaron JM (2016) Use of the electrohydrodynamic process to develop active/bioactive bilayer films for food packaging applications. Food Hydrocolloids 55(2016):11–18

Farage M, Miller KW, Elsner P, Maibach HI (2008) Intrinsic and extrinsic factors in skin aging: a review. Int J Cosmet Sci 30(2):87–95

Farage MA, Miller KW, Elsner P, Maibach HI (2013) Characteristics of the aging skin. Adv Wound Care 2(1):5–10

Farris, P.K. (2018). Topical skin care cosmetic patient master techniques in facial rejuvenation, second edition. E-Book, pp 68–72.e62

Farris P, Krutmann J, Li YH, McDaniel D, Krol Y (2013) Resveratrol: a unique antioxidant offering a multi-mechanistic approach for treating aging skin. J Drugs Dermatol 12(12):1389–1394

Ganceviciene R, Liakou AI, Theodoridis A, Makrantonaki E, Zouboulis CC (2012) Skin anti-aging strategies. Dermato-Endocrinology 4(3):308–319

Ganiari S, Choulitoudi E, Oreopoulou V (2017) Edible and active films and coatings as carriers of natural antioxidants for lipid food. Trends Food Sci Technol 68(2017):70–82

Godoy RS, Lanés LEK, Castro BD, Weber V, Wingen N, Pires MM, Oliveira GT, Maltch L (2019) Oxidative stress resistance in a short-lived Neotropical annual killifish. Biogerontology 2019:1–13

Goodman GJ, Armour KS, Kolodziejczyk JK, Santangelo S, Gallagher CJ (2018) Comparison of self-reported signs of facial aging among Caucasian women in Australia versus those in the USA, the UK and Canada. Australas J Dermatol 59(2):108–117

Gorbach SL (2000) Isoflavonoids for treatment and prevention of aging skin and wrinkles. Google Patents

Hameed A, Fatima GR, Malik K, Muqadas A, Fazal-ur-Rehman M (2018) Scope of nanotechnology in cosmetics: dermatology and skin care products. J Med Chem Sci 2(1):9–16

Howard D (2018) What is a free radical? Dostupno na adresi: Datum pristupa, 3. https://www.dermalinstitute.com/us/library/22_article_What_Is_A_Free_Radical_.html

Hughes B (2018) Going natural. Professional Beauty (Mar/Apr 2018), p 110

Humbert P, Louvrier L, Saas P, Viennet C (2018) Vitamin C, aged skin, skin health. Vitamin C. IntechOpen, Rijeka, pp 1–20

Huth S, Schmitt L, Marquardt Y, Heise R, Lüscher B, Amann PM, Baron JM (2018) Effects of a ceramide containing water-in-oil ointment on skin barrier function and allergen

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Article No. : 9865	☐ LE	☐ TYPESET
MS Code : BGEN-D-20-00003R1	☑ CP	☑ DISK

penetration in an IL-31 treated 3D model of the disrupted skin barrier. Exp Dermatol 27(9):1009–1014

Ibrahim M, Ahmed IA, Mikail MA, Ishola AA, Draman S, Isa ML, Yusof AM (2017) *Baccaurea angulata* fruit juice reduces atherosclerotic lesions in diet-induced hypercholesterolemic rabbits. Lipids Health Dis 16(134):1–8

Ibrahim M, Mikail MA, Ahmed IA, Abdul Ghani R (2018) Phenolic-rich *Baccaurea angulata* modulates inflammatory biomarkers of atherosclerosis. J Nutr Metab 2018:1–8

Jarrar MH (2018) Anti-aging effectsofretinol and alpha hydroxy acid on elastin fibers of artificially photo-aged human dermal fibroblast cell lines. World Acad Sci Eng Technol Int J Med Health Biomed Pharm Eng 9(4):1–4

Jin Y, Kim JH, Hong HD, Kwon J, Lee EJ, Jang M, Lee SY, Han AR, Nam TG, Hong SK, Huh TL (2018) Ginsenosides Rg5 and Rk1, the skin-whitening agents in black ginseng. J Funct Foods 45:67–74

Joshi K, Fedders J (2018) Increase SPF efficiency and enable better aesthetics. S Afr Pharm Cosmet Rev 45(7):30–31

Kadlecova A, Makova B, Artal-Sanz M, Strnad M, Voller J (2019) The plant hormone kinetin in disease therapy and healthy aging. Ageing Res Rev 55(2019):100958

Kadry MO (2019) Liposomal glutathione as a promising candidate for immunological rheumatoid arthritis therapy. Heliyon 5(7):e02162

Karimi M, Sadeghi R, Kokini J (2017) Pomegranate as a promising opportunity in medicine and nanotechnology. Trends Food Sci Technol 69:59–73

Kawada C, Kimura M, Masuda Y, Nomura Y (2015) Oral administration of hyaluronan prevents skin dryness and epidermal thickening in ultraviolet irradiated hairless mice. J Photochem Photobiol B 153(2015):215–221

Khuphe M, Ingram N, Thornton PD (2018) Exploiting poly (α-hydroxy acids) for the acid-mediated release of doxorubicin and reversible inside–out nanoparticle self-assembly. Nanoscale 10(29):14201–14206

Kowalska H, Czajkowska K, Cichowska J, AndrzejLenart A (2017) What's new in biopotential of fruit and vegetable by-products applied in the food processing industry? Trends Food Sci Technol 67(2017):150–159

Kruglikov IL, Zhang Z, Scherer PE (2019) Caveolin-1 in skin aging from innocent bystander to major contributor. Ageing Res Rev. https://doi.org/10.1016/j.arr.2019.100959

Lambers H, Piessens S, Bloem A, Pronk H, Finkel P (2006) Natural skin surface pH is on average below 5, which is beneficial for its resident flora. Int J Cosmet Sci 28(5):359–370

Lan CCE, Hung YT, Fang AH, Wu CS (2019) Effects of irradiance on UVA-induced skin aging. J Dermatol Sci 94(1):220–228

Lee DH, Oh JH, Chung JH (2016) Glycosaminoglycan and proteoglycan in skin aging. J Dermatol Sci 83(3):174–181

Li H, Wang M, Williams GR, Wu J, Sun X, Lv Y, Zhu LM (2016) Electrospun gelatin nanofibers loaded with vitamins A and E as antibacterial wound dressing materials. RSC Adv 55(6):50267–50277

Li WH, Wong HK, Serrano J, Randhawa M, Kaur S, Southall MD, Parsa R (2017) Topical stabilized retinol treatment induces the expression of HAS genes and HA production in human skin in vitro and in vivo. Arch Dermatol Res 309(4):275–283

Limbert G, Masen MA, Pond D, Graham HK, Sherratt MJ, Jobanputra R, McBride A (2019) Biotribology of the ageing skin: why we should care. Biotribology 17(2019):75–90

Liu Y, Liao Y, Wei S, Zhang H, Wang X (2019a) Nanoparticles based on sodium alginate and β-conglycinin: self-assembly and delivery of Phyllanthus urinaria phenolic compounds. J Food Process Preserv 43(1):1–8

Liu Y, Gao W, Koellmann C, Le Clerc S, Hüls A, Li B, Peng Q, Wu S, Ding A, Yang Y, Jin L (2019b) Genome-wide scan identified genetic variants associated with skin aging in a Chinese female population. J Dermatol Sci 96(1):42–49

Lodén M (2003) Role of topical emollients and moisturizers in the treatment of dry skin barrier disorders. Am J Clin Dermatol 4(11):771–788

Mahant S, Rao R, Nanda S (2018) Nanostructured lipid carriers: Revolutionizing skin care and topical therapeutics. Design of nanostructures for versatile therapeutic applications. Elsevier, Amsterdam, pp 97–136

Maione F, Russo R, Khan H, Mascolo N (2016) Medicinal plants with anti-inflammatory activities. Nat Prod Res 30(12):1343–1352

Malik A, Hoenig LJ (2019) Can aging be slowed down? Clin Dermatol 37(4):306–311

Martin AR, Lin M, Granka JM, Myrick JW, Liu X, Sockell A, Atkinson EG, Werely CJ, Möller M, Sandhu MS, Kingsley DM (2017) An unexpectedly complex architecture for skin pigmentation in Africans. Cell 171(6):1340–1353

Martinez FAC, Balciunas EM, Salgado JM, González JMD, Converti A, de Souza Oliveira RP (2013) Lactic acid properties, applications and production: a review. Trends Food Sci Technol 30(1):70–83

Mendes AC, Gorzelanny C, Halter N, Schneider SW, Chronakis IS (2016) Hybrid electrospun chitosan-phospholipids nanofibers for transdermal drug delivery. Int J Pharm 510(1):48–56

Mikail MA, Ahmed IA, Ibrahim M, Hazali N, Rasad MS, Ghani RA, Hashim R, Wahab RA, Arief SJ, Isa ML, Draman S (2016) *Baccaurea angulata* fruit inhibits lipid peroxidation and induces the increase of antioxidant enzymes activities. Eur J Nutr 55:1435–1444

Mir SA, Dar BN, Wani AB, Shah MA (2018) Effect of plant extracts on the techno-functional properties of biodegradable packaging films. Trends Food Sci Technol 80(2018):141–154

Moeini R, Memariani Z, Asadi F, Bozorgi M, Gorji N (2019) Pistacia genus as a potential source of neuroprotective natural products. Planta Med 85(17):1326–1350

Nguyen TN, Rajapakshe K, Avdieiev S, Nicholas C, Chitsazzadeh V, Welsh E, Fang B, Koomen J, Coarfa C, Einspahr J, Tsai KY (2018) A proteome-transcriptome-miRnome integrated analysis identifies similarity between UV-exposed skin and wounding skin (abstract): In: Proceedings of the American Association for Cancer Research Annual Meeting 2018; 2018 Apr 14–18. AACR, Chicago, IL. Philadelphia (PA); Cancer Res 2018;78(13 Suppl):Abstract nr 406

Pan L, Zhang S, Gu K, Zhang N (2018) Preparation of astaxanthin-loaded liposomes: characterization, storage stability and antioxidant activity. CyTA 16(1):607–618

Journal : Medium 10522 | Dispatch : 4-3-2020 | Pages : 18
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MS Code : BGEN-D-20-00003R1 | ✔ CP | ✔ DISK

Patra JK, Das G, Lee S, Kang SS, Shin HS (2018) Selected commercial plants: a review of extraction and isolation of bioactive compounds and their pharmacological market value. Trends Food Sci Technol 82(2018):89–109

Pérez-Masiá R, Lagaron JM, Lopez-Rubio A (2015) Morphology and stability of edible lycopene-containing micro- and nanocapsules produced through electrospraying and spray drying. Food Bioprocess Technol 8(2):459–470

Petruk G, del Giudice R, Rigano MM, Monti DM (2018) Antioxidants from plants protect against skin photoaging. Oxid Med Cell Longev. https://doi.org/10.1155/2018/1454936

Pillaiyar T, Manickam M, Namasivayam V (2017) Skin whitening agents: medicinal chemistry perspective of tyrosinase inhibitors. J Enzyme Inhib Med Chem 32(1):403–425

Poljšak B, Dahmane R, Godic A (2012) Intrinsic skin aging: The role of oxidative stress. Acta Dermatovenerol 21(2012):1–4

Pullar J, Carr A, Vissers M (2017) The roles of vitamin C in skin health. Nutrients 9(8):866

Rajagopalan P, Jain AP, Nanjappa V, Patel K, Mangalaparthi KK, Babu N, Cavusoglu N, Roy N, Soeur J, Breton L, Pandey A (2018) Proteome-wide changes in primary skin keratinocytes exposed to diesel particulate extract: a role for antioxidants in skin health. J Dermatol Sci 91(3):239–249

Ramalhete C, Mulhovo S, Lage H, Ferreira MJU (2018) Triterpenoids from *Momordica balsamina* with a collateral sensitivity effect for tackling multidrug resistance in cancer cells. Planta Med 84(18):1372–1379

Rattan SIS (2008) Hormesis in aging. Ageing Res Rev 7(2008):63–78

Ray L, Gupta KC (2018) Role of Nanotechnology in Skin Remedies. Photocarcinog Photoprot 2018:141–157

Rehman A, Ahmad T, Aadil RM, Spotti MJ, Bakry AM, Khan IM, Zhao L, Riaz T, Tong Q (2019) Pectin polymers as wall materials for the nano-encapsulation of bioactive compounds. Trends Food Sci Technol 90(2019):35–46

Rusu MA, Simedrea R, Gheldiu AM, Mocan A, Vlase L, Popa DS, Ferreira ICFR, I.C.F.R. (2019) Benefits of tree nut consumption on aging and age-related diseases: mechanisms of actions. Trends Food Sci Technol 88(2019):104–120

Safdar A, Zakaria R, Ab Aziz CB, Rashid U, Azman KF, K. (2019) Goat milk attenuates mimetic aging related memory impairment via suppressing brain oxidative stress, neurodegeneration and modulating neurotrophic factors in D-galactose-induced aging model. Biogerontology 2019:1–14

Schagen SK, Zampeli VA, Makrantonaki E, Zouboulis CC (2012) Discovering the link between nutrition and skin aging. Dermato-Endocrinology 4(3):298–307

Sethi A, Kaur T, Malhotra SL, Gambhir ML (2016) Moisturizers: the slippery road. Indian J Dermatol 61(3):279–287

Shapiro SS, Saliou C (2001) Role of vitamins in skincare. Nutrition 17(10):839–844

Shin HJ, Beak HS, Kim SI, Joo YH, Choi J (2018) Development and evaluation of topical formulations for a novel skin whitening agent (AP736) using Hansen solubility parameters and PEG-PCL polymers. Int J Pharm 552(1–2):251–257

Shishir MRI, Karim N, Gowd V, Zheng X, Chen W (2019) Liposomal delivery of natural product: a promising approach in health research. Trends Food Sci Technol 85(2019):177–200

Shishir MRI, Xie L, Sun C, Zheng X, Chen W (2018) Advances in micro and nano-encapsulation of bioactive compounds using biopolymer and lipid-based transporters. Trends Food Sci Technol 78(2018):34–60

Smit N, Vicanova J, Pavel S (2009) The Hunt for Natural Skin Whitening Agents. Int J Mol Sci 10(12):5326–5349

Stamatas GN, de Sterke J, Hauser M, von Stetten O, van der Pol A (2008) Lipid uptake and skin occlusion following topical application of oils on adult and infant skin. J Dermatol Sci 50(2):135–142

Strnadova K, Sandera V, Dvorankova B, Kodet O, Duskova M, Smetana K, Lacina L (2019) Skin aging: the dermal perspective. Clin Dermatol 37(4):326–335

Tarun J, Susan J, Suria J, Susan VJ, Criton S (2014) Evaluation of pH of bathing soaps and shampoos for skin and hair care. Indian J Dermatol 59(5):442–444

Thiele JJ, Ekanayake-Mudiyanselage S (2007) Vitamin E in human skin: organ-specific physiology and considerations for its use in dermatology. Mol Aspects Med 28(5–6):646–667

Tobin DJ (2017) Introduction to skin aging. J Tissue Viability 26(1):37–46

Tran D, Townley JP, Barnes TM, Greive KA (2015) An anti-aging skincare system containing alpha hydroxy acids and vitamins improves the biomechanical parameters of facial skin. Clin Cosmet Investig Dermatol 8(2015):9–17

Trojahn C, Dobos G, Lichterfeld A, Blume-Peytavi U, Kottner J (2015) Characterizing facial skin aging in humans: disentangling extrinsic from intrinsic biological phenomena. BioMed Res Int. https://doi.org/10.1155/2015/318586

Tsatsou F, Trakatelli M, Patsatsi A, Kalokasidis K, Sotiriadis D (2012) Extrinsic aging: UV-mediated skin carcinogenesis. Dermato-Endocrinology 4(3):285–297

Vaughn AR, Clark AK, Sivamani RK, Shi VY (2018) Natural oils for skin-barrier repair: ancient compounds now backed by modern science. Am J Clin Dermatol 19(1):103–117

Vierkötter A, Hüls A, Yamamoto A, Stolz S, Krämer U, Matsui MS, Morita A, Wang S, Li Z, Jin L, Krutmann J (2016) Extrinsic skin ageing in German, Chinese and Japanese women manifests differently in all three groups depending on ethnic background, age and anatomical site. J Dermatol Sci 83(3):219–225

Wang X, Wu J (2019) Modulating effect of fatty acids and sterols on skin aging. J Funct Foods 57(2019):135–140

Wang X, Yu DG, Li XY, Bligh SW, Williams GR (2015) Electrospun medicated shellac nanofibers for colon-targeted drug delivery. Int J Pharm 490(1–2):384–390

Watson AD, Okano TN, Akira N (2018) Methods of regulating skin health and appearance with a combination of flavonoid and vitamin B3: United States, (US9913792B2), 1–22

Wen P, Zhu DH, Wu H, Zong MH, Jing YR, Han SY (2016) Encapsulation of cinnamon essential oil in electrospun nanofibrous film for active food packaging. Food Control 59(2016):366–376

Journal : Medium 10522		Dispatch : 4-3-2020	Pages : 18
Article No. : 9865		☐ LE	☐ TYPESET
MS Code : BGEN-D-20-00003R1		☑ CP	☑ DISK

Wen P, Zong MH, Linhardt RJ, Feng K, Wu H (2017) Electrospinning: a novel nano-encapsulation approach for bioactive compounds. Trends Food Sci Technol 70(2017):56–68

Xu X, Xiao W, Zhang Z, Pan J, Yan Y, Zhu T, Tang D, Ye K, Paranjpe M, Qu L, Nie H (2018) Anti-pruritic and anti-inflammatory effects of oxymatrine in a mouse model of allergic contact dermatitis. J Dermatol Sci 91(2):134–141

Yagi M, Yonei YJ (2017) Glycative stress and anti-aging: 6. Glycative Stress Kidney Dis 4(1):275–278

Yang J, Ciftci ON (2017) Encapsulation of fish oil into hollow solid lipid micro- and nanoparticles using carbon dioxide. Food Chem 231(2017):105–113

Yao ZC, Chang MW, Ahmad Z, Li JS (2016) Encapsulation of rose hip seed oil into fibrous zein films for ambient and on demand food preservation via coaxial electrospinning. J Food Eng 191(2016):115–123

Zhao T, Yan X, Sun L, Yang T, Hu X, He Z, Liu F, Liu X (2019) Research progress on extraction, biological activities and delivery systems of natural astaxanthin. Trends Food Sci Technol 91(2019):354–361

Zouboulis CC, Makrantonaki E, Nikolakis D (2019a) When the skin is in the center of interest: An aging issue. Clin Dermatol 37(4):296–305

Zouboulis CC, Ganceviciene R, Liakou AI, Theodoridis A, Elewa R, Makrantonaki E (2019b) Aesthetic aspects of skin aging, prevention, and local treatment. Clin Dermatol 37(4):365–372

Journal : **Medium 10522**	Dispatch : **4-3-2020**	Pages : **18**
Article No. : **9865**	☐ LE	☐ TYPESET
MS Code : **BGEN-D-20-00003R1**	☑ CP	☑ DISK