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REVIEW ARTICLE

Depigmentation and Anti-aging Treatment by Natural Molecules

Abdelnaser Zaid* and Rowa' Al Ramahi

Pharmacy Department, Faculty of Medicine and Health Sciences, An-Najah National University, Nablus, Palestine

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Abstract: Natural molecules are becoming more accepted choices as cosmetic agents, many products in the market today claim to include natural components. Plants include many substances that could be of a value in the whitening of the skin and working as anti-aging agents. A wide range of articles related to natural skin whitening and anti-aging agents have been reviewed. Many plant-derived and natural molecules have shown to affect melanin synthesis by different mechanisms, examples include Arbutin, Ramulus mori extract, Licorice extract, Glabridin, Liquiritin, Kojic acid, Methyl gentisate, Aloesin, Azelaic acid, Vitamin C, Thioctic acid, Soya bean extracts, Niacinamide, α and β-hydroxy acids, Lactic acid, Chamomile extract, and Ellagic acid. Some of the widely used natural anti-aging products as natural antioxidants, collagen, hyaluronic acid, and coenzyme Q can counteract the effects of reactive oxygen species in skin cells and have anti-aging properties on the skin. It was concluded that many natural products including antioxidants can prevent UV-induced skin damage and have whitening and anti-aging effects. It is very important to develop and stabilize appropriate methods for the evaluation of the whitening and anti-aging capacity of natural products and their exact mechanism of action to ensure real efficacy based on evidence-based studies. The attention should be oriented on the formulations and the development of an appropriate vehicle to ensure suitable absorption of these natural products in addition to evaluating the suitable concentration of these molecules required having the desired effects without causing harmful side effects.

Keywords: Natural products, antioxidants, skin whitening, photoaging, anti-aging, formulation.

1. INTRODUCTION

The achieved advancement in dermatological studies and the improvements in the quality of life consequently resulted in a marked increase in the use of cosmetic preparations especially among women. Indeed, consumers of cosmetics could be classified into two categories; those who prefer the use of decorative cosmetics such as makeup, while the second category prefers the use of functional cosmetics (cosmeceuticals) such as whitening and anti-aging products that inhibit skin pigmentations and prevent premature wrinkles. Skin anti-aging strategies are highly demanded all over the world. Some methods are even invasive and require surgeries or injections [1]. The dermatologic studies- taking in consideration the market demand- were oriented toward an accurate comprehension of the physiology and biochemistry of the complete pigmentation process of the skin and skin aging, for a better understanding of the mechanism of action of the whitening and anti-aging agents of the skin. Great efforts are done to reach safe and less invasive methods and products.

Natural molecules are a major target in this field due to the idea among people that natural products are safe. Natural products include molecules either from plant sources or animal sources.

The color of the skin depends on three factors: the keratin layer, which gives a yellow to white foundation color depending on the thickness of the keratin layer; the superficial blood circulation, which gives reddish to bluish color where its intensity depends on the number, dilation, and deepness of the blood vessels. But the most important factor in the determination of skin color is given by the presence and ratio of several chromophores in the skin [2]. Oxyhaemoglobin (bright red), reduced hemoglobin (bluish red) and bilirubin (yellow) are found in the blood capillaries of the dermis. Melanin is produced from tyrosine and takes two forms: (i) eumelanin; gives a brown-black color and is the more common form and (ii) pheomelanin which produces a yellow or red color (Fig. **1**). This last one also has an important protective function from the ultra-violate (UV) radiations [2, 3].

Melanin is synthesized by the melanocytes that are found in the basal layer of the epidermis. These cells represent 13% of the cellular population of the epidermis. Particularly in the part of the skin exposed to the sun rays like hand and face (2000-2500/mm^2), while in the remaining part of the skin, they are near 1000-1500 mm^2 [4]. Normally, black skin has the same number of melanocytes as blond, red and white skin, but the black skin melanocytes are greatly more active in the synthesis of melanin. Another difference is that the melanin granules are present in the corneal layer, while in the blond skin, they are found in the basal layer of the epidermis only [3]. The number of melanocytes depends on the age. In fact, the number decreases 10-20% every 10 years. The genetic factor influences the number and type of the produced melanosomes rather than the number of melanocytes [5]. Also, certain hormones can influence these parameters [5]. The melanocytes stimulating hormone (MSH) produced by the adenohypophysis accelerates melanin synthesis. β-FGF (fibroblast growth factor), HGF (Hepatocytes Growth Factor) activate tyrosine kinase receptors [5]. Also, estrogen and progesterone increase melanin production, especially in women's face, abdomen, genitals and the areola of the mammalian which remain irreversibly hyperpigmented after first pregnancy [5, 6]. Also, exposure to UV light determines the modification of skin color causing an immediate photo-oxidation of the melanin which is stored in the melanosomes of the most superficial layer [6].

In fact, the prolonged exposure to the UV light causes also an activation of the synthesis process of melanin and acceleration of its transformation to keratinocytes [7]. Historically, during the past centuries, many substances were involved in the cosmetic field to produce bleaching effect to the human skin, such as the milk of goats used by Cleopatra and the milk of the donkeys used by Pop-

*Address correspondence to this author at Department of Pharmacy, Faculty of Medicine and Health Sciences, An-Najah National University, P.O.Box 7, Nablus -, Palestine; Tel: 0097292345113; Fax: 0097292345982;
E-mail: anzaid@najah.edu

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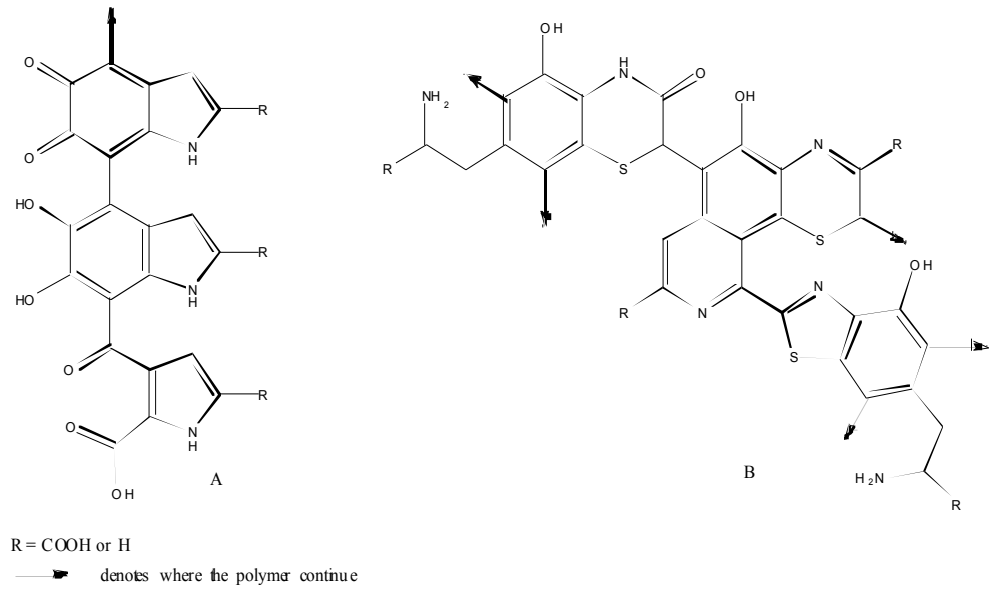

Fig. (1). Chemical structures of eumelanin (**A**) and pheumelanin (**B**).

pea [8]. In these two cases, the whitening agent involved is the lactic acid which is present in the milk. In the Mediterranean region which is rich of citrus fruits, lemon juice which is rich of citric acid and vitamin C has been used to eliminate the black spots without knowing that Vitamin C is responsible for this activity. Nowadays, many typical whitening agents in the market target the melanocytes.

Regarding skin aging, it happens due to many factors such as the biologic progression of cells with years, in addition to external factors as excessive exposure to UV radiation, tobacco smoking, nutritional deficiencies, pollution and hormonal imbalances that lead to the degradation of skin cells [9]. One of the major factors that participate in skin aging is exposure to sunlight (UV radiations) which is called photoaging. Free radicals attach skin structures and destroy collagen and elastic fibers. Free radicals and inflammation weaken repair mechanisms and result in collagen and elastic fiber breakdown. Aging of skin causes skin roughness, wrinkling, pigmentation change, loss of elasticity, and decreased firmness [9, 10]. These changes are mainly apparent in the face because aging is accelerated in areas subjected more to the sun. Reactive Oxygen Species (ROS) type free radicals are related not only to skin aging but also to skin cancer. So, any natural molecule with antioxidant effect may have a possible role in fighting skin aging and cancer, thousands of products have been tested for their antioxidant effects. According to the "mitochondrial theory of aging" being the main site of ROS generation, mitochondria are thought to be part of a process in which continuous accumulation of ROS damaged mtDNA and proteins induces electron transport chain (ETC) dysfunction, which in turn leads to an enhanced ROS production [11]. Molecules that have anti-oxidant properties are expected to protect skin against free radical damage which may repair the function of mitochondria [12]. The skin care market based on natural products is rapidly growing. The aim of this review is to aid in understanding the mechanism of action of some of the widely used whitening and anti-aging natural molecules or extracts and their possible efficacy.

2. SKIN WHITENING AGENTS

The ideal whitening agent should have a potent, rapid bleaching activity with no side-effects and give an irreversible elimination of undesired pigment. The depigmentation effect of whitening agents can be achieved by acting on the melanization process of the skin. In fact, this melanization consists of many steps, thus whitening agents may interfere with one or more steps of this process. They may affect (a) the transcription and activity of tyrosinase including tyrosinase-related protein-1 (TRP-1), tyrosinase-related protein-2 (TRP-2), and/or peroxidase enzymes; (b) the uptake and distribution of melanosomes in recipient keratinocytes and (c) degradation of melanin and melanosome further to the pigmented keratinocytes.

2.1. Old Generation Whitening Agents

2.1.1. Mercury

Red mercuric oxide, mercuric chloride and ammoniated mercury have depigmentation activity. These salts were used for many years as bleaching agents due to their high capacity and low cost. These salts are still used as ancient skin–bleaching products in some countries [13]. The red mercury oxide and mercury chloride were the first whitening agent to be employed, but the majority of the formulations included mercury chloride and ammoniated mercury. Mercury chloride was formulated as a lotion, but it caused exfoliative effect to the skin. The ammoniated mercury is a white powder, insoluble in water and alcohol. It has good chemical stability and it inhibits tyrosinase enzyme possibly by the replacement of the copper ion which is required for the tyrosinase activity or by combining with the protein structure of the tyrosinase enzyme, causing inhibition of melanin synthesis. Mercury is absorbed transcutaneously. In fact, the amount of absorbed mercury through the skin is about 20 times that taken by food and thus toxicity is a major concern. Indeed, the absorbed mercury is oxidized to form water-soluble salts with the hematic protein leading to the toxic effect of mercury [14]. Therefore, the well-known toxicity of mercury combined with its high skin penetration capacity was the main cause to ban the use of mercury in the formulations. Mercury compounds were replaced by hydroquinone which despite its light irritant effect was considered innocuous at the systemic level and does not cause environmental contamination [15].

2.1.2. Hydroquinone (HQ)

Hydroquinone (Fig. **2**) is considered the most popular whitening agent introduced in use since 1961. The depigmentation effect was discovered for the first time by chance. In fact, Oettel noticed that when HQ was fed to black-haired cats, their coat turned grey after 6-8 weeks [16]. Also, he noticed that the hands of women who worked in leather tanneries and were in contact with monobenzyl ether of hydroquinone (a derivative of hydroquinone), used as antioxidant, were lighter than normal [16]. Therapeutic efficacy of

hydroquinone alone or in association with other compounds has been approved in several studies [16, 17]. Because hydroquinone is one of the most famous whitening agents, it has been considered as a reference in evaluating other depigmenting products [18, 19]. Indeed, hydroquinone inhibits melanogenesis by acting at the level of several steps: (1) as an alternative substrate to the tyrosinase, which converts it into 2-hydroxybenzoquinone, which is a selective cytotoxic agent for melanocytes [16]; (2) also HQ produces membranous cytoplasmic destruction of melanocytes, probably by the conversion of hydroquinone to quinines and ROS by tyrosinase enzyme, which initiates a series of reactions resulting in oxidative damage [7, 20]. This results in melanocytes death and the net result is a delay in melanin pigment production, but this is not an irreversible process. However, because long-term treatments with HQ may be hazardous, the use of hydroquinone in cosmetics has been banned by the European Committee (24th Dir. 2000/6/EC) and it is available now as prescription only treatment. In fact, the use of concentrated formulations of hydroquinone (more than 5%) causes skin irritation effects like erythmatosis and desquamation [20, 21]. These side effects are decreased when concentration of < 5% hydroquinone was used [19].

2.2. Skin Whitening Natural Products

Many whitening agents have been developed and are currently available in the cosmetic market; however, those from natural origin are considered more fascinating and are expected to dominate in the cosmeceutical market. In fact, growing number of bioactive compounds such as flavonoids, phenols, coumarins and other derivatives have been obtained from natural sources and evaluated for skin whitening effects [22, 23]. Here, we will discuss a group of molecules or extracts with potential or confirmed skin depigmentation effects, sometimes the active ingredient for this effect is well defined so it will be discussed as a molecule, in other studies they discuss the efficacy of using certain herb or extract without defining one active ingredient, both types of studies are included here. When available, the safety and other biological effects will be discussed. Moreover, the different mechanisms of action of the products will be reviewed and reported. These mechanisms include; inhibition of tyrosinase enzyme, interference with mitochondria activity and DNA synthesis in melanocytes, exploiting the antioxidant capacity of certain products to inhibit the oxidative reaction which transforms tyrosine into melanin, the transfer of mature melanosomes into keratinocyte from melanocytes which is mediated through the protease-activated receptor (PAR-2), the exfoliative action of L(+) Lactic acid and the anti-inflammatory activity of certain products that might retard and prevent skin hyperpigmentations induced by inflammation.

2.2.1. Arbutin

Attention has been oriented to natural products since most attempts to produce a good whitening agent using synthetic chemical agents have failed. Extracts of arbutin *in uvae-Ursi (bearberry)* which contains arbutin, methylarbutin, and hydroquinone glucopyranoside have been considered among the most important natural agents used. In fact, arbutin is naturally occurring hydroquinone β-D-glucopyranoside, which is available in the leaves of *uvae-Ursi* of the *Erica and other Ericaceae* [24-26]. Pure arbutin is obtained by the extraction process from the above-mentioned plants, but it can also be obtained synthetically. Chemically, arbutin is a glucosylated hydroquinone (Fig. **2**) obtained by substitution of one of the hydroxyl groups of hydroquinone with a pentose, hexose, amine glucose or uronic acid. The bleaching capacity of this derivative is shown at noncytotoxic concentration because it is not hydrolyzed by the skin enzymes to give hydroquinone [26]. As this glycoside is not hydrolyzed by skin enzymes to give hydroquinone, it has low melanocytotoxic effects. Arbutin was found to induce a decrease of tyrosinase activity and interferes with the uptake of tyrosine into melanocytes [27]. It is considered as a hydroquinone prodrug and thus its mechanism of action is similar to hydroquinone (IC50 = 17 mM) and it consists of competitive inhibitory activity. Indeed arbutin competes with L-DOPA to the interaction with the tyrosinase enzyme [28]. Technically, arbutin has good water solubility and better chemical stability compared with hydroquinone and in cosmetic formulations, arbutin can be used as extract or as a pure powder.

2.2.2. Ramulus Mori Extract

Morus alba is a well-known plant in Eastern Asia. It can reach up to 15 meters in height. All parts of this plant have been used in the oriental traditional medicine as antipyretic and antihypertensive preparations [28]. The alcoholic extract of its young branches has a good anti-tyrosinase activity due to its content of 2-(2,4-dihydroxyphenyl)-5,7dihydroxy-3,8-bis(3-methyl-2-butenyl)4H-1benzopyran-4-one (Fig. **2**)[28]. This alkaloid has a better bleaching activity than arbutin and kogic acid [29].

2.2.3. Licorice Extract

The *licorice extract* is a yellow to brown colored powder with a characteristic odor. This powder is extracted from the roots of *Glycyrrhiza glabra Linn* or *glandulifera regel*, *Glycyrrhiza uralensis fisher*, *Glycyrrhiza inflates batalin* or other associated species like *Leguminosae*. The extract contains glabridin, glabrene, formomentine and glabrous (Fig. **2**) [30, 31]. This extract has demonstrated an antioxidant activity equal to tocopherol. Furthermore, it has antibacterial activity against dermal microorganisms, typical of acne (Staphylococcus, Pseudomonas, Penicillium)[30]. The whitening activity of this extract is due to its content of glabridin and liquiritin which have a different mechanism of action [32, 33]. *In vitro*, the inhibitory activity of *licorice extract* is 120 times, 30 times and 7 times the activity of ascorbic acid, kogic acid and hydroquinone respectively. *In vivo* experiments, showed the good safety of this extract, since it showed no irritant or any toxic effects. In addition, it showed good activity in case of post-inflammatory hyperpigmentation which was treated for 4 months with 1% w/v cream [30].

2.2.4. Glabridin

Glabridin is the main component of the hydrophobic fraction of *licorice extracts*, it was found to decreases tyrosinase activity in melanoma cells. It has an anti-inflammatory effect as it inhibits cyclooxygenase activity and superoxide anion production. The whitening activity of glabridin is given by its action on three enzymes: tyrosinase and the co-enzyme tyrosinases (Tyr_1 and Tyr_2), which are essential for the synthesis of melanin. It has inhibitory activity against tyrosinase enzyme, it blocks Dopa tautomerase enzyme and inhibits the conversion of Dopa to DHI and thus the formation of melanin is inhibited [33, 34].

2.2.5. Liquiritin

Liquiritin (Fig. **2**) is the second important whitening agent of the *licorice extract*. This agent acts on the dispersion and homogenization of melanin which can result in skin whitening and/ or better homogenization of the skin color, resulting in a better look. This flavonoid glucoside induced a significant improvement of skin hyperpigmentation in patients with melasma [33-35].

2.2.6. Kojic acid and Kojic dipalmitate ester

Kojic acid a 5-hydroxy-2-hydroxymethyl-4-pyran-4-one (Fig. **2**) is a white and colorless powder. It is water soluble and very unstable. Usually tends to change its color from yellow to brown when chelating ions like iron. It is oxidized upon exposure to air and high temperature [35]. Kojic acid has no toxicity and irritation capacity and thus it is largely used in many whitening formulations. It is a natural agent which was initially extracted from *rice bran* after its spontaneous fermentation. Nowadays, it is industrially obtained by the fermentation of the residue oil of cacao. Kojic acid was also known for its antibiotic and insecticide activity. Recent studies demonstrated that kojic dipalmitate ester has a high antity-

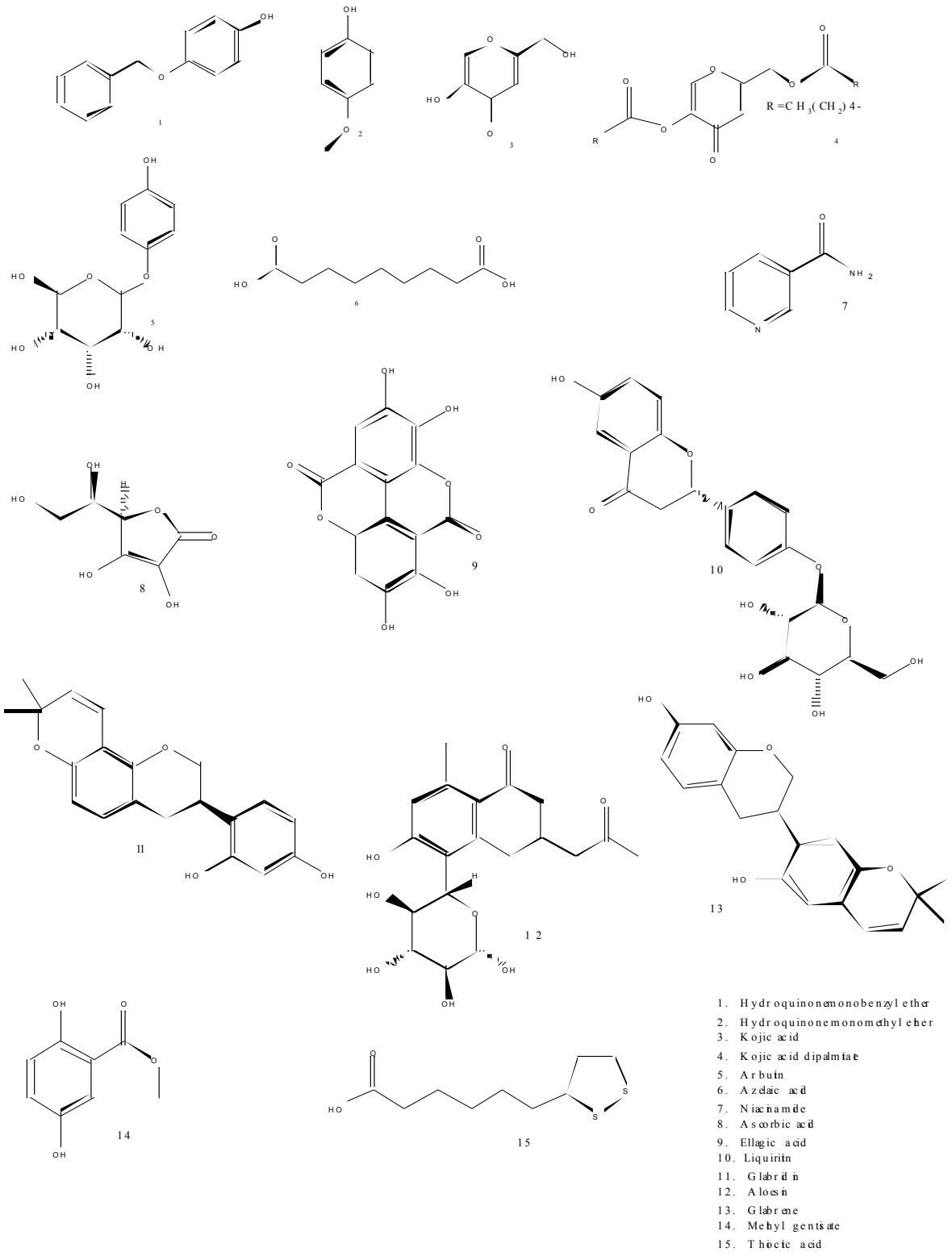

Fig. (2). Chemical structures of some whitening agents.

rosinase activity and higher chemical stability than Kojic acid. Also, this ester is more active than hydroquinone. Ester is oil soluble and thus it is mixed with the oily phase at 70^{o}C during formulation procedure. The palmitate ester is light, pH and air stable. The depigmentation activity of kojic acid is attributed to inhibition of tyrosinase activity by chelation with the copper ion of this enzyme. This leads to the inhibition of the tautomerization of Dopa to DHICA (5,6-dihydroxyindol-2-carboxylic acid) [35, 36], Kojic acid has the capacity to destroy the formed melanin by its antioxidant activity [36]. Furthermore, kojic acid stimulates the leucocytes and eliminates free radicals which were produced in the body cells and released into the circulation and tissues. Therefore, kojic acid is considered an important anti-aging agent also able to delay the undesired process which causes epidermal degradation [21, 36].

2.2.7. Methyl Gentisate (MG)

Gentiana lutea Linn (Gentianaceae), universally known as *gentian*, is commonly utilized in many folkloric and alternative medicine for its anti-inflammatory and wound healing properties [37]. MG is the methyl ester of gentistic acid or 2,5 dihydroxy benzoic acid (Fig. **2**). This agent is a naturally occurring analog of HQ, extracted from *Gentiana's* roots, It was found to inhibit melanin synthesis in murine melanocytes without cytotoxicity [38]. It inhibits tyrosinase following the intracellular release of HQ or by a direct effect on the enzyme through the binding copper ions. The efficacy of this compound as a skin bleaching agent was confirmed in clinical studies [39]. In fact, this agent is present in the cosmetic market as a cream [40]. The manufacturer claims that this MG based formulation has effectiveness comparable to HQ without causing undue skin irritation. The formulation of this agent into a cosmetic emulsion should take into consideration its oxidation and hydrolysis tendencies, thus an appropriate antioxidant and a neutral pH should be recommended.

2.2.8. Aloesin

This agent is a naturally occurring hydroxychromone derivative. It is extracted from *Aloe vera*. The mechanism of action of this whitening agent is attributed to (i) inhibition of tyrosinases without causing toxicity probably by working as a competitive inhibitor on Dopa oxidation; [41] (ii) and as a non-competitive on tyrosine hydroxylase activity. When aloesin was combined with arbutin, the combination was able to inhibit UV-induced melanogenesis in a synergistic manner *in vivo* [41]. Since this derivative is an ester, therefore it should be important to control the pH of the formulation in order to avoid hydrolysis, which may interfere with its absorption and distribution.

2.2.9. Azelaic Acid (AzA)

Azelaic is a natural product produced by the *Pityrosporum ovale*, which is the microorganism responsible for the skin disease known as Pityriasis Versicolor [42]. This disease is manifested as spots which are poor of melanin, because of the competitive tyrosinase inhibition of the azelaic acid. *In vitro*, this acid inhibits tyrosinase activity and may also interfere with mitochondria activity and DNA synthesis in melanocytes [43]. Later on, AzA has demonstrated to be a good antibacterial agent and a good reductase inhibitor of α-reductase enzymes, which is responsible for the formation of a pustule. Furthermore, AzA inhibits oxygen function in the biological system, such as the oxidation of the aromatic compounds like tyrosine and reduces the cytotoxic effects produced by free radicals. Clinically, AzA has been used to treat melasma and to arrest the progression of lentigo maligna to melanoma [43, 44]. Its use for the treatment of acne was also reported [45].

2.2.10. Vitamin C and magnesium-L-ascorbyl-2-phosphate

The role of compounds with reducing activity can be appreciated from the fact that these agents are able to interact with O-quinones, thus avoiding the oxidative polymerization of melanin intermediates, or with copper at the active site. Moreover, the free radicals, which are produced in the skin due to UV light exposure, can be trapped or scavenged by these redox agents. In fact, the scavenging of these free radicals inhibits possible second messengers, which are able to stimulate melanogenesis [46, 47]. Due to the instability problems, the use of vitamin C in cosmetic formulations as a whitening agent was introduced recently. In fact, it is used as an ester of the palmitic or benzoic acid. Recently, it was developed as magnesium phosphate (Fig. **2**). Its antioxidant capacity is exploited to inhibit the oxidative reaction which transforms tyrosine into melanin and inhibit the tyrosinase enzyme by reducing it. Indeed ascorbic acid inhibits melanin synthesis by reducing the o-quinone formation and oxidized melanin [46, 48, 49]. Ascorbic acid acts synergistically with vitamin E in many oxidation steps in the synthesis of melanin [49]. However, ascorbic acid is easily decomposed in the presence of aqueous solution, therefore magnesium-L-ascorbyl-2-phosphate (MAP) was produced in order to resolve this inconvenience. The MAP is a stable hydrophilic derivative of vitamin C, which is considered a prodrug because *in vivo* it releases L-ascorbic acid in the presence of skin phosphatases. However, this agent dissociates easily to give anions that have difficult skin penetration. Therefore, iontophoresis was used to enhance the transcutaneous penetration of MAP. The MAP has three important properties: inhibitory effect of melanogenesis; promotion of the collagen synthesis; and free radical scavenging. It has been demonstrated that MAP has undisputed bleaching activity on the skin which is affected by hyperpigmentation disturbances [50]. Also, this activity has been shown on healthy skin without any pigmentation, without interfering with the physiological growth and development of the skin [50].

2.2.11. Thioctic acid (TA)

Thioctic acid (Fig. **2**) is a α-lipoic acid, which is a disulfide derivative of octanoic acid. These agent effects include (i) quenching of free radicals; (ii) metal chelation, such as copper; (iii) interaction and regeneration of other antioxidants; (iv) effects on gene expression and apoptosis and (v) redox regulation of thiol groups of the protein. Clinically, TA has been suggested to prevent oxidative damage induced by UV light. This last effect results in the down-regulation of NF-κβ activation. Also, inhibition of tyrosinase activity is probably performed by chelating the copper ions, was also reported [51].

2.2.12. Soya bean extracts

An essential step in skin pigmentation is the transfer of mature melanosomes into keratinocyte from melanocytes. This step is mediated through the protease-activated receptor (PAR-2) [48]. Indeed, when dark-skinned Yucatan microswine were topically treated with serine protease inhibitors, like *soybean* trypsin inhibitor or Bowman-Birk protease inhibitor by using a formulation with liposomal delivery system, they exerted a significant skin whitening effect without showing any toxic effects. In fact, *soybean milk extracts* also decreased the melanin retention within the swine epidermis and prevented UVB induced pigmentation *in vivo*, similar to soybean trypsin inhibitor, with no need to add any delivery vehicle [48, 52].

2.2.13. Niacinamide

Niacinamide is the biologically active form of vitamin B3. It is likely to act via an inhibition of the transfer of melanosomes from melanocytes into keratinocytes. In fact, it inhibits both *in vitro* and *in vivo* melanogenesis, most likely through the abolition of melanosome transfer [53]. In addition, vitamin B3 has no effect on purified tyrosinase, therefore, skin darkening is decreased in the co-culture system or in reconstructed epidermis and not in melanocyte monocultures [21].

2.2.14. α- & β-hydroxy acids

Also, the acceleration of epidermal turnover can produce the same results, which were seen in the above method. Retinoic acid, α- and β-hydroxy acids and free fatty acids are called exfoliant chemicals because of their capacity to stimulate the cell renewal facilitating the elimination or the removal of black pigmented keratinocytes, leading to melanin pigment loss [54]. In fact, the visibility of age spots was reduced significantly using topical application of creams or lotions that contain these agents. But the size and number of these spots were not reduced, thus these formulations can be useful in the treatment of melanosome [55].

α-hydroxy acids have been exploited in the cosmetic field for many years as exfoliants. Sodium lactate has been hypothesized to be one of the skin own natural moisturizers. The stimulating of epidermal turnover or exfoliative effect was proven in recent studies. These studies have shown that low concentrations of α- & β-hydroxy and carboxylic acids have the potential to give long-term

skin improvement. This activity is due to the decrease of pH of the skin, as the neutralized acids lost their capacity to exfoliate the skin.

2.2.15. L(+) Lactic acid

In 1996 Smith, W.P. published the results of his studies on the effects of topical treatment of L(+) lactic acid on the skin. This author has suggested that topical applications of 12% L(+) lactic acid can induce changes in both the dermal and epidermal layers, while lower concentrations of this agent produce superficial effects only. This author has also demonstrated that such changes are likely tied into the clinical or subclinical alteration of the skin barrier. However lactic acid also has inhibition capacity towards tyrosinase activity and a number of *in vitro* studies suggest the use of this agent in whitening creams. Moreover, Smith W.P. reported that the use of a combination of L(+) lactic acid at 8,8% with 1% ascorbic acid, adjusted to pH 5, has documented whitening effects when examined in controlled clinical trials. In this study, Smith supposes that the exfoliative action of L(+) Lactic acid in some way contributes to the whitening effects of the tested combination since the same base formulation containing 1% ascorbic acid alone did not produce similar results to the combination [54].

2.2.16. Chamomile extract

Chamomile is a member of the family of *Asteraceae* or *Compositae*. It is widely described by two diversity; *Matricaria chamomilla* (*viz*. German chamomile) and *Chamaemelum Nobile* (Roman chamomile) [56]. *Chamomile* contains several classes of bioactive components, which are extracted and exploited in many cosmetics and medicinal products [57]. It contains up to 2% volatile oil which usually has a good shelf life and maintains its potency despite its fading. Several secondary metabolites were identified in this herb, such as terpenoids and flavonoids [58, 59]. Terpenoids α-bisabolol and its oxide azulenes including chamazulene and acetylene by-products are considered the main components of the essential oil available in the *Matricaria chamomilla* flowers. The extracted essential oil from the *Chamaemelum Nobile* contains lower quantities of chamazulene than *Matricaria chamomilla* and it is usually composed of angelic and tiglic acid esters. In addition, it contains farnesene and α-pinene. *Chamaemelum Nobile* contains sesquiterpene, nobilin, and 3-epinobilin. The major bio-active ingredients are bisabolol, α-bisabolol, terpenoids and flavanoids [60, 61]. Apigenin is the most promising compound among the available flavonoids in the flower of *Chamaemelum nobile*. Free apigenin is available in very limited quantities, but mostly available in different forms of glycosides [62-64]. In alternative and traditional medicine, *chamomile* has been exploited to treat inflammatory disorders of the skin. In addition, it showed an interesting antioxidant, astringent and healing activities [65]. In fact, it is currently used in the treatment of skin wounds, ulcers, eczema, skin irritations, burns, cracked nipples, canker sores, other skin disorders and many other internal diseases such as colic, croup, and fevers in children [66-68]. Regarding the role in skin pigmentation, the exposure of keratinocytes to UV-light and/or pro-inflammatory stimuli leads to the release of mediators, such as interleukin-1α (IL-1α) and endothelin 1 (ET-1)[69]. These mediators are able to induce melanogenesis. Therefore, the use of anti-inflammatory agents could be a useful method for the retardation and prevention of skin hyperpigmentations induced by inflammation. Chamomile extract avoids ET-1 induced DNA synthesis. This mechanism produces hypopigmentation. Therefore, topical application of cosmetic formulations enriched with *M. chamomile* extract could be a good method for skin bleaching [70].

2.2.17. Ellagic Acid (EA)

Ellagic acid (EA) has a polyphenol structure that is widely found in many plants (Fig. **2**). EA is a natural compound that can be found in different plants such as *cherries, strawberries, blackberries, raspberries, and walnuts*. In recent years, EA has created very important commercial interest since it has shown several important therapeutic benefits to human beings [71]. These benefits include antioxidant, anti-mutagenic, antimicrobial properties as well as its capacity in inhibiting the human immunodeficiency virus (HIV) [72-75]. In addition, EA demonstrated its ability to interfere with the development of different types of cancers, by its capacity to interplay important sites that facilitate the formation of complex proteins which are important in the propagation of metastatic cells [76]. In 2004, Losso et al. assessed the cytotoxic and anti-proliferative capacity of EA in breast, colon, lung, and prostate cancer, and demonstrated that EA can inhibit the proliferation of these tumors in doses of 1 -100 micromol/L [77]. Moreover, EA demonstrated some activity in skin bleaching. In fact, it can prevent pigmentation caused by sunburn. It is another copper chelator, which is a noncompetitive tyrosinase enzyme inhibitor, this is the major mechanism of action for its depigmentation effect, another mechanism of action of EA was also suggested which is its ability to have ROS scavenger effect [27].

2.2.18. Ginseng

Ginseng extract (GE) is typically characterized by the presence of ginsenosides and gintonin. GE is obtained from the root of the *Panax* family like Chinese ginseng (*P. notoginseng*), Korean ginseng (*P. ginseng*), as well as the American ginseng (*P. quinquefolius*). Despite its use in Asian traditional and folkloric medicines over centuries in many fields, current clinical research is uncertain about its pharmacological effectiveness because large number of studies can be found, but few have been high quality [78, 79]. Ginsenosides are the major active components of ginseng, in addition to phenolic compounds, polysaccharides, and proteins [80]. However, regarding its effect on the skin, various studies have reported the ability of GE to work as a skin whitening agent. In fact, P-coumaric acid, which is usually extracted from the fresh leaves of *ginseng Panax*, demonstrated higher capacity in preventing the oxidation of L-tyrosine than the inhibition of tyrosinase which was achieved by L-DOPA [81]. In addition, using various concentrations of *Radix Ginseng* and *Radix trichosanthis* demonstrated to inhibit the activity of tyrosinase and melanin content but increased cell proliferation slightly in B16 melanoma cells. This can increase the prospect that this combination can be effective as a skin-bleaching bioactive agent in the cosmetic field [82]. Another potential role is its effectiveness as anti-aging agent, a study by Lee et al, when HaCaT keratinocytes and human dermal fibroblasts were exposed to UVB radiations, *Panax ginseng* was found to reduce the nitric oxide production and inducible nitric oxide synthase mRNA synthesis and showed anti-inflammatory activity which was confirmed by its inhibitory effects on the elevated cyclooxygenase-2 and tumor necrosis factor-α transcription which was induced by UVB-irradiation in HaCaT cells, so they concluded a potential role against photoaging and damage of dermal cell caused by UVB [83].

2.2.19. Rubia cordifolia (RC)

RC is a breed of flowering plant; the species to which RC belongs is *Rubiaceae*. It contains a red pigment which is extracted from its roots. From a chemical point of view, CT is rich of glucosides such as Purpurine and Manjisthin, as well as lime salts, resins, and pigments. According to the Indian Ayurvedic texts, CR is famous for its great benefit to the skin as well as its capacity to bleach dark spots [84]. In fact, Alcoholic extracts of CR demonstrated interesting inhibition of the activity of tyrosinase enzyme which could explain its use as a skin whitening agent in Indian cosmetic preparations [85].

2.2.20. Mesua ferrea (MF)

MF is a slow-growing tree that belongs to the family of *Calophyllaceae*. Despite the fact that MF is not famous as a skin care tree but the phytochemical assessment of this tree has demonstrated its potential pharmacological and cosmetic use since it showed antioxidant and blood purifying effect [86]. Regarding the phytochemical contents, MF contains phenyl coumarins [87], xanthones

[88], triterpenoids [89] as well as flavanoids which are mainly responsible for its biological and therapeutic activities. In fact, according to a study that has been conducted by Jayanthi et al. this tree has potent antioxidant activity which can be equivalent to that given by ascorbic acid [90]. Recently, another study has demonstrated that its extract can display exceptional tyrosinase inhibition activity and protection against UV rays comparable with arbutin rendering it a great candidate for use in whitening creams [91].

2.2.21. Prunus cerasoides (PC)

PC is also known as wild Himalayan and sour *cherry* that belongs to the species of *Rosaceae* and the genus *Prunus*. It is a temporary *cherry* tree which is found in East, South and Southeast Asia. The use of *PC* in cosmetic and skin care products was well reported in both Ayurveda and biomedicine. A new flavanone glycoside Puddumin-B, (naringenin-4-methyl-ether -7-O-β-D-galactoside) has been isolated from PC [92]. This flavone showed interesting skin whitening effect by inhibiting the tyrosinase activity which makes it a suitable candidate for skin bleaching [93]. However, more studies are needed to confirm this effect and to reach the suitable formulation for this use.

2.2.22. Hemidesmus indica (HI)

HI is a plant species that belongs to the *Apocynaceae* family. It is found in South Asia. It has woody and aromatic roots. It is commonly employed as a blood purifier and for various skin ailments [94]. The biological activity like its antioxidant effect in many *in vitro* and ex vivo models was assessed using a methanolic extract of HI root [95]. In fact, this organic extract has demonstrated interesting tyrosinase suppression effect using l-DOPA as enzyme substrate [84]. A recent phytochemical screening on root extracts showed that HI is rich in 2-hydroxy-4-methoxybenzaldehyde, which is a principal aromatic phenolic compound that showed a potential inhibitory effect against the tyrosinase enzyme which may prove its skin potential bleaching effect [96].

2.2.23. Vetiveria zizanoides (VZ)

VZ is a perennial and ecofriendly cluster herb. It has many folkloric therapeutic uses in many Asian countries. Its extracted essential oil (*vetiver* oil) has extensive applications in the cosmetic field [97]. This aromatic oil has more than 150 different compounds such as β-vatirenene, cedr-8-en-13-ol, α-gurjunene, dehydro-aromadendrene and α-amorphene. This oil showed the significant antioxidant effect as well as capacity to suppress the β-MSH-induced melanogenesis, which causes a decrease in the production of melanin through inhibition of tyrosinase and the simultaneous block of oxidative stress in B16 melanoma cells [98]. Accordingly, *vetiver* oil could be considered as a potential candidate to become an ingredient in the future whitening cosmetic formulation.

2.2.24. Chalcones (CNs)

Chalcones (CNs) are natural compounds that are widely distributed in edible fruits, and vegetables [99]. Chemically, they bear an aromatic ketone which represents the core for a variety of important bioactive compounds. In fact, CNs demonstrated antiseptic and anticancer activities. In addition, they demonstrated anti-inflammatory properties. Moreover, their tyrosinase inhibition activity was studied by Nerya et al. demonstrating that CNs could show interesting skin whitening potency [100].

3. SKIN ANTI-AGING NATURAL PRODUCTS

This part discusses some of the widely used and studied natural anti-aging molecules including a group of natural antioxidants, collagen, hyaluronic acid, and Coenzyme Q. It is impossible to include all molecules with possible skin anti-aging properties because thousands of plant parts and extracts have been evaluated for possible efficacy.

Strategies of natural molecules in fighting skin aging include: 1) the ability to act as antioxidants and scavenge free radicals, this includes flavonoids and phenolic compounds, examples of plant extracts that have been studied and used for this effect include but not limited to *grape, green tea, turmeric, licorice, coffee, thyme, rosemary* and *oregano* [1], 2) another mechanism is the protection of skin matrix through the inhibition of enzymatic degradation; inflammatory mediators as interleukins and tumor necrosis factors mediate collagenolytic effects by stimulation of matrix metalloproteinases, examples of plant extracts that have been studied and showed potential matrix protective action include *wild yam, soybean, coffee, burdock,* and *areca nut palm*. 3) Some plants have been able to promote collagen synthesis in the skin; examples include *amla, burdock, camellia, ginseng,* and *cinnamon*. 4) In addition to that, some plants can improve skin tightness and elasticity, this effect might be due to synergistic properties including their antioxidant, anti-inflammatory and UV protective effects, examples *licorice, turmeric, pomegranate, amla, aloe, dill* and *sichuan pepper* [1, 101]. The reader may notice that some plants and molecules were discussed as whitening agents also; this is because some natural molecules could show whitening and anti-aging characteristics. Also, it is good to mention that this review tries to include the most common natural compound with possible skin anti-aging effects but not all of them because every day more and more extracts and molecules are being tested for possible useful effects, so it is im-

Table 1. Mechanism of action of natural molecules and extracts with potential skin whitening effect.

Mechanism of Action	Natural Molecules and Extracts
Inhibition of tyrosinase activity	Arbutin, Ramulus mori extract, Kojic acid and Kojic dipalmitate ester, Licorice extract, Glabridin, Methyl gentisate, Aloesin, Azelaic acid, Lactic acid, Thioctic acid, Ellagic acid, Gensing, Rubia cordifolia, Mesua ferrea, Hemidesmus indica, Vetiveria zizanoides
Acts on the dispersion and homogenization of melanin	Licorice extract, Liquiritin
Inhibition of melanin synthesis by reducing the o-quinone formation and reduces oxidized melanin	Vitamin C
Inhibition of the transfer of melanosomes from melanocytes into keratinocytes	Soya bean extracts, Niacinamide
Exfoliants which stimulate cell tunover	α and β-hydroxy acids
Ati-inflammatory effect inhibits endothelin 1 induced DNA synthesis	Chamomile extract

possible to include them all.

3.1. Natural Antioxidants

Exposure to UV light triggers the production of ROS in skin cells, this increases oxidative stress and results in photoaging. Nearly all creatures have developed mechanisms to protect themselves from radiations. Plants include many compounds with antioxidant activity to protect themselves from the UV effects [102]. A healthy diet rich in vitamins, polyunsaturated fatty acids, and polyphenols from plant sources has been shown to contribute to the prevention of age-related diseases [9]. Supplementation with dietary antioxidants and/ topical antioxidant-based lotions before exposure to the sun have been studied as strategies to avoid skin aging.

Many potential antiaging molecules have been extracted from plants and evaluated for their antioxidant effect, examples include phenolic compounds, carotenoids and ascorbic acid derived from different plant species, they were able to protect the skin by preventing UV penetration, reducing oxidative stress and inflammation and influencing several survival signaling pathways, this may protect skin from UV-induced erythema, early aging, and even irradiation-induced cancer [9, 102, 103]. Phenolic compounds include flavonoids (catechins, isoflavones, proanthocyanidins, and anthocyanins), phenolic acids (benzoic, gallic, and cinnamic acids), and stilbenes derived from plants such as *tea, grape, bergamot, fern block, rooibos, grapefruit,* and *red-orange* [9]. Curcumin is a polyphenol derived from the *turmeric* spice. It is well known for its anticarcinogenic, anti-inflammatory, and antioxidant activity [102]. The United States Food and Drug Administration (FDA) has labeled curcumin supplements safe for ingestion and pharmacologic use [10].

Carotenoids include *β*-carotene, lycopene, canthaxanthin, and lutein that are derived from different plant sources such as *tomato, carrots,* and algae and capsanthin and capsorubin from *red pepper* [9].

Thousands of studies evaluating potential skin anti-aging effects in plant extracts can be found. In a review by Tundis et al, many phytomolecules were able to inhibit tyrosinase, collagenase, hyaluronidase, and elastase, or were able to scavenge free radicals from skin cells, others showed activity in preventing trans-epidermal water loss and contributed to protecting skin from wrinkles. These molecules included curcumin, carnosic acid, curculigoside, mangiferin, glycyrrhizic acid, asiaticoside, rosmarinic acid, tectorigenin, and tyrosol. So they have concluded that extracts and pure compounds from *Fabaceae*, *Asteraceae* and *Zingiberaceae* families are promising for use in products for skin aging [104].

In another study to test the effect of topical herbal based products among 110 subjects, they compared products that included prescription tretinoin, physician strength idebenone, polyhydroxy, kinetin, lactic and glycolic acids in reversing signs of photoaging and concluded that herbal based products were safe and effective in reversing photoaging signs and symptoms [105]. The challenge today is to develop suitable formulations able to deliver effective doses of the active ingredient into the epidermis. Many types of nano-formulations, such as nanostructured lipid carriers, liposomes, and nano-emulsions are being studied and have great potential to solve the problem of poor solubility of some compounds [102]. Also, studies are needed to evaluate the combination of more than one natural product with different complementary beneficial activities which may be a promising method in fighting skin aging.

The major problem with natural botanical extracts is to reach stable formulations that provide the required medicinal efficacy. However, their instability and short half-life, complicated extraction methods, and difficult analysis of components have always been a problem. That is why it takes a long time to convert them into proper effective products [106]. Examples of common natural products with anti-aging properties which will be discussed here include green tea polyphenols, aloe vera, curcumin, sulforaphane, honokiol, apocynin, quercetin, coffee silverskin, wheat grain, and gingko. They mainly have this effect due to their antioxidant, anti-inflammatory effects and decreasing ultraviolet-induced skin photoaging.

3.2. Green tea polyphenols

Green tea (*Camellia sinensis*) is used widely all over the world especially in Asian countries, it includes many polyphenols that have shown antiwrinkle, antioxidant, and anti-inflammatory effects [107, 108]. *Green tea* includes many polyphenols including catechins, gallocatechin, epigallocatechin (EGC), and epigallocatechin-3-gallate (EGCG) [102]. In animal studies, topical or oral forms of tea polyphenols were able to protect against UVB-induced carcinogenesis and inflammation. Giving *green tea* orally to SKH-1 hairless mice resulted in a decrease of edema, counteraction of antioxidant depletion and a decrease in inflammation explained by the decrease in cyclooxygenase-2 (COX-2) expression after exposure to UV B radiations [109]. Tea polyphenols photo-protective effect is due to decreasing ROS and counteracting UVB-induced immunosuppression in the skin both locally and systemically [110]. Topical application of EGCG in mice could counteract UV induced alterations by blocking UVB-induced infiltration of CD11b+ cells into the skin; reducing IL-10 production in the skin and in draining lymph nodes (DLN), in addition to increasing IL-12 production in DLN [111]. In a study in mice, water extracts of green, white and black tea were tested, treated mice exhibited diminished epidermal thickness and increased collagen and elastic fiber content and reduced expression of MMP-3, a collagen-degradative enzyme. *Green, white, and black tea* were compared and it was found that the anti-wrinkle activity of *white tea* and *black tea* is equally greater than that of green tea [112]. When *green tea* was combined with *Ginkgo biloba*, extracts showed a moisturizing effect and improved skin elasticity [113]. In a comparative study among 33 men, *green tea* and *lotus* combined in multiple emulsions applied topically for 60 days showed a superior synergistic anti-aging effect than each agent alone [114]. These studies suggest that combining more than one herbal extract including different antioxidant constituents might have a synergistic effect. In clinical practice, formulation to improve the bioavailability of active compound are needed [110].

3.3. Aloe vera

Aloe vera containing products are widely used formulations for skin and hair care, leaf extract of *aloe vera* contains many active components such as proteins, minerals, carbohydrates, and vitamins [107]. *Aloe vera* gel is obtained from the pulp of a tropical cactus, the family of the plant is the lily family, it has anti-inflammatory, antibacterial, antifungal, antiviral and moisturizing effects [102, 115]. *Aloe vera* gel may be used to decrease inflammation. In a trial among 60 patients, *aloe vera* gel improved mild to moderate acne vulgaris. The antibacterial and anti-inflammatory properties of *Aloe vera* gel may be of value in this field [116]. In a study on HaCaT keratinocytes, they found that *aloe vera* could decrease both *in vitro* and *in vivo* photodamage, this was not due to anti-radical properties, the protection showed by *aloe vera* was explained by the maintenance of membrane integrity in both mimetic membranes and intracellular organelles. The increased lysosomal stability led to a decrease in lipofuscinogenesis and cell death [117]. The efficacy of *aloe vera* gel in decreasing ultraviolet-induced skin photoaging was approved in many animal studies [118, 119]. When *aloe vera* was given as oral supplement to mice, this led to a reduction in UVB induced apoptosis of epithelial cells and a reduction in matrix metalloproteinases (MMP-2, MMP-9, MMP-12, and MMP-13) in UVB-exposed skin in addition to a reduction of pro-inflammatory cytokines (IL-1β and TNF-α), this led improvement in skin dryness, epidermal thickness, and wrinkle formation [118]. In another study, daily ingestion of *aloe vera* gel powder containing aloe sterols in ovariectomized mice, significantly decreased acceleration in skin aging, the mechanisms for this effect included reducing the expres-

sion of MMPs and increasing hyaluronan synthase (HAS) and epidermal growth factor (EGF) in the skin [119]. In a study among 30 healthy females, after aloe gel intake for 90 days, the facial wrinkles and elasticity improved. Type I procollagen mRNA levels increased and the MMP-1 mRNA levels decreased [120]. In a study among Japanese women, *aloe vera* gel powder containing 40 μg Aloe sterols significantly reduced facial wrinkles in women aged ≥40 years, and aloe sterols could stimulate collagen and hyaluronic acid production by human dermal fibroblasts [118]. Aloe vera was combined with other natural molecules and the results were promising, it was combined with curcumin for topical delivery and that resulted in enhanced antioxidant effect [106].

3.4. Curcumin

Turmeric is a commonly used spice. Curcumin is the primary component of *turmeric* (*Curcuma longa*), it has a yellow pigment which gives the special yellow color. it has shown anti-inflammatory, antioxidant, antibacterial, anti-cancer and anti-proliferative properties [121, 122]. The active components of *turmeric* in addition to curcumin include bisdemethoxycurcumin, demethoxycurcumin tetrahydrocurcumin, and turmerones, all of these components have anti-inflammatory and anti-proliferative activity [122, 123] Curcumins have been studied and used for many skin problems as infection, acne and cancer [121, 124]. Curcumin is a selective and non-competitive phosphorylase kinase inhibitor which plays a key role in activating inflammatory pathways in photo-damaged and burned skin, so curcumin gel was able to produce rapid healing of burns and photo-damaged skin [125]. Curcumin showed anti-photoaging and anti-cancer activity on the skin, this effect is explained by its ability to attenuate oxidative stress and suppress inflammation [124]. In a study to examine the anti-wrinkle effects of three curcuminoids from *Curcuma longa* in keratinocytes and fibroblasts and evaluate the anti-inflammatory effects which could be useful in anti-aging treatment. They found that three curcuminoids could inhibit the UV-B-induced TNF-α mRNA expression. Mainly, both demethoxycurcumin and bisdemethoxycurcumin inhibited UV-B-induced NF-κB activation in HaCaT keratinocytes and reduced the expression of MMP-1 in both keratinocytes and fibroblasts. So they concluded that curcuminoids have anti-wrinkle activity, the mechanism was the inhibition of UV-B induction in keratinocytes and TNF-α induction in fibroblasts [126]. In another recent study, they tested the ability of curcumin to protect human dermal fibroblasts against ultraviolet A (UVA) induced photoaging, they found that it could reduce the accumulation of ROS and restore the activity of antioxidant defense enzymes, so they concluded a potential benefit in skin photoprotection [127]. The major problem with curcumin is its low bioavailability, low aqueous solubility, and chemical instability, so new and effective strategies to improve pharmacokinetic profile and increase its bioavailability are needed [121]. Curcumin has rapid plasma clearance which causes limited therapeutic benefits, trials to complex it with other substances or develop new formulations to improve bioavailability is going on and could solve the problem [123].

3.5. Sulforaphane (SL)

In 2002, Conaway et al conducted an epidemiological and clinical studies to assess the effect of functional food such as *broccoli, cauliflower, red cabbage, brussels sprout*s or *cabbage* on the development of certain types of tumors, such as tumors of the gastrointestinal tract and of the respiratory tract and skin cancer. The study provided conclusive evidence demonstrating that populations with a diet rich in the above edible plants or herbs are less prone to develop these tumors. The inhibition of carcinogenic and therapeutic effect that this type of diets provide have been attributed to the huge content of phytochemicals that are chemically characterized in that by bearing an isothiocyanate type functional group [128]. In fact, Sulforaphane (SL) is considered as one of the most popular phytochemicals of the isothiocyanate class. The IUPAC name of SL is (R_s)-1-isothiocyanato-4-(methylsulfonyl)-butane and for the first time, it was isolated from broccoli, in 1992 [129]. This chiral molecule contains isothiocyanate and sulphoxide functional groups and it is considered one of the main inducers of phase 2 detoxifying enzymes. In addition, its high cancer preventive activity was extensively proved. Therefore, the interest of the scientific community toward this kind of compounds and other related compounds that can improve the therapeutic and pharmacological characteristics thereafter has hugely increased especially in the last two decades [130]. This natural antioxidant also exerts antidiabetic, antimicrobial, and protective effect against UV-light-induced skin carcinogenesis. Precisely, it was proved that SL provides protection against UV radiation, thus preventing sun damage, degeneration caused by ROS and the development of skin cancer [130, 131]. In fact, SL extracts topically applied on the skin of mouse showed anti-inflammatory effect since protected against UVR-induced inflammation and edema. This was achieved by the activation of Nrf2 and subsequent up-regulation of phase 2 antioxidant enzymes [132]. In addition, SL demonstrated its effectiveness as anti-aging due to the recent studies which have shown that the activity of Nrf2 declines during the aging process. The causes for the decreased Nrf2 activity is still not understood, however, there is a prove that Nrf2 could lose the capacity to bind to the antioxidant response element (ARE) sequence in the antioxidant genes [133]. Mainly, the capacity of Nrf2 to bind to the cis-element is probably reversible by Nrf2 agonists such as an α-lipoic acid [133] and SL [134]. SL demonstrated to reestablish the transactivation capability of Nrf2 and to give cytoprotection against UVB-induced damage of human lens epithelial cells by enhancing the expression of phase 2 enzymes and also by expanding the antioxidant enzyme catalase [134]. The recovery of the activity of Nrf2 in aging cells, as well as cells exposed to UVB, gives the proof-of-concept that this natural product is a very promising ingredient in the upcoming anti-aging drugs and cosmetics [135].

3.6. Quercetin (QN)

Quercetin (QN) is chemically (3,3′,4′,5,7-pentahydroxyflavone) and it is considered one of the most abundant dietary flavonoids that belong to the flavonols subgroup [136]. It is available in several plants and foods, including *American elder, apples, green tea, buckwheat tea, onions, berries, ginkgo biloba, St. John's wort,* and others herbs and plants. The plant extract of QN is the principal constituent of many potential anti-allergic drugs and supplements [137]. QN is also an auspicious constituent that can prevent diseases that are caused by erroneous lifestyle [138]. QN extracts are now mostly used as a nutraceutical product and to treat many diseases such as obesity, diabetes, circulatory and blood vessels the conditions, including inflammation, as well as mood troubles [139]. QN showed comparable anti-allergic potential as a Chinese herbal formula that has been related to stopping anaphylaxis to peanuts in mice models [140]. QN is most commonly administered orally in order to help in treating heart dysfunctions and tumors. However, there is a limited scientific evidence to sustain these findings and uses [136]. Its strong antioxidant activity comes from the many hydroxyl groups available in its structure. Moreover, QN showed effectiveness in decreasing or attenuating the undesired skin conditions related to psoriatic lesions in a psoriasis-like mouse model. It was proven that this effect appeared by decreasing the serum levels of TNF-α, IL-6, and IL-17 and by increasing activation of superoxide dismutase, and GSH catalase. Down-regulation of NIK, IKKa, NFkB, and RelB expression were correlated with these effects [141]. The characteristics of QN give it huge potential to impede UVR-induced skin disorders. Unfortunately, its unsuitable physicochemical properties such as poor stability, skin permeability, and water solubility were considered as the major obstacle toward its formulation and consequent use in topical cosmeceutical products [142]. Accordingly, more suitable carriers for QN including its formulation with biodegradable polymeric nanoparticles have come up as an auspicious transdermal delivery system. In fact, nanoparticle formulation bearing polymers such as poly (D, L-lactide-co-

glycolide) (PLGA) has demonstrated to improve QN skin delivery in mice, causing a significant decrease in the UV-induced damage [143]. Another interesting colloidal formulation was the development of QN liposomal nanoparticles, which have also been assessed and they appear to be of important value in percutaneous delivery. It was proposed that liposomes adhere to the surface of the skin and afterward mix with the lipid cushion of the stratum corneum, rising the partitioning of QN. In addition, an oleic acid-based liposomal formulation containing QN and resveratrol were developed as wound healing formula. Their effectiveness was assessed using an *in vivo* model. They showed a significant decrease in ROS and the counteraction of the inflammatory responses caused by TPA. The data showed significant improvement in the delivery of the polyphenols, which result in better and faster tissue healing and wound closing, which also might suggest its use in the cosmetic field as antiaging products [144].

3.7. Honokiol (HL)

Magnolia Officinalis (MO) is a famous traditional slow growing tree in China for thousands of years. It belongs to the *Magnoliaceae* family, and it is used to cure cacochylia and cough. Modern pharmacological studies show that *M. officinalis* has an anti-inflammatory, anti-asthma and aid food digestion [145]. Recently, its activity as antiaging was demonstrated since it contains honokiol (HL), which is a small molecule with a hydroxyl biphenolic structure [146]. During the recent years, western medicine started to recognize its many pharmacological characteristics which include its anti-inflammatory [147, 148], antiangiogenic [149], anticarcinogenic [150, 151], antiseptic [148] and antioxidant [152] activities. In fact, the anti-inflammatory activity of HL caused by ROS is well known and it was shown to safeguard HaCat keratinocytes and human fibroblasts against the toxic and negative effects of cigarette smoke. This was actually achieved by decreasing the inflammatory mediator IL1-α and degradation of collagen [153]. Moreover, its role in the reduction of inflammation was also shown to safeguard against UVR; UVB induced expression of inflammatory mediators including COX2, IL-1, and IL-6 was significantly reduced in a mouse model [147]. In addition, HL regulates the expression of the cell cycle of proteins in melanoma. This results in anti-tumor effects [154]. In fact, the activation of immunosuppression by UVR performs an essential role in the development of skin carcinogenesis. Recently, topical application of HL demonstrated to invert UV-induced immunosuppression, significantly reducing the elimination or suppression of contact sensitiveness in CeH/HeN mice. This effect was demonstrated to be attributed to the inhibition of COX-2 expression and consecutive generation of PGE2. In addition, the study also demonstrated significant evidence that HL can forbid UVB-induced DNA hyper-methylation [155] since DNA hyper-methylation is involved in altering many genes that are involved in the induction or promotion of a tumor. Accordingly, this freshly defined aspect of HL suggests that HL has a huge potential to be used in the cosmetics field as anti-aging and sun-protection products.

3.8. Coffee Silverskin (CSS)

Coffee is considered the most popular beverage worldwide since its consumption is increasing regularly. This beverage is usually prepared after several steps of *coffee* production, which in last generates a colossal amount of solid black waste composed of abnormal or damaged beans, hulls, husks, coffee silverskin (CSS), and defective *coffee* grounds. CSS is the main by-product of *coffee* roasting industries and it is a thin membrane layer which directly covers the *coffee* grains, which detached from the *coffee* beans during the process of roasting [156]. In comparison with other *coffee* by-products, CSS is a nearly stable product since it has low moisture content [156, 157]. CSS may be considered as a new interesting source of bioactive phytochemical compounds that could be extracted and further exploited in food, cosmetic and pharmaceutical industries [158]. In fact, CSS is rich of soluble dietary fibers [156, 157], cellulose, xylose, galactose, arabinose, and mannose [159]. Moreover, it contains a high amount of protein and minerals including; potassium, magnesium, and calcium [158]. In addition, it contains an appreciable amount of fats such as triacylglycerols, diacylglycerols, esterified sterols, free sterols, free saturated, and polyunsaturated fatty acids [160, 161]. According to Costa et al, CSS contains four tocopherols (α, β, γ, and δ) and three tocotrienols (β, γ, and δ) [158]. Other important bioactive compounds present in CSS are chlorogenic acids, caffeine, and melanoidins along with others compounds, such as galactomannans and arabinogalactans [158, 162, 163]. Due to these nutritional and phytochemical-chemical compounds, antioxidant and other several bioactive compounds, highly purified grade of CSS is currently emerging as an exceptionally interesting material to be exploited in the cosmetic, food and pharmaceutical industries [164]. Recently, Martinez-Saez et al. [163] used CSS to produce a novel antioxidant beverage for the control of body weight. In the cosmetic industries, Rodrigues and colleagues reported new approaches in order to produce anti-aging skin products enriched with CSS [165-167]. In fact, the cosmeceutical companies are looking for new interesting bioactive compounds, due to the high consumer need for more natural, cheap and environmentally amicable products achieved by sustainable stuff that enhance the appearance of healthy skin. Therefore, CSS can be considered as a potential future candidate to replace synthetic chemicals as bioactive ingredients in cosmeceutical products due to their high content of antioxidants, phenolic compounds, melanoidins and caffeine [167]. Indeed, Iriondo-DeHond et al. have conducted a new approach to assess the anti-aging effect of CSS extracts against accelerated aging [168]. In fact, they found that nematodes *C. elegans* (animal models) treated with CSS extract in a concentration of 1 mg/mL showed a significantly improved longevity compared with those grown on a standard diet and this improved longevity was comparable to those nematodes fed with a concentration of chlorogenic acid or vitamin C around 0.1 μg/mL. On the other side, the assessed concentrations of extracts of CSS did not show any cytotoxicity and a CSS extract of about 1 mg/mL produced resistance to the cells of the skin when they were exposed to oxidative damage by t-BOOH. Moreover, other authors reported that the anti-aging activities of CSS may be due to its antioxidants complex that acts in a synergistic combination with each other [168, 169]. Accordingly, it could be suggested that CSS extracts have the potential properties to be used as a bioactive ingredient in skin cosmetic formulas to decrease the development of intracellular ROS in keratinocytes and therefore increasing skin health. In addition, extracts of CSS could protect against skin photoaging induced by UVC radiation. Moreover, skin inflammation which is considered as a skin response to burn, wound, infection or destruction. In fact, ROS contributes to the signaling cascades responsible for the pro-inflammation process and to the subsequent production of interleukin-1β (IL-1β), and TNF2016-α [170]. Moreover, augments the expression of collagenase and/or elastase enzymes, which causes a decrease in the elasticity and tensile strength of the skin. Accordingly, ROS, interleukins, and cytokines play synergistically during the process of skin inflammation, which induces the proliferation of keratinocyte and enrolment of monocyte to the injury side [171]. Accordingly, the anti-inflammatory effect of chlorogenic acid and caffeic acid, which are available in extracts of CSS has been assessed. The results showed that two compounds can inhibit the induced IL-8 production, which may suggest an important anti-inflammation effect [172]. In addition, Melanoidins which are also available in CSS demonstrated important antioxidant, antimicrobial and anti-inflammatory activities [169]. To the best of our knowledge, only studies on coffee grains and coffee-based beverages have reported the anti-inflammatory effect of melanoidins. Recently, Paur et al. [170] demonstrated that extracts of dark-roasted *coffee* beans can inhibit the activity of NF-κB by more than 80%, in LPS-induced NF-κB activation. Similar findings were re-

ported by another study that was conducted by Vitaglione et al. on the reduction of the expression of TNF-α [173].

3.9. Apocynin (AN)

Apocynin (AN) is an aromatic compound that bears a ketone group and it is available in many plants. Its IUPAC name is 1-(4-Hydroxy-3-methoxyphenyl)ethan-1-one. In fact, it is considered as a member of the family of acetophenones. AN also known as acetovanillone, since its organic structure is related to natural compound vanillin. It has been extracted from a variety of plant sources and was assessed for its variety of pharmacological characteristics including its role as a mild nonopioid analgesic, and as a non-steroidal anti-inflammatory drug [174]. Precisely, it is most commonly extracted from the root of the *Picrorhiza kurroa*, a medicinal herb. AN is well known also as inhibitor of the activity of NADPH oxidase (Nox) and play its activity by inhibiting the formation of the complex of NADPH oxidase [175]. In fact, AN is usually involved as a standard Nox inhibitor and it was demonstrated that it goes through dimerization in a peroxidase-facilitated manner. The obtained homodimers exhibits higher antioxidant activity than AN the monomeric form [176]. The therapeutic use of AN was investigated in different health statuses such as neurodegenerative disease, arthritis, asthma, and cardiovascular problems in addition to anti-inflammatory activity [177, 178]. Recently, it was investigated also for its anti-cancer capacity [179] as in skin and prostate tumors, where the ROS are considered a major contributor to cancer pathogenesis. It was found that AN blocked the production of ROS and decreased the development of oxidative DNA damage in a model of rat prostate carcinogenesis. These effects were related with the inactivation of the MEK-ERK1/2 pathway. In addition, the down-regulation of cyclin D1 and G0/G1 call cycle arrest were also involved [180]. Apocynin has shown a strong effect on inhibiting UVB-induced carcinogenic signaling, suggesting potential useful effect against inflammation and skin carcinogenesis. In one study, apocynin significantly decreased the UVB-induced activation of AP-1 and NF-kB in JB6 P+ cells and could suppress the promoter activity of UVB-induced COX-2. These effects were then confirmed *in vivo* using topical application of apocynin in a two-stage mouse model. The results showed that apocynin could delay the onset of UVB-induced skin tumors and significantly reduced the total number of these tumors [181]. Apocynin was also able to attenuate the production of inflammatory mediators in keratinocytes, including the Akt, mTOR and NF-kB pathways [178]. In addition to that, apocynin has produced therapeutic effects in many disease models. Moreover, the multiple activities of this COX2 inhibitor suggests the need for further exploration of its use in skin photo-protection.

3.10. Wheat Grain

Wheat grain is widely used in food manufacturing as well as in pharmaceutical and cosmetic fields since it is considered an excellent source of vitamins, minerals, polyunsaturated fatty acids, and phenolic compounds [182]. Although whole *wheat* contains important concentrations of bioactive components and nutrients, the most nutrient-dense part of the *wheat* grain is the internal part of the grain (germ) [183]. The germ is extracted from the grains of *wheat* during the process of refining of the flour [183]. In ancient time, the use of *wheat* germ was limited, and it was, most likely utilized in animals feeding preparations [184]. The germ is very rich in oil that contains a high amount of bioactive components, including tocopherols, policosanols, sterols, and omega-3 fatty acid (alpha-linolenic acid, ALA) [184, 185]. These bioactive compounds have illuminated the interest of researchers toward the potential health benefits of *wheat* germ oil (WGO) in the pharmaceuticals and cosmetics fields. In fact, these components found in WGO have demonstrated a variety of therapeutical effects, such as anti-inflammation, sun-protection, and antioxidant activities [186-189]. Precisely, the ALA component which is available in high amounts in WGO has been reported to decrease the manufacturing and expression of cytokines and eicosanoids genes (TNFα, IL-1β, and IL-6) which are responsible for the proinflammatory process [190, 191]. In addition, the bioactive form of TFs, α-TF, was found to exert an anti-inflammation role by blocking phospholipase A2 and decreasing the production of TNFα and IL-6 in differentiated THP-1 cells [192, 193]. Moreover, WGO is rich in policosanols which are a mixture of aliphatic alcohols that showed cholesterol-lowering activity and have been utilized against atherosclerosis since they reduce cholesterol levels by suppressing the levels of total LDL [185, 194]. These findings of anti-inflammatory properties exhibited by bioactive compounds found in WGO may reflect the potential of WGO as an anti-inflammatory agent especially in skin disorders such as eczema and psoriasis. In addition, the relationship between skin condition and diet on skin aging has been proven since the ancient time [195]. Accordingly, the high amounts of TF which are available in WGO can be of great interest for use in skin aging prevention. Recently, the use of WGO in a mixture with other vegetable oils such as *carrot, olive* oil, and *jojoba* oil in different ratio was suggested to achieve a cosmetic product with multipurpose effects such as anti-wrinkle, whitening, anti-aging, and sunscreen effect on skin, since this oil could give wonderful anti-wrinkle and sunscreen effects on skin [186].

3.11. Gingko

Gingko Extracts (GEs) are obtained by extraction of these phytochemical components from the leaves of the *gingko tree*. GEs demonstrated great activity as free radical scavenger when applied to the skin which renders it an interesting natural extract in skin anti-aging products. In addition, GEs are rich in flavone glycosides, especially kaempferol and quercetin by-products, which could block the activity of tyrosinase enzyme by chelating copper in the enzyme [196, 197].

3.12. Vitamin C

Vitamin C (ascorbic acid) is a water-soluble vitamin. Skin needs a high concentration of vitamin C which is important in stimulating collagen synthesis and protecting from UV-induced photodamage [198]. These two properties of vitamin C make it an important agent for healthy skin. Many anti-aging products in the market today include vitamin C either as topical or oral form. Oral vitamin C supplementation leads to an increase in its plasma and skin content [10]. Topical vitamin C also has shown antiaging, antipigmentary and photoprotective effects, although clinical studies to prove efficacy are limited [199]. Absorption of topical preparations is a challenge, it seems that the absorption of topical formulations depends on the concentration of vitamin C in plasma, if it is low the absorption will be good [198]. Efforts are going on to develop derivatives and formulations to improve absorption. Vitamin C is a potent antioxidant and essential cofactor and electron donor during collagen hydroxylation encouraging the maturation of collagen, several studies have shown that oral administration of vitamin C significantly inhibited wrinkle formation, skin atrophy, and loss of elasticity through increasing collagen and elastic fiber in animals and human [198, 200]. With vitamin C it is important to ensure its stability in the formulations because it is highly sensitive to heat and pH changes [199].

3.13. Vitamin E (Vit. E)

Tocopherol/s (TF) complex is a group of 8 compounds called vitamin E (Vit. E) complex. TF is an oil-soluble compound that has antioxidant and consequently free-radical scavenger activities, especially that highly reactive singlet oxygen [195]. Vitamin C and E can act in a synergistic way. In fact, a chain reaction of lipid peroxidation in membranes containing polyunsaturated fatty acids is activated when UV-induced compounds oxidize cellular content. The antioxidant D-α-TF is oxidized to the TF radical in this mechanism and it is reconstructed by ascorbic acid to D-α-TF [201, 202]. In addition, other molecules such as glutathione and coenzyme Q10 can also recycle TF as well as ascorbic acid [195]. Similar to vita-

min C, TF is available in many natural sources and existing endogenous non-enzymatic antioxidants. In fact, higher extents of TF are available in many edible plants and their products such as vegetables, *wheat* germ oil, *sesame* oil, and other seeds. The consumption of natural Vit. E products impede the cross-linking of collagen and the peroxidation of lipids, which are both involved and related to skin aging [195]. With the above-described process, D-α-TF is playing an important role in stabilizing the cell membrane since it can inhibit the oxidation of polyunsaturated fatty acids, including arachidonic acid available in membrane phospholipids. In the majority of the studies available in the literature, topical application of Vit E was defined to decrease erythema, sunburned cells, chronic UVB-induced skin damage, and skin cancers [203]. In addition to that, deficiency of Vit. E was correlated with a syndrome of edema with seborrhoeic changes or papular erythema, dryness and depigmentation in infants [204]. Several clinical studies are available in the literature to assess the effects of TF. However, data appears to be disputable, but large doses of oral Vit. E could affect the response to UVB in humans [205]. It was found that a daily oral administration of moderate doses of α-TF for 3-week caused a significant increase in the levels of Vit. E when measured in skin sites such as the face which is rich of sebaceous glands [206]. A combination of both vitamins C and E administered orally, partly with other photoprotective agents, caused a dramatic increase in the photoprotective effects compared with monotherapies. Accordingly, many experts recommended that this synergetic coaction of many antioxidants should be taken into account in future studies on skin photoprotection [207].

3.14. Vitamin F

Essential fatty acids (EFAs), known as vitamin F, are long-chain polyunsaturated fatty acids obtained from linoleic, linolenic, and oleic acids that human being cannot synthesize them. Therefore, humans, as well as other animals, must consume EFAs through daily dietary intake, since their body needs them to keep good health status. Only two fatty acids are known to be essential for humans; alpha-linolenic acid (an omega-3 fatty acid) and linoleic acid (an omega-6 fatty acid) [208]. Some other fatty acids were classified as "semi-essential" since they can be converted to EFAs only after being subjected to certain developmental or disorders such as docosahexaenoic acid (an omega-3 fatty acid) and gamma-linolenic acid (an omega-6 fatty acid) [209]. These last two omega fatty acid are available in several sources of vegetables and animal sources as *soya* oil, *canola* oil, *chia* seeds, *pumpkin* seeds, *sunflower* seeds, *avocados, walnuts, sesame* seeds, leafy vegetables, fish and shellfish, salmon and albacore tuna. Vit. F is fundamental for the synthesis of tissue lipids and has an essential role in the regulation of cholesterol levels, in addition to that EFAs are considered as precursors of prostaglandins [210]. In 2007, the relationship between linoleic acid intakes and skin aging has been assessed among 4 thousand women. The appearance of skin-aging was defined as having a senile dryness, skin atrophy as well as wrinkled appearance. A lower tendency of senile dryness and skin atrophy were associated with higher consumption of food rich in linoleic acid [211]. In another study, the impact of fish oil on UVB-induced prostaglandin metabolism was assessed. In this study, 13 patients with polymorphic light eruption were given for three months food supplements of fish oil rich in omega-3 polyunsaturated fatty acids. The study showed a decrease in UV-induced inflammation, likely because of the lowered prostaglandin-E2 levels [212]. Furthermore, oral administration of a mixture of antioxidant likes pycnogenol, Vit. C, Vit. E and evening primrose oil caused significant inhibition in the formation of wrinkles caused by chronic exposure to UVB irradiation on hairless mouse skin [213].

3.15. Collagen

This protein is present as a major extracellular matrix component in the skin, muscle, cartilage, tendons, and bone [214]. With time, collagen production in the skin decreases, many local and oral collagen products are available in the market, for oral products, it is very important to prove that collagen peptides can be absorbed [215] because many doctors argue that collagen is a protein, so in the gastrointestinal tract it will be degraded to amino acids and will be useless. Several studies have demonstrated increased collagen synthesis in the skin as a result of daily oral ingestion of collagen peptides [215-218]. This can be explained by the increase in peptides needed for collagen synthesis in the blood after ingestion of oral collagen. In a study among 69 women aged 35-55 years that were randomized to receive 2.5 g or 5.0 g of collagen peptides or placebo once daily for 8 weeks. At the end of the study, skin elasticity in both collagen peptide dosage groups showed a statistically significant improvement in skin elasticity and no side effects were noted throughout the study [217]. Another randomized controlled study used low-molecular-weight collagen peptide and was among 64 subjects who were randomized to receive 1000 mg Low molecular-weight Collagen peptide daily or placebo for 12 weeks, they concluded that the supplement could improve human skin hydration, elasticity, and wrinkling [218].

3.16. Hyaluronic acid (HA)

Both natural and photoaging processes appear to cause an imbalance between HA synthases and hyaluronidases, decreasing the integrity and amount of HA with increasing age [216]. Hyaluronic acid (HA) is important in various biological processes such as skin repairmen, wound healing, tissue regeneration, anti-inflammatory, and immunomodulation. A recent review revealed that HA based formulations exhibit remarkable anti-aging, anti-wrinkle, anti-nasolabial fold, space-filling, and face rejuvenating properties. This has been achieved via soft tissue augmentation, improved skin hydration, collagen, and elastin stimulation, and face volume restoration [219].

3.17. Coenzyme Q 10 (CoQ10)

CoQ10 or ubiquinone is a potent antioxidant synthesized endogenously to decrease ROS, DNA damage, and aging, the body tries to counteract these processes with natural substances such as CoQ10. It is important for electron transport in the mitochondrial respiratory chain [11, 220]. When supplementation with CoQ10 was administered, an increase in the respiratory parameters has been shown in epithelial tissue derived from human skin biopsies [11] and its anti-wrinkling effects on human and animal skin have been strongly supported [221-223]. It is available also as topical formulations with have shown beneficial effects on the skin [224], several studies have tried to improve its topical absorption, some suggested the potential use of nanoemulsion as a vehicle for enhancing solubility and permeability of CoQ10 and thus improving its anti-wrinkle efficiency [225], Yadav et al suggested proniosomal gel formulation [226], while Yue et al showed that nanostructured lipid carrier displayed a stronger capability to penetrate the stratum corneum and permeate the dermis after a topical skin application [220].

3.18. Propolis

Propolis (bee glue) is a plant resin collected by honeybees. Its chemical composition and biological activity is very complex and varies according to the sources of plants from which the bees developed this honey and the area of collection. Propolis extracts contain many chemical components which include polyphenols, especially flavonoids as quercetin, pinocembrin, formononetin, and coumaric acid [227, 228]. Propolis has photoprotection against UVB and UVA at and can be used as an active component in sunscreens as it was approved by measuring sun protection factor (SPF) level [229]. In a study in HaCaT cells, propolis was able to significantly reduce UVA-induced ROS production and to protect against UV induced apoptosis by scavenging free radicals [230]. In another study to evaluate its anti-photoaging potential, Pretreatment of human dermal fibroblasts with propolis extract before exposure to UVB increased the viability of UVB-irradiated cells

Table 2. Natural molecules and extracts with potential skin anti-aging effect.

Mechanism of Action	Natural Molecules and Extracts
Antioxidant and anti-inflammatory effects	Green tea polyphenols, Aloe vera, Curcumin, Sulforaphane, Quercetin, Honokiol, Coffee silverskin, Apocynin, Wheat grain, Gengko, Vitamin C, Vitamin E, Coenzyme Q10
Increasing collagen synthesis and improving elasticity	Vitamin C, Collagen, Hyaluronic acid
Modulation of the skin immune system	Probiotics

and decreased the number of β-galactosidase positive cells as senescent cells among them. It also increased the expression of FOXO3A and NGF genes in irradiated and non-irradiated cells. So they concluded that propolis extract has anti-photoaging potential and this property, in addition to its strong antioxidant activity, may be due to its effects on the upregulation of longevity-associated genes [231]. In addition to the effect on the UV absorption, topical propolis has shown a clear anti-inflammatory activity when applied to mice skin [232], these anti-inflammatory and antioxidant properties make it an attractive natural dermatologic product. Another promising example on its use for skin problems is the use in wound healing, in one study propolis and other honey products were loaded into chitosan nanofibers and tested against multidrug-resistant *Pseudomonas aeruginosa*. Results demonstrated antibacterial activity against all tested bacterial strains. *In vivo* testing revealed enhanced wound-healing results and cytotoxicity testing proved improved biocompatibility, suggesting their potential use in wound-healing dressings [233]. It is still unclear what components contribute to propolis's unique useful properties, making it an excellent source for new research for more potential benefits for the skin.

3.19. Probiotics

Probiotics, intestinal living microorganisms, play a beneficially effect on human health through the improvement of the microbial balance of the intestine [234]. They have been classified as a dietary supplement that can contribute a significant positive effect on an individual's health status [235]. These reported benefits include the gastrointestinal tract (GIT), the metabolic disorders, such as type 2 diabetes mellitus as well as to the cardiovascular system. Moreover, earlier studies have reported the effect of probiotics on some immune disorders, such as atopic dermatitis and inflammatory bowel diseases since probiotics were identified to play an important role in the changes of the host immune feedback [236]. As a matter of fact, Probiotics like *Lactobacilli* and *Bifidobacterium* may pass through the membrane of the GI mucous and trigger the process of phagocytosis for several days in the certain abdominal organs like spleen [237, 238]. In fact, certain recent studies demonstrated that probiotics might enhance the lipid profile in the human body [239-241]. On the other hand, non-digestible food components that can stimulate the growth and or activity of microbiota in the GIT, and thus improve human's health were first defined as prebiotics [242-246] Furthermore, prebiotics can locally improve the production of vitamin B complex, and promote short-chain fatty acids that may lower blood ammonia, decrease glucagon level, enhance glucose tolerance and improve insulin sensitivity [247, 248]. Thus, administration of prebiotics may play a regulatory role in metabolic diseases which surely return with the positive improvement of the general health status and the skin appearance of the human body. According to Schouten et al. a diet rich in prebiotic demonstrated a significant reduction in acute allergic skin response in recipient mice [249]. The availability of alternatives to antibiotics to treat skin ailments is receiving huge interest in research. Indeed, it has been found that the skin's microbiota plays a beneficial role as well as to the GIT microflora. Therefore, the opportunity to inflect the microbiota more selectively is receiving high interests. As we mentioned earlier, the UV exposure is known to negatively affect the skin conditions as well as the functions of the human immune system [250]. In fact, recent clinical studies that used probiotics such as *Lactobacillus johnsonii* NCC 533 in order to modulate the skin immune homeostasis that was modified by UV exposure in humans showed that certain types of probiotics could help in the protection of the skin homeostasis throughout modulation of the skin immune system [251, 252]. This field of research seems to be an interesting subject with potential benefits on the skin.

CONCLUSION AND RECOMMENDATIONS

During the last years, several plant extracts have been assessed, and many bioactive compounds were classified as potential skin-whitening agents. In the same contest, thousands of natural extracts were evaluated for their potential effect as skin antiaging agents. It is clear that natural products represent an interesting source of bioactive compounds that can be employed in topical treatments in order to decrease or to prevent skin hyperpigmentation as well as to retard the skin aging process and improve the overall appearance of human skin. In fact, more and more *in vitro* studies are demonstrating that these natural bioactive compounds or ingredients may also furnish additional protective activities, through their biological activities such as their antioxidant effect and protective activity of skin collagen from UV irradiation. Unfortunately, only a few extracts or bioactive compounds have been incorporated into the topical cosmetic formulation to be applied on the skin, often due to the absence of the required human clinical trials that demonstrate the efficacy and safety of these products. Therefore, it is very important to develop and stabilize appropriate clinical methods for the evaluation of the whitening and anti-aging capacity of natural products to ensure real efficacy based on evidence-based studies. In addition, it is important to develop appropriate research methodologies for a better understanding of the mechanism of action of these substances. In fact, limited clinical studies to prove the efficacy of these molecules can be found in the literature, and if they are present, the number of included subjects is limited, so more clinical studies with suitable numbers of subjects are highly recommended.

LIST OF ABBREVIATIONS

UV	=	Ultra violate
MSH	=	melanocytes stimulating hormone
FGF	=	fibroblast growth factor
HGF	=	Hepatocytes Growth Factor
ROS	=	Reactive Oxygen Species
ETC	=	electron transport chain
TRP-1	=	tyrosinase-related protein-1
HQ	=	Hydroquinone
DHICA	=	(5,6-dihydroxyindol-2-carboxylic acid
MG	=	Methyl Gentisate
AzA	=	Azelaic Acid
MAP	=	magnesium-L-ascorbyl-2-phosphate

TA	=	Thioctic acid
PAR-2	=	protease-activated receptor
IL-1α	=	interleukin-1α
ET-1	=	endothelin 1
EA	=	Ellagic Acid
RC	=	Rubia cordifolia
MF	=	Mesua ferrea
PC	=	Prunus cerasoides
HI	=	Hemidesmus indica
VZ	=	Vetiveria zizanoides
EGC	=	epigallocatechin
EGCG	=	epigallocatechin-3-gallate
MMP	=	matrix metalloproteinases
QN	=	Quercetin
PLGA	=	lactide-co-glycolide
HL	=	honokiol
CSS	=	coffee silverskin
AN	=	Apocynin
WGO	=	wheat germ oil
GE	=	Gingko Extract
EFAs	=	Essential fatty acids.

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