Chapter

Vitamin E in Human Skin: Functionality and Topical Products

Claudineia Aparecida Sales de Oliveira Pinto, Tércio Elyan Azevedo Martins, Renata Miliani Martinez, Thamires Batello Freire, Maria Valéria Robles Velasco and André Rolim Baby

Abstract

Vitamins are part of the antioxidant system of human skin, and are detectable in different layers, so the topical application can be an alternative to maintain the functionality of the system. The capacity of the antioxidant gradient of keratinocytes is associated with attenuation of the action of related free radicals in both esthetics and health. These problems arise from extrinsic aging and are related to the risk of cancer. Vitamin E has been proven to have antioxidant and moisturizing properties in the skin and can protect against the damage of UVB radiation, with emphasis on the reduction of acute erythema and photoaging. The choice for the use of topical vitamin E, compared to the oral is given by the safety as mild irritation and it has potential for multifunctional topical formulations. The purpose of the chapter is to review the topical use of formulations with vitamin E, addressing the development, safe use and evaluation of effectiveness.

Keywords: vitamin E, skin, protection, antioxidant, cosmetology

1. Introduction

Vitamin E is the most well-known fat-soluble non-enzymatic antioxidant, mainly for its ability to inhibit the activity of pro-oxidant agents generated by reactive oxygen species (ROS). Vitamin E can eliminate free radicals induced by endogenous and/or exogenous agents such as ultraviolet radiation, drugs and pollution agents, avoiding their deleterious effects. The antioxidant activity of vitamin E is directly linked to its ability to inhibit the lipid peroxidation in unsaturated fatty acids, incorporating itself into cell membranes, which effectively inhibits lipid peroxidation [1, 2].

The antioxidant activity of vitamin E (alpha-tocopherol) has its property due to its ability to react mainly with the peroxyl radical ($HOH^{\bullet}$) and singlet oxygen ($^1O_2$), which favors lipid peroxidation. The free radical scavenging reaction occurs through the formation of a stable, low-energy radical, tocopheroxyl, which does not have the capacity to react with the free radical-forming agent [3]. Alpha-tocopherol

is the main agent capable of removing peroxyl radicals from lipid membranes, such as membranes or low-density lipoproteins (LDL) [4].

It is a classic dermatological ingredient used alone in its purified form, alpha-tocopherol or by its derivatives. However, the conversion to the purified (isolated) form is required in skin to obtain the desired effects. Topical applications are designed for treating melasma, protecting against ultraviolet radiation (UVR) and improving aging damages [5, 6], The association of vitamin E with other antioxidants increase the effects in skin [7].

Some studies suggest that a poor diet of vitamin E could be related with skin disorders. Oral supplementation of vitamin E is recommended in many skins' therapies, such as: yellow nail syndrome, epidermolysis bullosa, cutaneous ulcers, pressure ulcers and burns, sub corneal pustular dermatosis, scleroderma, morphea, calcinosis cutis, Raynaud's phenomenon, and inflammatory diseases. The oral supplementation of vitamin E could reduce the pigmentation in melasma and contact dermatitis lesions, too demonstrated remission of atopic dermatitis, prevention of sunburn reaction as well as the subsequent chronic skin damage [5]. Vitamin E combined with other antioxidants has shown positive results topically in the photoprotection, as well as delay the growth of the melanoma by promoting the apoptosis of tumor cells and inhibiting VEGF-mediated angiogenesis. Other results with alpha-tocopherol: improvement in periorbital fine lines, roughness, radiance, skin tone, elasticity, density, collagen production and overall appearance by clinical evaluations of skin. Topical application of tocopherol acetate significantly reduces the severity of erythema, edema and skin sensitivity associated with sunburn by UVB [8]. It is difficult to determine the *in vivo* antioxidative activity of vitamin E because it is naturally present in the skin, but future studies with the isolated form and its derivatives can be explored in topical products [9].

2. Topical products (cosmetics x medicines)

Skin products can be classified as medicines, cosmetics and cosmeceuticals, however, the teaching line between the categories is tenuous, being widely discussed by dermatologists, pharmacists and beauticians. Medicines and cosmetics are already widely discussed and accepted by world regulatory agencies; however, the term cosmeceutical is used as a marketing appeal and is not recognized as an official legal category. Skin products considered to be cosmetics are generally defined as products to clean, beautify, promote attractiveness, or change appearance, while medicines are intended for the diagnosis, cure, mitigation, treatment or prevention of diseases, which can affect the structure or any function of the skin. Regulatory agencies in different countries seek to organize the offer of products to ensure the safety for users.

Topical products that contain vitamin E can be classified as medicines or cosmetics, depending on their purpose. If the product is intended to lubricate the skin, it will be considered cosmetic and if it has therapeutic use as a healing agent, it will be a medicine. There are legal limits on the daily consumption of vitamin E as a supplement, however, for most international regulatory agencies, such as the NHS, FDA, Health Canada the limits for topical use are not described [10].

3. Types of vitamin E for topical applications

The antioxidant alpha-tocopherol acetate is the most common form of vitamin E in skin care products. In 2001, the Scientific Committee on Cosmetic and Non-Food

Products for Consumers (SCCNFP) presented its opinion during the 18th Plenary Meeting. At the time, SCCNFP believed that alpha-tocopherol acetate did not pose a threat to consumer health and therefore did not propose any restrictions or use conditions [11].

The Cosmetic Ingredients Review Panel (CIR) in 2002 has assessed the safety of 14 tocopherols and tocotrienols and concluded that these ingredients are safe when used in cosmetics. The Panel further reviewed data from clinical and animal studies to determine the safety of tocopherols and tocotrienol ingredients and considered it appropriate to extrapolate existing information to conclude on the safety of all tocopherols and tocotrienols [12].

Since vitamin E can absorb ultraviolet light to produce free radicals, there is a possibility that strong exposure to sunlight after topical application may cause skin reactions. However, vitamin E concentrations between 0.1–1.0% are generally considered to be safe and effective for increasing vitamin E levels in the skin, but higher levels of α-tocopherol have been used with no apparent side effects [8]. Vitamin E as alpha-tocopherol or tocopherol acetate is used in over-the-counter products in concentrations ranging from 1.0 to 5.0% [13–15].

Vitamin E is the main fat-soluble antioxidant in the body with biological activity and it is the collective name for the eight mains naturally occurring substances such four tocopherols and four tocotrienols. The eight analogues of vitamin E share similar chemical antioxidant activity, however, they are distinguished by their individual physico-chemical and biological effects at the molecular level in humans and higher animals. Alpha tocopherol is the most active, being considered an important asset in protecting cell membranes from lipid peroxidation promoted by free radicals [13–15].

Alpha-tocopherol is practically insoluble in water and this characteristic can difficult the development of topical products with high water content. In addition, this molecule is easily oxidized by atmospheric oxygen. Vitamin E acid acetate and succinate esters are applicable for clinical use due to their high oxidation stability but require the use of surfactants to improve the water solubility. Alpha-tocopherol is solubilized by large amounts of surfactants, but the hydrolysis of acetate is the limiting step in terms of its concentration during bioavailability [15].

The antioxidant properties of vitamin E are attributed to its free aromatic hydroxyl group; thus, the esters of vitamin E need to be hydrolyzed during absorption by the skin to exhibit this activity. In the biologically inactive esterified form, vitamin E acetate is more used because of its greater stability, acting as a prodrug, being hydrolyzed in active free vitamin E (alpha-tocopherol) after penetration into the skin. The bioconversion of vitamin E into the active form can be influenced by the technology involved in the development of formulations, by the target layer of the skin and exposure to ultraviolet rays. The stratum corneum seems to have less efficiency in the bioconversion of esters of vitamin E when compared to the nucleated epidermal layers. Thus, alpha-tocopherol should provide more efficient antioxidant protection for skin surface lipids and skin barrier constituents than vitamin E esters. However, in the nucleated epidermis the bioconversion of vitamin E acetate to active free form occurs at a much higher rate. In this sense, the choice of which vitamin E molecule to be used must consider the target layer of the skin and include product development strategies so that the activity of vitamin E is fully utilized [15, 16].

4. Vitamin E in skin damage

Vitamin E, more specifically alpha tocopherol, is considered one of the main fat-soluble and non-enzymatic antioxidant agents of natural origin, due to its

advantages in terms of the protective activity against physical and chemical damage promoted by free radicals (FR). Vitamin E is an antioxidant capable of binding to the membrane in various tissues [17, 18]. Therefore, it is involved in several oxidative mechanisms in epidermis and dermis, catalyzed by ultraviolet radiation (UVR) and pollutants (**Figure 1**).

4.1 Oxidative stress: lipid peroxidation and free radicals' formation

The first studies related to the damage caused by the formation of FR on the skin, promoting lipid peroxidation, date from the 1950s and 1960s. To avoid the damages, the use of natural and synthetic substances was suggested in order to prevent the formation of FR [19, 20].

Reactive oxygen species (ROS) such as superoxide ($O_2^{-\bullet}$), hydroxyl radicals ($OH^{\bullet}$), peroxyl ($HOH^{\bullet}$) and singlet oxygen ($^1O_2$), can be formed by endogenous (physiological) processes such as inflammation, physical activity in excess, nutritional disorder, hereditary issues, neoplasms, and even, by processes related to exogenous sources such as UVR and pollution agents. In the skin, the main damage related to lipid peroxidation generated by FR from exogenous sources is the activation of melanogenesis and damage to collagen fibers [19, 21, 22].

The lipid peroxidation of the epidermis cells occurs through the action of the ROS, which has the ability to bind to the unsaturated bonds present in the polyunsaturated fatty acids of the cell membrane phospholipids [22, 23]. The process starts between polyunsaturated fatty acids (PUFA) and the oxygen radical, obtaining a lipid radical, which causes a rearrangement process in the presence of molecular oxygen, becoming a peroxy lipid radical. The lipid peroxyl radical is also capable of attacking unsaturated lipids, generating new radicals, such as the lipid radical as in the first stage of the reaction and the lipid hydro peroxide radical, thus promoting a cyclic reaction. Thus, it is necessary to use substances capable of interacting with cell membranes and to extinguish the free radicals formed, such as vitamin E [24, 25].

In a more detailed way, the mechanism involved in the lipid peroxidation process occurs through a chain reaction of the polyunsaturated fatty acids (PUFA) of biological membranes, which due to the large amount of unsaturation, become extremely susceptible to attack by free radicals. The process begins with the activity

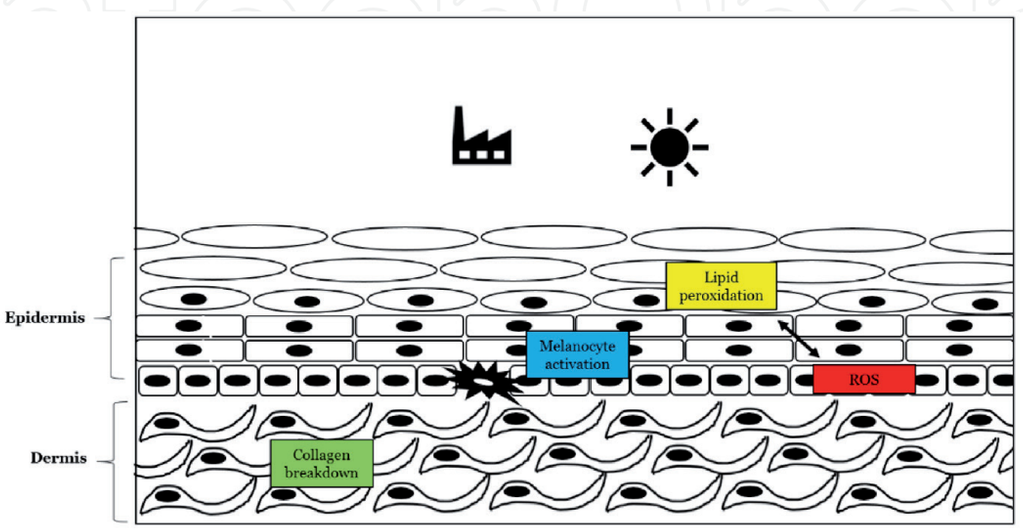

Figure 1.
Oxidative mechanisms involving vitamin E in human skin exposed to ultraviolet radiation and pollution. ROS, reactive oxygen species.

of the free radical like OH*, which extracts H from PUFA resulting in the radical PUFA*. After the molecular rearrangement of a conjugated diene, the molecule is susceptible to attack by O_2, resulting in a peroxyl radical (PUFAOO*). PUFAOO* can extract H from the adjacent PUFA, thus propagating a chain reaction. Self-oxidation occurs continuously, which can seriously affect the functionality of the tissue [26].

The action of pollutants and UV radiation (UVR) on the skin has already been studied, but the mechanisms involved are still uncertain, knowing that the damage is initially related to the composition of the skin's sebum and the quality of the stratum corneum, which may lead to the formation of wrinkles, hyperchromies (spots), wrinkles and accelerated extrinsic aging and dermatological diseases such as atopic dermatitis, related to lipid peroxidation [27–29].

The chronic and acute damage to the skin caused by UVR (UVB and UVA) are related to the direct absorption of rays and indirectly through photosensitization reactions. Mostly (> 95%), UVA radiation, more specifically UVAI (340–400 nm), has the major ability to penetrate the skin and it causes deeper damage. The aggression of UVA radiation targets collagen and supporting fibers, in addition to cellular DNA. The DNA damage is related to the mutagenic power of UVA radiation, which can act directly or indirectly through photosensitization reactions [30].

Studies prove the mutagenic power of UVA through direct oxidation reactions of DNA nucleic acids with ROS, which can lead to simple disruptions of the DNA strands or to disruptions in symmetrical positions in the two strands. Several studies (*in vivo* and *in vitro*) have evaluated the damage to DNA bases caused by oxidative stress, such as the oxidation of purine and guanine [31, 32].

As the UVR, polluting agents have harmful effects on the skin by increasing the oxidative stress and decreasing the physiological enzymatic and non-enzymatic antioxidant capacity. With the formation of FR and ROS, an interaction occurs with the lipid layer membrane, initiating the cascade reactions of lipid peroxidation and the release of pro-inflammatory mediators, which result in the accumulation of neutrophils and phagocytic cells, that also generate radicals free, thus promoting a cyclical reaction. Oxidative stress initiates a series of quite complex biological processes that result in DNA damage, activation of transcription factors such as activating protein 1 (AP1) and the nuclear factor Kappa-B (NF-KB) and even some pathways of signaling involved in cell growth and differentiation and degradation of dermal connective tissue. Pollutants are also capable of inducing functional changes in lipids, DNA, skin proteins, favoring the acceleration of skin aging, inflammatory processes and dermatological pathologies [33, 34].

4.2 Free radicals and the activation of melanogenesis

Melanogenesis can be considered as the first skin defense, being directly influenced by the skin phototype and, consequently, by the amount and type of melanin present. Melanocytes are particularly vulnerable to excessive oxidative stress from ROS due to their pro-oxidant state and the melanin synthesis involves oxidation reactions and generation of superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2), promoting oxidative stress. The initiation of melanin synthesis occurs by a single route, with the conversion of tyrosine to dopa by the catalytic activity of the enzyme tyrosinase, releasing $O2^-$, which also oxidizes dopa to dopaquinone with the release of $O2^-$. From the obtaining of dopaquinin, a specific orthoquinone, capable of reacting with nucleophilic compounds, the synthesis follows two distinct pathways, eumelanogenesis and pheomelanogenesis, which respectively produce the darkest and lightest melanin monomers (red-yellow) [35, 36].

The homeostasis of human melanocytes in the epidermis is maintained mainly through a complex paracrine network, involving growth factors and cytokines synthesized by epidermal keratinocytes and dermal fibroblasts and modulated by UV radiation. Keratinocyte-derived endothelin-1 is a potent mitogen and a melanogenic factor capable of reducing H_2O_2 generation and apoptosis in human UV-irradiated melanocytes [37]. The α-MSH melanocortin and adrenocorticotropic hormone (ACTH) are synthesized by keratinocytes and melanocytes and stimulate the synthesis of eumelanin, as well as the survival and proliferation of melanocytes by binding and activating the melanocortin 1 receptor (MC1R). The MC1R is a receptor located on the surface of melanocytes with the ability to bind to protein G. Studies show that the treatment of human melanocytes in culture with α-MSH, results in a decrease in the generation of H_2O_2, due to exposure to UV rays [35].

With the production of ROS, oxidative stress formed can interrupt melanocyte homeostasis, compromising their survival or even leading to malignant pathogens. Thus, the balance between the pro and antioxidant properties of melanin in the skin is mainly determined by the proportions of eumelanin and pheomelanin, the levels of melanin intermediates and the concentrations of reactive metals in the melanosome microenvironment. The generation of H_2O_2 in response to the action of UV radiation is inversely proportional to the constitutive pigmentation, suggesting a natural antioxidant effect of melanin [35, 38]. The inhibition of melanogenesis occurs in several stages, such as the inhibition of the enzyme tyrosinase that acts in several phases of the melanin production cascade, and also influences the post-transcriptional concentration of tyrosinase and other enzymes related to melanogenesis, such as tyrosinase-related protein 1 (TRP1) and DOPA chrome tautomerase (TRP2) [39].

4.3 Role of vitamin E in skin's oxidative stress

The mechanism of action of vitamin E (**Figure 2**) regarding the antioxidant activity in the skin is directly related to the chemical mediation of the phenolic hydroxyl (OH) of its structure, capable of donating H to the peroxyl radical (PUFAOO*), resulting in the formation of a stable lipid species (PUFAOOH). Thus, when donating the hydroxyl H, vitamin E becomes a relatively non-reactive free

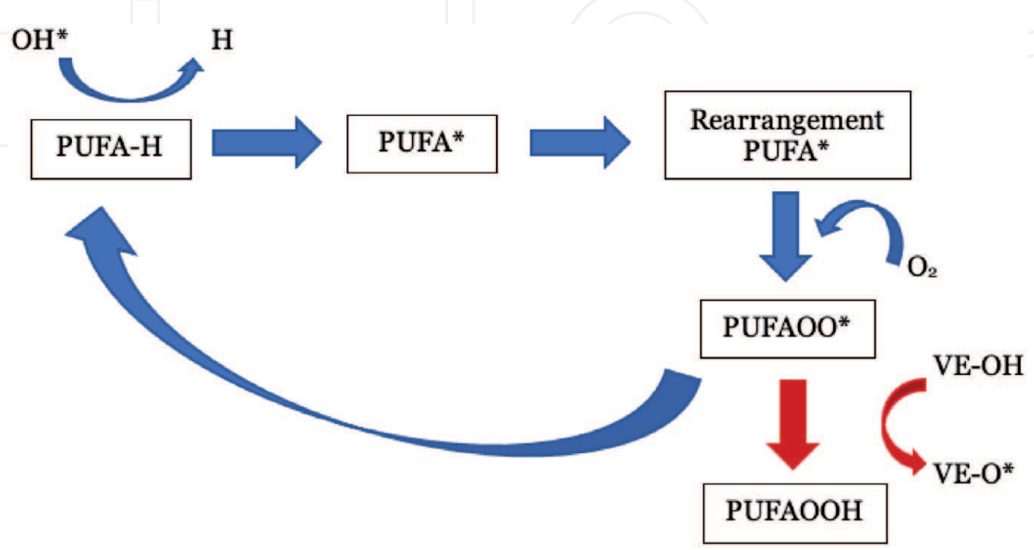

Figure 2.
Mechanism of lipid peroxidation and vitamin E in cells. PUFA, polyunsaturated fatty acids; PUFA, lipid radical; PUFAOO*, Peroxy lipid radical; OH*, oxygen radical - hydroxyl; O_2, oxygen; VE-OH, Vitamin E, alpha-tocopherol; VE-O*, radical tocopheroxyl.*

radical, as the unpaired electron moves to the aromatic ring. Thus, with electronic displacement, incorporation occurs in biological membranes, being located awfully close to the polyunsaturated fatty acids of the cell membrane phospholipids, interrupting the chain reaction. Vitamin E stops the reaction by the ability to donate hydrogen from the OH group to the unsaturated lipid or to the lipid peroxyl radical (PUFOO *), forming the low-energy tocopheroxyl stable radical (VE-O *), which in turn does not present the ability to act as a free radical forming agent [40, 41]. Vitamin E also has antioxidant activity involving other lipid radicals, acting directly on the radical's singlet oxygen and superoxide anion [19].

Studies have shown the activity of vitamin E in the modulation of damage caused by FR mediated by the action of UVR on the skin, such as lipid peroxidation, photoaging, immunosuppression and photocarcinogenesis [42]. Vitamin E is able to reduce the inflammatory reactions of the skin, attenuating the production of prostaglandin involved in the process, pro-inflammatory cytokines, cyclooxygenase-2 (COX-2) and NADPH oxidase [43–45].

In addition to its anti-inflammatory capacity, vitamin E is also able to modulate the protein kinase C (PKC) and phosphatidylinositol 3-kinase (PI3-K) signaling pathways and to reduce the increase in collagenase expression. PKC modulation may be representative in terms of cell growth control, however, the interaction between vitamin E (alpha-tocopherol) and PKC protein does not occur directly, assuming that it occurs preventively to its action at the cellular level [45, 46].

Vitamin E has the ability to significantly suppress collagen degradation by inhibiting metalloprotein 1 (MMP-1), involved in the initial process of collagen hydrolysis [44]. It can be identified in deeper layers of the skin, supposing its activity to minimize the photocarcinogenesis process, being considered as one of the main antioxidants of the human epidermis. Another characteristic of vitamin E is its use as an early and very sensitive marker for oxidative damage promoted by the environment [47, 48]. Thus, vitamin E prevents the lipoperoxidation of cell membranes and the degradation of fatty acids that are essential for the proper functioning of the body and skin [8, 49, 50].

Vitamin E can eliminate FR induced by UVA radiation, protect endogenous antioxidants from degrading processes, prevent lipid peroxidation and reduce immunosuppression caused by UVR. To increase protection against erythema and sunburn, the association of vitamins E and C is indicated, presenting potential against skin aging and skin cancer. Another activity of vitamin E on the skin is its application before sun exposure, avoiding the formation of the cyclobutane pyrimidine dimer (CPD) induced by UVB [46].

In general, exposure excessive to pollution and ultraviolet radiation promotes a greater production of free radicals, thus requiring an oral and/or topical supplementation of antioxidant substances, such as vitamin E, thus, the endogenous mechanism is not sufficient to prevent deleterious skin damage [51].

5. Topical treatments with vitamin E

After vitamin E depletion, oral intake is the best way to replenish the stock of this antioxidant in skin. In fact, oral supplementation brings cosmetic effects after 8–12 weeks. For alpha-tocopherol alone, a photoprotection effect by reduction of human skin malondialdehyde concentration was observed [52]. The combination of vitamin E with other antioxidants is very beneficial for skin treatments. Alpha-tocopherol in combination with ascorbic acid increased UVB photoprotection in the human epidermis [53, 54]. The same combination showed a reduction in UV-induced inflammation [55]. Good outcomes for treating chloasma were seen

with the same mixture during double blinded clinical trials [56]. When more antioxidants act together, strong outcomes are seen, such as reduction of UVB-induced wrinkle and increased collagen synthesis [57] and treatments of melasma [58, 59]. Despite the benefits to skin appearance, oral intake is not considered cosmetic treatment for its systemic effects.

Topical delivery also plays an important role in restock vitamin E. It is widely used in its purified forms or indirectly using vegetable seed oils [60]. It is a classical ingredient in dermatology and still used in cosmetics worldwide in a recent growth tendency. Cosmetics containing vitamin E are most valuable in the USA, UK and France. The top cosmetic claims used in labels and the categories are in **Figure 3** [61].

The lipophilic nature of vitamin E requires an oily or alcoholic phase at the topical formulation. In cosmetics, the main drivers capable of delivering this type of molecule are serums, tonics, oils and especially emulsions. For vitamin E alone, hydro-alcoholic solution of alpha-tocopherol showed a reduction of UV-induced erythema in the epidermis [62] and the reduction on the number of epidermal sunburn cells. While O/W and W/O emulsions containing alpha-tocopherol acetate increased skin hydration and water-binding capacity in the stratum corneum [63]. Vitamin E is also used as coadjutant in other topical products to improve physical–chemical characteristics or to donate different effects. One of the most studied associations is with vitamin C, due its primary replenisher of vitamin E mechanism in skin. Vitamin C regenerates the oxidized form of vitamin E to its reduced form [64, 65]. A similar mechanism is expected using other antioxidants. **Table 1** shows examples of associations of vitamin E and other molecules. The type of molecule and/or type of formulation is chosen depending on the target to address.

The metabolization of derivatives into the active form of vitamin E (alpha-tocopherol) occurs at a far extend in the nucleated epidermis [6]. Therefore, the conversion is highly dependent on the delivery system of cosmetic preparations into controlling skin permeation [14]. To address this issue, several innovations on cosmetic formulations have appeared during the last decade.

The use of chemical permeation enhancers (e.g. alcohol, surfactants, terpenoids) is a good strategy to change stratum corneum polarity and fluidity. Likewise, the use of devices that create micron-scale pores in skin (e.g. iontophoresis, microneedles) is also available in clinics [78]. The benefits of using those techniques is to maintain the original formulation. However, adaptations may be needed to maintain stability in the case of adding chemical agents. Another strategy is to change the formulation completely by using new delivery systems to encapsulate vitamin E.

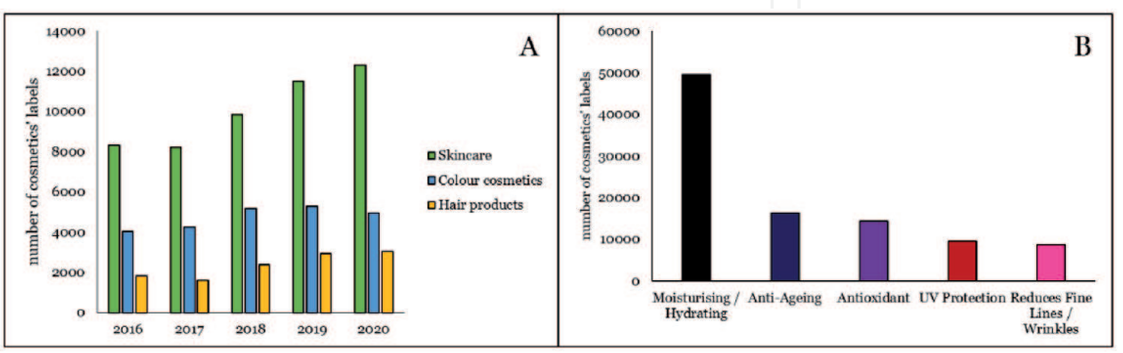

Figure 3.
Evolution of the most explored categories using tocopherol in cosmetics' labels between 2016 and 2020 (A). Claims used in cosmetics' labels containing tocopherol between 2016 and 2020 (B).

Vitamin E	Combined molecule	Effect	Model	Reference
Alpha-tocopherol (1%)	L-ascorbic acid (15%)	Synergic protection against erythema and sunburn cell formation	Aqueous solution applied to pig skin	[66]
Tocopheryl acetate (1%)	L-ascorbic acid (20%) + *Rubus idaeus* leaf cell culture (0.0005%)	Improved the appearance of aging skin (Skin color, elasticity, radiance, smoothness, scaliness and wrinkles)	Commercial serum applied *in vivo*	[67]
Tocopheryl acetate	Bioflavanoids from *Gingko biloba* + ascorbyl tetraisopalmitate + retinyl palmitate	Protected the skin from UV damage by reduction on the number of sunburn cells	Emulsion containing 5% of the mixture *in vivo*	[68]
Vitamin E	*L. plantarum*	A good antibacterial activity against *S. aureus* and *P. aeruginosa* with a sustained release of probiotic cells over 24 h	Dressing	[69]
Vitamin E 5 IU	vitamin A (10 000 IU) + vitamin D (1000 IU) + vitamin B1 (50 mg) + vitamin B2 (12.7 mg) + vitamin B6 (15 mg) + vitamin C (500 mg) + nicotinamide (100 mg) + dexpanthenol (vitamin B5) (25 mg)	Reduction of age spots and melasma	*In vivo* application of the multivitamin by iontophoresis	[70]
Vitamin E	Resveratrol + Baicalin	Improvement on the periorbital fine lines, roughness, radiance, skin tone, elasticity, density, and overall appearance	*In vivo*	[71]
Vitamin E	Photostable filters (octyl methoxycinnamate, avobenzone and 4-methylbenzilidene camphor) + vitamins A (1,700,000 UI/g) and C [2% (w/w) ascorbyl tetraisopalmitate]	The formulation with filters showed better stability comparing with the vitamins alone	*In vivo* In mouse skin	[72]
Vitamin E	Amniotic membrane mesenchymal stem cell	Decreased the diameter of lesions	In chronic leprosy	[73]
Vitamin E	Ferulic acid + Vitamin C	Suggests preventing skin cancer	Topically solution in the skin of white Yorkshire pigs	[74]
Vitamin E	Vitamin C	Prevention of inflammation due lipid peroxidation caused by *Propionibacterium acnes* leakage through follicles and sebaceous glands in *acne vulgaris*	*In vivo*	[5]

Vitamin E	Combined molecule	Effect	Model	Reference
Alpha-tocopherol	Ferulic acid	Inhibition of melanization	*In vitro* application of alpha-tocopheryl ferulate	[75, 76]
Delta-tocopherol glucoside (0.05%)	Retinaldehyde (0.05%) + glycylglycine oleamide (0.1%)	Improvement on the elastin fiber production and a protection effect of the elastin and fibrillin fiber network against UV-induced alterations	*In vitro* and *ex vivo*	[77]

Table 1.
Examples of association between vitamin E and other active molecules.

Micro and nanoemulsions are strong candidates for its permeation capacity. Nevertheless, reduced sizes may have systemic effects, which is not allowed for cosmetics. Regulatory issues must be address in controlling the particle size. Vitamin E microemulsions (256 nm) reach dermis, however with the aid of surfactants [79]. More recently, bigels are a viable cosmetic formulation. These biphasic systems formed by hydrogels and organogels show good spreadability and emollient and moisturizing effect, besides its transdermal capacity [80]. However, bigels containing alpha-tocopherol showed no difference against regular emulsions for hyperpigmentation and inflammatory markers in in vivo tests [81]. More tests are required to evaluate the benefits and safety of new cosmetic formulations.

6. Safety and efficacy of topical products with vitamin E

Many products in the cosmetic market have vitamin E in its composition. The definition of optimal dosage of vitamin E in cosmetics products depends on the derivative molecule and the type of formulation.

6.1 Safety of Vitamin E

Studies with animals to evaluate safety is common in many countries, especially in oral products. In animal experiments, 200 mg/kg was administered orally to frogs, rabbits, cats, dogs, and monkeys, with repeated application to mice over a period of 10–61 days. In food of rats, 4.000 mg/kg of Vitamin E was added and, in these experiments, was not mutagenic, teratogenic nor carcinogenic properties [82].

The toxicity of vitamin E is very low, because in clinical studies, a daily dosage of 100–300 mg of vitamin E was considered harmless, even when their use extends over a long period of time. Double-blind studies demonstrated that large oral doses of up to 3,200 USP-Units/day led to no consistent adverse effects. They mentioned that the optimal human plasma concentration of vitamin E is between 1.0 and 1.5 mg/dl [82].

Numerous genotoxicity studies were conducted with tocopherol, tocopheryl acetate, tocopheryl phosphate (MTP), and tocopheryl succinate. The only remarkable result was tocopheryl succinate with only a weak positive in a sister chromatid exchange assay in the presence of metabolic activation [12].

Tocopherol and tocopheryl acetate are generally recognized as safe food ingredients [12]. According to Brigelius-Flohe et al. [83], vitamin E supplements for pregnancy usually contain only small doses of vitamin E, although adverse effects have not been observed at higher doses. The original report on tocopherols indicated that tocopheryl succinate, up to 75 mg/d in the diet did not have reproductive or developmental effects in rats. In relation to tocopheryl acetate, 1.6 g/kg/d, generally did not have any reproductive or developmental effects in rabbits, hamsters, rats, or mice [84]. There is no published report documenting adverse fetal effects due to use of topical vitamin products. Topical application of vitamin E can rarely cause contact dermatitis, erythema multiforme, and xanthoma [5].

Vitamin E and its derivatives are widely used in many cosmetic and dermatologic products, in general, papers with side effects such as allergic or irritant skin reactions are rare. In clinical studies, tocopherol and tocopherol acetate were found to be safe for use in topical skin formulation since irritant or sensitizing reactions were found only in very small percentages [85]. Tocopheryl acetate was not irritating to rabbit eyes in one study, but it produced weak-to-moderate conjunctival irritation in another study [86]. Positive patch test results of alfa-tocopherol are rare and need to be critically reviewed. However, the derivative (alpha-tocopheryl linoleate), demonstrated allergic popular and follicular contact dermatitis in 1000 cases, reported in Switzerland by a line cosmetic in 1992. This compound was easily oxidized under the storage condition [8]. According to Baumann and Spencer [87], 33% of the patients studied developed a contact dermatitis to the vitamin E. The ingredients considered safe to use in cosmetics were Ascorbyl tocopheryl acetate, Ascorbyl tocopheryl maleate, Dioleyl tocopheryl methylsilanol, Potassium ascorbyl tocopheryl phosphate, Sodium tocopheryl phosphate, Tocopherol, Tocophersolan, Tocopheryl acetate, Tocopheryl linoleate, Tocopheryl linoleate/oleate, Tocopheryl nicotinate, Tocopheryl phosphate, Tocopheryl succinate and Tocotrienols. remembering that the concentrations and conditions of use in the safety tests must be observed [12].

Tocopheryl acetate, 0.2 mL applied under an occlusive patch for 24 hours prior to irradiation, was not phototoxic in a study in 11 participants [84]. According to ECHA [86], animal and clinical testing concluded that tocopheryl acetate was not photoallergenic or phototoxic. The dermal LD50 of tocopheryl acetate is >3 g/kg bw in albino rats. Five animals per group were dosed with 1 or 3 g/kg bw undiluted tocopheryl acetate in vegetable oil under an occlusive patch for 24 hours. Slight erythema was observed 24 to 48 hours after exposure. Slight abrasion was observed in one low dose female, two high-dose females, and two high-dose males [86]. The acute dermal toxicity of mixed tocopheryl phosphates (MTPs) was determined in New Zeal and rabbits; the dermal LD50 was greater than 1,130 mg/kg bw MTP in female rabbits [88].

An aqueous gel containing 1,130 mg/kg bw MTP (918 mg/kg bw a-tocopherol equivalents) was applied to the clipped dorsal skin of 5 male and 5 female rabbits for 24 hours using surgical gauze. At 24 hours, slight-to-well-defined erythema was observed in 4 of 5 males and all females, and slight-to-moderate edema was observed in 2 of 5 males and all females. Signs of irritation were not observed at days 7 and 14 [12].

6.2 Efficacy of Vitamin E for topical formulations

According to Costa [89], vitamin E has a wetting action and in an *in vitro* study, it was found that if it was applied on living skin equivalent cultures also reduced the Transepidermal Water Loss (TEWL), so improving barrier function [72]. Lin *et al* [66], reported that a stable aqueous solution of 15% vitamin C (L-ascorbic

acid) and 1% vitamin E (alpha-tocopherol) when applied topically to pig skin, daily for 4 days, could provide quadruples photoprotection for skin. This was observed by skin biopsy specimens processed for routine histology. The entire 8 mm center section of the histologic ribbon was analyzed, and the results expressed as sunburn cells/mm.

An *in vivo* study with resveratrol, baicalin and Vitamin E topic formulation demonstrated activation of endogenous antioxidants with ROS scavenging, simultaneously. This was observed by percutaneous absorption, biopsies, and biomarkers. A significant improvement was observed in periorbital fine lines, roughness, radiance, skin tone, elasticity, density, and overall appearance by clinical evaluations that were performed by an expert clinical grader at baseline and for 8–12 weeks. In addition to the increase in collagen production (18.9%) in dermal thickness detected by ultrasound measurements [71].

Topical application of tocopherol acetate significantly reduces the severity of erythema, edema and skin sensitivity associated with sunburn by UVB. Magnetic resonance images showed that there was no increase in skin thickness associated with edema. However, the cytotoxic effects of UV exposure as measured in Chinese hamster embryo cells can also be reversed by the presence of other antioxidants as well as a-tocopherol, ascorbic acid, butylated hydroxytoluene (BHT) and GSH. However, before exposure UV these components do not protect against cytotoxicity. In this study, it was observed that high dietary levels of vitamin E can restore the level of incorporation of thymidine dimers into DNA, in UV-exposed epidermal cells in relation to control non irradiated cells. The DNA was isolated and determined by the method of Gendominico Record et al. 1991 [90].

Gaspar and Campos [72], evaluated photoprotective formulations with a combination of photostable (octyl methoxycinnamate, benzophenone-3 and octocrylene or photoinstable filters (octyl methoxycinnamate, avobenzone and 4-methylbenzilidene camphor), both in addition to A, C and E. vitamins The combination of photostable filters showed a better response compared to the others. The filter components and vitamins were quantified by HPLC analysis and spectrophotometry. The formulation containing only vitamins, showed irritation and hairless in mouse skin, this was observed by histopathology.

Ferulic acid, by protecting vitamins C and E, can prevent UV-induced thymine dimer formation when applied topically to skin evaluated by fluorescence microscope coupled with a camera. Studies mentioned a presence of mutations in thymine dimer in keratoses and squamous cell carcinomas of skin, so this result requires that this combination can prevent skin cancer [74]. The photoprotective actions demonstrated by the topical application of alpha-tocopherol in mice may not be restricted to the action of itself [91]. It is likely that the dimers formed from UVB photo-oxidation of alpha-tocopherol, and perhaps the trimers as well, may themselves confer photoprotection, this was observed by similarities in the UV absorbance spectrum. Vitamin E slowed melanoma growth by promoting tumor cell apoptosis and inhibiting VEGF-mediated angiogenesis. The mechanism of the *in vivo* antitumor effect of VES was determined by immunohistochemical detection of proliferation and apoptosis [8].

6.3 Skin disorders

Some studies suggest that a poor diet of vitamin E could be related with skin disorders. Oral supplementation of vitamin E is recommended in therapy of yellow nail syndrome in a dosage of 1000 IU once a day for a period of 6 months; epidermolysis bullosa (300–600 IU/day); in cutaneous ulcers with treatment of pressure sores in doses of 800 IU/L gradually increasing to 1600 IU/L; in wound healing with zinc and

vitamin C for pressure ulcers and burns; in subcorneal pustular dermatosis (d-alpha-tocopheryl acetate) 100 IU/day, gradually increasing to 400 IU/day for 4 weeks; in scleroderma, morphea, calcinosis cutis, and Raynaud's phenomenon respond to vitamin E in a range from 200 to 1200 IU per day; in Hailey–Hailey disease with derivative of vitamin E *d-* alpha-tocopheryl acetate in doses of 800–1200 IU/L by clinically evaluation [5].

Vitamin E has been reported to be effective in inflammatory diseases with attenuation of pro-inflammatory cytokine TNF, evaluated by a section of skin mice by quantitative ELISA kit [64]. In a combination of oral vitamins, A, C, and E with or not proanthocyanidin there was a significant reduction of pigmentation in melasma and pigmented contact dermatitis lesions in two randomized clinical double-bind study [5, 92]. Oral vitamin E (400 IE/day) for 8 months, improvement and near remission of atopic dermatitis and a 62% decrease in serum IgE levels [93]. In oral combination with carotenoids (ß-carotene and lycopene), vitamins C and E, selenium and proanthocyanidins there was decreases the UV-induced expression of Metalloproteinases 1 and 9, that means prevention of sunburn reaction as well as subsequent chronic skin damage, evaluated by clinical trials [94].

In chronic leprosy a topical combination of vitamin E and with an amniotic membrane mesenchymal stem cell decreased the diameter of these lesions, evaluated by randomized controlled trial and monitored weekly [73]. In a dressing based on the association of Vitamin E and *L. plantarum* showed a good antibacterial activity against *S. aureus* and *P. aeruginosa* and guaranteed a sustained release of probiotic cells over 24 h, suggesting a successful and ecologically sustainable alternative to the cotton in wound care [69].

Chung *et al*. [85], demonstrated that a topical occlusive pretreatment with 5% vitamin E for 24 h protected against UV-induced upregulation of human macrophage metalloelastase in human skin *in vivo*. There was improving photoprotection of sunscreens against free radical formation in viable epidermal layers in the cultured human dermal fibroblasts. In a topical tocoretinate, hybrid compound of retinoic acid and tocopherol was reduced the clinical symptoms of lichen and macular amyloidosis [5].

Studies show that there was an improvement in the healing of wounds in diabetic rats by topical vitamin E [95]. According to Kuriyama et al. [9], some animal's studies even suggest that topical vitamin E at a concentration of 20% suppressed allergic and irritant contact dermatitis, exerting a comparable effect to 0.5% prednisone ointment. Those skin conditions are generally self-reported as dry skin [96].

With the onset of xerosis, several inappropriate situations can arise, such as the release of inflammatory mediators, hyperproliferation of keratinocytes and interruption of epidermal differentiation, in addition to changes in lipid structure and enzymatic activity [97]. Skin aging, specifically after age 65, presents several constitutional and functional changes in all layers of the skin, such as cellular senescence, decreased proliferative capacity, decreased ability to repair cellular DNA, abnormalities related to chromosomes, loss of telomeres, DNA extranuclear related mutations, oxidative stress and genetic mutations, promoting the formation of wrinkles, loss of elasticity and dryness of the skin [98, 99]. According to Rhie et al., 2001, the alpha-tocopherol concentration in the epidermis is negatively affected with aging and especially with photoaging, in this case the levels found are even lower when compared to young skin [100].

Over the years, the main histological changes occur with the basal cells, which suffer from dyscrasia, presenting an increase in volume and size, which can be accentuated by the action of UV radiation. As for the functionality of the basal cells, there is a decrease in mitotic activity and an increase in the cell cycle time and

the cell migration time, which can promote changes in the outermost layer of the skin. The horny extract does not change its thickness, however, the replacement of lipids happens slowly, which significantly affects the function of barrier, protection and maintenance of natural hydration [101, 102].

Thus, the topical use of vitamin E is adequate for its recognized antioxidant and protective activities, favoring the improvement of the skin barrier due to its lipophilic character and also, effectively avoiding lipid peroxidation by protecting cell membranes from the action of free radicals [103]. Gehring et al. [63] evaluated the hydration capacity of the stratum corneum by the use of vitamin E (5%) in water/oil and oil/water emulsions, demonstrating moisturizing activity in the stratum corneum, in addition to providing indications that indicate retention of water in the stratum corneum. Gonullu and collaborators [104] also report that the topical use of vitamin E for a period of two to four weeks can improve the ability of water to retain in the skin, favoring hydration.

While aging decreases keratinocyte proliferation, the abnormal hyperproliferation those cells are seen in psoriasis. Psoriasis is a chronic inflammatory process of the skin which affects 1–2% of the population and can affect the quality of life. It is most characterized by the presence of erythematous plaques with silvery scale on various regions of the body including the scalp, extensor regions of the extremities, and intertriginous areas of the skin [19, 105, 106]. Studies on the influence of vitamin E on psoriasis include oral and topical treatment evaluation of the vitamins combination, minerals, among others (vitamins A, C, D, E, B1, B2, B3, B5, B6, B12, magnesium, zinc, selenium, folic acid, copper, lysine and proline), that act on oxidative stress, energy metabolism, the immune system and optimized collagen formation. The consumption of olive oil, a vitamin E source, is also associated with improvement in psoriasis symptoms, acting positively in the suppression of serum levels of metalloproteinase-3 (MMP-3), protein of the cartilage olimeric matrix (COMP) as well as the levels of pro-inflammatory cytokines (TNF-α, IL-1β and IL-17) [107]. Topical treatments include the application of products added with plant extracts containing vitamin E and other derivatives, the results are representative in relieving the symptoms of psoriasis induced in the mouse model, suppressing the levels of Interleukin-22 involved in extensive proliferation of keratinocytes and pathogenesis of psoriasis. The critical importance of the interleukin axis for the pathogenesis of psoriatic disease has resulted in new biological treatments targeting these cytokines, indicating that vitamin E is a component of interest in the treatment of psoriasis [106–109].

7. Discussion

Antioxidants consumed orally or topically may impact several organs in the body and among them, the skin. Systemic or centralized effects of these molecules can be modulated by the administration pathway and cellular machinery involved in their metabolization. When compared with other natural bioactive compounds, vitamin E has a specific mechanism of activation in skin due its lipophilicity. Alpha-tocopherol is the active molecule, but several derivatives are available in the market to address solubility, cost and pharmacotechnical necessities. The acetate and succinate esters exhibit better oxidation stability and are often associated with surfactants to improve water-solubility. The hydrolyzation of those molecules is mandatory to achieve biological effects and is mainly driven by enzymatic complexes in skin. The application of derivatives is an interesting alternative for slow delivery of this vitamin since the necessity of activation may lead to accumulation and a reservoir effect [110].

The natural lipophilicity of vitamin E impacts also its biological effects in skin. Vitamin E structure forms complexes with lipids in the cellular membrane and therefore acts promptly against the ROS formation due UV or pollution exposure [111]. The reduction/blockage of oxidative stress' cascade protects skin against several damages visible as wrinkles, melasma and cancer. Besides the lipid peroxidation, vitamin E has an important role in DNA integrity and epigenetic gene modulation [112]. As a natural component of the healthy tissue, vitamin E is associated with impaired skin treatments, such as psoriasis, dry skin, atopic dermatitis and other skin disorders related to oxidative stress and inflammation [5].

The presence of vitamin E is expected in skin, which makes permeation experiments, bioavailability studies and quantification analysis more challenging. Raman confocal spectroscopy showed good sensibility to evaluate the health benefits and safety of vitamin E in human skin *in vivo* [113]. This technique can elucidate the extend of vitamin E overcoming skin barrier and achieving the nucleated epidermis for bioconversion. The complex mechanism of action of vitamin E depends on other bioactive molecules, especially vitamin C. As the primary replenisher of vitamin E in skin, the benefits of using those vitamins cannot be investigated separately and a wider look of the literature is required to make a fair comparison [114]. Further investigation using Raman could bring more data about the mechanisms and contribution of each ingredient. Nevertheless, it is very common that topical products present a combination of molecules acting synergistically to achieve better results.

The cosmetic market is always releasing innovative products despite vitamin E is considered a very classic dermatological active. New delivery systems focused on better absorption, deeper permeation or simpler hydrolysis are the R&D main targets. Since vitamin E is generally recognized as safe (GRASA) food ingredient and used in over-the-counter products with broader concentration range (1.0 to 5.0%), there is little regulatory concern about the exploration of this molecule in cosmetics and supplements. The focus of this chapter is topical applications and therefore, the oral toxicity data was not extensively covered. Safety assessment of alpha-tocopherol and its most used esters showed no phototoxicity, no genotoxicity and no ocular and dermal sensibilization [12]. The use of vitamin E in topical applications is a safe, effective and well accepted worldwide, especially in association with other antioxidants.

8. Conclusions

Vitamin E, more specifically alpha-tocopherol, can be considered a substance with antioxidant activity with the ability to protect long-chain unsaturated fatty acids. It is also capable of playing an important role in a wide variety of physiological and biochemical functions, mediated by the antioxidant function or by its stabilizing effect on cell membranes, breaking down the peroxyl chain propagation reactions and eliminating the efficient lipid peroxyl radicals. Is has been used for decades and is still a very good a widespread ingredient for dermatological products and formulations, especially when associated with other antioxidants such as vitamin C. However, it is important to emphasize the need for more in-depth studies on the use of its derivatives and associations, regarding the conversion speed and the converted amount of vitamin E in skin. There are few studies related to the topical safety and efficacy of vitamin E in the literature, although it is widely used in cosmetics and dermatologic products. A low incidence of contact dermatitis has been reported. However, more studies would be needed for a conclusive answer regarding its topical safety. The definition of optimal dosage in cosmetics depends on the derivative molecule and the type of cosmetic formulation.

Author details

Claudineia Aparecida Sales de Oliveira Pinto[1*], Tércio Elyan Azevedo Martins[1,2], Renata Miliani Martinez[1], Thamires Batello Freire[1], Maria Valéria Robles Velasco[1] and André Rolim Baby[1]

1 Department of Pharmacy, School of Pharmaceutical Sciences, University of São Paulo, São Paulo, Brazil

2 Aesthetics and Cosmetics Course, Paulista University, São Paulo, Brazil

*Address all correspondence to: clausal@usp.br

IntechOpen

References

[1] Poljšak B, Fink R. The protective role of antioxidants in the defence against ROS/RNS-mediated environmental pollution. Oxid Med Cell Longev. 2014;2014:1-22.

[2] Pekiner BD. Vitamin E as an antioxidant. J Fac Pharm, Ankara. 2003;32(4):243-267.

[3] Yamaguchi R. Vitamin E: Mechanism of Its Antioxidant Activity. Food Sci Technol Int Tokyo. 1997;3(4):301-309.

[4] Lobo V, Patil A, Phatak A, Chandra N. Free radicals, antioxidants and functional foods: Impact on human health. Pharmacogn Rev. 2010;4(8):118-126.

[5] Keen MA, Hassan I. Vitamin E in dermatology. Indian Dermatol Online J. 2016;7(4):311-315.

[6] Thiele JJ, Hsieh SN, Ekanayake-Mudiyanselage S. Vitamin E: critical review of its current use in cosmetic and clinical dermatology. Dermatologic Surg. 2005;31:805-813.

[7] Galli F, Azzi A, Birringer M, Cook-Mills JM, Eggersdorfer M, Frank J, et al. Vitamin E: Emerging aspects and new directions. Vol. 102, Free Radical Biology and Medicine. Elsevier Inc.; 2017. p. 16-36.

[8] Thiele JJ, Ekanayake-Mudiyanselage S. Vitamin E in human skin: Organ-specific physiology and considerations for its use in dermatology. Vol. 28, Molecular Aspects of Medicine. 2007. p. 646-667.

[9] Kuriyama K, Shimizu T, Horiguchi T, Watabe M, Abe Y. Vitamin E ointment at high dose levels suppresses contact dermatitis in rats by stabilizing keratinocytes. Inflamm Res. 2002;51(10):483-489.

[10] National Institutes of Healthy. Vitamin E Fact Sheet for Health Professionals [Internet]. 2021 [cited 2021 Apr 14]. p. 1-1. Available from: https://ods.od.nih.gov/factsheets/VitaminE-HealthProfessional/

[11] SCCNFP. Opinion of the scientific committee on cosmetic products and non-food products intended for consumers concerning the use of alpha-tocopherol acetate in cosmetic products [Internet]. 2001 [cited 2021 Apr 19]. Available from: https://ec.europa.eu/health/archive/ph_risk/committees/sccp/documents/out148_en.pdf

[12] Fiume MM, Bergfeld WF, Belsito D V., Hill RA, Klaassen CD, Liebler DC, et al. Safety Assessment of Tocopherols and Tocotrienols as Used in Cosmetics. Int J Toxicol. 2018 Sep 1;37(2_suppl):61S-94S.

[13] Traber MG, Rallis M, Podda M, Weber C, Maibach HI, Packer L. Penetration and distribution of α-tocopherol, α- or γ-tocotrienols applied individually onto murine skin. Lipids. 1998;33(1):87-91.

[14] Manela-Azulay M, Bagatin E. Cosmeceuticals vitamins. Clin Dermatol. 2009 Sep;27(5):469-474.

[15] Zingg JM. Water-Soluble Vitamin E—Tocopheryl Phosphate. In: Advances in Food and Nutrition Research. Academic Press Inc.; 2018. p. 311-363.

[16] Thiele JJ, Hsieh SN, Ekanayake-Mudiyanselage S. Vitamin E: critical review of its current use in cosmetic and clinical dermatology. Vol. 31, Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.]. 2005.

[17] Burke K. Interaction of vitamins C and E as better cosmeceuticals. Dermatol Ther. 2007;20(5):314-321.

[18] Varma SD, Kovtun S, Hegde KR. Role of ultraviolet irradiation and oxidative stress in cataract formation-medical prevention by nutritional antioxidants and metabolic agonists. Eye Contact Lens. 2011;37(4):233-245.

[19] Nachbar F, Korting H. The role of vitamin E in normal and damaged skin. J Mol Med. 1995;73(1):7-17.

[20] Nada A, Krishnaiah YSR, Zaghloul AA, Khattab I. In vitro and in vivo permeation of vitamin e and vitamin e acetate from cosmetic formulations. Med Princ Pract. 2011;20(6):509-513.

[21] Boussouira B, Pham D. Squalene and Skin Barrier Function: From Molecular Target to Biomarker of Environmental Exposure. In: Skin Stress Response Pathways. 2016. p. 29-48.

[22] Martins TEA, Pinto CAS de O, de Oliveira AC, Velasco MVR, Guitiérrez ARG, Rafael MFC, et al. Contribution of topical antioxidants to maintain healthy skin—A review. Sci Pharm. 2020;88(2):1-17.

[23] Silva SAM, Michniak-Kohn B, Leonardi GR. An overview about oxidation in clinical practice of skin aging. An Bras Dermatol. 2017;92(3):367-374.

[24] Mayer P. The effects of vitamin E on the skin. Cosmet Toilet. 1993;108(99-109).

[25] Ayala A, Muñoz MF, Argüelles S. Lipid peroxidation: Production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. Oxid Med Cell Longev. 2014;2014:1-31.

[26] Rimbach G, Minihane A, Majewicz J, Fischer A, Pallauf J, Virgli F, et al. Regulation of cell signalling by vitamin E. Proc Nutr Soc. 2002;61(4):415-425.

[27] Valacchi G, Sticozzi C, Pecorelli A, Cervellati F, Cervellati C, Maioli E. Cutaneous responses to environmental stressors. Ann N Y Acad Sci. 2012;1271(1):75-81.

[28] Portugal-Cohen M, Oron M, Cohen D, Ma'or Z. Antipollution skin protection – A new paradigm and its demonstration on two active compounds. Clin Cosmet Investig Dermatol. 2017;10:185-193.

[29] Velasco MVR, Sauce R, de Oliveira CA, Pinto CAS d. O, Martinez RM, Baah S, et al. Active ingredients, mechanisms of action and efficacy tests antipollution cosmetic and personal care products. Brazilian J Pharm Sci. 2018;54(Special Issue):1-8.

[30] Delinasios GJ, Karbaschi M, Cooke MS, Young AR. Vitamin E inhibits the UVAI induction of "light" and "dark" cyclobutane pyrimidine dimers, and oxidatively generated DNA damage, in keratinocytes. Sci Rep [Internet]. 2018;8(1):1-12. Available from: http://dx.doi.org/10.1038/s41598-017-18924-4

[31] Drouin R, Therrien JP. UVB-induced Cyclobutane Pyrimidine Dimer Frequency Correlates with Skin Cancer Mutational Hotspots in p53. Photochem Photobiol. 1997;66(5):719-726.

[32] Iwamatsu Y, Aoki C, Takahashi M, Teranishi M, Ding Y, Sun C, et al. UVB sensitivity and cyclobutane pyrimidine dimer (CPD) photolyase genotypes in cultivated and wild rice species. Photochem Photobiol Sci. 2008;7(3):311-320.

[33] Soeur J, Belaïdi JP, Chollet C, Denat L, Dimitrov A, Jones C, et al. Photo-pollution stress in skin: Traces of pollutants (PAH and particulate matter) impair redox homeostasis in keratinocytes exposed to UVA1. J Dermatol Sci. 2017;86(2):162-169.

[34] Cooper S, Bowden G. Ultraviolet B Regulation of Transcription Factor Families: Roles of Nuclear Factor-kappa B (NF-κB) and Activator Protein-1 (AP-1) in UVB-Induced Skin Carcinogenesis. Curr Cancer Drug Targets. 2007;7(4):325-334.

[35] Denat L, Kadekaro A, Marrot L, Leachman S, Abdel-Male Z. Melanocytes as Instigators and Victims of Oxidative Stress. J Invest Dermatol. 2014;134(6):1512-1518.

[36] Herrling T, Jung K, Fuchs J. The role of melanin as protector against free radicals in skin and its role as free radical indicator in hair. Spectrochim Acta - Part A Mol Biomol Spectrosc. 2008;69(5):1429-1435.

[37] Kadekaro AL, Kavanagh R, Kanto H, Terzieva S, Hauser J, Kobayashi N, et al. α-melanocortin and endothelin-1 activate antiapoptotic pathways and reduce DNA damage in human melanocytes. Cancer Res. 2005;65(10):4292-4299.

[38] Baldea I, Mocan T, Cosgarea R. The role of ultraviolet radiation and tyrosine stimulated melanogenesis in the induction of oxidative stress alterations in fair skin melanocytes. Exp Oncol. 2009;31(4):200-208.

[39] Kamei Y, Otsuka Y, Abe K. Comparison of the inhibitory effects of vitamin e analogues on melanogenesis in mouse B16 melanoma cells. Cytotechnology. 2009;59(3):183-190.

[40] Kramer KA, Liebler DC. UVB induced photooxidation of vitamin E. Chem Res Toxicol. 1997;10(2):219-224.

[41] Grams G, Eskins K. Dye-Sensitized Photooxidation of Tocopherols. Correlation between Singlet Oxygen Reactivity and Vitamin E Activity. Biochemistry. 1972;11(4):606-608.

[42] Burke K, Clive J, Combs Jr GF, Commisso J, Keen CL, Nakamura R. Effects of topical and oral vitamin E on pigmentation and skin cancer induced by ultraviolet irradiation in Skh:2 hairless mice. Nutr Cancer. 2000;38(1):87-97.

[43] Wu S, Gao J, Dinh QT, Chen C, Fimmel S. IL-8 production and AP-1 transactivation induced by UVA in human keratinocytes: Roles of d-α-tocopherol. Mol Immunol. 2008;45(8): 2288-2296.

[44] Park K. Role of micronutrients in skin health and function. Biomol Ther. 2015;23(3):207-217.

[45] Ricciarelli R, Maroni P, Özer N, Zingg JM, Azzi A. Age-dependent increase of collagenase expression can be reduced by α-tocopherol via protein kinase C inhibition. Free Radic Biol Med. 1999;27(7-8):729-737.

[46] Butt H, Mehmood A, Ali M, Tasneem S, Anjum MS, Tarar MN, et al. Protective role of vitamin E preconditioning of human dermal fibroblasts against thermal stress in vitro. Life Sci [Internet]. 2017;184:1-9. Available from: http://dx.doi.org/10.1016/j.lfs.2017.07.002

[47] Shindo Y, Witt E, Han D, Epstein W, Packer L. Enzymic and non-enzymic antioxidants in epidermis and dermis of human skin. J Invest Dermatol [Internet]. 1994;102(1):122-124. Available from: http://dx.doi.org/10.1111/1523-1747.ep12371744

[48] Thiele J, Schroeter C, Hsieh S, Podda M, Packer L. The antioxidant network of the stratum corneum. Curr Probl Dermatol. 2001;29(1):26-42.

[49] Thiele JJ, Traber MG, Polefka TG, Cross CE, Packer L. Ozone-exposure depletes vitamin E and induces lipid peroxidation in murine stratum corneum. J Invest Dermatol. 1997;108(5):753-757.

[50] Puri P, Nandar SK, Kathuria S, Ramesh V. Effects of air pollution on the skin: A review. Indian J Dermatol Venereol Leprol. 2017;83(4):415-423.

[51] Petruk G, Giudice R Del, Rigano MM, Monti DM. Antioxidants from plants protect against skin photoaging. Oxidative Medicine and Cellular Longevity. Hindawi Limited; 2018. p. 1-11.

[52] Mcardle F, Rhodes LE, Parslew RAG, Close GL, Jack CIA, Friedmann PS, et al. Effects of oral vitamin E and beta-carotene supplementation on ultraviolet radiation – induced oxidative stress in human skin. Am J Clin Nutr. 2004;80(1): 1270-1275.

[53] Placzek M, Gaube S, Kerkmann U, Gilbertz KP, Herzinger T, Haen E, et al. Ultraviolet B-induced DNA damage in human epidermis is modified by the antioxidants ascorbic acid and D-α-tocopherol. J Invest Dermatol [Internet]. 2005;124(2):304-307. Available from: http://dx.doi.org/10.1111/j.0022-202X.2004.23560.x

[54] Eberlein-könig B, Placzek M, Przybilla B. Protective effect against sunburn of combined systemic ascorbic acid (vitamin C) and d- α -tocopherol (vitamin E). J Am Acad Dermatol. 1998;45-48.

[55] Fuchs J, Kern H. Modulation of UV-light-induced skin inflammation by D-alpha-tocopherol and L-ascorbic acid: a clinical study using solar simulated radiation. Free Radic Biol Med. 1998;25(9):1006-1012.

[56] Hayakawa R, Ueda H, Nozaki T, Izawa Y, Yokotake J, Yazaki K, et al. Effects of combination treatment with vitamins E and C on chloasma and pigmented contact dermatitis. A double blind controlled clinical trial. Acta Vitaminol Enzym. 1981;3(1): 31-38.

[57] Cho H, Lee M, Lee JW, No K, Park S, Lee H, et al. by chronic ultraviolet B irradiation. Photodermatol Photoimmunol Photomed. 2007;23(5):155-162.

[58] Aladrén S, Garre A, Valderas-mart P, Piquero-casals J. Efficacy and Safety of an Oral Nutritional (Dietary) Supplement Containing Pinus pinaster Bark Extract and Grape Seed Extract in Combination with a High SPF Sunscreen in the Treatment of Mild-to-Moderate Melasma : A Prospective Clinical Study. Cosmetics. 2019;6(15):1-13.

[59] Handog EB, Amor D, Galang VF, Leon-godinez MA De, Chan GP. Pharmacology and therapeutics A randomized , double-blind , placebo-controlled trial of oral procyanidin with vitamins A , C , E for melasma among Filipino women. Int J Dermatol. 2009;48:896-901.

[60] Chen B, McClements DJ, Decker EA. Minor components in food oils: a critical review of their roles on lipid oxidation chemistry in bulk oils and emulsions. Crit Rev Food Sci Nutr. 2011;51(10):901-916.

[61] Mintel [Internet]. [cited 2021 Mar 12]. Available from: https://www.mintel.com/global-new-products-database

[62] Dreher F, Denig N, Gabard B, Schwindt DA, Maibach HI. Effect of topical antioxidants on UV-induced erythema formation when administered after exposure. Dermatology. 1999;198(1):52-55.

[63] Gehring W, Fluhr J, Gloor M. Influence of vitamin E acetate on stratum corneum hydration. Arzneimittelforschung. 1998;48:772-775.

[64] Al-Niami F, Yi Zhen Chiang N. Topical Vitamin C and the Skin : J Clin

Aesthetic Dermatology. 2017;10(7):14-17.

[65] Traber MG, Stevens JF. Vitamins C and E: Beneficial effects from a mechanistic perspective. Free Radic Biol Med. 2011;51(5):1000-1013.

[66] Lin JY, Selim MA, Shea CR, Grichnik JM, Omar MM, Monteiro-Riviere NA, et al. UV photoprotection by combination topical antioxidants vitamin C and vitamin E. J Am Acad Dermatol. 2003;48(6): 866-874.

[67] Rattanawiwatpong P, Wanitphakdeedecha R, Bumrungpert A, Maiprasert M. Anti-aging and brightening effects of a topical treatment containing vitamin C, vitamin E, and raspberry leaf cell culture extract: A split-face, randomized controlled trial. J Cosmet Dermatol. 2020;19(3):671-676.

[68] Maia Campos PMBG, Gianeti MD, Kanashiro A, Lucisano-Valim YM, Gaspar LR. In Vitro Antioxidant and In Vivo Photoprotective Effects of an Association of Bioflavonoids with Liposoluble Vitamins. Photochem Photobiol. 2006;82(3):683.

[69] Cerchiara T, Giordani B, Melgoza LM, Prata C, Parolin C, Dalena F, et al. New Spanish Broom dressings based on Vitamin E and *Lactobacillus plantarum* for superficial skin wounds. J Drug Deliv Sci Technol [Internet]. 2020;56(December 2019):101499. Available from: https://doi.org/10.1016/j.jddst.2020.101499

[70] Choi YK, Rho YK, Yoo KH, Lim YY, Li K, Kim BJ, et al. Effects of vitamin C vs. multivitamin on melanogenesis: Comparative study in vitro and in vivo. Int J Dermatol. 2010;49(2):218-226.

[71] Farris P, Yatskayer M, Chen N, Krol Bs Y, Oresajo C. Evaluation of Efficacy and Tolerance of a Nighttime Topical Antioxidant Containing Resveratrol, Baicalin, and Vitamin E for Treatment of Mild to Moderately Photodamaged Skin Christian Oresajo L'Oréal Evaluation of Efficacy and Tolerance of a Nighttime Top [Internet]. Vol. 13, Article in Journal of drugs in dermatology. 2014. Available from: https://www.researchgate.net/publication/271538214

[72] Gaspar LR, Campos PMBGM. Photostability and efficacy studies of topical formulations containing UV-filters combination and vitamins A, C and E. Int J Pharm. 2007;343(1-2): 181-189.

[73] Prakoeswa CRS, Natallya FR, Harnindya D, Thohiroh A, Oktaviyanti RN, Pratiwi KD, et al. The efficacy of topical human amniotic membrane-mesenchymal stem cell-conditioned medium (hAMMSC-CM) and a mixture of topical hAMMSC-CM + vitamin C and hAMMSC-CM + vitamin E on chronic plantar ulcers in leprosy: a randomized control trial. J Dermatolog Treat. 2018 Nov 17;29(8):835-840.

[74] Lin FH, Lin JY, Gupta RD, Tournas JA, Burch JA, Selim MA, et al. Ferulic acid stabilizes a solution of vitamins C and E and doubles its photoprotection of skin. J Invest Dermatol [Internet]. 2005;125(4):826-832. Available from: http://dx.doi.org/10.1111/j.0022-202X.2005.23768.x

[75] Funasaka Y, Komoto M, Ichihashi M. Depigmenting effect of α-tocopheryl ferulate on normal human melanocytes. Pigment Cell Res. 2000;13(SUPPL. 8):170-174.

[76] Ichihashi M, Funasaka Y, Ohashi A, Chacraborty A, Ahmed NU, Ueda M, et al. The inhibitory effect of DL-alpha-tocopheryl ferulate in lecithin on melanogenesis. Anticancer Res. 1999;19(5A):3769-3774.

[77] Rouvrais C, Bacqueville D, Bogdanowicz P, Haure MJ, Duprat L, Coutanceau C, et al. A new dermocosmetic containing retinaldehyde, delta-tocopherol glucoside and glycylglycine oleamide for managing naturally aged skin: Results from in vitro to clinical studies. Clin Cosmet Investig Dermatol. 2017;10:35-42.

[78] Kim B, Cho H, Moon SH, Ahn H, Bae S, Cho H. Transdermal delivery systems in cosmetics. Biomed Dermatology. 2020;4(10):1-12.

[79] Praça FG, Viegas JSR, Peh YH, Garbin TN, Medina WSG, Bentley MVLB. Microemulsion co-delivering vitamin A and vitamin E as a new platform for topical treatment of acute skin inflammation. Mater Sci Eng C [Internet]. 2020;110(August 2019):110639. Available from: https://doi.org/10.1016/j.msec.2020.110639

[80] Shakeel A, Farooq U, Iqbal T, Yasin S, Lupi FR, Gabriele D. Key characteristics and modelling of bigels systems: A review. Mater Sci Eng C. 2019;97(December 2018):932-953.

[81] Martinez RM, Magalhães WV, Sufi BS, Padovani G, Nazato LIS, Robles MV, et al. Vitamin E-loaded bigels and emulsions : Physicochemical characterization and potential biological application. Colloids Surfaces B Biointerfaces. 2021;201(111651).

[82] Kappus H, Diplock AT. Tolerance and safety of vitamin e: a toxicological position report [Internet]. Vol. 13, Free Radical Biology & Medicine. 1992 [cited 2021 Apr 19]. Available from: https://www.sciencedirect.com/science/article/abs/pii/089158499290166E

[83] Brigelius-Flohé R, Kelly FJ, Salonen JT, Neuzil J, Zingg J-M, Azzi A. The European perspective on vitamin E: current knowledge and future research. Am J Clin Nutr. 2002;76(4):703-716.

[84] Fiume MZ. Final report on the safety assessment of tocopherol, tocopheryl acetate, tocopheryl linoleate, tocopheryl linoleate/oleate, tocopheryl nicotinate, tocopheryl succinate, dioleyl tocopheryl methylsilanol, potassium ascorbyl tocopheryl phosphate, and tocophe. Vol. 21, International Journal of Toxicology. 2002. 51-116 p.

[85] Chung HJ, Young Seo J, Kyoung Lee M, Chul Eun H, Heung Lee J, Kang S, et al. Ultraviolet Modulation of Human Macrophage Metalloelastase in Human Skin In Vivo. 2002.

[86] European Chemicals Agency. 3,4-Dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyldecyl)-2H-benzopyran-6-yl acetate. 2013.

[87] Baumann LS, Spencer J. The Effects of Topical Vitamin E on the Cosmetic Appearance of Scars. Vol. 25, Dermatol Surg. 1999.

[88] Libinaki R, Ogru E, Gianello R, Bolton L, Geytenbeek S. Evaluation of the safety of mixed tocopheryl phosphates (MTP)-A formulation of α-tocopheryl phosphate plus α-di-tocopheryl phosphate. Food Chem Toxicol. 2006;44(7):916-932.

[89] Costa A. Tratado Internacional de Cosmecêuticos. 1st ed. Koogan G, editor. Rio de Janeiro; 2012. 744 p.

[90] Fryer MJ. Evidence for the photoprotective effects of vitamin e. Vol. 58. 1993.

[91] Krol ES, Kramer-Stickland KA, Liebler DC. Photoprotective actions of topically applied vitamin E [Internet]. Vol. 32, Drug Metabolism Reviews. 2000. Available from: www.dekker.com

[92] Sarkar R, Arora P, Garg Kv. Cosmeceuticals for hyperpigmentation: What is available? J Cutan Aesthet Surg. 2013;6(1):4.

[93] Tsoureli-Nikita E, Hercogova J, Lotti T, Menchini G. Evaluation of dietary intake of vitamin E in the treatment of atopic dermatitis: a study of the clinical course and evaluation of the immunoglobulin E serum levels. Int J Dermatol. 2002;41(3):146-150.

[94] Greul A-K, Grundmann J-U, Heinrich F, Pfitzner I, Bernhardt J, Ambach A, et al. Skin Skin Pharmacology andApplied Physiology Skin Pharmacology andApplied Skin Physiology Photoprotection of UV-Irradiated Human Skin: An Antioxidative Combination of Vitamins E and C, Carotenoids, Selenium and Proanthocyanidins [Internet]. Vol. 15, Skin Pharmacol Appl Skin Physiol. 2002. Available from: www.karger.com/journals/sph

[95] Ibrahim N 'Izzah, Wong SK, Mohamed IN, Mohamed N, Chin KY, Ima-Nirwana S, et al. Wound healing properties of selected natural products. Vol. 15, International Journal of Environmental Research and Public Health. MDPI AG; 2018. p. 1-23.

[96] Thyssen JP, Johansen JD, Zachariae C, Menné T, Linneberg A. Xerosis is associated with atopic dermatitis, hand eczema and contact sensitization independent of filaggrin gene mutations. Acta Derm Venereol. 2013;93(4):406-410.

[97] Vaz S, Silva R, Amaral MH, Martins E, Sousa Lobo JM, Silva AC. Evaluation of the biocompatibility and skin hydration potential of vitamin E-loaded lipid nanosystems formulations: In vitro and human in vivo studies. Colloids Surfaces B Biointerfaces [Internet]. 2019;179(November 2018):242-9. Available from: https://doi.org/10.1016/j.colsurfb.2019.03.036

[98] Fisher GJ, Kang S, Varani J, Bata-Csorgo Z, Wan Y, Datta S, et al. Mechanisms of photoaging and chronological skin aging. Arch Dermatol. 2002;138(11):1462-1470.

[99] Makrantonaki E, Zouboulis CC. Characteristics and pathomechanisms of endogenously aged skin. Dermatology. 2007;214(4):352-360.

[100] Rhie GE, Mi HS, Jin YS, Won WC, Kwang HC, Kyu HK, et al. Aging- and photoaging-dependent changes of enzymic and nonenzymic antioxidants in the epidermis and dermis of human skin in vivo. J Invest Dermatol [Internet]. 2001;117(5):1212-1217. Available from: http://dx.doi.org/10.1046/j.0022-202x.2001.01469.x

[101] Lavker RM. Structural alterations in exposed and unexposed aged skin. Vol. 73, The Journal of Investigative Dermatology. 1979. p. 59-66.

[102] Yaar M, Gilchrest BA. Skin aging: Postulated mechanisms and consequent changes in structure and function. Clin Geriatr Med. 2001;17(4):617-630.

[103] Nada A, Zaghloul A, Hedaya M, Khattab I. Stability of vitamin E and vitamin E acetate containing cosmetic preparations. J Glob Pharma Technol. 2012;4(03):1-8.

[104] Gönüllü Ü, Sensoy D, Üner M, Yener G, Altinkurt T. Comparing the moisturizing effects of ascorbic acid and calcium ascorbate against that of tocopherol in emulsions. J Cosmet Sci. 2006;57(6):465-473.

[105] Vaule H, Leonard SW, Traber MG. Vitamin E delivery to human skin: Studies using deuterated α-tocopherol measured by apci LC-MC. Free Radic Biol Med. 2004 Feb 15;36(4):456-463.

[106] Usedom E, Neidig L, Allen HB. Psoriasis and Fat-soluble Vitamins: A Review. J Clin Exp Dermatol Res. 2017;08(05):1-6.

[107] Parlapally S, Cherukupalli N, Bhumireddy SR, Sripadi P, Anisetti R, Giri CC, et al. Chemical profiling and anti-psoriatic activity of methanolic extract of Andrographis nallamalayana J.L.Ellis. Nat Prod Res. 2016;30(11): 1256-1261.

[108] Aparicio-Soto M, Sánchez-Hidalgo M, Cárdeno A, Rosillo MÁ, Sánchez-Fidalgo S, Utrilla J, et al. Dietary extra virgin olive oil attenuates kidney injury in pristane-induced SLE model via activation of HO-1/Nrf-2 antioxidant pathway and suppression of JAK/STAT, NF-κB and MAPK activation. J Nutr Biochem. 2016;27:278-288.

[109] Sýs M, Švecová B, Švancara I, Metelka R. Determination of vitamin E in margarines and edible oils using square wave anodic stripping voltammetry with a glassy carbon paste electrode. Food Chem. 2017;229:621-627.

[110] Marra F, Ostacolo C, Laneri S, Bernardi A, Sacchi A, Padula C, et al. Synthesis, hydrolysis, and skin retention of amino acid esters of α-tocopherol. J Pharm Sci. 2009;98(7):2364-2376.

[111] Kamal MA, Raghunathan VA. Modulated phases of phospholipid bilayers induced by tocopherols. Biochim Biophys Acta - Biomembr [Internet]. 2012;1818(11):2486-2493. Available from: http://dx.doi.org/10.1016/j.bbamem.2012.06.016

[112] Zappe K, Pointner A, Switzeny OJ, Magnet U, Tomeva E, Heller J, et al. Counteraction of oxidative stress by Vitamin E affects epigenetic regulation by increasing global methylation and gene expression of MLH1 and DNMT1 dose dependently in Caco-2 cells. Oxid Med Cell Longev. 2018;2018.

[113] Mazurek S, Pichlak K, Szostak R. Quantitative determination of vitamins a and e in ointments using raman spectroscopy. Processes. 2021;9(1):1-9.

[114] Pullar JM, Carr AC, Vissers MCM. The roles of vitamin C in skin health. Nutrients. 2017;9(866):1-27.