Chapter

Vitamin E and Derivatives in Skin Health Promotion

Júlia Scherer Santos, Guilherme Diniz Tavares and Thaís Nogueira Barradas

Abstract

Vitamin E is fundamental for a proper function of human cells. Mostly obtained from vegetable oils, it has antioxidant and non-antioxidant actions. At times, its oral intake or skin application are employed. Oral intake is recommended in some cases. Differently, the topical application is a part of daily skin routine. Both in oral or in topical formulations, it is employed in its isoforms or derivatives. Tocopherols and tocotrienols are isoforms while derivatives are synthetic forms. In pharmaceutical and cosmetic formulations, vitamin E and its derivatives are widely used due to its antioxidant and photoprotective properties. However, the clinical success treatment is often impaired by its low skin penetration, high lipophilicity, and chemical instability. A rational formulation design in the development of novel vitamin E dosage forms is required. In this chapter, the most successful and innovative approaches towards Vitamin E and its derivatives loaded in formulations for skin health promotion are reviewed. Conventional and nanoparticle-based formulations enable vitamin E chemical stabilization, and they are suitable vehicles for its release on the skin. Further, nano-sized carriers can increase vitamin E content in formulations as well as favor its skin penetration.

Keywords: antioxidant, tocopherols, tocotrienols, skin, health

1. Introduction

Neurodegenerative and metabolic diseases progression is related to oxidative stress [1, 2], a condition where there is a lower ability of endogenous antioxidants to scavenge free radicals [3] resulting in free radicals increase. Most frequent free radicals are the reactive oxygen species (ROS) such as singlet oxygen, hydrogen peroxide and hydroperoxide. ROS are formed endogenously [4] and its production is raised by some environmental factors [3]. Major internal sources are mitochondrial oxidative reactions, phagocytosis by macrophages and xenobiotics metabolization [4]. Environmental factors include pollution, ultraviolet radiation and smoking [3]. Free radicals damage DNA, protein and lipids [4] and their increase is involved in diabetes progression [1] and in Alzheimer and Parkinson's diseases onset [2]. In addition, cystic fibrosis patients are more prone to oxidative stress owing to vitamin E deficiency [3].

Some endogenous antioxidants are glutathione peroxidase, vitamin C and vitamin E [4]. Vitamin E is a non-enzymatic endogenous antioxidant [4] preventing atherosclerosis due to reduction of low density lipoprotein (LDL) oxidation. Beyond from antioxidant, it has a fundamental role in neurological and immune system function [4]. Accordingly, oral intake of vitamin E would be an interesting

alternative treatment to oxidative related diseases to improve patients quality of life [5, 6]. Apart from oral intake, natural sources of this vitamin are the vegetable oils. Wheat germ oil, sunflower oil, rice bran oil, canola oil and palm oil are some representants rich in vitamin E. Nuts and fresh foods contain vitamin E, but in smaller amounts [4].

1.1 Vitamin E isoforms and derivatives

A sum of 4 tocopherols isomers and 4 tocotrienols isomers compose vitamin E. Isomers are named as alpha, beta, gamma and delta and their chemical structures are shown in **Figure 1**. Tocopherols and tocotrienols differ only in their side chain. Tocotrienols have an unsaturation on its side chain. In respect to isomers, the nomenclature is due to substitutions in R_1 and R_2 positions. Alpha isomers have a methyl group both at R_1 and R_2 while delta isomers do not have any methyl group. Instead, beta and gamma isomers have one single methyl group, in R_1 or in R_2. Regardless of the source, vegetables contain a mixture of isoforms and one of them is predominant [7, 8]. Isoforms are obtained through extraction from vitamin E- rich vegetables such as wheat (shown in **Figure 1**) whose principal isoform is alpha-tocopherol [7]. Chemical synthesis is employed to obtain alpha-tocopherol [7, 8].

Commercially, vitamin E is available mainly as alpha-tocopherol [9, 10] or tocopheryl acetate [11–13] which are used above all to oral [14, 15] and skin [10, 12, 16] applications, respectively. Among vitamin E derivatives are tocopheryl acetate, tocopheryl glucoside and tocopheryl phosphate. Tocopheryl acetate is the most used vitamin E derivative [17] also named as tocopherol acetate or vitamin E acetate [18]. It is obtained through tocopherol modification to improve stability since tocopherol is a labile form. However, tocopheryl acetate is biologically inactive and it must be converted to tocopherol in skin and intestine. Often, there is no mention about tocopheryl acetate isomer as alpha-tocopheryl acetate is the most used [8].

Regarding human use, there is no standardization about vitamin E dose neither in oral intake [14, 15] nor in skin formulations [10, 19, 20]. Although its deficiency in adults is unusual [4], its oral intake may be recommended in cystic fibrosis

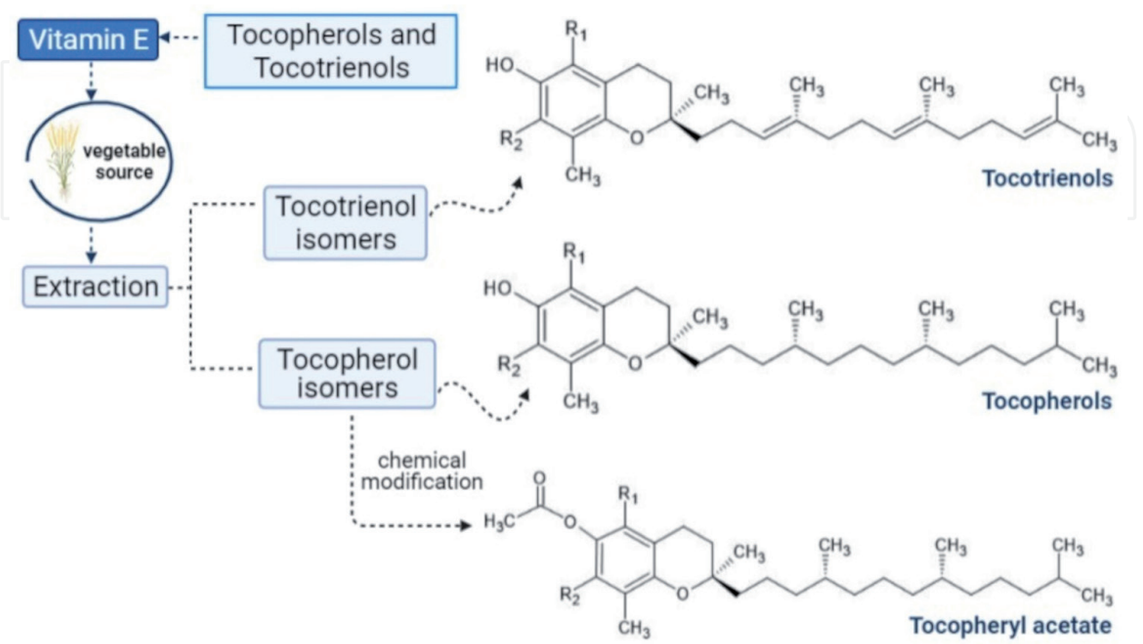

Figure 1.
Extraction of vitamin E isoforms, chemical structure of Tocopherols, Tocotrienols and Tocopheryl acetate. Created in BioRender and ACD/ChemSketch.

Skin effect	Mechanism of action	References
Photoprotection	Lipid peroxidation reduction	[23–25]
	Endogenous antioxidants protection	[24–26]
	Erythema decrease	[27, 28]
	Inflammation reduction	[29]
Cancer prevention	Pyrimidine dimers reduction	[30]
Reduction of melanoma progression	Apoptosis induction	[31, 32]
	Cell cycle arrest	[32]
Improvement of melasma	Reduction of tyrosinase activity	[33, 34]
	Down-regulation of TYRP-2 expression	[34]
	Down-regulation of TYR, TYRP-1, TYRP-2*	[35]
Reduction of Skin Aging	Increased collagen expression	[36, 37]
	Decrease metalloproteinases expression	[37]

**TYR: Tyrosinase, TYRP-1: tyrosinase-related protein-1, TYRP-2: tyrosinase-related protein- 2.*

Table 1.
General skin effects and mechanisms of vitamin E isoforms and derivatives.

patients [21]. Oral supplementation is equally used to reduce ultraviolet damage to skin [14, 15]. Furthermore, its combination with other antioxidants is a common approach. Vitamin C is the most used one [15, 19, 20] because it regenerates oxidized vitamin E [22]. Oxidized vitamin E if not properly regenerated may promote lipid peroxidation instead of preventing it [4]. The association of several antioxidants is then extremely important to reduce oxidative stress.

1.2 Benefits on skin health and dermatological diseases

The knowledge about vitamin E effects is essential to guide its use in dermatological treatments. **Table 1** shows some skin effects and mechanisms of action to vitamin E isoforms and derivatives. Photoprotection was approached mostly in earlier studies [23, 27, 28] while current ones approach mostly skin diseases [31, 35]. The antioxidant activity accounts for many skin effects including photoprotection [23–25], skin aging reduction [36, 37] and pyrimidine dimers reduction. The latter effect is important to prevent cancer onset [30]. Moreover, as reactive oxygen species are involved in the pathogenesis of psoriasis and atopic dermatitis [38–40], the topical application of vitamin E isoforms would be likewise beneficial in these diseases.

In relation to isomers, earlier researches were directed mainly to alpha-tocopherol whose action is lipid peroxidation reduction [24]. Nowadays, research is focused on tocotrienols [31] and tocotrienol-rich fraction [35–37] which are able to reduce melanoma progression [31, 32], melanogenesis [35] and skin aging [36, 37]. Tocotrienol-rich fraction (TRF) is a mixture of tocotrienols and alpha-tocopherol [41] allowing to combine the pharmacological benefits of several isomers. Further studies over tocotrienols and TRF are required to prove their efficacy in skin diseases treatments.

2. Vitamin E in skin care formulations

Conventional formulations [42] and nanotechnological-based formulations [16, 43] have been used to deliver vitamin E and its derivatives into the skin due

to its moisturizing, photoprotective, antioxidant [44, 45] and anticancer properties [46]. Some formulations applied to skin care are summarized in **Table 2**. Mainly sunscreens and anti-aging commercial products contain this vitamin [42]. Additionally, some cosmetic brands have explored the "anti-pollution" claim in their labels. As pollution triggers oxidative stress, the "anti-pollution" effect prevents skin damage induced by pollutants [19].

Nevertheless, several limitations impact vitamin E isoforms and derivatives bioavailability. Their bioactivity in different target sites, such as the skin is affected. Vitamin E is an unstable molecule because it undergoes oxidation, especially the light-triggered phenomena [60]. In this sense, novel drug delivery systems have been extensively investigated to improve vitamin E bioavailability, solubility, stability and biodistribution. Consequently, a better skin penetration can be accomplished [61, 62].

2.1 Conventional formulations

Emulsions and hydroalcoholic gel are the most common conventional formulations bearing either tocopherol, tocopheryl acetate or other esters (succinate, nicotinate, linoleate, and phosphate). The isoform α-tocopherol is the one with the best cost–benefit ratio [42]. One single α-tocopherol molecule is capable of neutralizing 2 peroxidil radicals which is responsible for lipid oxidation initiation. Then, a delay in the development of several oxidation-based disorders could be achieved [38]. Despite being less effective than tocopherol, tocopheryl acetate is widely used in formulations intended to skin delivery [42].

In sunscreens formulations, vitamin E and its derivatives increase the sun protection factor [47] and contribute to the photostabilization of chemical filters [49]. After skin permeation, they can minimize the oxidative stress harmful effects

Skin formulation	Skin care application	Vitamin E isoform or derivative	Reference
Conventional formulations	Photoprotection	α-tocopherol	[10, 47]
		Tocopheryl acetate	[48, 49]
		Tricotrienol-rich fraction	[25]
	Melasma	Tocopheryl acetate	[50]
	Anti-pollution	α-tocopherol	[19]
	Skin aging	Tocopheryl acetate	[51]
	Acne vulgaris	Tocopheryl phosphate	[52]
Nanotechnology-based systems	Photoprotection	Tocopheryl acetate	[43, 53]
		α-tocopherol	[54, 55]
	Wound healing	Tocopheryl acetate	[56, 57]
	Dermatitis	α-tocopherol	[58, 59]
		γ-tocotrienol	[59]
	Skin aging	α-tocopherol	[9]
	Moisturization	Tocopheryl acetate	[16]
		α-tocopherol	[9]

Table 2.
Vitamin E isoforms and derivatives in conventional forms and nanotechnology-based systems.

caused by UV radiation [48, 63]. In the latter case, an adequate vehicle is important since it can influence its permeation. In this regard, especially o/w (oil- in-water) emulsions have been used as the vehicle of choice [64]. From this perspective, a report showed that o/w emulsion containing vitamin E prevented erythema induction and reduced inflammatory damage caused by UV exposure in healthy volunteers [48].

In anti-aging formulations, vitamin E and its derivatives act as antioxidants, scavenging free radicals, the principal accelerators of skin aging [65]. As regards to α-tocopherol, it decreased expression lines, wrinkles, and freckles induced by photoaging in a study performed *in vivo* [66]. In addition, α-tocopherol smooths the skin, increases the stratum corneum ability to maintain its humidity and accelerates the epithelialization process [67]. For these purposes of use, most commercially available formulations are emulsions o/w, both in creams and lotions.

Furthermore, the association of vitamin E and its derivatives with other ingredients increased the effectiveness of different dermocosmetic treatments [45]. In this sense, the application of a lotion combining α-tocopherol phosphate, ascorbyl 2-phosphate 6-palmitate, and glyceryl-octyl-ascorbic acid reduced the complications of acne vulgaris [52]. On the other hand, in a randomized controlled trial, a cream containing hydroquinone, buffered glycolic acid, vitamins C and E, and sunscreen was safe and effective in melasma treatment [50]. Recently, a serum containing vitamin C, tocopheryl acetate and raspberry leaf cell culture extract had anti-aging and brightening effects on the skin, with significant improvement of skin color, elasticity, and radiance. The smoothness, scaliness, and wrinkles were also improved by topical use of the product once a day, during eight weeks [51].

2.2 Nanotechnology-based formulations

Bioactives molecules and lipophilic vitamins release on or into the skin by topical products comprise a challenging task owing to the characteristics of the stratum corneum barrier. Thereby, the drug accumulates on the skin surface. Besides, vitamin E low stability by its direct exposure to UV radiation can limit conventional formulations effectiveness [58]. Therefore, when it comes to topical administration, nanostructured drug vehicles have shown advantages over conventional delivery systems. The most investigated nanostructured carriers for vitamin E comprise liposomes, nanoemulsions, polymer nanoparticles and lipid-based nanoparticles [54].

Liposomes are self-assembled vesicles composed by one or more hydrophobic bilayers constituted by amphiphilic phospholipids which originate an aqueous core domain. Phospholipids contain phosphorus in their composition [68]. Diversely, nanoemulsions are thermodynamically unstable surfactant-stabilized systems composed of nano-sized micelles bearing an oily nucleus [69]. Polymer nanoparticles, whether nanocapsules or nanospheres, are colloidal artificially prepared spherical carriers surrounded by a polymer membrane. Nanocapsules contain an oily core and nanospheres contain a polymeric matrix [70]. Besides, chitosan obtained from shrimp and crab shells [71] is employed to form polymeric nanoparticles. In these nanoparticles, there is a matrix formed by chitosan and tripolyphosphate. The latter is used as a crosslinking agent [58]. Elseways, lipid nanoparticles either solid lipid nanoparticles (SLN) or nanostructured lipid carriers (NLC) have a lipophilic bioactive entrapped. SLN are formed by a solid lipid-based core while NLC are formed by a mixture of solid and liquid lipids [72]. **Figure 2** shows the general structures of some nanocarriers used to deliver vitamin E into skin.

Concerning liposomes, an optimized composition [73], a proper selection of preparation methods and a suitable particle size range [74] are essential as skin

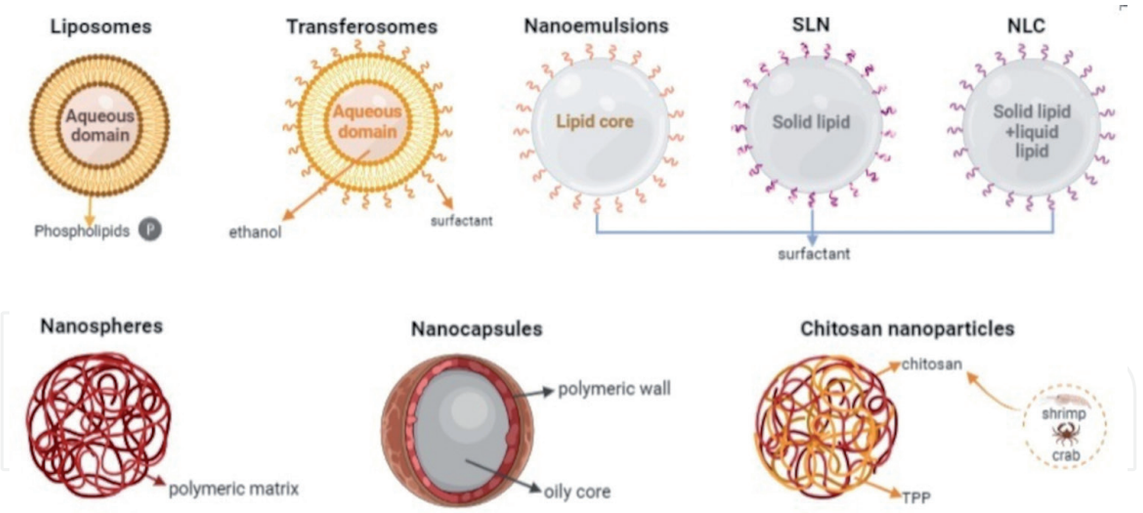

Figure 2.
Structure of some vitamin E nanocarriers. SLN: Solid lipid nanoparticles. NLC: Nanostructured lipid carriers. TPP: Tripolyphosphate. Created in BioRender.

penetration will be affected by these factors. Regarding biological activity, vitamin E-loaded liposomes inhibited lipid peroxidation more effectively than free vitamin E [74]. Lately, tocopherol acetate-loaded transferosomes optimized wound healing process [56]. As transferosomes are elastic liposome-like ultra-deformable vesicles, a higher diffusion across the stratum corneum can be accomplished [75, 76]. Topical administration of vitamin E-loaded liposomes are also interesting to enable a high drug penetration and transdermal release into skin tumors [68].

Lipid nanoparticles ability to increase sunscreens efficacy was previously shown [53, 55]. Tocopherol acetate-loaded SLN increased sunscreen UV-blocking effect [53]. Moreover, alpha-tocopherol and sunscreens loaded in NLC and SLN increased vitamin E photostability. Additionally, nanoencapsulated vitamin E promoted a better photoprotection than nanoparticle-based formulation without Vitamin E [55]. Besides, tocopheryl acetate and idebenone loaded in NLC provided a skin hydration increase because lipids have occlusive properties. Vitamin E loaded in NLC reduced skin pigmentation which was attributed to the photoprotective effect of Vitamin E [43].

An innovative nanocomposite dressing for burn wound healing containing vitamin E- loaded polymer nanoparticles allowed a vitamin controlled release [57]. In another report, α-tocopherol loaded to nanospheres was crosslinked to cellulose fiber to obtain a novel cosmetic fabric with potential application to atopic dermatitis patients [58]. As to nanoemulsions, tocopherol-loaded nanoemulsions increased skin delivery *in vitro* and they protected vitamin E from UV-triggered degradation [54]. More recently, α-tocopherol and γ-tocotrienol were loaded in nanoemulsions to treat dermatitis as an attempt to avoid the use of steroid anti-inflammatory drugs. This nanotechnological formulation could be in the future an alternative to dermatitis patients [59].

Lastly, clinical trials are essential to complement in *vitro assays*. According to human experiments, different nanosystems could be employed to ensure a more immediate or a more prolonged skin hydration [16]. Beyond skin moisturization, lipid nanoparticles improved human skin elasticity and firmness [9]. Importantly, a protocol clinical trial proposes the use of a formulation containing vitamin E-loaded NLC to reduce radiodermatitis in breast cancer patients. Since radiodermatitis is a recurrent radiotherapy side effect, the use of this topical formulation could improve cancer treatment as there would be lower patients quitting radiotherapy treatment [77].

3. Conclusion

Reactive oxygen species are implicated in systemic and skin diseases pathogenesis. Hence, topical use as well as oral intake of antioxidants should be encouraged to reduce stress oxidative effects. Vitamin E isomers and derivatives are widely known for their antioxidant activity. Tocopherols and tocotrienols isomers are found in vegetable oils. Elseways, vitamin E derivatives are synthetic forms obtained from natural isomers. Endogenously, alpha-tocopherol scavanges reactive oxygen species and owed to this effect, the oral supplementation of vitamin E is beneficial to prevent the appearance and progression of diseases. In relation to cutaneous effects, both oral and topical formulations provide a photoprotection against harmful ultraviolet radiation. Moreover, despite tocotrienols potential application in melanoma treatment, their skin effects are not fully understood.

Majority of skin care formulations contain alpha-tocopherol isoform or tocopherol acetate derivative whose effects are mainly due to their scavenging ROS ability. Therefore, the reduction of skin aging, melasma and cancer prevention can be achieved by different vitamin E pathways on the skin. As conventional forms and nanotechnology-based systems bearing vitamin E are useful in skin diseases treatment, their use is essential to skin health promotion and maintenance. Nevertheless, its therapeutic effectiveness is limited. Vitamin E loaded in nanostructured delivery systems can significantly increase antioxidant-based therapy effectiveness. In the future, there will be a need for well-designed controlled trials to support the benefits of nanotechnology-based products containing this vitamin.

Author details

Júlia Scherer Santos*, Guilherme Diniz Tavares and Thaís Nogueira Barradas
Faculty of Pharmacy, Department of Pharmaceutical Sciences, Federal University of Juiz de Fora, Juiz de Fora, Brazil

*Address all correspondence to: julia_scherer_santos@hotmail.com

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