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Review Article

The Epitome of Antioxidants Against UV Photodamage: Vitamin E Use in Skin Protection

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Abstract

Since its discovery, there has been ongoing discourse regarding the physiological significance and therapeutic potential of vitamin E, particularly in combating cell damage caused by free radicals. As a prominent antioxidant in the body, vitamin E plays a crucial role in reducing lipid peroxidation within cell membranes, making it a focal point for researchers in dermatology. The unique cellular functions of vitamin E have been linked to its antitumorigenic and photoprotective properties, garnering attention for its potential efficacy in addressing UV-related skin conditions. This literature review aims to illuminate the efficacy of vitamin E, spanning its topical applications to oral supplementation for the protection against photodamage, through an examination of past research in dermatology. A comprehensive analysis of 44 studies from the PubMed database and ScienceDirect, spanning from 1990 to 2022 and references up to 2024, was conducted to gather insights from clinical trials and investigations focusing on potential therapeutic uses of vitamin E in managing UV-induced skin disorders. This review article includes a diverse range of studies-such as experimental research, randomized controlled trials, clinical studies, and double-blind trials-to comprehensively examine the wide-ranging effects of Vitamin E in protecting against UV-induced photodamage. This includes photodamage, nonmelanoma skin cancer, radiodermatitis, and age-related skin changes.

Keywords: Vitamin E; α-Tocopherol; UV Photodamage; Antiaging; Skin Cancer

Introduction

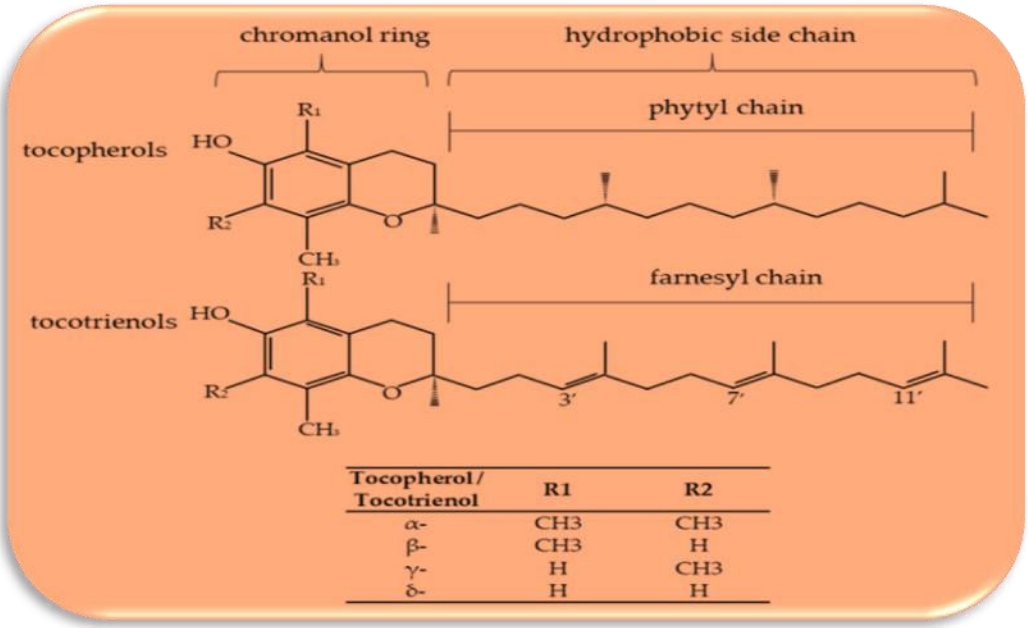
Vitamin E is a term that encompasses a group of fat-soluble compounds discovered by Evans and Bishop in 1922. This group, known as Tocochromanols, includes two main subclasses: Tocopherols with saturated side chains and Tocotrienols with unsaturated side chains [1]. Among these, Tocopherols are the predominant and active form of vitamin E in the human body, with Tocotrienols present to a lesser extent [2]. There are eight naturally occurring forms of vitamin E: alpha, beta, gamma, and delta classes of both Tocopherols and Tocotrienols, which plants synthesize from homogentisic acid. In humans, alpha and gamma Tocopherols are found in the serum and red blood cells, with alpha tocopherol being the most prevalent due to its rapid metabolism and the presence of a specific transfer protein called alpha-tocopherol transfer protein [1]. This protein has a strong binding affinity for alpha-tocopherol, contributing to its higher concentration compared to other tocopherol classes [1].

Physiologic Role of Vitamin E in the Human Body

Vitamin E, across its various forms, acts as a potent antioxidant by neutralizing lipid peroxyl radicals through donating hydrogen from the phenolic group on the chromanol ring [3]. In the context of healthy skin, vitamin E serves as a photoprotective agent, shielding the skin from damage caused by UV radiation [2]. Furthermore, after UV exposure, topical application of vitamin E demonstrates anti-inflammatory effects, reducing skin erythema and edema. Studies conducted with cultured keratinocytes have shown that both α-tocopherol and γ-tocotrienol can diminish inflammatory prostaglandin synthesis, interleukin production, and

the induction of cyclooxygenase-2 and NADPH oxidase triggered by UV light exposure [4][5]. Additionally, they mitigate inflammatory responses to lipid hydroperoxide exposure [6]. The generation of reactive oxygen species has been associated with various diseases such as cancer, aging, arthritis, and cataracts. Given its antioxidant properties, vitamin E presents itself as a promising candidate for addressing chronic conditions linked to free radical generation and reactive oxygen species [1].

Fig. 1 adapted from Tocopherols and Tocotrienols-Bioactive Dietary Compounds; What Is Certain, What Is Doubt? [7].



Tocopherol/ Tocotrienol	R1	R2
α-	CH3	CH3
β-	CH3	H
γ-	H	CH3
δ-	H	H

Figure 1: Tocopherol and Tocotrienol.

Vitamin E in UV Photodamage Protection

UV photodamage is caused by the exposure of UV radiation, which can be sourced from the sun or artificial sources such as tanning beds. This damage can lead to the formation of free radicals, known as Reactive Oxygen Species (ROS), and oxidizing stress which causes changes in the cellular function. UV radiation is classified into three primary types depending on its wavelength of penetration: Ultraviolet A (UVA) (315-40 0nm), Ultraviolet B (UVB) (280-315), Ultraviolet C (UVC) (100-280). Almost all UV radiation reaches the earth, but in this article, we will focus on UVA and UVB as the main types for photodamage.

The photochemical reaction starts when the skin absorbs the UV radiation through a mechanism where the environment is oxygen-rich atmosphere which helps the radiation to be coupled and cause distress on the skin. For photodamage to occur, it needs to be absorbed by chromophores, which is the beginning cascade for photoaging and skin cancer [8]. In this photochemical reaction, DNA changes take place as follows depending on the type of UV light.

UVB is almost entirely absorbed in the first layer of the skin, which is the epidermis, and tends to form changes in one of the DNA strands. These changes are found to be in between the pyrimidine bases, which results in thymine dimers such as pyrimidine or cyclobutene [9]. Thymine dimers are known to produce mutations in DNA and form carcinomas that have been found in tumor suppressor gene p53. An example of the UVB effect can be seen in sunburn conditions or skin erythema, which suggests the reason for the beneficence of sunscreen use to protect the skin cell membrane. In comparison to UVB, UVA is absorbed by the dermal layers of the skin and produces indirect DNA changes. Due to its higher wavelength, UVA is found to be more potent than UVB activity. For example, UVA is prone to cause tumor promotion, whereas UVB causes tumor initiation. UVA tends to form more lipid peroxidation and promotes the synthesis of Matrix Metalloproteinase (MMP). The Results of changes can be best seen in patients with immunosuppression or organ transplantation, who are subject to UVA damage. In addition to UVA indirect damage, photohemolysis can be seen due to erythrocytes being photosensitized by endogenous porphyrins [10].

In skin defense, antioxidants work together harmonically to protect skin integrity from metabolic or cellular changes that occur over time from oxidative stress. Their arrangements are found in the cell according to their molecular weight and their enzymatic activity. Antioxidant enzymes are found in both extracellular and intercellular spaces. However, enzyme activity was predominantly present in the skin epidermis compared to the dermis. These antioxidants are arranged in accordance with their roles in a cell: vitamin E (tocopherol) in the membrane, vitamin c (L-ascorbic acid) in the cytoplasmic fluid phase, glutathione in cellular compartments, and ubiquinol in mitochondria. Vitamin E was known for its protection against lipid peroxidation that was produced by ROS. In addition to its presence in cells, one study shows that vitamin E concentrates with the increase of the depth of stratum corneum [11,12]. Where sebaceous glands are present in the deepest layers of the skin, they show high concentration of vitamin E [13,14].

As an essential nutrient, vitamin E is one of the main antioxidants that protect cells from lipid peroxidation. Vitamin E is known for its skin barrier-stabilizing properties and anti-inflammatory effects [15]. Since there are eight naturally occurring compounds of vitamin E, the main isomer that is commercially used is α-tocopherol. A study has shown that up to 120 molecules were deactivated by one molecule of α-tocopherol [10]. Topical and systemic oral vitamin E use grew in the market due to its biological potency to protect skin against diseases and for maintaining cellular and molecular functions. One of the known uses of vitamin E is for the protection against UV photodamage. Studies have shown both topical and systemic use worked synergistically to give the ultimate protection when given in the right concentration. As in topical use, vitamin E exerts its effects on skin tissues when given in the right amount. After UV exposure, a decrease in vitamin E concentration was noted in numerous studies. To avoid such events, repeated application of topical vitamin E, whether before or after UV exposure, can help reduce the depletion of vitamin E over time. One study shows that when hairless mice were pretreated with 5% tocopherols before UVB exposure, 75% of skin wrinkling and skin carcinogenesis tumors were decreased. Yet, there have been no positive effects towards UVA radiation [16].

Oral vitamin E has shown some significance in use, but no major significant changes were observed [17]. Daily ingestion of 400 IU of oral alpha-tocopherol over a course of six months has shown no significant protection against UV radiation [18]. Another study has shown that when feeding mice different doses of vitamin E, the group with higher vitamin E intake tended to have lower lipid peroxidation and inhibited the suppression of DNA synthesis, yet the difference was not significant compared to the other group. The results of the study suggested that topical use was more effective due to its direct application [19].

Vitamin E in Combination Formulas: Topical Route vs Systemic Route

Oral Vitamin E: Studies have shown formulas containing vitamin E and other antioxidants result in protecting the skin from photodamage. A formulation of vitamin C, vitamin E, B-carotene, lycopene, and carnosic acid in the form of oral supplementation has shown a photoprotective effect, and the formation of oxidative stress from UVA in skin fibroblasts is prevented by vitamin E [20][21]. A combination of a-tocopherol and b-carotene has yielded positive results in decreasing phototoxicity and erythema [22], while others have shown no photoprotection in supplementation [23-25]. A combination of oral intake with vitamin E (2 g) and vitamin C (3 g) has shown a 1.5-fold protection increase against phototoxicity [26]. Others have found that adding melatonin increased the protection and erythemal reaction [27].

Topical Vitamin E: Contrary to oral formulas, a combination of vitamin C, vitamin E, and oxybenzone (UVA sunscreen) resulted in prominent adaptivity for phototoxic damage [28,29]. Other solutions, such as 15% L-ascorbic acid and 1% alpha-tocopherol, have been proven to decrease cellular apoptosis in sunburn cells and provided fourfold protection against UV radiation [30]. While systemic use of vitamin E and vitamin C can reduce sunburn events caused by UV-induced skin reactions [31]. Topical vitamin C, vitamin E, and ferulic acid show improved results in protection from photodamage and DNA mutations against skin cancer [30]. Vitamin E and Q10 have shown to reduce UVB irradiation and an interesting formula for anti-aging, as well as NAC and Vitamin E [32-34].

Vitamin E Sorbate: New Isomer in Commercial Use?

In addition to combination formulas, another form of vitamin E is emerging in terms of its positive use and results compared to tocopherol. A study shows that tocopherol sorbate treatment was found to be highly protective against UV radiation and the formation of free radicals compared to tocopherol. The data later suggests a new emerging sunscreen formula to be seen in commercial use [35]. Another form has been found to have promising results, and that is vitamin E phosphate, which can help

prevent erythema and protect the skin before and after UV exposure [36]. A combination of tocopherol and tocotrienols has been used as a pretreatment, where results suggest no reaction against UV radiation compared to vitamin A [37]. UV filters, along with a combination of vitamin E, vitamin E, and vitamin A, have shown hopeful results for skin irritation that was caused by sun exposure [27]. Furthermore, a study trial was conducted on a new vitamin E prodrug in the isoform of y-tocopherol-glucoside. The outcomes design indicated the long-term use of vitamin E in a slow and prolonged matter for the release of its antioxidant properties [38].

Evolution of Vitamin E in Sunscreen

With its neutralizing and antioxidant properties, vitamin E continues to prove its potential in providing skin protection through its biologic activity [39]. In recent years, numerous companies have promised to provide sunscreens that have UVA and UVB filters in their formulas. Vitamin E acetate is commonly used in commercial cosmetic formulas due to its active form and its viability on human skin [40]. In addition to the quality of vitamin E in preserving the shelf life of the product, it is seen best when applied topically to the epidermis, where the concentration accumulates to 25% on the skin compared to when taken orally [41]. Their effect on the cell membrane with proliferation can further provide moisture and stability to the integrity of the intercellular lipids in the stratum corneum [41].

In 1997, an experiment was done to show a rising form of vitamin E: α-tocopherol, which was proven to be ahead of the most commonly used form of tocopherol acetate in sunscreens with the characteristic of preventing UVB photocarcinogenesis in mouse skin [42]. In addition to the α-tocopherol form, hydrogel formulas containing vitamin E are on the rise in their use against UV radiation, especially post-sunbath. In contrast, vitamin E lipogels are suitable for local use, such as in anti-aging cosmetic products [43].

Vitamin E in Skin Cancer

Skin cancer is one of the most common cancers diagnosed worldwide, with statistics showing more than 1.5 million cases reported in 2020 [44]. One of the most common causes of skin cancer is UV radiation, which leads to the development of melanoma, basal cell carcinoma, and squamous cell carcinoma. With the characteristic of vitamin E in its antioxidant activity and its fat solubility in their structure, it has been known for providing neutrality to oxidative stress, DNA damage, and maintenance of the cellular membrane integrity of the tissues [45]. Moreover, reviews and studies are on the rise for vitamin E benefits against skin cancer, which sheds light on hope for treating the disease.

UV induced Skin Cancer

Numerous studies have investigated the effectiveness of vitamin E on UV-induced skin cancer, from its topical use to oral supplementation. One study experimented on ninety-two hairless female mice by applying vitamin E lotion with its different isomers (α-tocopherol (Eol), α-tocopherol succinate (Esuc) lotion, and oral α-tocopherol acetate (Eac)) before the exposure of UV light. Results have shown Eol was the most protective with 75% and no blisters were formed, Esuc was less protective with 33%, and oral Eac resulted in 25% [46]. However, another study used forty hairless mice to experiment with the different results of topically applying vitamin E versus vitamin E topical formulations with vitamin C and ferulic acid (C-E FERULIC) and UVB vehicles. Mice treated with vitamin E demonstrated an increase in multiplicity compared to vehicle with 14.9% and tumor growth with 16.6%. C E Ferulic has resulted in more promising results [47]. In addition to UV-induced skin tumors, a study about chemical-induced skin tumors presented with a regress of tumors with vitamin E supplementation [48]. Furthermore, more experimental studies are needed specifically for diverse types of tumors to determine the effectiveness of vitamin E use.

Non-melanoma Skin Cancer

Non-melanoma skin cancer (NMSC) is a type of skin cancer that is caused by the epidermis of the skin rather than the melanocyte. NMSC is divided into two groups: basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). With it being the most common reported type of skin cancer around the globe, bcc is the most common skin cancer case that has been reported. BCC is commonly caused by sunlight exposure to the epidermis of the skin, and fair skin and age can be two of the common risks.

Epidemiology statistics reveal the important protective effects of antioxidants, including vitamin E, vitamin C, vitamin A, and b-carotene. Vitamin A has shown results in treating skin malignancies. While b-carotene has also shown results of protection from skin cancer, Vitamin E is known as an inhibitor of skin tumor initiation. Through topical application, vitamin E has shown

immunosuppression in UV-induced skin damage as well as a reduction in the formation of skin cancer [49]. Retinoids, or vitamin A, have been demonstrated to be favored in treating skin cancer. However, adding vitamin E can provide protection from vitamin A nonenzymatic destruction and enhance the results further for the treatment [49]. A case-control study has shown the levels of vitamin A, vitamin E, selenium, and carotene had no significant difference among the citizens of Seattle and NMSC patients, as well as melanoma patients [50]. In contrast to diet-uptake serum levels, a study has shown a reduction in tumor yield of up to 30% as well as a reduction in skin blistering in mice that are supplemented with vitamin E [51]. Other studies have found vitamin E to act as a pro-oxidant when treating BCC and have also found positive results when treating other epithelial tumors [51,52]. Further studies should be made on the other isomers of vitamin E to prove their efficiency in skin cancer treatment.

Palmar-plantar Erythrodysesthesia and Vitamin E Treatment

Hand foot syndrome, or Palmar-Plantar Erythrodysesthesia (PPE), is skin condition that is caused as a side effect of chemotherapy in breast cancer patients. A study, one of its kind, shows the use of 300 mg/d of vitamin E without reducing the chemotherapeutic dosage in six clinical cases. The results were promising, as most of the patients demonstrated that their skin lesions disappeared between a week and ten days of use. Despite this, further studies are needed to understand the effect of vitamin E on PPE [53].

Radiodermatitis

Radiation Dermatitis is a skin condition and a common side effect of exposure to radiation therapy. Patients experience erythema, dryness, pain, edema, and pruritus. A study demonstrated the use of vitamin E with nanoparticle cream versus a cream with lipid nanoparticles (without vitamin E) and a group without nanoparticles or vitamin E cream. Patients undergoing radiotherapy saw an insignificant difference in effectiveness. However, a protective effect was seen for the vitamin E nano-encapsulated group during the onset of radiodermatitis [54].

Antiaging Savior: Vitamin E

From the destruction of collagen and elastin to the loss of skin elasticity and integrity [55]. Aging is a natural, gradual process that starts in early adulthood and includes a combination of environmental, genetic, and lifestyle factors that contribute to its activity. Aging characteristics share sagging of the skin, dryness, wrinkles, and fine lines. One of the external causes where the antioxidant interest comes into play is sun exposure, pollution, smoking, and poor nutrition.

Two profound phenomena that have been found to contribute to aging are glycation and oxidation. Glycation is an ideal concept to study when discussing aging physiology. It is found in various aging processes, including cataracts, decreased myocardial contractility, and diabetes. It is formed in the process of glucose binding to proteins and lipids in two ways: endogenous and exogenous. Endogenous forms occur when proteins bind to red blood cells in the bloodstream. While exogenous foods tend to form AGE-advanced glycation end products when consuming foods that contain high glucose or fructose, AGEs are by-products of this reaction, and they are known for their stability and their difficulty in being eradicated from the body. Through this process, glycation can crosslink with collagen and elastin, which can make it difficult to recover the normal physiologic change. In contrast to foods containing glucose, newly formed self-tanning creams have been found to contain dihydroxyacetone, which contains sugar that crosslinks proteins in the stratum corneum [56]. However, one of the ways to avoid such events is to engage in a low-glucose diet and avoid tanning in all its forms to protect the skin from aging.

The oxidation process is the second phenomenon, where oxygen tends to form oxidative free radicals when metabolized by tissues. This is where antioxidants such as vitamin E and vitamin C come into play in protecting the skin from antiaging, where the function of the antioxidants can be complemented by enzymatic and non-enzymatic systems [56]. The primary antioxidant is vitamin E, and it is considered the most important antioxidant. It has been known that the generic pathway of aging is through protein kinase C, which is heavily affected by vitamin E [56]. Vitamin E functions in protecting the cell membrane from lipid chain reactions or damage from phospholipase A, lysophospholipids, and free fatty acids [57]. In addition to its function, vitamin E works perfectly with vitamin C as a secondary antioxidant to provide its full potential. Vitamin C helps to regenerate vitamin E from free radicals, as it can be depleted in the process [57].

Vitamin E is commonly found to be higher in regions of the body with more sebum production, such as the forehead or the face region, compared to the rest of the human body [55]. The use of vitamin E against anti-aging can be done by topically applying

sunscreen, since it has proven its efficiency in protecting the skin from UV radiation and its by-products of free radicals [58]. Sunscreen with vitamin E does not necessarily mean it decreases antiaging, but it can help maintain the presence of vitamin E on skin by preventing the formation of photoproducts that can lead to photoaging. The combination of vitamin E, vitamin C, and selenium, when applied topically, has been found to provide strong reverification of photodamage to the skin and improve photoaged skin [59].

The Future and Challenges of Vitamin E From UV Photodamage

Vitamin E is widely recognized with its potential as an antioxidant against UV induced skin damage. However, certain challenges were raised during clinical trials of its application. As in Vitamin E alone, it has shown to be unstable and has higher degradation when not combined with another antioxidant [26]. In addition to instability, its efficacy has been proven poor when delivered as a monotherapy without its combination to another antioxidant such as Vitamin C or ferulic acid [23,29,30,37]. Regarding inconsistent results, further studies should be conducted to understand Vitamin E formulation in UV photodamage protection [26].

In Vitamin E topical formulation, challenges arise in terms of its delivery and penetration to the skin. Vitamin E can degrade under UV radiation when delivered alone, which reduces its effectiveness [27,29]. Multiple studies have suggested various approaches in Vitamin E delivery to preserve its metabolic stability as well as its penetration in the skin. One study has found prodrug approach has improved Vitamin E topical bio efficacy and stability [38]. Through nanoparticle delivery systems, Vitamin E controlled release formulations as well as oxidative degradation effectiveness against UV photodamage proved possibility of the usage of Vitamin E in sunscreens [41]. Another study pointed how the base of the topical formulation can control the potential antioxidants effects of Vitamin E when used as in lipogels are more stable in delivery to skin compared to hydrogels [43]. Through encapsulation and controlled release of Vitamin E approach, results are better enhanced as Vitamin E alone is one of the challenging antioxidants to stabilize and deliver topically [59].

In contrast to topical formulation stability, oral supplementation requires further studies as it's exposed to multiple factors that need to be addressed in clinical trials to recommend the most effective dosage for skin diseases. Challenges range from its absorption, isoforms, forms of delivery, and older patients' physiological absorption. In terms of absorption and isoforms, a study conducted has shown that α-tocopherol has been selectively retained by liver and the other forms of Vitamin E (γ, δ) are excreted more rapidly, which affects overall bioavailability [5,8,10]. A study has shown that Vitamin E coupled with dietary fat shows better efficacy in bioavailability when compared to used alone [6]. Certain skin diseases have shown to favor topical applications when compared to the effectiveness against oral supplementation [55]. Supplementation formulation is also important to impact the release of Vitamin E effectiveness such as in emulsified forms as it enhances its oral bioavailability [39]. Older patients' physiological absorption plays a role in the absorbance of Vitamin E and tissue distribution, which further raises questions in oral dosage supplementation appropriate for patient need [34].

The future of vitamin E in managing UV-induced photodamage appears promising, particularly due to the advances in formulation science and continuous understanding of its synergistic role with other antioxidants. Research is growing to focus on enhancing stability, penetration, and targeted delivery of vitamin E through nanoencapsulation, liposomal systems, and esterified derivatives like tocopheryl acetate and phosphate. These innovations aim to overcome current limitations in topical application, such as degradation and limited bioavailability. With the current shift towards multi-antioxidants formulation, combining vitamin E with other compounds like vitamin C, ferulic acid, and coenzyme Q10 has shown greater efficacy in photoprotection. Oral supplementation continues to be explored, though future directions may emphasize personalized nutrition that affects absorption and metabolism. Additionally, emerging evidence on the distinct roles of tocotrienols and non-α isoforms may pave the way for broader-spectrum vitamin E interventions. With increasing interest in photoaging and skin cancer, the development of more sophisticated delivery platforms and integrated antioxidant strategies will likely define the future of vitamin E-based skin protection.

Conclusion

Despite a century of research on vitamin E, there remains a need for more comprehensive information to effectively combat UV-induced skin damage. While numerous studies have been conducted, many skin conditions have not yet been thoroughly assessed for their responsiveness to vitamin E. Leveraging technology and combining vitamin E with other antioxidants can

enhance its efficacy. However, there is a lack of controlled clinical trials establishing precise dosages and clinical applications for oral and topical vitamin E, despite advancements in formulations for cosmetic and skin care products. The future of vitamin E utilization holds promise, especially in the realm of UV photodamage. Innovations like nanotechnology and new gauze materials offer opportunities for enhanced delivery and efficacy. Yet, further research is necessary to understand vitamin E's mechanisms of action in various skin diseases and optimize dosage regimens. Given its affordability, more studies are needed to be carried out to explore vitamin E's potential as a preventative measure or adjunct treatment for UV-induced skin damage. In essence, while initially discovered in food, vitamin E continues to be a rich area for exploration and development across medical disciplines.

Conflicts of Interest

The author declares no conflict of interest in this paper.

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