PROSPECTS
IN PHARMACEUTICAL SCIENCES

Prospects in Pharmaceutical Sciences, 22(3), 76-80
https://prospects.wum.edu.pl/

Review

VITAMIN E: OVERVIEW OF HISTORY OF DISCOVERY, MECHANISM OF ACTION, ROLE AND DEFICIENCY

Aleksandra Kowalska[1]

[1] *Department of Organic and Physical Chemistry, Faculty of Pharmacy, Medical University of Warsaw, 02-097 Warsaw, Poland.*

Correspondence, e-mail: aleksandra.kowalska@student.wum.edu.pl

Received: 25.07.2024 / Accepted: 25.07.2024 / Published: 05.08.2024

ABSTRACT

Vitamin E, a collective term for tocopherols and tocotrienols, is vital for numerous biological functions, particularly due to its antioxidant properties. Tocopherols and tocotrienols share a common structure but differ in their side chains, influencing their bioactivities. Despite extensive research highlighting the potential in treating neurodegenerative diseases, cardiovascular disorders, and cancer, the clinical application of vitamin E is often limited by its poor bioavailability. Dietary sources of vitamin E include vegetable oils, nuts, seeds, and certain animal products, with α-tocopherol being the most abundant form in plasma. High doses of vitamin E can interact with medications like aspirin and warfarin, necessitating medical supervision. Deficiency in vitamin E, particularly in children, can lead to significant health issues, emphasizing the importance of adequate intake. This review explores the chemical properties, historical discovery, bioavailability, dietary sources, recommended intakes, and biological activities of vitamin E, highlighting its therapeutic potential and the challenges in its application.

KEYWORDS: vitamin E, tocopherol, tocotrienol

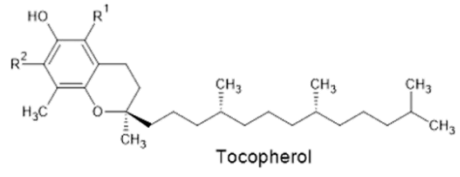
1. Introduction

Vitamin E, a group of fat-soluble compounds with potent antioxidant properties, plays a crucial role in human health and disease prevention. First discovered in 1922 by Evans and Bishop, vitamin E has since been the subject of extensive research due to its diverse biological functions. This essential nutrient, obtained exclusively from dietary sources, is primarily composed of two classes of molecules: tocopherols and tocotrienols [1]. As a key component of the body's antioxidant defense system, vitamin E protects cell membranes and other fat-soluble parts from free radical damage. Its antioxidative properties have been linked to potential benefits in various health conditions, including cardiovascular diseases, cancer, and neurodegenerative disorders [2].

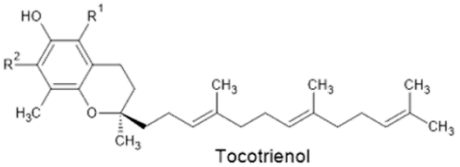
This paper aims to provide a comprehensive overview of the current understanding of vitamin E's role in human health, its potential therapeutic applications, and the challenges in translating research findings into clinical practice.

2. Chemical Structure

Tocopherol refers specifically to the methyl-substituted derivatives of tocol and should not be used interchangeably with the term 'vitamin E'. Tocochromanols are composed of two similar series: tocopherols, which have a fully saturated side chain, and tocotrienols, which have an unsaturated side chain.



Tocopherol



Tocotrienol

	R1	R2
α-	$-CH_3$	$-CH_3$
β-	$-CH_3$	-H
γ-	-H	$-CH_3$
δ-	-H	-H

Fig 1. Chemical structures of tocopherols and tocotrienols

Tocopherols and tocotrienols share a common chemical structure, characterized by a lengthy isoprenoid side chain connected at the 2 position of a 6-chromanol ring [1]. Tocotrienols are distinct from tocopherols because they have a farnesyl side chain instead of a saturated isoprenoid C16 side chain. Tocopherols found in nature exist in the RRR-configuration, whereas the synthesized version consists of eight distinct stereoisomers and is referred to be all-rac-α-tocopherol. Tocotrienols have a single chiral stereocenter at C-2, and naturally occurring tocotrienols only have the 2R,3'E,7'E configuration [3].

3. History of Discovery

The discovery of vitamin E occurred in 1922 by Herbert McLean Evans and Katharine Scott Bishop at the University of California, Berkeley. During the investigation of rat fertility, researchers made a significant finding that identified a crucial fat-soluble component necessary for healthy pregnancies [4]. In 1931, Olcott and Mattill were the first to elucidate the antioxidant role of vitamin E, which has since been acknowledged as its primary and crucial biological activity [5]. In 1936, α-tocopherol was initially separated and the term tocopherol was proposed to Evans by George M. Calhoun, a Greek professor at the University of California, where Evans and his colleagues were employed. The term was derived from the Greek terms *tokos*, which refers to progeny, and *phero*, which means to bear [6].

4. Bioavailability and Pharmacokinetics

According to European Medicines Agency's terms, bioavailability is the extent to which an active ingredient is absorbed from a medicine and becomes available in the body. Unfortunately, despite the promising results of in vitro and in vivo studies of applications in treatment of various diseases, the use of vitamin E may be limited due to its poor bioavailability. Those limitations are caused mainly by the parameters of solubility, absorption, distribution and rate of elimination.

As vitamin E belongs to lipid-soluble group of vitamins, its absorption highly depends on dietary fat in food and body, bile salts and pancreatic enzymes. When taken orally, vitamin E is incorporated into chylomicrons, a large lipoproteins high in triglycerides that are made mostly of cholesterol and fatty acids, in the intestines and travels through lymph nodes to reach the circulation. Vitamin E can travel to the liver or tissues after it is enclosed in chylomicrons. Lipids and vitamin E are transferred to tissues through the hydrolysis of chylomicrons by lipoprotein lipase enzymes in the bloodstream [7].

According to recent studies, when tocotrienols were supplemented orally, it took three to four hours to reach the peak plasma concentration (T_{max}), whereas tocopherol reached its T_{max} about six hours after a meal. The results of these investigations also showed that, in comparison to tocotrienols, α-tocopherol had a significantly higher peak plasma concentration (C_{max}) (1.82–2.92 μM for α-tocopherol and 0.89–1.92 μM for tocotrienols). The elimination half-life ($t_{1/2}$) of α-tocopherol in humans was found to be roughly 20 hours; however, the $t_{1/2}$ varied between 2.3 and 4.4 hours for different tocotrienol isomers. For this reason, it is typically advised to take tocotrienols supplements twice a day in order to maintain their bioactive levels [8].

5. Metabolism of vitamin E

Over the past two decades, significant progress has been made in comprehending the metabolism of vitamin E and discovering novel activities of its metabolites. It is now understood that vitamin E forms are metabolized through ω-hydroxylation to produce 13'-OH and 13'-COOH. The 13'-COOH is then broken down through ß-oxidation into different carboxychromanols, including the final metabolite CEHCs and conjugated carboxychromanols. CYP4F2 has been identified as the primary enzyme responsible for starting the metabolism of different forms of vitamin E by ω-hydroxylation [9]. Research conducted on CYP4f14 mutant mice has shown that the process of ω-hydroxylase-initiated metabolism is accountable for more than 70% of the production of ω-series metabolites of vitamin E [10]. Furthermore, molecular and animal investigations have elucidated the biological activities and specific targets of 13'-COOHs. Specifically, 13′-COOHs act as inhibitors of both COX-1 and COX-2 enzymes, as well as 5-LOX enzyme, resulting in anti-inflammatory actions. 13′-COOHs exhibit anticancer properties, influence the buildup of lipids within cells, and stimulate nuclear receptors such as PPARs and PXR [11]. These receptors are recognized for their role in regulating lipid and drug metabolism, respectively [12].

Metabolites and their predecessors exhibit distinct actions. For example, 13′-COOHs have the ability to block the activity of COXs and 5-LOX, while tocopherols do not have a direct inhibitory effect on 5-LOX or COX-2. Tocotrienols, specifically δTE and γTE, have been found to hinder the activation of nuclear factor (NF)-κB and seem to be more potent than δTE-13′-COOH in impeding the proliferation of cancer cells [13].

6. Sources of vitamin E

The primary dietary sources of α-tocopherol consist of vegetable oils, fat spreads derived from vegetable oils, nuts and seeds, some fatty fish, egg yolk, and whole grain cereals. The relative amounts of the four tocopherols differ depending on the food source, with α-tocopherol and γ-tocopherol being the most abundant. Vegetable oils range in their levels of various tocopherol forms. Wheat germ, sunflower, olive, and rapeseed oils are rich in α-tocopherol. Wheat germ oil has ß-tocopherol, while soybean, maize, and rapeseed oils include γ-tocopherol. Soybean oil is a source of δ-tocopherol [14].

7. Recommended intakes

The Dietary Reference Intakes (DRIs) created by the Food and Nutrition Board (FNB) at the Institute of Medicine of The National Academies provide guidelines for the intake of vitamin E and other nutrients. DRI, or Dietary Reference Intake, is a comprehensive phrase that refers to a collection of benchmark values utilized to determine and evaluate the recommended nutrient consumption for individuals in good health. The numbers, which differ based on age and gender, encompass the Recommended

Dietary Allowance (RDA), Adequate Intake (AI), Estimated Average Requirement (EAR), and Tolerable Upper Intake Level (UL). The FNB's recommendations for vitamin E pertain specifically to α-tocopherol, which is the sole form of vitamin E found in plasma. The FNB derived these recommendations mostly from serum levels of the nutrient that offer sufficient defense in a test assessing the viability of red blood cells when exposed to hydrogen peroxide, a reactive oxygen species. The naturally occurring form of vitamin E is known as RRR-α-tocopherol (often labeled as d-α-tocopherol), while the artificially generated version is called all rac-α-tocopherol (usually labeled as dl-α-tocopherol) [15].

The Recommended Daily Allowances (RDAs) for vitamin E are expressed in milligrams (mg) and may be found in Table 1. One milligram of vitamin E (α-tocopherol) is equal to one milligram of RRR-α-tocopherol or two milligrams of all rac-α-tocopherol.

Table 1. Recommended Dietary Allowances (RDAs) for Vitamin E (α-Tocopherol). Based on Medicine, I.o., Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. 2000, Washington, DC: The National Academies Press. 528.

Age	Males	Females	Pregnancy	Lactation
0-6 months	4 mg	4 mg		
7-12 months	5 mg	5 mg		
1-3 years	6 mg	6 mg		
4-8 years	7 mg	7 mg		
9-13 years	11 mg	11 mg		
14+ years	15 mg	15 mg	15 mg	19 mg

8. Biological properties of vitamin E

Vitamin E is being commonly known for its antioxidant properties. As antioxidant activity is facilitated by the hydroxyl group on the chromanol ring, which readily donates a hydrogen atom to reduce free radicals, both tocopherols and tocotrienols are potent antioxidants. They have the ability to scavenge free radicals and reactive oxygen species (ROS) [16].

Apart from its antioxidant qualities, vitamin E also has anti-inflammatory properties and therefore researchers are very interested in examining vitamin E's medicinal potential for the prevention and treatment of several diseases because of these characteristics.

Vitamin E's neuroprotective effects were proven in clinical trials of multiple neurological maladies such as traumatic brain injury, Alzheimer's disease and Parkinson's disease.

- In people with serious head injuries (n = 100), a randomised double-blind controlled experiment found that intramuscular injection of vitamin E (400 IU/day) significantly reduced mortality when compared to the groups receiving vitamin C and a placebo [17].

- Vitamin E was observed to slow down the advancement of Alzheimer's disease in animal models by blocking the activation of the p38 signaling pathway, which stops tau hyperphosphorylation caused by amyloid beta (Aß) [18].

- In another study it was proven that supplementation (200 mg/kg) could lower the high levels of DNA damage. All of these findings point to the possibility of using vitamin E as an alternate AD treatment [19].

- In the meantime, dietary consumption of vitamin E and ß-carotene was linked to a lower risk of Parkinson's disease, according to a two-population cohort research [20].

The potential of vitamin E, particularly tocotrienols, to prevent metabolic syndrome and cardiovascular diseases (CVDs) has also been extensively researched [21].

- Proinflammatory cytokine release, body weight, liver weight, insulin and fat content, and elevated fasting blood glucose in obese mice fed a high-fat diet were all markedly reduced when γ-tocotrienol (50 mg/kg) was supplemented [22].

- Researchers found that TRF supplementation (200 mg/kg/day) strengthened vascular walls and decreased oxidative stress and fasting blood glucose in diabetic rats [23].

- In an animal model of atherosclerosis, vitamin E treatment (100 mg/kg) significantly lessened atherosclerotic plaques, however only at the early stages [24].

Moreover, vitamin E is frequently utilized in dermatology due to its antioxidant and UV radiation protection properties, which offer photoprotection and postpone the aging of the skin [25].

Vitamin E has anti-cancer qualities that show promise for use in cancer treatments. These properties include inhibiting the growth of cancer cells, blocking angiogenesis, modifying growth factors, encouraging cell cycle arrest, and causing apoptosis. Multiple in vitro investigations involving diverse cell lines (breast, lung, liver, pancreas, skin, and bladder malignancies) have reported these unique features of tocotrienols [26].

- Past studies have shown that δ-tocotrienol (200 mg/kg) greatly improved the effectiveness of gemcitabine in preventing the growth and survival of pancreatic cancer both in vitro and in vivo by suppressing NF-kB activity [27].

- A different study using mouse melanoma xenografts revealed that treatment with 100 mg/kg of δ-tocotrienol significantly decreased the tumour volume and postponed the tumour's progression [28].

By stimulating bone production and osteoblast (bone-forming cell) activity as well as inhibiting osteoclasts (cells mediating the bone resorption process), vitamin E, especially tocotrienols, is helpful in enhancing bone strength [29].

- In an animal model of post-menopausal osteoporosis, a study applying a combined therapy of lovastatin (750 µg/kg) and annatto-derived tocotrienols (60 mg/kg) revealed that the treatment caused higher bone volume, decreased eroded surface, decreased osteoclast surface, and increased osteoblast surface as compared to the untreated group [30].

- Using the same animal model, a different study showed that TRF supplementation (60 mg/kg) decreased lipid peroxidation during the early stages of fracture healing by lowering the amounts of free radicals that cause the delayed healing process [31].

Tocotrienols are also very beneficial for conditions like osteoarthritis and rheumatoid arthritis that cause inflammation-mediated bone loss.

- It was demonstrated in an animal model of osteoarthritis that supplementing with 100 mg/kg of tocotrienol produced from annatto reduced cartilage breakdown, which may stop the disease from progressing [32].

9. Interactions with medical products

Many individuals frequently consume Vitamin E as a dietary supplement, operating on the belief that it may have beneficial effects on their health without causing any harm. Nevertheless, the ingestion of high-dose vitamin E supplements can potentially cause interactions with the medications aspirin, warfarin, tamoxifen, and cyclosporine A, potentially modifying their effects. Patients administered with these medications should ask for advice from their doctor and undergo drug efficacy testing if they desire to take vitamin E supplements. In most cases, medications do not interact with vitamin E, even when taken in large quantities, and no such interactions have been reported [33].

10. Vitamin E deficiency

Vitamin E deficiency (VED), which is more prevalent in children, is hardly discussed in the literature. Adequate consumption of Vitamin E is crucial for the proper functioning of this key nutrient within the body. Serum α-tocopherol is commonly employed as a biochemical marker to evaluate the prevalence of VED. Vitamin E deficiency (VED) is linked to symptoms caused by the inability to absorb fat properly, which can result in peripheral neuropathy and an increase in the breakdown of red blood cells. The decreased levels of α-tocopherol can be attributed to the combination of vitamin E-deficient diets and insufficient intake of fats, proteins, and calories. Asia had the lowest occurrence of VED, whereas North America and Brazil had the highest incidence. The prevalence of VED indicates that this nutritional insufficiency is a significant public health issue in children and has received limited attention in the worldwide scientific literature [34].

The results of a study indicate that a lack of Vitamin E alters various networks of gene expression in zebrafish embryos. These networks include energy metabolism, oxidoreductase activity, intra- and intercellular communication, and developmental transcriptional control. This disruption occurs throughout important developmental periods [35].

11. Summary

Vitamin E, encompassing tocopherols and tocotrienols, is a crucial nutrient with diverse health benefits and significant therapeutic potential. Despite promising research, its efficacy can be hampered by poor bioavailability, often requiring dietary fat for optimal absorption. Tocopherols, found predominantly in vegetable oils, nuts, seeds, and some animal products, are essential for antioxidant defense and anti-inflammatory actions. Tocotrienols, while structurally similar, exhibit unique bioactivities, especially in neuroprotection, cardiovascular health, and cancer prevention. However, high doses of vitamin E may interact with certain medications, underscoring the importance of medical guidance. Deficiency in vitamin E, particularly in children, remains a public health concern due to its impact on neurological and cellular health, highlighting the need for adequate intake through diet or supplementation.

Conflicts of Interest: The author declare no conflict of interest.

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