

CHAPTER 1

Vitamin E: Structure, Properties and Functions

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1.1 Introduction

In 1922, Evans and Bishop demonstrated the existence of a hitherto unrecognized dietary factor essential for normal reproduction in the rat.¹ It was accepted at that time that the most striking function of vitamin E was to provide a normal gestation in a pregnant rat to prevent the resorption of the embryos which invariably occurred in its absence.² This unknown dietary factor X was found to be present in green lettuce, dried alfalfa leaves, wheat, and oats. Evans isolated the factor X from wheat germ oil, provided the chemical formula $C_{29}H_{50}O_2$ and proposed the name α -tocopherol in 1936.³ The structural formula for α -tocopherol was provided by Fernholz in 1938.⁴ Tocotrienols were discovered much later than tocopherol and named in the early 1960s.^{5,6}

Olcott found that the lipid fractions of vegetable oils contained antioxidants against the oxidative deterioration of lard.⁷ Since then, it has been unequivocally demonstrated that vitamin E acts as an essential antioxidant

in vivo as well as *in vitro* and plays an important role in the prevention of detrimental oxidative damage of biological molecules.^{8–11} More recently, the non-antioxidant functions of vitamin E, including cellular signaling, gene regulation, membrane processes, and nerve functions, have also received much attention.^{12–14} However, many issues are still controversial and remain to be elucidated. Sound information based on solid chemical evidence is essential for understanding the role of vitamin E *in vivo* as well as *in vitro*.

1.2 Homologues: Nomenclature and Structure

Vitamin E is a plant-derived, lipid-soluble substance whose molecular structure is comprised of a chromanol ring with a side chain located at the C2 position. Vitamin E refers to a group of eight different compounds: α -, β -, γ -, and δ -tocopherols and the corresponding four tocotrienols. The four tocopherols have a saturated phytyl side chain, while tocotrienols have an unsaturated isoprenyl side chain containing three double bonds at C3', C7', and C11'. The double bonds of tocotrienols' side chains at C3' and C7' have a *trans*-configuration. The α -, β -, γ -, and δ -forms differ with respect to the number and position of methyl groups on the chromanol ring. The α -forms of tocopherol and tocotrienol have three methyl groups at the C5, C7, and C8-positions of the chromanol ring, while the β - and γ -forms have two and the δ -forms have one methyl group as illustrated in Figure 1.1.

In addition to tocopherols and tocotrienols, tocomonoenols and tocodi-enols containing a single and two double bond unsaturation, respectively,

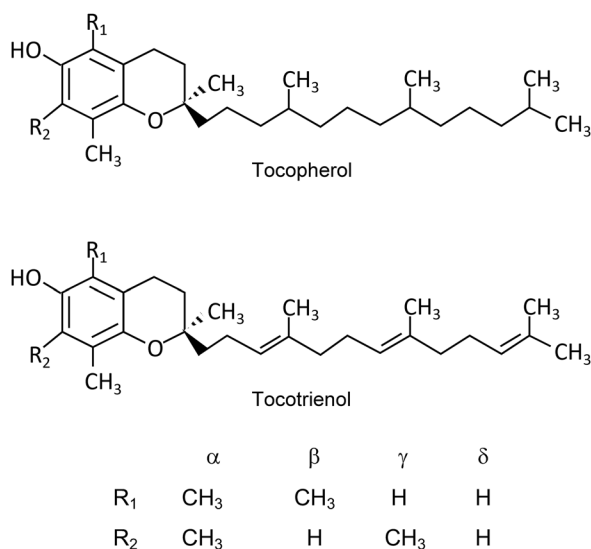


Figure 1.1 Chemical structure of vitamin E homologues.

have also been found in nature. For example, a tocomonoenol with a single double bond at carbon 11', 2,5,7,8-tetramethyl-2-(4',8',12'-trimethyltrideca-11'-enyl)-6-chromanol, was isolated from palm and rice bran oils.¹⁵ Since then, several groups have detected tocomonoenols in plants and plant foods, such as α -tocomonoenol in palm oil,^{16–22} pumpkin seed oil (*Cucurbita pepo* L.),²³ and sunflower oil (*Helianthus annuus*),²⁴ γ -tocomonoenol in pumpkin seed oil,^{22,23} δ -tocomonoenol in kiwi (*Actinidia chinensis*),²⁵ and β -, γ -, and δ -tocomonoenol in the leaves of *Kalanchoe daigremontiana* and *Phaseolus coccineus*.²⁶ A tocomonoenol with an unsaturation at the isoprenoid-chain terminus was also found in the tissues of salmon.²⁷ Furthermore, tocodienols with two double bonds at carbon 7' and 11' were identified in palm oil.^{16,21}

Tocopherols contain three chiral carbons, one at C2 in the chromanol ring and two in the side chain at C4' and C8'. Naturally occurring α -tocopherol contains chiral carbons in the *R*-conformation, 2*R*, 4'*R*, and 8'*R*- α -tocopherol. α -Tocotrienol has one chiral center at C2 in the chromanol ring and natural tocotrienols occur as the *R*-isoform. On the other hand, the chemical synthesis of α -tocopherol produces an equimolar mixture of eight different stereoisomers: *RRR*, *SRR*, *RSR*, *RRS*, *RSS*, *SSR*, *SRS*, and *SSS*. The synthetic α -tocopherol is called all-rac- α -tocopherol. An equimolar mixture of *RRR*- α -tocopherol and *SRR*- α -tocopherol is called 2-ambo- α -tocopherol. The IUPAC names of *RRR*- α -tocopherol and *RRR*- α -tocotrienol are (2*R*)-2,5,7,8-tetramethyl-2-[(4*R*,8*R*)-(4,8,12-trimethyltridecyl)]chroman-6-ol and (2*R*)-2,5,7,8-tetramethyl-2-[(3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trienyl]-3,4-dihydrochromen-6-ol, respectively.

Ester forms of tocopherol and tocotrienols, including acetate, nicotinate, succinate, and phosphate, have been prepared and their action and potential applications have been studied. Vitamin E is easily oxidized when subjected to heat, light, and alkaline conditions, but esters are less susceptible to oxidation and therefore more appropriate for food, cosmetic, and pharmaceutical applications compared to the free form. Polyethylene glycol conjugates of tocopherols and tocotrienols have the ability to form miscible micelles in water due to amphiphilic properties and enhance bioavailability in animals and humans *via* improving their water solubility and absorption.²⁸ It was reported that *RRR*- α -tocopheryl polyethylene glycol 1000 succinate acted as a safe and effective form of vitamin E for reversing or preventing vitamin E deficiency during chronic childhood cholestasis.²⁹

1.3 Physicochemical Properties

The tocopherols are viscous oils at room temperature, insoluble in water but soluble in ethanol and aprotic solvents. Vitamin E is a slightly yellow to amber, nearly odorless, clear, viscous oil, which darkens on exposure to air or light by oxidation. The physicochemical properties of α -tocopherol, the most abundant and active form of vitamin E in humans, are summarized in

Table 1.1 Physicochemical properties of α -tocopherol.

IUPAC name	(2 <i>R</i>)-2,5,7,8-Tetramethyl-2-[(4 <i>R</i> ,8 <i>R</i>)-4,8,12-trimethyltridecyl]-3,4-dihydrochromen-6-ol
Molecular formula	C ₂₉ H ₅₀ O ₂
Molecular weight	430.7 g mol ⁻¹
Physical description	Slightly yellow to amber, nearly odorless, clear, viscous oil
Melting point	3 °C
Boiling point	235 °C
Solubility	Insoluble in water (1.9 × 10 ⁻⁶ mg L ⁻¹ at 25 °C), soluble in ethanol
Density	0.950 g cm ⁻³ at 25 °C
Partition coefficient	log <i>P</i> = 12.2
Stability	Unstable to UV light, alkaline, and oxidation
Dissociation constant	p <i>K</i> _a = 10.8
UV absorption maximum	292 nm in ethanol
Fluorescence	Excitation 290–295 nm, emission 320–335 nm
BDE (O–H) ^a	77.1 kcal mol ⁻¹

^aBond dissociation energy.³¹

Table 1.1.³⁰ The melting point of *RRR*- α -tocopherol is 3 °C. The optical rotations of tocopherols are very small and depend on the nature of the solvent. The ultraviolet absorption spectra of tocopherols and tocotrienols in ethanol show an absorption maximum at 292–298 nm, while the infrared spectra show OH (2.8 ± 3.0 μ m) and CH (3.4 ± 3.5 μ m) stretching and a characteristic band at 8.6 μ m. α -Tocopherol is fluorescent with an emission maximum about 325 nm in a hydrophobic solution. The bond dissociation energy of α -tocopherol's O–H bond is 77.1 kcal mol⁻¹.³¹ The p*K*_a values for α -, β -, γ -, and δ -tocopherol in a micellar solution were reported as 13.1, 12.8, 12.7, and 12.6 respectively.³²

The partition coefficient of α -tocopherol is 12.2, while that for ascorbic acid is -1.85,³⁰ showing their lipophilic and hydrophilic characters, respectively.

1.4 Sources

Numerous foods provide vitamin E. Seeds and fruits are among the best sources of vitamin E. Green leafy vegetables are also important sources. Only plants and photosynthetic organisms are able to synthesize vitamin E.^{33,34} The synthesis is facilitated by enzymes to produce stereospecific tocopherols: *RRR*-tocopherols.³⁵ Tocopherols and tocotrienols can be extracted and purified or concentrated from vegetable oils and other higher plant materials. Dietary supplements are another source of vitamin E. Most vitamin E supplements contain substantially higher amounts of vitamin E than foods. Vitamin E in dietary supplements and fortified foods is often esterified to prolong its shelf life while protecting its antioxidant properties.

Table 1.2 The contents of tocopherols (T) and tocotrienols (T3) in representative edible oils. Adapted from ref. 36–41.^a

Oil	α T	β T	γ T	δ T	α T3	β T3	γ T3	δ T3
Corn	18–25	1	44–75	2–3	1	0	1–2	<1
Olive	11–17	<1	1	<1	<1	<1	<1	<1
Palm	6–42	<1	<1	<1	5–26	<1	11–36	3–8
Rapeseed	18–24	<1	37–51	<1	0	0	0	0
Rice bran	1–15	0–2	0–8	0–2	0–13	0–2	1–23	0–2
Soybean	9–12	1	61–69	23–26	0	0	0	0
Sunflower	32–59	0–2	1–4	<1	<1	0	0	0
Wheat germ	151–192	31–65	0–52	<1	2–3	0–8	0–1	<1

^aIn mg per 100 g oil. Major components are shown in bold.

The contents and composition of tocopherols and tocotrienols in natural oils vary markedly between the plant species and even within the same species. Tocopherols are widely distributed in higher plants, whereas tocotrienols occur only in some non-photosynthetic tissues. Some examples of the contents in natural edible oils adopted from several reports^{36–41} are shown in Table 1.2. α -Tocopherol is the major tocopherol in palm, olive, and sunflower oils, whereas the contents of γ -tocopherol in some edible oils such as corn, rapeseed, and soybean oils are higher than α -tocopherol.

The major sources of tocotrienols are palm, rice, and annatto, the ratio of tocopherol–tocotrienol in each being 25 : 75, 50 : 50, and 0.1 : 99.9, respectively.⁴² Palm oil contains considerable amounts of α -, γ -, and δ -tocotrienols. γ -Tocotrienol is the major vitamin E isoform in the oil extracted from rice bran^{39,43} while β -tocopherol is one of the major isoforms found in wheat germ oil.^{36,37} Interestingly, the lipid fraction of annatto (*Bixa orellana* L.) seeds contained only tocotrienols, mainly δ -tocotrienol, but no tocopherols.⁴⁴

1.5 Chemical Synthesis

Due to wide applications in the pharmaceutical, food, and cosmetic industries, about 35 000 tons of vitamin E is manufactured per year worldwide.⁴⁵ All-racemic- α -tocopherol, all-rac- α -tocopherol, an equimolar mixture of all eight stereoisomers, is industrially the most important product and is prepared either by total synthesis or originates from natural sources. It is mainly applied as an acetate ester. The industrial synthesis consists of three major parts: the preparation of 2,3,5-trimethylhydroquinone, the production of the side chain component, and the condensation reaction.⁴⁵

Pure *RRR*- α -tocopherol is chemically prepared by semi-synthesis. Vegetable oils refined on a large scale and isolated by a combination of several separation methods contain mixtures of *RRR*-tocopherols, which are converted to *RRR*- α -tocopherol by permethylation reactions. The efforts and strategies to synthesize tocopherols and tocotrienols have been described in detail.⁴⁵

1.6 Analysis

Natural products contain mixtures of isomeric tocopherols and tocotrienols together with minor amounts of tocomonoenols and tocodienols. They are metabolized and oxidized to produce many kinds of compounds. The biological samples contain complicated mixtures of vitamin E isoforms and their metabolites and oxidation products. The identification and quantitation of vitamin E isoforms and their products are important for elucidating their role and functions. Sample preparation is the most time-consuming and important step in analysis, because it is the main source of errors. Many analytical methods including colorimetric, fluorometric, gas chromatographic (GC), high performance liquid chromatographic (HPLC),⁴⁶ GC-MS,⁴⁷ and HPLC-MS^{47,48} have been reported (see also Chapter 2). Concerning public documents for the quantitative determination method of vitamin E in active pharmaceutical ingredients, United States and European Pharmacopeia adopt the GC method, while Japanese Pharmacopeia adopts the HPLC method. Each of these methods has its merits and demerits. At the present time, HPLC methods are the most widely applied.

HPLC conditions for vitamin E analysis have been summarized in several reviews.^{46,47,49,50} Vitamin E and products are obtained from natural products, food matrices, and biological samples by direct extraction, solid-phase extraction, and saponification. Care should be taken to avoid artifactual oxidation and decomposition during preparation of samples and analysis. The use of electrochemical (amperometric), fluorometric (Ex. 290–295 nm, Em. 320–330 nm), or MS detection is much more sensitive and specific than the conventional UV detection. Tocol, 2-methyl-2-(4,8,12-trimethyltridecyl)-6-chromanol, may be the best compound to use as an internal standard because its characteristics are similar to vitamin E. Deuterium-labelled α -tocopherol acetate is commonly used as a standard in MS analysis. In most vitamin E analyses, atmospheric pressure chemical ionization (APCI) is used in the positive ionization mode. It may be noted that supercritical-fluid chromatography using CO₂ and ethanol as a mobile phase, NH₂ as a stationary phase, and mass spectrometry for the detection and quantification of vitamin E homologues has been proposed as a “greener” analytical strategy.^{51,52}

1.7 Functions and Applications

Vitamin E is a physiologically essential micronutrient and has been applied in various fields including medicine, pharmaceuticals, cosmetics, and foods. Vitamin E is assumed to play an important role in the promotion of health and prevention and/or treatment of some diseases and disorders. The daily recommended intake is 15 mg (22.4 IU, International Unit) for adults [<https://ods.od.nih.gov/factsheets/VitaminE-HealthProfessional/>].

Multiple functions of vitamin E have been demonstrated or proposed, including (1) antioxidant by scavenging free radicals, especially peroxy radicals, and singlet oxygen, (2) membrane stabilization by forming complexes

with destabilizing molecules so as to prevent disturbance of the amphipathic balance within the structure, (3) physiological regulator of enzyme activity, cellular signaling, cell proliferation, and gene expression, which is not directly related to antioxidant action, (4) inhibition of platelet coagulation, (5) prevention of diseases including neurological disorders, cardiovascular diseases, age-related eye and skin damage, and infertility, and (6) biocompatible modifier of biomaterials and medical devices, for example in high molecular weight polyethylene used in hip and knee implants. It has been argued that tocotrienols possess additional positive health effects beyond those of tocopherols including, for example, induction of immune responses and lowering of serum cholesterol levels.^{53–55}

Among these functions, the role of vitamin E as an antioxidant against free radical-mediated lipid peroxidation has been unequivocally demonstrated and it appears that this is the most important physiological function of this vitamin. Vitamin E also inhibits air oxidation of foods, oils, and industrial materials to extend their lifetime. The physiological significance of other functions that are not related to antioxidant function must be established in a future study.

Vitamin E is widely used as a dietary supplement, by itself or together with other micronutrients such as vitamin C, to promote health and to reduce the risk of or prevent diseases that are assumed to arise from detrimental oxidative modification of biological molecules. Vitamin E is used to fortify some foods and beverages.

Deficiency of vitamin E is uncommon as typical diets appear to provide sufficient amounts, although malnutrition and genetic disorders may result in vitamin E deficiency. Premature babies of very low birth weight might be deficient in vitamin E. Further, people with fat-malabsorption disorders⁵⁶ and inherited disorders in which the liver's α -tocopherol transfer protein (α -TTP) is defective or absent⁵⁷ or there are decreased levels of selenoproteins⁵⁸ are more likely to become vitamin E deficient and require high doses of supplemental vitamin E.

The potential role of vitamin E against periodontal disease,⁵⁹ nonalcoholic steatohepatitis,⁶⁰ and sarcopenia⁶¹ has received attention. Insufficient micronutrient intake (vitamins and phosphorus) was significantly associated with severity of periodontal disease.⁶² A systematic review showed significant improvement of periodontal parameters by vitamin E and lycopene.⁶³ Vitamin E may mitigate age-associated skeletal dysfunction and enhance muscle regeneration, thus attenuating sarcopenia.⁶⁴

Vitamin E is also used for biomedical materials. α -Tocopherol is blended to a dialysis membrane for clinical management of chronic hemodialysis patients to improve stability and functions.⁶⁵ Vitamin E-blended ultra-high molecular weight polyethylene (UHMWPE) has been developed as a material for use in total knee and hip replacements.⁶⁶ α -Tocopherol is accepted to improve oxidation resistance while maintaining wear resistance and fatigue strength.

The poor water solubility of vitamin E has greatly limited its application. Investigations to improve both oral and topical encapsulation and formulations of vitamin E have been widely carried out and various delivery systems

for vitamin E have been developed to overcome this problem and to enhance solubility, permeation, and bioavailability. Liposomes,⁶⁷ nano-emulsions, and lipid nanoparticles⁶⁸ are some examples.⁶⁹ The tocopheryl ester of polyethylene glycol and tocopheryl phosphate are water soluble. Polyethylene conjugates of tocotrienols have also been studied.²⁸

Dietary polyphenols such as quercetin are converted to glucoside and/or sulfate derivatives, or their *O*-methyl derivatives, during absorption into the body, and presents as these conjugated metabolites in circulating blood. Formation of the metabolites of tocopherol such as glucoside, sulfate, and *O*-methyl derivatives *in vivo* has not been reported but α -tocopherol glucoside was synthesized from 2-hydroxymethyl-2,5,7,8-tetramethylchroman-6-ol and maltose by transglycosylation with α -glucosidase from *Saccharomyces* species.⁷⁰ The glycosylated product, 2-(α -D-glucopyranosyl)methyl-2,5,7,8-tetramethylchroman-6-ol, is water soluble and acts as a radical scavenging antioxidant.^{70,71} δ -Tocopherol glucoside was prepared and its effects during its topical application on skin were studied.⁷²

One important question is whether or not each vitamin E isoform exerts its own specific function which is not shared with other isoforms. It has been argued that tocotrienol exerts some functions that tocopherol does not, and that tocopherol interferes with such tocotrienol functions.⁴² These important issues must be clarified in future studies.

1.8 Stability

Vitamin E is stable at ambient temperature, but it is readily oxidized at high temperature, under light or in an alkaline medium. Frying is one of the most common methods of food preparation and during the frying process, usually between 160–190 °C, vitamin E is oxidized to give complicated mixtures of products including tocored (5,6-tocopheryldione) and dimers that are assumed to be formed by a recombination of tocopheroxyl radicals. α -Tocopherol is oxidized to α -tocopheroxyl radical by transition metal ions such as ferric ions (Fe^{3+}) and cupric ions (Cu^{2+}).

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