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Vitamin E_{xcellent}

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Abbreviations

α-$TO^{\bullet}$, α-Tocopherol radical
$AscH^{-}$, Ascorbate
DHAsc, Dehydroascorbate
GSH, Glutathione
GSSG, Glutathione disulfide.
H, Hydrogen
$LOO^{\bullet}$, Lipid peroxyl radicals
Me, Methyl group
$^1O_2$, Singlet oxygen

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I. Abstract

Vitamin E is an important antioxidant that protects cells from free radical damage. Alpha-tocopherol is the major lipid-soluble, chain-breaking antioxidant, protecting mammalian membranes and lipoproteins from damage. Evidence suggests that an adequate intake of vitamin E prevents or minimizes free-radical damage associated with specific diseases and might promote the function of the immune system. This paper will focus on the main features of vitamin E and its role as an antioxidant compound.

II. Introduction

Biological antioxidants are natural molecules that can prevent the uncontrolled formation of free radicals and reactive oxygen species, or inhibit their reactions with biological structures. Antioxidants work in several ways: they may reduce the energy of the free radical, stop the free

radical from forming in the first place, or interrupt an oxidizing chain reaction to minimize the damage of free radicals [3].

Vitamin E, was discovered by Evans and Bishop in 1922 as a micronutrient essential for reproduction in rats [1]. It was rediscovered in the 1950s as factor 2 by Klaus Schwarz and placed in the context of cellular antioxidant systems together with sulfur amino acids (factor 1) and selenium (factor 3)[2]. Because α-tocopherol is the form of vitamin E that appears to have the greatest nutritional significance, it will be the primary topic of the following discussion.

III. Types of antioxidants

Antioxidants are either chemical traps for oxidizing free radicals and reactive oxygen species, or physical quenchers of excited species like singlet oxygen and triplet states of photosensitizers.

Hydrophilic scavengers are found in cytosolic, mitochondrial and nuclear aqueous compartments. Among these, ascorbate and glutathione are the most important free radical scavengers and their intracellular concentrations are typically between 1 and 10 mM [4].

Hydrophobic scavengers are found in lipoproteins and membranes, where they either interrupt the propagation step of lipid peroxidation by destroying peroxyl radicals $ROO^{\bullet}$, or block the formation of hydroperoxides from singlet oxygen $^1O_2$. These include vitamin E, carotenoids, and possibly ubiquinol, the reduced form of coenzyme Q [5].

IV. Structure and forms of vitamin E

The term vitamin E describes a family of eight antioxidants, four tocopherols, alpha (α), beta (β), gamma (γ) and delta (δ), and four tocotrienols (also α, β, γ, and δ). Alpha -tocopherol is the

only form of vitamin E that is actively maintained in the human body and is therefore, the form of vitamin E found in the largest quantities in the blood and tissue (Figure 1) [6].

a) Tocol

The term tocol is the trivial designation for 2-methyl-2-(4,8,12-trimethyltridecyl)chroman-6-ol (Figure 1, $R^1 = R^2 = R^3 = H$).

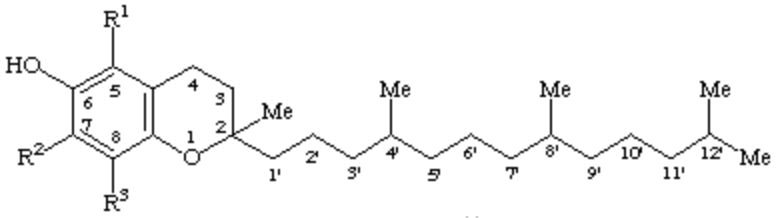

Figure 1 shows the basic structure of tocol. Different R groups designate different tocopherols (Adapted from [6]).

b) Tocopherol(s)

The term tocopherol(s) should be used as a generic descriptor for all mono, di, and trimethyltocols. Thus, this term is not synonymous with the term vitamin E.

b.1. α-tocopherol, or 5,7,8-trimethyltocol (Figure 1, $R^1 = R^2 = R^3 = Me$).

b.2. β-tocopherol, or 5,8-dimethyltocol (Figure 1, $R^1 = R^3 = Me$; $R^2 = H$).

b.3. γ-tocopherol, or 7,8-dimethyltocol (Figure 1, $R^1 = H$; $R^2 = R^3 = Me$).

b.4. δ-tocopherol, or 8-methyltocol (Figure 1, $R^1 = R^2 = H$; $R^3 = Me$).

The only naturally occurring stereoisomer of α-tocopherol has the configuration 2*R*,4'*R*,8'*R* according to the sequence-rule system (Figure 2) [6].

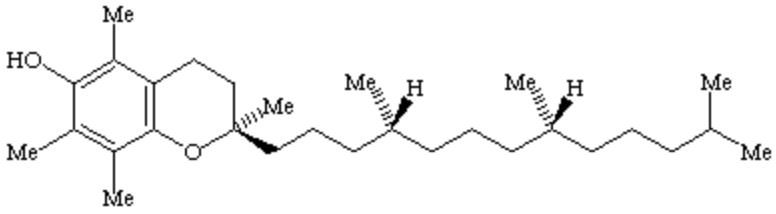

Figure 2 Naturally occurring sterioisomer of α-tocopherol (Adapted from [6]).

c) Tocotrienols

Tocotrienols have three double bonds in the hydrophobic side chain. Side chain nomenclature is the same as for tocopherols. The compound shown in figure 3 is the basic structure of tocotrienols or 2-methyl-2-(4,8,12-trimethyltrideca-3,7,11-trienyl)chroman-6-ol. Only the *all-trans* (*E*,*E*)-tocotrienol has been found occurring in nature.

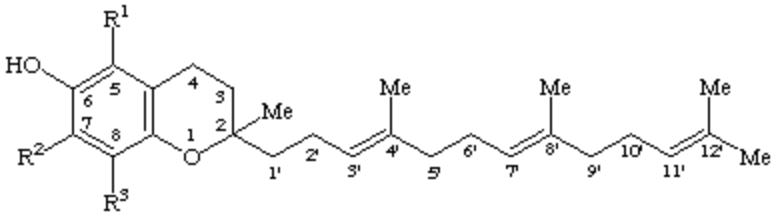

Figure 3 the structure of tocotrienol. ($R^1 = R^2 = R^3 =$ H), 2-methyl-2-(4,8,12-trimethyltrideca-3,7,11-trienyl)chroman-6-ol.

V. a **-Tocopherol- peroxyl radical interaction**

Alpha-tocopherol and tocotrienols are efficient scavengers of peroxyl radicals in phospholipid bilayers. It scavenges lipid peroxyl radicals $LOO^{\bullet}$ through hydrogen atom transfer (eq.1). The α-$TO^{\bullet}$ radical might also react with a further peroxyl radical to give non radical products (eq.2), *i.e.* one molecule of α-tocopherol is capable of terminating two peroxidation chains [7].

$$\alpha\text{-TOH} + LOO^{\bullet} \longrightarrow \alpha\text{-}TO^{\bullet} + LOOH \qquad (1)$$

$$LOO^{\bullet} + \alpha\text{-}TO^{\bullet} \longrightarrow \alpha\text{-TocOOL} \qquad (2)$$

Tocopherols and tocotrienols scavenge lipid peroxyl radicals much faster (k is about 10^6 $M^{-1}s^{-1}$) than these radicals can react with adjacent fatty acid side-chains (k is about 10^2 $M^{-1}s^{-1}$) or with membrane proteins.

Ham and Liebler (1997), induced lipid peroxidation in rat livers using *tert*-butylhdroperoxide and described the reaction product of α-tocopherol with peroxyl radicals as shown in Figure 4.

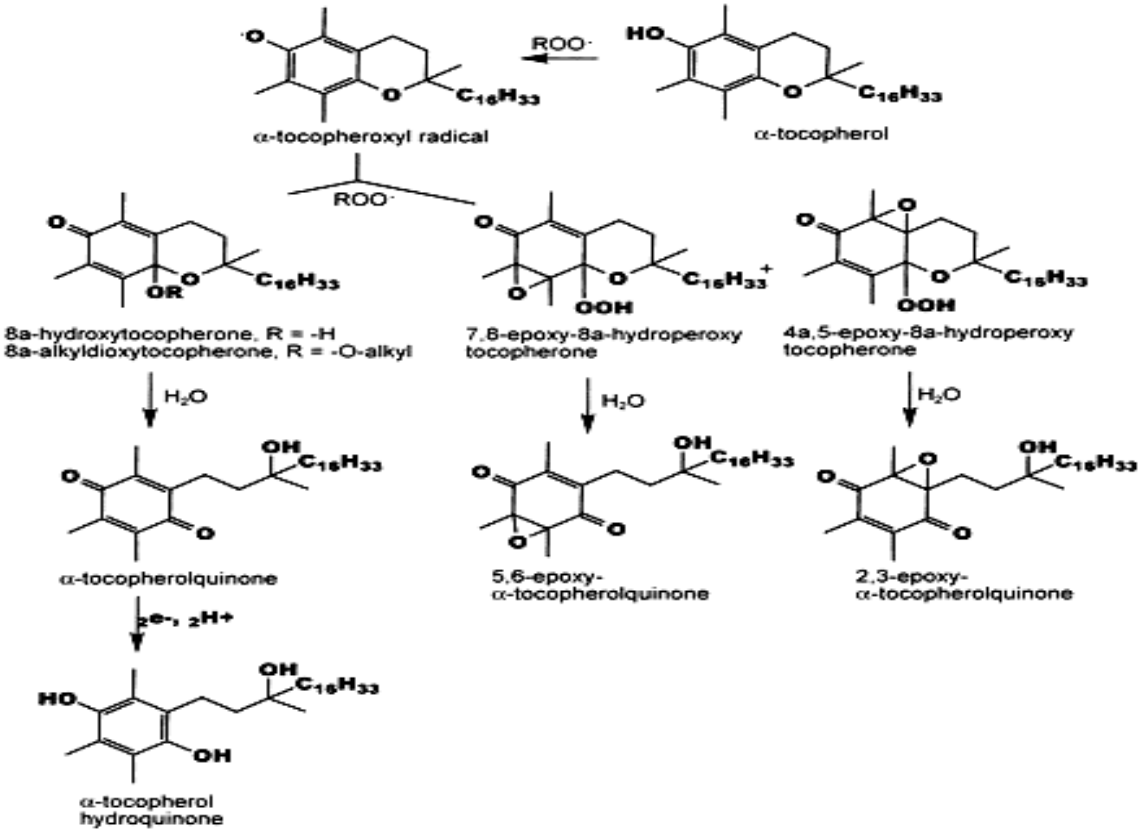

Figure 4
Reactions of α-tocopherol with peroxyl radicals. α-tocopherolquinone is a key intermediate. See text for more details (Adapted from [8]).

Tocopheryl radicals may be recycled to tocopherol or can undergo further oxidation by a series of mechanisms. All 8a-substituted tocopherones eventually hydrolyze to α-tocopherolquinone via the intermediate 8a-hydroxytocopherone, which also maybe formed by electron transfer from the tocopheroxyl radical to a peroxyl radical or by disproportionation of tocopheroxyl radicals. One of key product of lipid peroxidation is α-tocopherolquinone (Figure 4). Traces of α-tocopherolquinone are found in animal (including human) tissues. It is metabolized by reduction to hydroquinone which itself can exert antioxidant properties and can

be conjugated with glucuronic acid and excreted in bile or degraded in the kidneys to α-tocopheronic acid, followed by conjugation and excretion in urine [8].

VI. Vitamin E and human diseases

Interest in the use of antioxidants for the treatment of human disease, and in the role of dietary antioxidants in the prevention of disease development, has been sustained for at least two decades. In 1996, the Cambridge Heart Antioxidant Study (CHAOS) reported that in over 2000 patients with angiographically proven coronary atherosclerosis that vitamin E supplementation (400–800 IU/day) for slightly under 2 years significantly (P<0.005) reduced the incidence of cardiovascular death and nonfatal myocardial infarction by 77% (9). Also, it was shown that severe vitamin E deficiency leads to neuromuscular abnormalities characterized by spinocerebellar ataxia. The peripheral neuropathy likely occurs due to free radical damage to the nerves and a dying back of the sensory neurons [10]. Alpha-tocopherol has been shown to enhance specific aspects of the immune response that appear to decline as people age. For example, 200 mg of synthetic α-tocopherol (equivalent to 100 mg of RRR-α-tocopherol) daily for several months increased the formation of antibodies in response to hepatitis B vaccine and tetanus vaccine in elderly adults [12]. These observational studies have suggested that supplemental α-tocopherol might have value in the treatment of some diseases.

VII. Vitamin E is excellent antioxidant

One of the main features of a good antioxidant is its ability to be renewed. The regeneration of α-tocopherol in membranes is coupled to vitamin C and glutathione (GSH). The enzyme glutaredoxin regenerates ascorbate ($AscH^-$) from dehydroascorbate (DHAsc) at the expense of GSH. The phenoxyl radicals α-$TO^\bullet$ that are produced on reaction of α-TOH with

lipid peroxyl radicals $LOO^{\bullet}$ are efficiently scavenged by ascorbate at the water/membrane interface (Figure 5) [7].

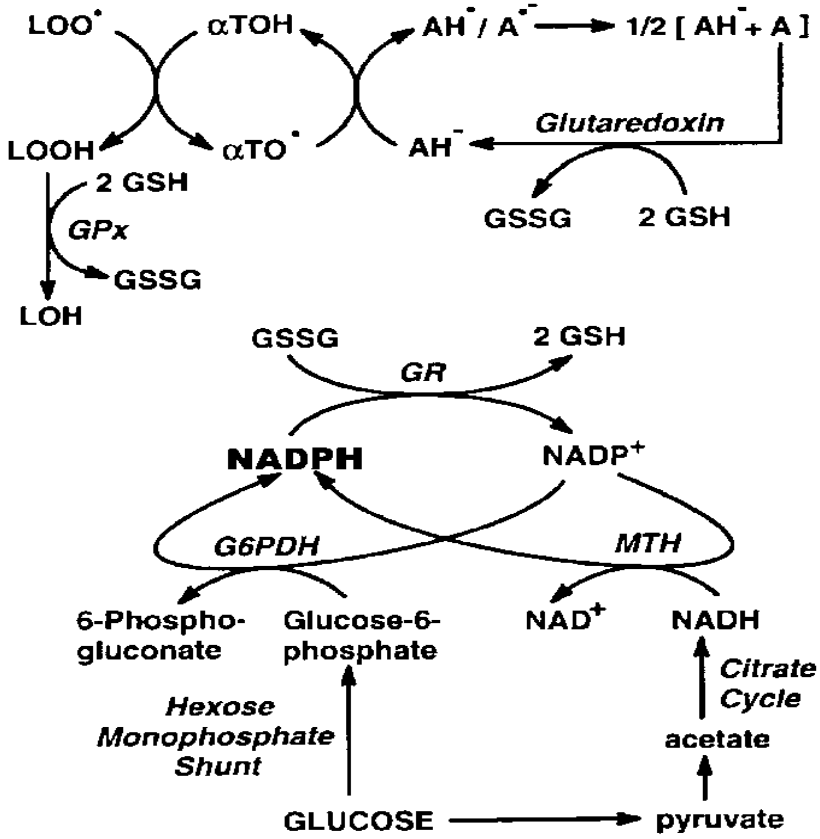

Figure 5 Co-operative interaction of vitamin E, vitamin C, GSH and glutathione peroxidase. The phenoxyl radical α-$TO^{\bullet}$ produced upon scavenging of lipid peroxyl radicals $LOO^{\bullet}$ is reduced back to α-tocopherol by ascorbate at the membrane/water interface. Hydroperoxide degradation by phospholipid hydroperoxide glutathione peroxidase or another glutathione peroxidase, and ascorbate regeneration by glutaredoxin both produce GSSG, which is reduced back to GSH by NADPH-dependent glutathione reductase (Adapted from [7]).

VIII. Assays of vitamin E

Various laboratory techniques have been used to assess vitamin E status in humans and animals including gas chromatography-mass spectroscopy (GC-MS) and high-performance liquid chromatography (HPLC). HPLC was described by many authors as a method of measuring vitamin E in plasma, platelets and erythrocytes. Figure 6 shows an example of HPLC chromatogram, where α-tocopherol acetate was used as an internal standard. The level of α-tocopherol in the plasma of normal adults was found to be 8.66 μg/ml compared to 6.03 μg/ml and 2.18 μg/ml for both platelets and erythrocytes respectively [11].

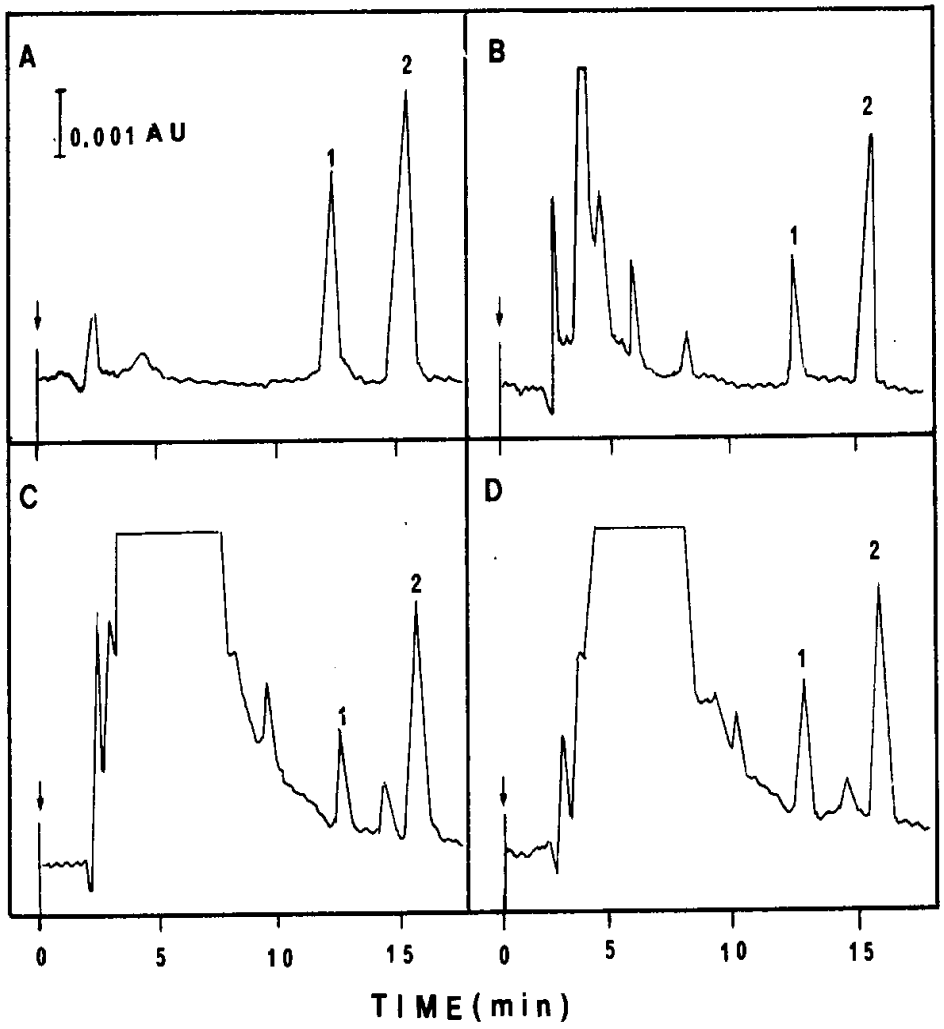

Figure 6 HPLC chromatograms of standard mixture (A), plasma (B), platelet (C), and erythrocyte (D) extracts. Peaks: 1=α-tocopherol, 2= α-tocopherol acetate, AU=Absorbance unit. (Adapted from [11]).

IX. Summary

In summary, vitamin E is the term for a group of tocopherols and tocotrienols, of which α-tocopherol has the highest biological activity. Different studies showed that vitamin E is likely to provide protection from heart disease. The regeneration of α-tocopherol in membranes is coupled to vitamin C and glutathione (GSH). The important role and great features of vitamin E can now justify the title of this report “Vitamin Excellent”.

X. References

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