Advances in Antioxidant Activity of Vitamin E

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ABSTRACT:

Vitamin E (α-tocopherol) is now well accepted as nature's most effective lipid-soluble, chain breaking antioxidant, protecting cell membranes from peroxidative damage. Free-radical mediated pathology has been implicated in the development of degenerative diseases and conditions. Vitamin E has a protective role in preventing or minimizing free-radical damage associated with specific diseases and processes, including cancer, aging, circulatory conditions, arthritis, cataract, pollution and strenuous exercise. Research evidence suggests that an adequate intake of vitamin E can provide protection from the increasing high free-radical concentrations caused by air pollutants and current lifestyle patterns. Topical application of a combination of vitamin E and C has been suggested as a protective measure against UV-induced skin damage.

INTRODUCTION

The major function of vitamin E (α-tocopherol) is that of a lipid-soluble antioxidant. Its deficiency symptoms depend on the vitamin content, uptake and turnover as well as susceptibility to and the degree of oxidative stress in a given tissue. Vitamin E concentrations depend on the presence of other antioxidants to maintain the levels of α-tocopherol in its unoxidized state. It is vital for healthy cell structure, for slowing the effects of aging process on cells, and for maintaining the activities of certain enzymes. Specific vitamin-E deficiency symptoms (e.g. fetal resorption, muscular dystrophy and encephalomalacia) have been observed in experimental animals fed with vitamin-E deficient diets. Vitamin E therapeutic indications include the clinical conditions characterized by low serum tocopherol levels and increased fragility of red blood cells to hydrogen peroxide. The biochemical, hematological and clinical aspects of vitamin E have been discussed in detail.

LITERATURE REVIEW

Antioxidant chemistry of Tocopherols

Several tocopherols (α-, β-, γ-, δ-) have been isolated which possess 4′, 8′, 12′ trimethyltridecyl-saturated side chain or have an unsaturated side chain attached to a chromanol nucleus. The polyunsaturated tocopherols have been termed as "tocolochrols". The tocopherols are diterpenoid natural products biosynthesized from a combination of four isoprenoid units. The most well known of the tocopherols is α-tocopherol, which possesses the greatest biological or antioxidant activity. In 2000, the Food and Nutrition Board (FNB) defined α-tocopherol as the only form that meets human E requirements because only α-tocopherol has been shown to reverse human vitamin E deficiency symptoms. Vitamin E supplements often contain α-tocopherol esters, including α-tocopheryl acetate, or succinate. The ester form of α-tocopherol is not an antioxidant and thus has a long shelf life. Vitamin E esters are readily hydrolyzed in the gut and are absorbed as α-tocopherol.

α-Tocopherol is an unstable compound and its oxidation by air results in the formation of an epoxide which then produces a quinone that is inactive. It is destroyed fairly rapidly by sunlight and artificial light containing the wavelengths in the UV region. All vitamin E forms act as lipid-soluble chain-breaking antioxidants. Vitamin E is a potent peroxyl radical scavenger and especially protects phospholipids of biological membranes and plasma lipoproteins. When lipid hydroperoxides are oxidized to peroxo radicals (ROO•), these react 1000 times...
faster with vitamin E (Vit E-OH) than with (RH). The chromanol hydroxyl group reacts with a peroxyl radical to form a hydroperoxide and the chromanoxyl radical (Vit E-O•):

\[ \text{ROO}^- + \text{Vit E-OH} \rightarrow \text{ROO}^+ \text{Vit E-O}^- \]  

In the presence of vitamin E,

\[ \text{ROO}^- + \text{Vit E-OH} \rightarrow \text{ROOH} + \text{Vit E-O}^- \]  

(1)

In the absence of vitamin E,

\[ \text{ROO}^- + \text{RH} \rightarrow \text{ROOH} + \text{R}^- \]  

\[ \text{R}^- + \text{O}_2 \rightarrow \text{ROO}^- \]  

(2)

(3)

In this manner, vitamin E acts as a chain-breaking antioxidant and prevents further autooxidation of lipids.

Vitamin E interacts with other antioxidants to remain in the unoxidized form. The chromanoxyl radical, Vit E-O•, reacts with vitamin C (or other reductants serving as hydrogen donors, AH), oxidizing the other antioxidant and reducing vitamin E which is the biologically active form.

\[ \text{Vit E-O}^- + \text{AH} \rightarrow \text{Vit E-OH} + \text{A}^- \]  

(4)

Biologically important antioxidants that regenerate chromanols (Vitamin E compounds) from chromanoxyl radicals include ascorbate (vitamin C) and thiols, especially glutathione. The other antioxidants are then reduced by various metabolic processes. Thus by recycling vitamin E is restored by other antioxidants. Since the α-tocopheroxyl radical can readily be reduced to α-tocophenol, the amount of recycled vitamin is likely to be much larger than the amount that is further oxidized.

The eminent vitamin biochemist R. J. Williams has emphasized that "Lipid peroxidation, the formation of harmful peroxides, from the interaction between oxygen and highly unsaturated fats (polyunsaturates) needs to be controlled in the body. Both oxygen and the polyunsaturated lipids are essential to our existence, but if the protection against peroxidation is inadequate serious damage to various body proteins may result. Vitamin E is thought to be the leading agent for the prevention of peroxidation and the free radical production. Providing plenty of vitamin E and ascorbic acid, both harmless antioxidants, is indicated as a possible means of preventing premature aging, especially if one's diet is rich in polyunsaturated acids".

Antioxidant Activity of Tocopherols

Vitamin E is now well accepted as nature's most effective lipid-soluble, chain-breaking antioxidant, protecting cell membranes from peroxidative damage. Free-radical mediated patholgy has been implicated in the development of degenerative diseases and conditions. Packer\textsuperscript{15} has reviewed the protective role and requirements of vitamin E and the other antioxidants in preventing or minimizing free-radical damage associated with specific diseases and lifestyle patterns and processes, including cancer, aging, circulatory conditions, arthritis, cataract, pollution and strenuous exercise. Research evidence suggests that an adequate intake of vitamin E and the other antioxidants (e.g. vitamin C) can provide protection from the increasing high free-radical concentrations caused by air pollutants and current lifestyle patterns.

The bioactivities of RRR-α-, β-, γ-, and δ-tocopherols (T) and R-α-tocotrienol (Rα-TT) have been determined in rat resorption-gestation tests. The ranking order was RRR-α-T > RRR-β-T > RRR-γ-T > R-α-TT > RRR-δ. Quantities of immunoglobulin G (IgG) in plasma of α-tocopherol depleted rats were reduced upon supplementation with the vitamin from palm-oil residue. The phenolic hydroxyl group of the chromanol moiety of vitamin E can transfer the hydrogen to free radicals formed randomly or by metabolic processes during lipid peroxidation. The tocopherol radical is apparently reconverted to tocopherol by vitamin C. Thus vitamin E protects lipids in membranes, proteins such as enzymes and DNA by acting as a free-radical scavenging, chain-breaking antioxidant\textsuperscript{16}.

Among the various antioxidants with vitamin E activity, only α-tocopherol is preferentially recognized by the α-tocopherol transfer protein (α-TTP) and is transferred to plasma. Hepatic α-TTP is required to maintain plasma and tissue α-tocopherol concentrations to regulate its antioxidant activity\textsuperscript{17}. It has been shown that α-tocopherol regulates key events in the cellular pathogenesis of atherosclerosis. The inhibition of protein kinase (PKC) activity by α-tocopherol is the basis of the vascular smooth muscle cell growth inhibition by the vitamin\textsuperscript{18}. The biological
activity of various natural vitamin E forms\textsuperscript{19,20} is reported in Table 1.

**DISCUSSION**

In the light of the literature reviewed above it is evident that α-tocopherol is the most biologically active form and possesses greatest antioxidant activity. It has been stated that the antioxidant and anti-inflammatory properties of α-tocopherol produce potential beneficial effects with regard to cardiovascular disease. Its supplementation in human subjects and animal models has been shown to decrease lipid peroxidation and superoxide (O\textsubscript{2}\textsuperscript{-}) production by impairing the assembly of nicotinamide adenine dinucleotide phosphate (reduced form) oxidase as well as by decreasing the expression of scavenger receptors (SR-A and CD 36), particularly important in the formation of foam cells\textsuperscript{21}. α-Tocopherol supplementation at high doses decreases C-reactive protein (CRP) and release of proinflammatory cytokine, the Chemokine IL-8 and PAT-1 levels and has implications in the prevention of cardiovascular disease\textsuperscript{22}.

The order of antioxidant effectiveness of low concentrations of vitamin E analogues, in preventing cumene hydroperoxide-induced hepatocyte lipid peroxidation and cytotoxicity was 2,2,5,7,8-pentamethyl-6-hydroxychromane (PMC) > troglitazone > Trolox C > α-tocopherol > γ-tocopherol > δ-tocopherol. Mathematical equations have been derived for three-parameter quantitative structure-activity relationships (QSARs), which describe the correlation between antioxidant and prooxidant activity of vitamin E analogues and their lipophilicity (log P), ionization potential (E\textsubscript{HOMO}) and dipole moment\textsuperscript{23}.

α-Tocopherol has been shown to conduct specific cellular functions including its action as a radical scavenger, as a prooxidant and as an anti-alkylation agent through various mechanisms. To the last group belong protein kinase C and 5-lipoxygenase inhibition at post-translational level, as well as α-tocopherol activation of protein phosphatase 2A and diacylglycerol kinase\textsuperscript{24,25}.

The previous workers have shown that the tocotrienol subfamily of natural vitamin E possesses powerful neuroprotective, anticancer and cholesterol-lowering properties that are often not exhibited by tocopherols.

At nanomolar concentration, α-tocotrienol prevents neurodegeneration\textsuperscript{26}. Micromolar concentrations of α-tocotrienol function as an antioxidant as verified in a model involving linoleic acid-induced oxidative stress and cell death\textsuperscript{27}. It modulates 12-lipoxygenase which has a central role in executing glutamine-induced neurodegeneration\textsuperscript{28}.

Vitamin E analogues such as α-tocopheryl succinate belong to the group of "mitocans" (mitochondrially targeted anticancer drugs) and are selective for malignant cells, cause destabilization of mitochondria and suppress cancer in preclinical models\textsuperscript{29}. Phenylhydrazine oxidation resulting in free iron release followed by free radical generation has increased the frequency of cancer. A study has been made towards the dose-dependent response of phenylhydrazine and the role of vitamin E following phenylhydrazine induced toxicity within the lymphoid tissue (spleen)\textsuperscript{30}.

Another important aspect of the use of α-tocopherol is the systemic or topical application of a combination of antioxidants ascorbic acid and α-tocopherol as a protective measure against UV-induced skin damage\textsuperscript{31}. Ferulic acid, a potent ubiquitous plant antioxidant has been found to stabilize a solution of vitamin C and E and increase its photoprotection of skin oxidative stress and cancer\textsuperscript{32}. Ubiquinone, idebenone and kinetin are ineffective in photoprotection of skin in comparison to a topical antioxidant combination of vitamin C and E with ferulic acid\textsuperscript{33}.

**CONCLUSION**

Recent research on vitamin E has emphasized its role as a most effective lipid-soluble chain-breaking antioxidant protecting cell membranes from peroxidative damage. It minimizes free-radical damage associated with specific diseases including cancer, aging, circulatory disorders, arthritis, cataract and pollution. Vitamin E has been shown to conduct specific cellular functions including its action as a radical scavenger, as a prooxidant and as an alkylating agent in cancer therapy.
### Table 1: Biological Activity of Natural Vitamin E Forms

<table>
<thead>
<tr>
<th>Vitamin E forms</th>
<th>Biological Activity *</th>
<th>USP units (IU) mg⁻¹</th>
<th>Compared to RRR-α -T (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α - Tocopherol</td>
<td></td>
<td>1.49</td>
<td>100</td>
</tr>
<tr>
<td>β - Tocopherol</td>
<td></td>
<td>0.75</td>
<td>50</td>
</tr>
<tr>
<td>γ - Tocopherol</td>
<td></td>
<td>0.15</td>
<td>10</td>
</tr>
<tr>
<td>δ - Tocopherol</td>
<td></td>
<td>0.05</td>
<td>3</td>
</tr>
<tr>
<td>α - Tocotrienol</td>
<td></td>
<td>0.75</td>
<td>50</td>
</tr>
<tr>
<td>β - Tocotrienol</td>
<td></td>
<td>0.08</td>
<td>5</td>
</tr>
<tr>
<td>γ - Tocotrienol</td>
<td>Not known</td>
<td></td>
<td>Not known</td>
</tr>
<tr>
<td>δ - Tocotrienol</td>
<td>Not known</td>
<td></td>
<td>Not known</td>
</tr>
</tbody>
</table>

* USP: United State Pharmacopeia; IU: international unit; α -T: α -Tocopherol
REFERENCES


19. Pryor, W. A. Vitamin E Abstracts, VERIS (The Vitamin E Research and Information Service), LaGrange, IL, 1995, p. VII.


