Cellular Protection and Therapeutic Potential of Tocotrienols

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Abstract: Tocotrienols, components belonging to vitamin E members, are used as potent therapeutics in the treatment of several diseases. Recent studies suggested tocotrienol to have better activity in many situations compared to tocopherols. Tocotrienols have been shown to lower the atherogenic apolipoprotein B and lipoprotein plasma levels. Additionally, tocotrienols with their anti-tumor effect together with anti-angiogenic and anti-thrombotic effects may serve as effective agents in cancer therapy. Besides these effects, some properties such as water insolubility and low stability limit the usage of tocotrienols in the clinic. However recent studies tried to increase the bioavailability with esterification and combination use. These efforts for the clinical usage of tocotrienols which may help them to take a wide place in the clinic and additional studies are needed to identify their therapeutical mechanisms.

Keywords: Tocotrienols, atherosclerosis, Alzheimer's disease, cancer, therapy.

INTRODUCTION

Tocotrienols are classified as isoforms of vitamin E and exist in α, β, γ , and δ derivatives as tocopherols do. Vitamin E was discovered in green leafy vegetables and Burton and Ingold reviewed that α-tocopherol has an activity as a chain-breaking antioxidant and both the phenolic head and phytyl tails in its structure contributed to the biological properties of the vitamin E molecule. Vitamin E is a fat soluble nutrient that emerged as essential. Since it is essential, the body can not manufacture vitamin E and it must be provided externally from foods and supplements. Besides their antioxidant activities, vitamin E components have the potential to influence a broad range of mechanisms underlying human health and disease. In this direction, many studies were carried out to highlight the effects of Vitamin E components, especially tocotrienol, on the several age related diseases [1].

Structurally tocotrienols and tocopherols possess the same resemblance of a chromonal head and a side chain at the C-2 position. In addition, tocotrienols have an unsaturated isoprenoid side chain and tocopherols have saturated phytyl tail. The number and position of methyl groups located around the chromanol ring vary among the different tocopherols and tocotrienols, and account for the designation as α, β, γ , or δ-forms. As mentioned, vitamin E components should be externally provided by food and supplements. Tocotrienols are mainly concentrated in cereal grains such as rye, barley, oat and certain vegetable oils such as palm oil and rice bran oil [2].

Tocotrienols have been studied extensively for thier many therapeutic functions, including possible blood cholesterol lowering and cardioprotective effects, antioxidant activity, anticancer effects, and neuroprotective effects [3]. When compared with α-tocopherol, tocotrienols have been shown to display a better anti-tumor activity. For many years, α-tocopherol was considered as the most potent antioxidant vitamin E compound. But in more recent studies, α-tocotrienol was found to be a better antioxidant when compared to α-tocopherol [4,5]. Mechanisms to explain its higher activity were identified in a detailed study with their uniform distribution in the membrane lipid bilayer, efficient interaction of their chromanol ring with lipid radicals, and a higher recycling efficiency from chromanoxyl radicals [4]. Besides their antioxidant capacity, tocotrienols play important roles in the regulation of several pathways, and with these broad spectrum of effects, the value for the therapeutic efficiencies of tocotrienols increases day by day.

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AGE RELATED DISEASES AND BASIC MECHANISMS

During aging, neurodegenerative and cardiovascular diseases are developed because of the cellular changes. The mechanisms related to aging may help to develop therapeutic approaches against these age related diseases [6]. In the free radical theory of aging, introduced in 1956 by Denham Harman, it was proposed that aging occurs by the accumulation of free radical damage to tissues. In addition to this reactive species (RS) are known to be involved in age related diseases. These reactive species, reactive oxygen species (ROS) and reactive nitrogen species (RNS), effect redox status of the cell. Cellular components such as proteins, lipids, carbohydrates, and nucleic acids are damaged by RS [7]. Following several studies in many years, oxidative damage is strongly implicated in the pathogenesis of neurodegenerative and cardiovascular diseases including Alzheimer's disease and atherosclerosis [6].

Redox status of the cell is important in the progression of cardiovascular diseases, therefore superoxide ($O_2^{\cdot-}$), hydroxyl ($OH^{\cdot}$) and hydrogen peroxide (H_2O_2) and reactive nitrogen species (NO and peroxynitrite) are involved in cardiovascular diseases. While superoxide and hydroxyl radicals are more reactive, hydrogen peroxide is more membrane permeable. As the basic mechanism, these oxygen species are converted to each others by several mechanisms. $O_2^{\cdot-}$ is dismutated nonenzymatically or enzymatically by superoxide dismutase (SOD) to H_2O_2. Also various enzymes located in the plasma membrane, cytosol, peroxisomes and mitochondria catalyze ROS formation [8].

Atherosclerosis that is characterized by the accumulation of plasma lipoproteins that carry cholesterol and triglycerides in the arteries, is one of the major cardiovascular diseases [9]. In the process of this disease, phagocytic monocytes are rapidly transformed into macrophage foam cells, following the penetration into the subendothelial space and atherogenic lipoproteins like modified low density lipoprotein (LDL) are uptaken by receptor-mediated endocytosis mechanism [10,11]. Besides the formation of these foam cells, adaptive thickening of the intima is accepted as the main visible lesion at the early stage of the pathogenesis [12]. Several receptors play important role in the uptake of atherogenic lipids and lipoproteins and CD36 takes the most important place in the scavenger receptors by playing role in atherosclerotic process [9,11]. Redox status, as mentioned above, has a big role in the atherosclerotic lesion formation and several cell types such as macrophages, endothelial, smooth muscle and adventitial cells are

1381-6128/11 $58.00+.00

thought to be the sources of ROS formation in the vessel wall [13]. Mostly by lipid peroxidation and LDL oxidation are implicated [14,15] but there is also recent work representing protein oxidation in the vascular wall [9]. When looked through the redox signaling process in atherosclerosis; lipid rafts play an important role in transmembrane signaling [16], NFκB activation and adhesion molecules such as selectins, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) and chemokines such as monocyte chemoattractant protein-1 (MCP-1) expressions in the vascular endothelium play an important role, macrophage colony-stimulating factor (M-CSF) is an important factor regulating the survival, proliferation, differentiation, and chemotaxis of macrophages [17]. PKC was also shown to play important role in the disease and it has been shown in *in vivo* that hypercholesterolemia increases CD36 mRNA expression and PKC activity in rabbits [18,19].

Another important age-related disease is Alzheimer, which is the most common form of adult onset dementia. Neuropathology, includes numerous biochemical changes such as cholinergic deficits [20]; neuronal metabolic insult [21]; and oxidative stress or damage such as lipid peroxidation and protein oxidation [22]. Senile plaques (SP) and neurofibrillary tangles (NFT) are the major alterations in this disease and they represent an accumulation of intraneuronal and extracellular filamentous protein aggregates. Hyperphosphorylated tau in NFT and amyloid beta (Aβ) peptide, derived from amyloid precursor protein for SP are the major proteins in these formations [23]. This incidence of protein aggregate formations in Alzheimer's disease pushed the researchers to focus on the role of oxidative stress mainly protein oxidation in the process. The oxidative damage markers shown to be increased in Alzheimer's disease involve carbonyl modified neurofilament protein and free carbonyls [24], lipid peroxidation adduction products [25], advanced glycation end products [26] and nitration [27]. Protein carbonyls were shown to be increased in frontal pole and occipital pole in Alzheimer's disease patients compared with controls [25]. Mishto *et al.* [28] found an inhibition in the activity of trypsin-like proteasomal activity which occurred in hippocampus and cerebullum of Alzheimer's disease patients. Lovell *et al.* [29] observed increased levels of free and protein-bound HNE adducts in ventricular fluids of Alzheimer's disease patients. There was a significant increase in mitochondrial DNA oxidation in parietal cortex of Alzheimer's disease subjects compared with control groups [30]. Iron in a redox-active state, thought to play an important role in free radical production in Alzheimer's disease, was shown to be increased in NFT as well as Aβ deposits [31]. Iron catalyzes the formation of hydroxyl radical from H_2O_2 and also the formation of advanced glycation end products. Aβ itself, has been directly implicated in ROS formation through peptidyl radicals [32]. Advanced glycation end products and Aβ, activate specific receptors, such as the receptor for advanced glycation end products (RAGE) and the class A scavenger-receptor, to increase reactive oxygen production [33]. Additionally an increased nitrative stress on proteins in human AD brains has been reported [34]. Both nuclear and mitochondrial DNA have been modified by oxidative stress to increased levels of 8-hydroxy-2-deoxyguanosine and oxidized bases in cerebral cortex and cerebellum of AD patients as compared to age-matched control subjects [30]. Increased levels of malondialdehyde, a measure of lipid peroxidation, are found in human AD brains [35]. Numerous cellular and animal models of AD have been developed and considerable efforts have been taken to identify mechanisms of redox state-mediated gene regulation in relation to AD pathology. Also genetic factors (apolipoprotein E ε4 allele), germline mutations (amyloid-β protein precursor gene, presenilin-1 gene, and presenilin-2 gene), environmental causes, lifestyle-related factors (smoking) and certain health conditions such as diabetes, brain injury and hypercholesterolemia cause oxidative stress in AD patients [22].

TOCOTRIENOLS IN AGE RELATED DISEASES

Vitamin E is a fascinating natural resource that has the potential to influence health and disease related mechanisms and up to today many studies have been carried out to gain insight into the effects of Vitamin E components, especially tocotrienol, on the several age related diseases. There is an increasing interest on the hypocholesterolemic effect of tocotrienols. In human subjects with hypercholesterolemia tocotrienols were shown to lower serum cholesterol [36], lower both serum total cholesterol and low-density-lipoprotein cholesterol [37], lower plasma cholesterol level in hypercholesterolemic subjects [38] and tocotrienol-rich fraction of rice bran were shown to suppress serum cholesterol in a dose-dependently manner [39]. In another human study, dietary tocotrienols were shown to react with peroxyl radicals following incorporation into circulating human lipoproteins where they act as efficiently as the corresponding tocopherol isomers [40]. Palm tocotrienols were shown to protect ApoE± mice from diet-induced atheroma formation [41] and tocotrienols were shown to inhibit atherosclerotic lesions in ApoE-deficient mice [42]. It is thought that, the unsaturated side chain of tocotrienol allows for more efficient penetration into tissues that have saturated fatty layers such as the brain and liver [43]. Also tocotrienol administration reduced oxidative protein damage and extended the mean life span of C. elegans [44].

Hypocholesterolemic effect of α-tocotrienol was identified to inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA reductase, HMGR) enzyme which is the rate-limiting enzyme of the cholesterol biosynthetic pathway. The molecular mechanism of this inhibition was explained to be the proteolytic degradation of this enzyme which was stimulated by farnesol product increased by the side chain of α-tocotrienol [45]. On the other hand, in an animal study using hypercholesterolemic pigs who were fed a tocotrienol-rich diet and showed a 44% and 60% decrease in total serum cholesterol and LDL-cholesterol, respectively [46]. α-tocotrienol was shown to inhibit cholesterol synthesis in human liver cells and in these cells γ- and δ- tocotrienols were shown to possess significantly greater HMGR suppression confirming the effects of structural differences of methyl groups on the activity [47]. To confirm the role of tocotrienols on blood cholesterol, human trials were performed and supplementation of α, γ, δ-tocotrienols and α-tocopherol combination caused a significant decrease in total cholesterol [48]. Besides total or LDL-cholesterol, apolipoprotein B-100 (apoB), the protein moiety of LDL, is a better index of atherogenic risk [49]. Studies have shown that tocotrienol combination or only γ-tocotrienols can perform a reduction in apoB plasma levels [36,38]. The effects of tocotrienols on apoB levels have been explained to be by the upregulation of LDL receptors in the liver which facilitates the clearance of LDL-apoB from the bloodstream [50].

Fluvastatin and Atorvastatin, currently used hypolipidemic drugs, act via inhibiting the HMGR of the mevalonate pathway. Side-effects of these statins mainly on muscles and liver led researchers to investigate the therapeutic potentials of dietary α-, β-, γ- and δ-tocotrienols mixture named Tocomin. The data showed that Tocomin significantly reduced the levels of plasma and lipoprotein lipids, cholesterol, apoB, small dense (sd)-LDL as well as LDL in the hyperlipidemia-induced hamsters [51].

Tocotrienols have also shown to be effective on brain related and neurodegenerative diseases. When administered orally, tocotrienols are shown to cross the blood-brain barrier to reach brain tissue of rats; and also can reach fetal brain while pregnant mother is supplemented with tocotrienol. On cultured striatal neurons of rats, α-tocotrienol provided the most potent neuroprotection among vitamin E analogs [52]. Sen *et al.* showed that, for the protection against glutamate-induced neuronal death in mice by suppressing inducible pp60 c-src kinase activation, α-tocopherol was effective at high doses and in contrast α-tocotrienol was effective at nM concentrations [53]. This protection against glutamate-induced neuronal death was also shown to be via suppression of inducible 12-

lipoxygenase activation [54]. Tocotrienols can prevent the diabetes associated cognitive deficits by decreasing the oxidative stress and suppressing the NFkβ expression in diabetic rats [55]. Tiwari *et al*. [56] investigated the potential of tocopherol vs tocotrienol in preventing the streptozotocin (i.c.v) induced dementia in rats. This model of rat has been described as an appropriate animal model for sporadic Alzheimer type dementia characterized by a progressive deterioration of memory, and the presence of oxidative stress in the brain of rats [57]. α-Tocopherol as well as tocotrienol treated groups showed significantly less cognitive impairment in both the behavioral paradigms but the effect was more potent with tocotrienol. Both isoforms of vitamin E effectively attenuated the reduction in glutathione and catalase and reduced the malonaldehyde, nitrite as well as cholinesterase activity in the brains of ICV STZ rats in a dose dependent manner. The study demonstrates the effectiveness of vitamin E isoforms, in which tocotrienol is more potent in preventing the cognitive deficits caused by ICV STZ in rats and suggests its potential in the treatment of neurodegenerative diseases such as Alzheimer's disease [58].

TOCOTRIENOLS IN CANCER THERAPY

Cancer, as widely known, is a class of diseases in which cells show uncontrolled growth and may damage adjacent tissues, and sometimes show metastasis, or spread to other locations in the body via lymph or blood. Interest in the use of alternative and complementary therapies, mainly nutraceuticals as chemopreventive compounds, is increasing for cancer. In this direction, chemoprevention by nutraceuticals may decelerate tumor formation and also delay the progression of the disease from neoplasms. Regulation of signal transduction pathways related to tumor formation is thought to be the main point for the delay of the progression of cancer [58].

There is increasing evidence supporting the role of vitamin E in the cancer prevention. The main theory of the anti-cancerogenic effect of tocotrienols is the inhibition of lipid peroxidation and also with antioxidant activity they may prevent oxidative damage to DNA [59]. Anti-tumor property is also another notion to have chemo-preventive effect for tocotrienols. Tocotrienol administration to mouse, rat and human tumor cell lines has shown to undergo growth inhibition [60-62]. In human breast cancer, several administrations of tocotrienols were shown to inhibit the growth in culture which was independent from estrogen status [63]. This independent growth inhibition by tocotrienols brought great potential for the therapy of antiestrogen resistant breast cancer cells. The γ and δ forms of tocotrienol have demonstrated efficacy superior to that of vitamin E succinate in breast cancer cells regardless of the HER-2/Neu expression [64] and may serve as potent dietary chemoprotective compounds. In a clinical trial on breast cancer, 240 subjects with stage 1 or stage 2 breast cancers were selected for the five years clinical trial. The subjects were evenly divided into two groups; one group took placebo with Tamoxifen whereas the other group took palm tocotrienol-rich fraction with Tamoxifen. The outcome of the clinical trial is that tocotrienols prolong the lives of breast cancer patients and inhibit the recurrence of breast cancer [65].

In the prevention of cancer, the effect of tocotrienols on cell proliferation represents an important physiological role. The mechanism for the antiproliferative property of tocotrienols may be related to its prenylated side-chain involved in the production of isoprenoid intermediates from the mevalonate biosynthetic pathway [66]. These intermediates are thought to be involved in the prenylation of several signal transduction proteins including the Ras protein which is essential for normal cell growth. Recent studies have shown that γ -tocotrienols inhibit cell proliferation by decreasing Akt and activation of NF-κB, implicated in the regulation of cell growth, cell cycle, and apoptosis [67].

Barve *et al*. [68] reported the efficacy of a mixed-tocotrienol diet against prostate tumorigenesis in the transgenic adenocarcinoma mouse prostate (TRAMP) model. Results showed that mixed-tocotrienol-fed groups had a lower incidence of tumor formation along with a significant reduction. Furthermore, mixed tocotrienols significantly reduced the levels of high-grade neoplastic lesions as compared to the positive controls. This decrease in levels of high-grade neoplastic lesions was found to be associated with in increased expression of proapoptotic proteins BAD (Bcl2 antagonist of cell death) and cleaved caspase-3 and cell cycle regulatory proteins cyclin dependent kinase inhibitors p21 and p27. In contrast, the expression of cyclins A and E was found to be decreased in mixed-tocotrienol groups.

Campbell *et al*. [69] demonstrated that the γ and δ isoforms of vitamin E are effective growth inhibitors in both androgen-dependent and androgen-independent prostate cancer cells and tocotrienols are more effective at inducing growth arrest compared with the tocopherols. However, lower concentrations of γ-tocotrienol proved to induce apoptosis as demonstrated by fluorescence microscopy and caspase cleavage. Dietary fat intake has been positively correlated with an increased risk for prostate cancer [70]. γ-tocotrienol treatment in PC-3 cells resulted in the up-regulation of PPAR-γ, the master fat metabolism regulatory element [71], resulting in growth arrest that is partially dependent upon PPAR-γ. γ-tocotrienol is not an endogenous PPAR-γ ligand, but regulates PPAR-γ through the activation of 15(S)-Hydroxyeicosatetraenoic acid (15-S-HETE). Previous data have implicated γ-tocotrienol in modulating the NF-κB pathway; however, the TNFα pathway was the source of NF-κB activation and chronic myeloid leukemia cells were the target for γ-tocotrienol treatment [72]. It was also demonstrated that TGFβ2 (the source of NF-κB activation) and cell survival in PC-3 human prostate cancer [73] cells are down-regulated with γ-tocotrienol treatment. γ-tocotrienol is involved in more than the proteolytic processing of the TGFβ2 ligand, and more likely it is involved in the transcriptional regulation either directly or by down-regulation of a gene product involved in TGFβ2 transcriptional activity. γ-tocotrienol disruption of TGFβ2 transcription is further validated by the down-regulation of TGFβ receptor I and p-SMAD-2 signaling. the antiapoptotic inhibitor XIAP, which is up-regulated by the constitutive activation of NF-κB, is down-regulated in the presence of γ-tocotrienol treatment.

Antiangiogenic therapy mediated by food components is an established strategy for cancer chemoprevention. Growth factors play critical roles in tumor angiogenesis. Li *et al*. [74] used a conditioned medium containing growth factors from human gastric adenocarcinoma SGC-7901 cell conditioned medium as an angiogenic stimulus. The results showed that γ-tocotrienol significantly suppressed proliferation, migration and tube formation of human umbilical vein endothelial cells (HUVECs) induced by SGC-7901 cell conditioned medium in a dose-dependent manner. Moreover, the inhibitory effects of γ-tocotrienol on HUVECs were correlated with inducing the apoptosis and arresting cell cycle at the G_0/G_1 phase at a dose of 40 μmol/L γ-tocotrienol. In addition, γ-tocotrienol inhibited angiogenesis in HUVECs by down-regulation of β-catenin, cyclin D1, CD44, phospho-VEGFR-2 and MMP-9. The antiangiogenic effects of γ-tocotrienol on HUVECs may be attributable to regulation of Wnt signaling by decreasing β-catenin expression. These results suggested that γ-tocotrienol has a potential chemopreventive agent via antiangiogenesis.

Melanin is synthesized by tyrosinase and other enzymes in the tyrosinase family, such as tyrosinase-related protein (TRP)-1 and TRP-2, in melanosomes. δ-Tocotrienol might be useful as a therapeutic or preventive drug for hyperpigmentation and as a component of whitening and/or lightening cosmetics not causing severe side effect (reduction of cholesterol content and release of lysosomes/melanosomes). Michihara *et al*. [75] investigated the dose-dependent effect of δ-tocotrienol long term (48, 72 h) on the melanin content of cells treated with δ-tocotrienol, and whether cells treated with δ-tocotrienol for a long time show cytotoxicity. δ-

tocotrienol at up to 50 mM dose-dependently caused a reduction in melanin content by the decrease of TRP-1 and TRP-2 as well as tyrosinase, and no cytotoxicity [75].

Selvaduray *et al*. [76] showed that the anticancer effect of tocotrienols is linked to increased expression of interleukin-24 (IL-24) mRNA, a cytokine reported to have antitumor effects in many cancer models. Tocotrienol isomers (α-, γ-, δ-tocotrienol) and tocotrienol-rich fraction (TRF) inhibited the growth of the 4T1 murine mammary cancer cells. Tumor incidence and tumor load in TRF-supplemented BALB/c mice were decreased. The induction of the IL-24 mRNA in the 4T1 cells by vitamin E decreased mostly by δ-tocotrienol. The IL-24 mRNA levels in tumor tissues of BALB/c mice supplemented with TRF increased 2-fold when compared with control mice. Increased levels of IL-24 have been associated with inhibition of tumor growth and angiogenesis. Treatment of 4T1 cells with TRF and δ-tocotrienol significantly decreased IL-8 and vascular endothelial growth factor mRNA levels. These results also confirmed the potent anti-angiogenic and antitumor effects of tocotrienols that are associated with increased levels of IL-24 mRNA [76].

Vitamin E isoforms may influence cancer growth by modulating gene-regulatory functions through mechanisms unrelated to their antioxidant properties [77]. Taken together, by modulating cell cycle regulatory proteins, related genetic pathways and increasing expression of proapoptotic proteins, mixed tocotrienols suppress tumorigenesis in different models.

PRACTICAL APPROACHES FOR THE USAGE OF TOCOTRIENOLS IN THE CLINIC

Tocotrienols started to take wide place in the pharmaceutical industry for the treatment of different diseases. Since some clinical trials already took place [78-81] still studies are carried out to increase the bioavailability of these components.

In order to be effective in chemo-prevention of degenerative diseases, the bioavailability of tocotrienols must be sufficient at the respective organs or tissues. The bioavailability of tocopherols and tocotrienols is at least partly dependent on the relative binding affinity with α-tocopherol transfer protein (α-TTP) [82-84]. Tocotrienols require fats for absorption. The bioavailability of tocotrienols is significantly higher under fed conditions when compared with fasted conditions [85,86]. Therefore during the manufacturing process (Palm Neutroceuticals) in order to increase the bioavailability of the tocotrienol-rich fraction, the natural food emulsifiers monoacylglycerols and diacylglycerols should be intentionally retained. Tocotrienol-rich fraction produced by other manufacturers does not contain natural food emulsifiers as these have been destroyed during their destructive processing (transesterification).

Physicochemical and pharmacokinetic properties of tocotrienols may greatly limit their use as therapeutic agents. Chemical instability, poor water solubility, NPC1L1-mediated transport, and rapid metabolism of tocotrienols are examples of such hindrances which interfere with the therapeutic use of these natural products. Poor water solubility is a big problem for the preclinical trials of these compounds mainly in cell culture studies. Vitamin E esters like α-tocopheryl succinate were prepared to significantly improve chemical and metabolic stability, water solubility, and potency. Thus, 12 semisynthetic tocotrienol ester analogs 4-15 were prepared by direct esterification of natural tocotrienol isomers with various acid anhydrides or chlorides. Esters 4-15 were evaluated for their ability to inhibit the proliferation and migration of the mammary tumor cells. The most active ester 9 was 1000-fold more water-soluble and chemically stable versus its parent a-tocotrienol [87]. These findings strongly suggest that redox-silent tocotrienol esters may provide superior therapeutic forms of tocotrienols for the control of metastatic breast cancer. Natural vitamin E members are relatively unstable towards air, heat, light, alkali, and metal ions. Therefore, several synthetic stabilized vitamin E analogs, mainly esters, for example, α-tocopheryl acetate and tocopheryl succinate, were synthesized and became commercially available for use in supplements and cosmetics. Esters are less susceptible to oxidation and therefore more appropriate for food and pharmaceutical applications compared to the free form [88]. The poor bioavailability of γ-tocotrienol was attributed to its NPC1L1-mediated intestinal uptake and its lipophilicity and poor water solubility [89,90]. A commercially available water- soluble vitamin E ester was produced by esterification of polyethylene glycol-1000 onto RRR-α-tocopheryl succinate. This ester has the ability to form miscible micelles in water due to its amphiphilic properties. This approach enhanced tocopherols' bioavailability in animals and humans via improving their water solubility and absorption [91]. Esterification of tocotrienols affords redox-silent analogs, which will prevent their rapid metabolic inactivation via masking the free phenolic group required for chromanoxy radical formation. Generally, esters will slowly hydrolyze to release their parent natural phenol, which will decrease the rate of metabolism and enhance the metabolic stability of tocotrienols [92]. Intestinal or epidermal esterases will catalyze ester hydrolysis and thus can be considered as pro-vitamins or prodrugs of the natural tocotrienols. Esterification of tocotrienols is expected not only to maintain the bioactivity but also to improve thier solubility and chemical stability [93].

Supplements including tocotrienols and tocopherols take a wide place in the pharmaceutical markets. They can be easily provided and ordered via internet and produced under the name of famous companies and also under the individual names. This situation also arises the question of uncontrolled usage of these supplements.

CONCLUSION

There is an increasing interest on the use of natural compounds as therapeutic agents. A large body of evidence shows the connection between redox status of the cell and related signaling mechanisms in the progression of the diseases. Because of the effective role of Vitamin E components in several genetic pathways, and also as antioxidants, these components take the most important place in this therapeutic research. In the past, mainly tocopherols have been investigated but recently tocotrienols have shown to be more effective in the treatment of several diseases. Together with the new formulation, these compounds are believed to be used in the clinical trials.

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Received: June 2, 2011 **Accepted: June 21, 2011**