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## Tocotrienols: Vitamin E Beyond Tocopherols

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### Abstract

In nature, eight substances have been found to have vitamin E activity:  $\alpha$ -,  $\beta$ -,  $\gamma$ - and  $\delta$ -tocopherol; and  $\alpha$ -,  $\beta$ -,  $\gamma$ - and  $\delta$ -tocotrienol. Yet, of all papers on vitamin E listed in PubMed less than 1% relate to tocotrienols. The abundance of  $\alpha$ -tocopherol in the human body and the comparable efficiency of all vitamin E molecules as antioxidants, led biologists to neglect the non-tocopherol vitamin E molecules as topics for basic and clinical research. Recent developments warrant a serious reconsideration of this conventional wisdom. Tocotrienols possess powerful neuroprotective, anti-cancer and cholesterol lowering properties that are often not exhibited by tocopherols. Current developments in vitamin E research clearly indicate that members of the vitamin E family are not redundant with respect to their biological functions.  $\alpha$ -Tocotrienol,  $\gamma$ -tocopherol, and  $\delta$ -tocotrienol have emerged as vitamin E molecules with functions in health and disease that are clearly distinct from that of  $\alpha$ -tocopherol. At nanomolar concentration,  $\alpha$ -tocotrienol, not  $\alpha$ -tocopherol, prevents neurodegeneration. On a concentration basis, this finding represents the most potent of all biological functions exhibited by any natural vitamin E molecule. An expanding body of evidence support that members of the vitamin E family are functionally unique. In recognition of this fact, title claims in manuscripts should be limited to the specific form of vitamin E studied. For example, evidence for toxicity of a specific form of tocopherol in excess may not be used to conclude that high-dosage "vitamin E" supplementation may increase all-cause mortality. Such conclusion incorrectly implies that tocotrienols are toxic as well under conditions where tocotrienols were not even considered. The current state of knowledge warrants strategic investment into the lesser known forms of vitamin E. This will enable prudent selection of the appropriate vitamin E molecule for studies addressing a specific need.

### Keywords

antioxidant; redox; nutrient; supplement; neuroprotection

### Introduction to Vitamine and Vitamin E

In 1905, Englishman William Fletcher determined that if special factors (vitamins) were removed from food disease ensued. Fletcher was researching the causes of the disease Beriberi when he discovered that eating unpolished rice prevented Beriberi and eating polished rice did not. William Fletcher believed that there were special nutrients contained in the husk of the rice. Next year, English biochemist Sir Frederick Gowland Hopkins also discovered that certain food factors were important to health. In 1912, Polish scientist Cashmir Funk named the special nutritional parts of food as a "vitamine" after "vita" meaning life and "amine" from compounds found in the thiamine he isolated from rice husks. Vitamine was later shortened to vitamin when it was discovered that not all of the vitamins contain nitrogen, and, therefore, not all are

amines. Together, Hopkins and Funk formulated the vitamin hypothesis of deficiency disease - that a lack of vitamins could make people sick. Vitamin E was discovered in 1922 in green leafy vegetables by University of California researchers, Herbert Evans and Katherine Bishop. In 1924, Sure named it vitamin E. Because E supported fertility, it was scientifically named tocopherol. This comes from the Greek word *tokos* meaning childbirth, and *phero* meaning to bring forth, and the *ol* ending was added to indicate the alcohol properties of this molecule. In 1936 it was discovered that vitamin E was abundant in wheat germ oil. Two years later, it was chemically synthesized for the first time. The U.S. National Research Council sponsored studies on deficiencies of vitamin E, and based on the results E was designated an essential vitamin. Vitamin E emerged as an essential, fat-soluble nutrient that functions as an antioxidant in the human body. It is essential, because the body cannot manufacture its own vitamin E and foods and supplements must provide it. Since the elucidation of the chemical structure of vitamin E in 1938 by Fehholz and the synthesis of *dl*- $\alpha$ -tocopherol by Karrer in the same year, specific focus was directed on the chemical class of natural compounds that qualify to be vitamin E. At present, vitamin E represents a generic term for all tocopherols and their derivatives having the biological activity of RRR- $\alpha$ -tocopherol, the naturally occurring stereoisomer compounds with vitamin E activity (Traber and Packer, 1995; Traber and Sies, 1996). In nature, eight substances have been found to have vitamin E activity:  $\alpha$ -,  $\beta$ -,  $\gamma$ - and  $\delta$ -tocopherol; and  $\alpha$ -,  $\beta$ -,  $\gamma$ - and  $\delta$ -tocotrienol (Figure 1). Yet, of the 24000+ papers on vitamin E listed in PubMed, only just over 200 relate to tocotrienols (Table 1). The current handicap in knowledge of how tocotrienols may be implicated in human health and disease and the significance of filling that void in vitamin E research is discussed in this minireview.

## Biosynthesis of tocopherols and tocotrienols

Vitamin E are essential components of the human diet and are synthesized exclusively by photosynthetic organisms. Tocopherols consist of a chromanol ring and a 15-carbon tail derived from homogentisate (HGA) and phytyl diphosphate, respectively (Fig. 1). Condensation of HGA and phytyl diphosphate, the committed step in tocopherol biosynthesis, is catalyzed by HGA phytyltransferase (HPT). Tocotrienols differ structurally from tocopherols by the presence of three *trans* double bonds in the hydrocarbon tail (Fig. 1). Tocotrienols are the primary form of vitamin E in the seed endosperm of most monocots, including agronomically important cereal grains such as wheat, rice, and barley. Tocotrienols are also found in the seed endosperm of a limited number of dicots, including *Apiaceae* species and certain *Solanaeaceae* species, such as tobacco. These molecules are found only rarely in vegetative tissues of plants. Crude palm oil extracted from the fruits of *Elaeis guineensis* particularly contains a high amount of tocotrienols (up to 800 mg/kg), mainly consisting of  $\gamma$ -tocotrienol and  $\alpha$ -tocotrienol. Tocopherols, by contrast, occur ubiquitously in plant tissues and are the exclusive form of vitamin E in leaves of plants and seeds of most dicots. Transgenic expression of the barley HGGT (homogentisic acid transferase, which catalyzes the committed step of tocotrienol biosynthesis) in *Arabidopsis thaliana* leaves resulted in accumulation of tocotrienols, which were absent from leaves of nontransformed plants, and a 10- to 15-fold increase in total vitamin E antioxidants (tocotrienols plus tocopherols). Overexpression of the barley HGGT in corn seeds resulted in an increase in tocotrienol and tocopherol content of as much as six-fold. These results provide insight into the genetic basis for tocotrienol biosynthesis in plants and demonstrate the ability to enhance the antioxidant content of crops by introduction of an enzyme that redirects metabolic flux (Cahoon et al., 2003). Recently, another strategy involving genetic engineering of metabolic pathways in plants has proved to be efficient in bolstering tocotrienol biosynthesis (Rippert et al., 2004). In plants, phenylalanine is the precursor of a myriad of secondary compounds termed phenylpropanoids. In contrast, much less carbon is incorporated into tyrosine that provides p-hydroxyphenylpyruvate and homogentisate, the aromatic precursors of vitamin E. The flux of these two compounds has been upregulated by deriving their synthesis directly at the level of prephenate. This was

achieved by the expression of the yeast prephenate dehydrogenase gene in tobacco plants that already overexpress the *Arabidopsis* p-hydroxyphenylpyruvate dioxygenase coding sequence. A massive accumulation of tocotrienols was observed in leaves. These molecules, which were undetectable in wild-type leaves, became the major forms of vitamin E in the leaves of the transgenic lines. An increased resistance of the transgenic plants toward the herbicidal p-hydroxyphenylpyruvate dioxygenase inhibitor diketonitril was also observed. Thus, the synthesis of p-hydroxyphenylpyruvate is a limiting step for the accumulation of vitamin E in plants (Rippert et al., 2004).

### **Tocotrienols: A cameo role in the side-lines of tocopherol celebrity**

Often, the term vitamin E is synonymously used with  $\alpha$ -tocopherol. While the expression is correct it is incomplete and may be often misleading. d- $\alpha$ -Tocopherol (RRR- $\alpha$ -tocopherol) has the highest bioavailability and is the standard against which all the others must be compared. However, it is only one out of eight natural forms of vitamin E. Tocotrienols, formerly known as  $\zeta$ ,  $\epsilon$  or  $\eta$ -tocopherols (Fig. 1), are similar to tocopherols except that they have an isoprenoid tail with three unsaturation points instead of a saturated phytyl tail (Fig. 1). Interestingly, tocotrienols possess powerful neuroprotective, antioxidant, anti-cancer and cholesterol lowering properties that often differ from the properties of tocopherols (Table 1). Micromolar amounts of tocotrienol suppress the activity of HMG-CoA reductase, the hepatic enzyme responsible for cholesterol synthesis (Pearce et al., 1994; Pearce et al., 1992). Tocotrienols are thought to have more potent antioxidant properties than  $\alpha$ -tocopherol (Serbinova et al., 1991; Serbinova and Packer, 1994). The unsaturated side chain of tocotrienol allows for more efficient penetration into tissues that have saturated fatty layers such as the brain and liver (Suzuki et al., 1993). Experimental research examining the antioxidant, free radical scavenging effects of tocopherol and tocotrienols revealed that tocotrienols appear superior due to their better distribution in the fatty layers of the cell membrane (Suzuki et al., 1993). One major justification often used to side-line tocotrienol research is the relative inferiority of the bioavailability of orally taken tocotrienols compared to that of  $\alpha$ -tocopherol. The hepatic  $\alpha$ -tocopherol transfer protein ( $\alpha$ -TTP), together with the tocopherol-associated proteins (TAP) is responsible for the endogenous accumulation of natural  $\alpha$ -tocopherol. Although these systems have a much lower affinity to transport tocotrienols, it has been evident that orally supplemented tocotrienol results in plasma tocotrienol concentration in the range of 1  $\mu$ M (O'Byrne et al., 2000). Of note, such circulating levels of  $\alpha$ -tocotrienol are almost an order of magnitude higher than that required to protect neurons against a range of neurotoxic insults (Khanna et al., 2003; Sen et al., 2000). Despite such promising potential, tocotrienol research accounts for less than 1% of all vitamin E research published in PubMed. The unique vitamin action of  $\alpha$ -tocopherol, combined with its prevalence in the human body and the similar efficiency of tocopherols as chain-breaking antioxidants, led biologists to almost completely discount the "minor" vitamin E molecules as topics for basic and clinical research. Recent discoveries have forced a serious reconsideration of this conventional wisdom (Hensley et al., 2004).

### **$\alpha$ -Tocopherol: Riding the wave for five decades**

In 1950, Kamimura's treatment of frostbite using  $\alpha$ -tocopherol represents one of the earliest therapeutic applications of the vitamin (Kamimura, 1977). Early works of Tappel identified that  $\alpha$ -tocopherol effectively inhibits biological oxidation processes (Tappel, 1953, 1954, 1955; Zalkin and Tappel, 1960; Zalkin et al., 1960). It was soon realized that tocopherol deficiency in humans led to elevated levels of oxidative lipid damage and erythrocyte hemolysis (Horwitt et al., 1956). These observations set the stage for the emergence of tocopherol as a biological antioxidant (Green and Bunyan, 1969), a concept that drew widespread attention in the decades to follow. Two decades after the "biological antioxidant

theory” (Green and Bunyan, 1969) was reported, Burton and Ingold presented the first comprehensive review article discussing that  $\alpha$ -tocopherol has near optimal activity as a chain-breaking antioxidant and that both the phenolic head and phytyl tails contributed to the biological properties of the vitamin E molecule (Burton and Ingold, 1989).  $\alpha$ -Tocopherol gained recognition as the most important lipophilic radical-chain-breaking antioxidant in tissues *in vivo*. Deficiency of  $\alpha$ -tocopherol in membranes made them highly permeable and therefore vulnerable to degradation. Tocopherols seemed also to influence other important biophysical membrane characteristics, such as fluidity, in a manner similar to that of cholesterol. Studies of the antioxidant properties led to the recognition that during the reaction of  $\alpha$ -tocopherol with an appropriate oxidizing species,  $\alpha$ -tocopherol may be oxidized to  $\alpha$ -tocopheryl quinone (Seward et al., 1969). In latter studies where peroxidizing lipids were used to induce the formation of antioxidant radicals, electron spin resonance spectroscopy revealed that free radical interactions of *dl*- $\alpha$ -tocopherol generate *dl*- $\alpha$ -tocopheroxyl radicals. It was thus realized that  $\alpha$ -tocopherol is only available as an antioxidant for a short period of time (Lambelet and Loliger, 1984). Importantly, it was noted that the reaction kinetics and stability of the four tocopherols were not identical. The fast reacting *dl*- $\alpha$ -tocopherol reacted more rapidly and trapped free radicals more thoroughly and was therefore only available as an antioxidant for a short period of time as compared with the slowly reacting *dl*- $\delta$ -tocopherol. *dl*- $\beta$ - and *dl*- $\gamma$ -Tocopherols behaved in an intermediate way (Lambelet and Loliger, 1984). That ascorbate can transfer hydrogen to  $\alpha$ -tocopheroxyl radicals and thus regenerate  $\alpha$ -tocopherol (Bascetta et al., 1983) encouraged the concept of antioxidant recycling. Mass analysis studies demonstrated that tocopherol can be regenerated in human cell homogenates implying that maintenance of membrane tocopherol status may be an essential function of ascorbate and GSH which operate in concert to ensure maximum membrane protection against oxidative damage (Chan et al., 1991). While the concept of antioxidant recycling was extended to build the “antioxidant network” hypothesis (Packer and Suzuki, 1993), skepticism regarding whether such interactions take place *in vivo* stirred the field (Strain and Mulholland, 1992). In the late eighties, the discovery that oxidative modification of low-density lipoprotein is a key trigger for atherosclerosis represented a major breakthrough in biomedical research. The early nineties was thus a time when numerous laboratories studied mechanisms underlying the oxidation of LDL and the inhibition of such oxidation. Because  $\alpha$ -tocopherol was identified as the major antioxidant present in human lipoproteins, it received much attention as a suppressor of LDL lipid oxidation and as an epidemiological marker for ischemic heart disease. While most laboratories were excited about  $\alpha$ -tocopherol preventing LDL oxidation, Stocker et al published conditions under which  $\alpha$ -tocopherol may actually act as a pro-oxidant *via* the  $\alpha$ -tocopheroxyl radical (Bowry et al., 1995). This direct link established between vitamin E chemistry and health outcomes drew significant attention underscoring the potential adverse effects of redox-active antioxidant nutrients. Although the relevance of the proposed antioxidant network remained to be proven in *in vivo* systems, enthusiasm for therapeutic regimens including multiple antioxidant members of the network soared (Albanes et al., 1996; DeCosse et al., 1989; Fuchs and Kern, 1998; Hartman et al., 1998; Liede et al., 1998; McKeown-Eyssen et al., 1988; Mireles-Rocha et al., 2002; Porkkala-Sarataho et al., 2000; Rapola et al., 1998; Rapola et al., 1997; Salonen et al., 2000; Teikari et al., 1998; Teikari et al., 1997; Woodson et al., 1999) resulting in quite a few clinical trials at a time when basic scientists were still trying to grasp the fundamentals.

## Functional uniqueness of vitamin E family members: Caution against empirical claims

All eight tocopherols in the vitamin E family share close structural similarity (Fig. 1) and hence comparable antioxidant efficacy (Table 1). Yet, current studies of the biological functions of vitamin E continue to indicate that members in the vitamin E family possess unique biological

functions often not shared by other family members. One of the earliest observations suggesting that  $\alpha$ -tocopherol may have functions independent of its antioxidant property came from the study of platelet adhesion.  $\alpha$ -Tocopherol strongly inhibits platelet adhesion. Doses of 400 IU/day provide greater than 75% inhibition of platelet adhesion to a variety of adhesive proteins when tested at low shear rate in a laminar flow chamber. The antiadhesive effect of  $\alpha$ -tocopherol appeared to be related to a reduction in the number and size of pseudopodia upon platelet activation and led to the hypothesis that within the body vitamin E may exert functions beyond its antioxidant property (Steiner, 1993). That members of the tocopherol family may have functions independent of their antioxidant properties gained more prominence when vitamin E molecules with comparable antioxidant properties exhibited contrasting biological effects (Boscoboinik et al., 1991). At the posttranslational level,  $\alpha$ -tocopherol inhibits protein kinase C, 5-lipoxygenase and phospholipase A2 and activates protein phosphatase 2A and diacylglycerol kinase. Some genes (*e.g.* scavenger receptors,  $\alpha$ -TTP,  $\alpha$ -tropomyosin, matrix metalloproteinase-19 and collagenase) are specifically modulated by  $\alpha$ -tocopherol at the transcriptional level.  $\alpha$ -Tocopherol also inhibits cell proliferation, platelet aggregation and monocyte adhesion. These effects have been characterized to be unrelated to the antioxidant activity of vitamin E, and possibly reflect specific interactions of  $\alpha$ -tocopherol with enzymes, structural proteins, lipids and transcription factors (Zingg and Azzi, 2004).  $\gamma$ -Tocopherol represents the major form of vitamin E in the diet in the USA, but not in Europe. Desmethyl tocopherols, such as  $\gamma$ -tocopherol and specific tocopherol metabolites, most notably the carboxyethyl-hydroxychroman (CEHC) products, exhibit functions that are not shared by  $\alpha$ -tocopherol. The activities of these other tocopherols do not map directly to their chemical antioxidant behavior but rather reflect anti-inflammatory, antineoplastic, and natriuretic functions possibly mediated through specific binding interactions (Hensley et al., 2004). Metabolites of  $\gamma$ -tocopherol (2,7,8-trimethyl-2-(beta-carboxyethyl)-6-hydroxychroman), but not that of  $\alpha$ -tocopherol, provides natriuretic activity. Moreover, a nascent body of epidemiological data suggests that  $\gamma$ -tocopherol is a better negative risk factor for certain types of cancer and myocardial infarction than is  $\alpha$ -tocopherol (Wagner et al., 2004). Further evidence supporting the unique biological significance of vitamin E family members is provided by current results derived from  $\alpha$ -tocotrienol research. As illustrated in Table 1,  $\alpha$ -tocotrienol possesses numerous functions that are not shared by  $\alpha$ -tocopherol. For example, nanomolar concentrations of  $\alpha$ -tocotrienol uniquely prevents inducible neurodegeneration by regulating specific mediators of cell death (Khanna et al., 2003; Sen et al., 2000). In addition, tocopherols do not seem to share the cholesterol-lowering properties of tocotrienol (Qureshi et al., 1986; Qureshi et al., 2002). Tocotrienol, not tocopherol, administration reduces oxidative protein damage and extends the mean life span of *C. elegans* (Adachi and Ishii, 2000). Furthermore, tocotrienol but not tocopherol, suppresses growth of human breast cancer cells (Nesaretnam et al., 1995). Such expanding body of evidence indicating that members of the vitamin E family are functionally unique calls for a revisit of the current practices in vitamin E research. Research claims should be limited to the specific form of vitamin E studied. For example, evidence for toxicity of a specific form of tocopherol in excess may not be used to conclude that high-dosage vitamin E supplementation may increase all-cause mortality (Miller et al., 2005). Along these lines, it may not be prudent to express frustrations about the net yield of vitamin E research as a whole (Greenberg, 2005) when all that has been tested for efficacy on a limited basis in clinical trials is  $\alpha$ -tocopherol. Vitamin E represents one of the most fascinating natural resources that have the potential to influence a broad range of mechanisms underlying human health and disease. Yet, clinical outcomes studies have failed to meet expectations (Friedrich, 2004; Greenberg, 2005). The current state of knowledge warrants strategic investment into the lesser known forms of vitamin E with emphasis on uncovering the specific conditions that govern the function of vitamin E molecules *in vivo*. Outcomes studies designed in light of such information would yield lucrative returns.

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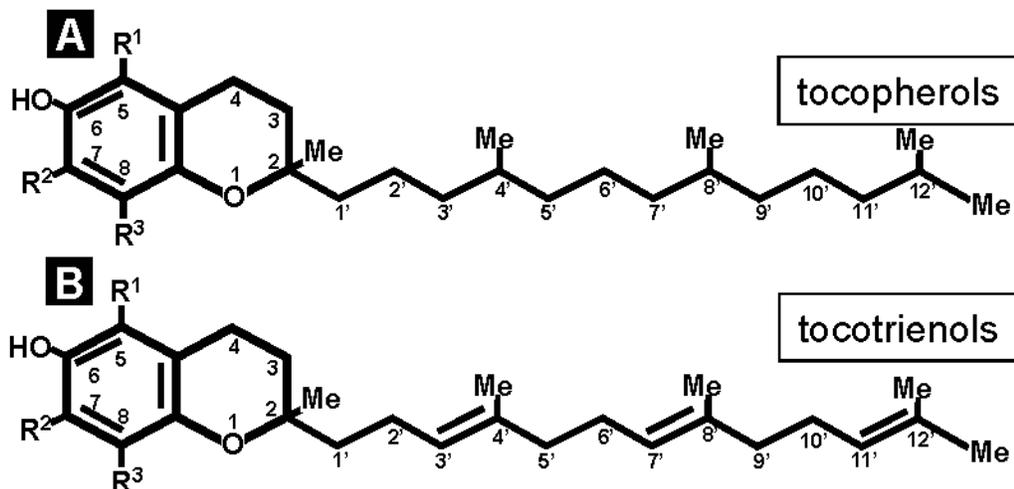
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**Figure 1. Vitamin E: variations and nomenclature**

**A**,  $R_1 = R_2 = R_3 = \text{Me}$ , known as  $\alpha$ -tocopherol, is designated  $\alpha$ -tocopherol or 5,7,8-trimethyltolcol;  $R_1 = R_3 = \text{Me}$ ;  $R_2 = \text{H}$ , known as  $\beta$ -tocopherol, is designated,  $\beta$ -tocopherol or 5,8-dimethyltolcol;  $R_1 = \text{H}$ ;  $R_2 = R_3 = \text{Me}$ , known as  $\gamma$ -tocopherol, is designated  $\gamma$ -tocopherol or 7,8-dimethyltolcol;  $R_1 = R_2 = \text{H}$ ;  $R_3 = \text{Me}$ , known as  $\delta$ -tocopherol, is designated  $\delta$ -tocopherol or 8-methyltolcol. **B**,  $R_1 = R_2 = R_3 = \text{H}$ , 2-methyl-2-(4,8,12-trimethyltrideca-3,7,11-trienyl) chroman-6-ol, is designated tocotrienol;  $R_1 = R_2 = R_3 = \text{Me}$ , formerly known as  $\zeta_1$  or  $\zeta_2$ -tocopherol, is designated 5,7,8-trimethyltocotrienol or  $\alpha$ -tocotrienol. The name tocochromanol-3 has also been used;  $R_1 = R_3 = \text{Me}$ ;  $R_2 = \text{H}$ , formerly known as  $\epsilon$ -tocopherol, is designated 5,8-dimethyltocotrienol or  $\beta$ -tocotrienol;  $R_1 = \text{H}$ ;  $R_2 = R_3 = \text{Me}$ , formerly known as  $\gamma$ -tocopherol, is designated 7,8-dimethyltocotrienol or  $\gamma$ -tocotrienol. The name plastochromanol-3 has also been used;  $R_1 = R_2 = \text{H}$ ;  $R_3 = \text{Me}$  is designated 8-methyltocotrienol or  $\delta$ -tocotrienol (Liebecq, 1992).

**Table 1**  
**TOCOTRIENOL: A NEW FACE OF VITAMIN E UNFOLDING**

<b>Neuroprotective</b>	2000	<i>Mouse</i> ; At nM concentrations $\alpha$ -tocotrienol, in contrast with $\alpha$ -tocopherol, protects against glutamate-induced neuronal death by suppressing inducible pp60 c-src kinase activation. $\alpha$ -Tocotrienol provided the most potent neuroprotection among all vitamin E analogs. Reported effects of tocotrienol independent of antioxidant property (Sen et al., 2000)
	2002	<i>Rat</i> ; Oral tocotrienol crosses the blood-brain barrier to reach brain tissue; more so for fetal brain while pregnant mother is supplemented with tocotrienol (Roy et al., 2002)
	2003	<i>Mouse</i> ; At nM concentrations $\alpha$ -tocotrienol, in contrast with $\alpha$ -tocopherol, protects against glutamate-induced neuronal death by suppressing inducible 12-lipoxygenase activation (Khanna et al., 2003)
	2003	<i>Mouse</i> ; Injected $\alpha$ -tocotrienol decreased the size of the cerebral infarcts 1 day after stroke; $\gamma$ -tocotrienol and delta- tocotrienol did not protect (Mishima et al., 2003)
	2003	<i>Human</i> ; Tocotrienols induced IKBKAP expression: a possible therapy for familial dysautonomia (Anderson et al., 2003)
	2004	<i>Rat</i> ; $\alpha$ -Tocotrienol provided the most potent neuroprotection among vitamin E analogs on cultured striatal neurons (Osakada et al., 2004)
<b>Hypocholesterolemic</b>	1986	<i>Chicken</i> ; Three double bonds in the isoprenoid chain essential for the inhibition of cholesterologenesis; tocopherols do not share this property (Qureshi et al., 1986)
	1991	<i>Human</i> ; Lowered serum cholesterol in hypercholesterolemics (Qureshi et al., 1991b); lowered both serum total cholesterol (TC) and low-density-lipoprotein cholesterol (Tan et al., 1991) <i>Pigs</i> ; Reduced plasma cholesterol, apolipoprotein B, thromboxane B2, and platelet factor 4 in pigs with inherited hyperlipidemias (Qureshi et al., 1991a)
	1992	<i>In vitro</i> ; Post-transcriptional suppression of HMG-CoA reductase by a process distinct from other known inhibitors of cholesterol biosynthesis (Pearce et al., 1992)
	1993	Regulate cholesterol production in mammalian cells by post-transcriptional suppression of 3-hydroxy-3-methylglutaryl- coenzyme A reductase (Parker et al., 1993)
	1994	<i>HepG2</i> ; The farnesyl side chain and the methyl/hydroxy substitution pattern of gamma-tocotrienol responsible for HMG CoA reductase suppression (Pearce et al., 1994)
	1995	isoprenoid-mediated suppression of mevalonate synthesis depletes tumor tissues of two intermediate products, farnesyl pyrophosphate and geranylgeranyl pyrophosphate, which are incorporated post-translationally into growth control- associated proteins (Elson and Qureshi, 1995)
	1995	<i>Human</i> ; Lowered plasma cholesterol level in hypercholesterolemic subjects (Qureshi et al., 1995)
	2001	<i>Chicken</i> ; The effects of a tocotrienol/lovastatin combination were no greater than that of tocotrienol alone, indicating that tocotrienol produced a maximum cholesterol lowering effect (Qureshi and Peterson, 2001)
	2001	<i>Swine</i> ; Tocotrienols suppress cholesterologenesis in hereditary hypercholesterolemic swine (Qureshi et al., 2001a)
	2001	<i>Human</i> ; Tocotrienol, not tocopherol, hypocholesterolemic in humans; claimed that tocotrienol is converted to tocopherol in vivo (Qureshi et al., 2001c)
	2002	<i>Human</i> ; Dose-dependent suppression of serum cholesterol by tocotrienol-rich fraction of rice bran in hypercholesterolemic humans (Qureshi et al., 2002)
	2002	<i>Hamster</i> ; Tocotrienols lower total cholesterol and low density lipoprotein plasma levels (Raederstorff et al., 2002)
	2003	<i>Rat</i> ; Suppression of hypercholesterolaemia in rats by tocotrienol-rich fraction isolated from rice bran oil (Iqbal et al., 2003)
ApoB level reduction in hypercholesterolemic subjects	1999	<i>Human</i> ; in HepG2 cells tocotrienol (not tocopherol) stimulates apoB degradation possibly as the result of decreased apoB translocation into the endoplasmic reticulum lumen (Theriault et al., 1999)
Anti-hypertensive	1992	<i>Rat</i> ; Depressed (better than $\alpha$ -tocopherol) age-related increase in the systolic blood pressure of spontaneously hypertensive rats (Koba et al., 1992)
Hypocholesterolemic and antioxidant	1993	<i>Rat</i> ; spares plasma tocopherol (Watkins et al., 1993)
Lowering blood pressure; antioxidant	1999	<i>SHR</i> ; Supplement of $\gamma$ -tocotrienol may prevent increased blood pressure, reduce lipid peroxides in plasma and blood vessels and enhanced total antioxidant status (Newaz and Nawal, 1999)
<b>Antioxidant</b>	1991	<i>In vitro</i> ; Better than $\alpha$ -tocopherol (Serbinova et al., 1991)
	1992	<i>In vitro</i> ; Facilitates antioxidant recycling (Kagan et al., 1992)
	1993	<i>In vitro</i> ; Tocotrienol is better than tocopherol; tocotrienol is located closer to the cell membrane surface (Suzuki et al., 1993)
	1993	<i>Human</i> ; Dietary tocotrienols become incorporated into circulating human lipoproteins where they react with peroxy radicals as efficiently as the corresponding tocopherol isomers (Suarna et al., 1993)
	1995	<i>Rat</i> ; Protects brain against oxidative damage (Kamat and Devasagayam, 1995)
	1995	<i>Human</i> ; Controls the course of carotid atherosclerosis (Tomeo et al., 1995)
	2002	<i>Human</i> ; $\alpha$ -Tocotrienol is more potent than $\alpha$ -tocopherol in protecting against free radical-induced impairment of erythrocyte deformability (Begum and Terao, 2002)
	2002	<i>Rat</i> ; Comparable effects of a tocotrienol-rich fraction and tocopherol in aspirin-induced lipid peroxidation mediated gastric lesions (Nafeeza et al., 2002)
	2003	<i>Rat</i> ; Antioxidant effects of $\gamma$ -tocotrienol in spontaneously hypertensive rats (Newaz et al., 2003)

	2003	Tocopherols and tocotrienols have comparable antioxidant properties; Some of the vitamin E formulations tested showed antioxidant activities superior to d-alpha-tocopherol (Naguib et al., 2003)
	2003	The corresponding tocopherols and tocotrienols exert comparable antioxidant activity; tocotrienols are more readily transferred between the membranes and incorporated into the membranes than tocopherols (Yoshida et al., 2003)
	2003	<i>Human</i> ; Topical $\alpha$ -tocotrienol supplementation inhibits lipid peroxidation in human skin (Weber et al., 2003)
	2004	<i>Human</i> ; Lack of oxidative stress in a selenium deficient area in Ivory Coast Potential nutritional antioxidant role of crude palm oil (Tiahou et al., 2004)
	2004	<i>Rat</i> ; Palm oil tocotrienol mixture better than $\alpha$ -tocopherol acetate in protecting bones against free-radical induced elevation of bone-resorbing cytokines (Soelaiman et al., 2004)
	2004	<i>Mice</i> ; Ricotrienol exerted a protective effect against oxidative damage in diabetes mellitus (Kanaya et al., 2004)
Antiaging/antioxidant	2000	<i>C. elegans</i> ; Tocotrienol, not tocopherol, administration reduced the accumulation of protein carbonyl and consequently extended the mean life span but not the maximum life span (Adachi and Ishii, 2000).
<b>Anti-cancer</b>	1989	<i>Mouse</i> ; Intraperitoneally injected tocotrienol prevented transplanted tumors (Komiyama et al., 1989)
	1989	<i>Rat</i> ; Tocotrienol-rich palm oil prevented chemically-induced mammary tumorigenesis (Sundram et al., 1989)
	1991	<i>Rat</i> ; Tocotrienol, but not tocopherol, was chemopreventive in mammary tumor model (Gould et al., 1991)
	1991	<i>Rat</i> ; Tocotrienol, chemopreventive in hepatic tumor model (Ngah et al., 1991)
	1993	<i>Rat</i> ; Tocotrienol, chemopreventive in hepatic tumor model (Rahmat et al., 1993)
	1994	<i>Human</i> ; Suppresses activation of Epstein-Barr virus early antigen expression in PMA-activated lymphoblastoid Raji cells (Goh et al., 1994)
	1995	<i>Human</i> ; Tocotrienol, not tocopherol, suppresses growth of a human breast cancer cell line in culture (Nesaretnam et al., 1995)
	1997	<i>Human</i> ; Inhibited proliferation of estrogen receptor-negative MDA-MB-435 and -positive MCF-7 breast cancer cells (Guthrie et al., 1997) <i>Mouse</i> ; Isoprenoids suppress the growth of murine B16 melanomas in vitro and in vivo (He et al., 1997)
	1998	<i>Human</i> ; Inhibit the growth of human breast cancer cells irrespective of estrogen receptor status (Nesaretnam et al., 1998)
	1999	<i>Human</i> ; Apoptosis and cell-cycle arrest in human and murine tumor cells are initiated by isoprenoids (Mo and Elson, 1999)
	1999	<i>Human</i> ; Naturally occurring tocotrienols and RRR- $\delta$ -tocopherol are effective apoptotic inducers for human breast cancer cells (Yu et al., 1999)
	2000	<i>Human</i> ; Tocotrienols inhibit growth of ZR-75-1 breast cancer cells (Nesaretnam et al., 2000)
	2000	<i>Mouse</i> ; Highly potent $\gamma$ - and $\delta$ -tocotrienol isoforms may play a physiological role in modulating normal mammary gland growth, function, and remodeling (McIntyre et al., 2000b)
	2000	<i>Mouse</i> ; highly malignant breast cancer cells were the most sensitive, whereas the preneoplastic cells were the least sensitive to the antiproliferative and apoptotic effects of tocotrienols (McIntyre et al., 2000a)
	2001	<i>Mouse</i> ; Tocotrienols are significantly more potent than tocopherols in suppressing EGF-dependent normal mammary epithelial cell growth. The inhibitory effects of specific tocopherol and tocotrienol isoforms on EGF-dependent normal mammary epithelial cell mitogenesis occurs downstream from the EGF-receptor and appears to be mediated, at least in part, by a reduction in PKC $\alpha$ activation (Sylvester et al., 2001)
	2002	<i>Mouse</i> ; Antiproliferative effects of tocotrienols in preneoplastic mammary epithelial cells do not reflect a reduction in EGF- receptor mitogenic responsiveness, but rather, result from an inhibition in early post-receptor events involved in cAMP production upstream from EGF-dependent MAPK and phosphoinositide 3-kinase/Akt mitogenic signaling (Sylvester et al., 2002)
	2003	<i>Rat</i> ; Suppression of 7,12-dimethylbenz[ $\alpha$ ]anthracene-induced carcinogenesis by tocotrienol-rich fraction isolated from rice bran oil (Iqbal et al., 2003)
	2003	<i>Mouse</i> ; Tocotrienol-induced apoptosis in mammary cancer cells is mediated through activation of the caspase-8 signaling pathway and is independent of caspase-9 activation (Shah et al., 2003)
	2004	<i>Mouse</i> ; Tocotrienol-induces caspase-8 activation, unrelated to death receptor apoptotic signaling, in neoplastic mammary epithelial cells (Shah and Sylvester, 2004)
	2004	<i>Rat</i> ; Tocotrienol induces apoptosis in dRLh-84 hepatoma cells (Sakai et al., 2004)
	2004	<i>Rat</i> ; Tocotrienol-rich fraction isolated from rice bran oil suppressed diethylnitrosamine and 2-acetylaminofluorene-induced hepatocarcinogenesis (Iqbal et al., 2004)
	2004	<i>Human</i> ; Tocotrienol disrupts mitochondrial function and causes apoptosis of breast cancer cells (Takahashi and Loo, 2004)
	2004	<i>Human</i> ; Pro-apoptotic properties of $\delta$ -tocotrienol in breast cancer cells (Shun et al., 2004)
	2004	<i>Human</i> ; Supplementation of tocotrienol rich fraction of palm oil significantly and specifically affected MCF-7 cell response after tumor formation <i>in vivo</i> by an antioxidant-independent mechanism (Nesaretnam et al., 2004)

	2004	<i>Human</i> ; Tocotrienol-rich fraction of palm oil activated p53, modulated Bax/Bcl2 ratio and induced apoptosis independent of cell cycle association in colorectal cancer RKO cells (Agarwal et al., 2004)
Modulating normal mammary gland growth, function, and remodeling	2000	<i>Mouse</i> ; Mammary epithelial cells more easily or preferentially took up tocotrienols as compared to tocopherols (McIntyre et al., 2000b)
<b>Antiangiogenic</b>	2004	<i>Human/Chicken</i> ; Tocotrienol, not tocopherol, inhibited angiogenesis and telomerase activity (Nakagawa et al., 2004)
	2004	<i>Bovine</i> ; Tocotrienol, not tocopherol, limited angiogenic responses <i>in vitro</i> (Miyazawa et al., 2004)
	2003	<i>Bovine</i> ; Tocotrienol, but not tocopherol, inhibited both the proliferation and tube formation of aortic endothelial cells (Inokuchi et al., 2003)
Antiproliferative and apoptotic	2000	<i>Mouse</i> ; Preneoplastic and neoplastic mammary epithelial cells: $\alpha$ - and $\gamma$ -tocopherol had no effect on cell proliferation (McIntyre et al., 2000a)
	2003	<i>Cancer cell lines</i> ; Not $\alpha$ -tocotrienol but $\gamma$ -tocotrienol was apoptogenic, and more so when succinylated. Shortening the aliphatic side chain of gamma-tocotrienol by one isoprenyl unit increased its activity (Birringer et al., 2003)
Hypocholesterolemic, antioxidant & antitumor	2000	<i>Chicken</i> ; The number and position of methyl substituents in tocotrienols affect their hypocholesterolemic, antioxidant, and antitumor properties; tocotrienol better than $\alpha$ -tocopherol (Qureshi et al., 2000)
Anti-atherogenic	2001	<i>Mouse</i> ; Palm tocotrienols protect ApoE +/- mice from diet-induced atheroma formation (Black et al., 2000)
	2001	<i>Mouse</i> ; Tocotrienols inhibit atherosclerotic lesions in ApoE-deficient mice (Qureshi et al., 2001b)
Serum lipoproteins; platelet function	1999	<i>Human</i> ; in men at risk for cardiovascular disease tocotrienol supplements used had no marked favorable effects (Mensink et al., 1999)
<b>Anti-inflammatory</b>	2002	<i>Human</i> ; Tocotrienols inhibit monocyte-endothelial cell adhesion (Chao et al., 2002)
	2002	<i>Human</i> ; Tocotrienol is the most effective vitamin E for reducing endothelial expression of adhesion molecules and adhesion to monocytes (Therault et al., 2002)
	2003	<i>Human</i> ; The efficacy of tocotrienol for reduction of VCAM-1 expression and adhesion of THP-1 cells to HUVECs was 10- fold higher than that of tocopherol (Noguchi et al., 2003)
Serum triglycerides	1999	<i>Rat</i> ; Lower in tocotrienol fed; higher IgM productivity of spleen lymphocytes and IgA, IgG, and higher IgM productivity mesenteric lymph node lymphocytes (Kaku et al., 1999)
Immune function	1999	<i>Rats</i> ; Feeding affects proliferation and function of spleen and mesenteric lymph node lymphocytes (Gu et al., 1999)
Transfer Protein	1997	$\alpha$ -Tocopherol transfer protein binds $\alpha$ -tocotrienol with 11% efficiency compared to $\alpha$ -tocopherol (Hosomi et al., 1997)
Lymphatic transport	1996	<i>Rat</i> ; preferential absorption of $\alpha$ -tocotrienol compared to $\gamma$ - and $\delta$ -tocotrienols and $\alpha$ -tocopherol (Ikeda et al., 1996)
<b>Drug metabolism</b>	2002	Tocotrienols inhibit human glutathione S-transferase P1-1 (van Haafien et al., 2002)
	2003	<i>Human</i> ; Vitamin E are able to activate gene expression via the pregnane X receptor (PXR), a nuclear receptor regulating a variety of drug metabolizing enzymes. Tocotrienols more potent than tocopherols (Landes et al., 2003)
	2004	<i>In vitro</i> ; Tocotrienols activate the steroid and xenobiotic receptor, SXR, and selectively regulate expression of its target genes (Zhou et al., 2004)
Eye	2004	<i>Rat</i> ; Preferential uptake of topically applied tocotrienol, over tocopherol, by ocular tissues (Tanito et al., 2004)
Bone	2002	<i>Rat</i> ; Tocotrienols are needed for normal bone calcification in growing female rats (Norazlina et al., 2002)
Obesity & Osteoporosis	2004	<i>Rat</i> ; Tocotrienol, not tocopherol, has the potential to be utilized as a prophylactic agent in preventing side effects of long- term glucocorticoid use (Ima-Nirwana and Suhaniza, 2004)
Diabetes	2002	<i>Rat</i> ; Tocotrienols-rich diet decreased advanced glycosylation end-products in non-diabetic rats and improved glycemic control in streptozotocin-induced diabetic rats (Wan Nazaimoon and Khalid, 2002)
<b>Natriuretic function</b>	2000	<i>Rat</i> ; An oral administration of $\gamma$ -tocotrienol increases plasma concentration of 2,7,8-trimethyl-2-(beta-carboxyethyl)-6- hydroxy chroman (LLU- $\alpha$ , gamma-CEHC), a natriuretic compound (Hattori et al., 2000)
	2003	<i>Rat</i> ; $\gamma$ -Tocotrienol is a natriuretic hormone precursor (Saito et al., 2003)
<b>Bioavailability</b>	1996	<i>Mouse</i> ; Supplemented tocotrienol not detected in the brain (Podda et al., 1996). See 2002* below.
	2000	<i>Human</i> ; Following supplementation, ~1 $\mu$ M tocotrienol detected in human plasma (O'Byrne et al., 2000)
	2000	<i>Rat</i> ; The skin is a unique tissue in respect to its ability to discriminate between various vitamin E analogs; it preferentially uptakes dietary tocotrienols (Ikeda et al., 2000)
	2001	<i>Humans</i> ; Increased absorption of the tocotrienols in the fed versus fasted state (Yap et al., 2001)
	2001	<i>Humans</i> ; Tocotrienols, like tocopherols, are metabolized to CEHC; however, the quantities excreted in human urine are small in relation to dose size (Lodge et al., 2001)
	2001	<i>Rat</i> ; Dietary sesame seeds elevate the tissue concentrations of orally taken tocopherols and tocotrienols (Ikeda et al., 2001)
	2002*	<i>Rat</i> ; Oral tocotrienol crosses the blood-brain barrier to reach brain tissue; more so for fetal brain while pregnant mother is supplemented with tocotrienol (Roy et al., 2002)

2002	<i>Human</i> ; In HepG2 cells, tocotrienols are metabolized essentially like tocopherols, i.e., by $\beta$ -oxidation followed by $\beta$ -oxidation of the side chain. Quantitatively, tocotrienols are degraded to a larger extent than tocopherols (Birringer et al., 2002)
2002	<i>Rat</i> ; Sesame lignans added to diet increased plasma and tissue concentrations of supplemented tocotrienols (Yamashita et al., 2002)
2002	<i>Rat</i> ; In epididymal adipose, renal adipose, subcutaneous adipose and brown adipose tissues and in the heart, the tocotrienol levels were maintained or increased for 24 h after intragastric administration. In the serum, liver, mesenteric lymph node, spleen and lungs, the tocotrienol levels were highest 8 h after the administration (Okabe et al., 2002)
2003	<i>Rat</i> ; Dietary $\alpha$ -tocopherol decreases $\alpha$ -tocotrienol but not $\gamma$ -tocotrienol concentration in rats (Ikeda et al., 2003)
2003	Tocotrienols are more readily transferred between the membranes and incorporated into the membranes than tocopherols (Yoshida et al., 2003)
2003	<i>Human</i> ; $\alpha$ -Tocotrienol accumulate in endothelial cells to levels approximately 10-fold greater than that of $\alpha$ -tocopherol (Noguchi et al., 2003)
2003	<i>Rat</i> ; Of the three tocotrienols, $\alpha$ -tocotrienol had the highest oral bioavailability, at about 27.7+/-9.2%, compared with $\gamma$ - and $\delta$ -tocotrienols, which had values of 9.1+/-2.4% and 8.5+/-3.5%, respectively. Tocotrienols were found to be negligibly absorbed when administered intraperitoneally and intramuscularly (Yap et al., 2003)
2003	<i>Human</i> ; The $t_{1/2}$ of tocotrienols is short, ranging from 3.8–4.4 h for $\gamma$ - and $\alpha$ -tocotrienol (Schwedhelm et al., 2003)
2004	<i>Human</i> ; Following the intervention with palm vitamin E, tocotrienols are detected in total blood plasma, TRP, LDL and HDL. Tocotrienols appeared in the blood stream at 2h interval & disappeared within 24 h. Tocotrienols concentration in total plasma plasma, TRP & LDL peaked between 4 to 6 h; in HDL, tocotrienol concentrations peaked at 8 h after supplementation. $\alpha$ -tocopherol was the major vitamin E detected in plasma. Tocotrienols have a very short duration of absorption & distribution in circulating blood (Fairus et al., 2004).

CEHC, carboxyethyl-hydroxychromans; EGF, epidermal growth factor; HDL, high density lipoprotein; HMG CoA reductase, 3-hydroxy-3-methylglutaryl coenzyme A reductase; HUVEC, human umbilical vein (derived) endothelial cells; IKBKAP, gene encoding IkappaB kinase complex-associated protein; LDL, low density lipoprotein; SHR, spontaneously hypertensive rats; TRP, triglyceride rich particles.