

## What's Wrong With Vitamin E?

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If you asked a group of scientists to name an antioxidant, most would point to vitamin E as the classic example of a compound that inhibits dangerous free radicals.

While numerous studies show that vitamin E suppresses free radicals, there is evidence that commercial vitamin E supplements do not provide adequate antioxidant protection.

Most vitamin E supplements consist primarily of alpha tocopherol. Recent studies indicate that a lot more than alpha tocopherol is needed to protect against degenerative disease.

To obtain optimal health benefits from vitamin E, a mixture of tocopherols (alpha, beta, delta, and gamma) and tocotrienols (alpha, beta, delta, and gamma) are required. Some of the functions of these vitamin E fractions are similar while others are completely different. When taken together, these various forms of vitamin E work synergistically as a team to provide maximum benefits.

In this article, we discuss scientific findings supporting the value of the full spectrum of vitamin E that includes the tocopherols and tocotrienols.

### The Tocotrienols

In 1995, Life Extension added a small amount of tocotrienols to a Coenzyme Q10 supplement used by most Life Extension Foundation members. Evidence at that time showed that tocotrienols could help protect against free radical-induced disease.

More recent research shows that tocotrienols may be the most important members of the vitamin E family. In an animal model of aging, tocotrienols extended lifespan by 19% while reducing protein carbonylation, a particularly toxic oxidation process indicative of aging.[1] Not only have tocotrienols demonstrated a superior antioxidant effect compared to alpha tocopherol (40-60 times more effective), but in a clinical study they have been shown to reverse carotid stenosis (narrowing of the carotid artery due to atherosclerosis), thus reducing the risk of stroke.



Tocotrienols have also been shown to reduce the level of LDL (the “bad” form of cholesterol) and apolipoprotein B, both of which are important risk factors for atherosclerosis and cardiovascular disease. Furthermore, tocotrienols have been shown to inhibit the growth of cancer cells. While tocotrienols are found in high concentration in palm oil and rice bran, palm-derived tocotrienols are better supported by research.

The difference in effect between tocopherols and tocotrienols is believed to be caused by a subtle difference in molecular structure. Tocotrienols have an isoprenoid instead of a phytyl side chain. Double bonds in the isoprenoid side chain allow tocotrienols to move freely and more efficiently within cell membranes than tocopherols, giving tocotrienols greater ability to catch and fight free radicals. This greater mobility also allows tocotrienols to recycle more quickly than alpha-tocopherol.

### Alpha versus Gamma Tocopherol

Several large studies have shown great benefits of vitamin E intake in reducing cardiovascular disease and death from heart attacks, while others have failed to show similar results.[2-8] This discrepancy may well be due to the fact that only alpha-tocopherol was studied in isolation, while gamma-tocopherol and toco-trienols were not considered.

This may also explain why vitamin E as found in food is more effective than alpha-tocopherol supplements in reducing death from cardiovascular disease.[9-10] Food provides a broader spectrum of the vitamin E family than conventional supplements. For example, vitamin E in the typical American diet contains considerably more gamma-tocopherol than alpha-tocopherol[11] in contrast to supplements that generally contain only alpha-tocopherol, or insignificant amounts of gamma-tocopherol, tocotrienols and other members of the vitamin E family.

Moreover, studies indicate that high dose alpha-tocopherol supplementation considerably decreases the absorption of gamma-tocopherol and reduces the effects of tocotrienols. One group of scientists observed that when human volunteers (age 30-60) were given 1,200 IU of synthetic alpha-tocopherol daily for 8 weeks, plasma gamma-tocopherol decreased in all subjects to 30-50% of initial values.[12] This is another indication of the importance of a balanced vitamin E intake.

A Swedish study found that patients with coronary heart disease had lower levels of gamma tocopherol and a higher alpha-to-gamma ratio than healthy age-matched subjects.[13]

While alpha-tocopherol has long been known as an important antioxidant, research has now shown that the complete vitamin E team is much more effective. The different vitamin E forms have complementary effects as free radical scavengers. Together they can fight a wider spectrum of free radicals than alpha-tocopherol alone.

One research group found that gamma-tocopherol is significantly more effective than alpha-tocopherol in inhibiting the powerful and harmful oxidizing agent peroxynitrite.[14] While alpha-tocopherol can to some extent inhibit free radical generation, gamma-tocopherol is able to trap and remove existing free radicals as well as highly toxic compounds such as peroxynitrite.[15] Gamma tocopherol can, therefore, protect cells against the mutagenic and carcinogenic effects of the very damaging reactive nitrogen species (See the antioxidant section).

### Tocotrienols and Lifespan Extension

Recent experimental research confirms the connection between tocotrienols, reduced oxidative damage, and increased life span. Palm-derived tocotrienols were chosen for a study of the aging process at the Life Science Research Center in Japan.[16] The study was conducted on a model organism commonly used in anti-aging research, the nematode known as *C. elegans* (*Caenorhabditis elegans*). This species of worm is widely used in basic life science research due to the fact that it has genetic sequences similar to humans.

The study demonstrated that tocotrienols, but not alpha-tocopherol, significantly extended the average life span of the organisms. Nematodes exposed to a tocotrienol enriched (80ug/ml) growth medium lived 19% longer than the control group. A lower concentration (8ug/ml) of tocotrienols extended their average lifespan by 9%. When alpha-tocopherol was tested instead of tocotrienols it had no effect on lifespan. The study also examined carbonylated proteins, which are destructive products of protein oxidation that accumulate during aging in both nematodes and humans. In humans about a third of proteins become carbonylated in the latter third of life, leading to serious degenerative changes in the structures and regulatory systems of the body, including for example the wrinkling of skin. (For further discussion of protein carbonylation, see Carnosine article on page 24 in the January 2001 issue of Life Extension magazine).

Protein carbonyl accumulation in the nematodes was a mirror image of their survival curve, increasing from 1.1nmol/mg protein in young animals to 2.8nmol/mg in "old age" (15 days). In the nematodes treated with tocotrienols protein carbonyls rose about half as much during the course of aging, to only 1.9nmol/mg at age 15 days.

Ultraviolet (UV B) irradiation of the nematodes shortened their average life span by 12%. However, when tocotrienols were added to the medium prior to irradiation, the irradiated nematodes lived as long as the non-irradiated control group. Interestingly, their lifespan increased even more when tocotrienols were added soon after irradiation, and exceeded that of the non-irradiated group, indicating that tocotrienols are more than chain-breaking antioxidants, and are, in fact, capable of repairing damage that has already occurred. Alpha-tocopherol did not lend significant protection from irradiation.

### Tocotrienols and Cardiovascular Disease

One of the most striking discoveries in tocotrienol research is their ability to clear atherosclerotic blockage (stenosis) in the carotid artery, giving them the potential to significantly reduce the risk of stroke. Stroke often occurs when atherosclerotic deposits travel upstream and cut off the blood supply to part of the brain.

Tocotrienols show promise as a natural and safe alternative to risky surgery for this condition because of their ability to reverse carotid stenosis, not merely stop its progression. This was demonstrated in a clinical trial testing the effect of tocotrienols on carotid atherosclerosis.[17] The results of this 18-month trial were remarkable.

Fifty patients with carotid stenosis were randomly assigned to receive either 160 mg daily of palm tocotrienols (gamma and alpha forms) with 64 mg of alpha-tocopherol in palm oil, or palm oil only as a placebo. After 6 months the dosage in the treatment group was increased to 240 mg of tocotrienols with 96 mg of alpha-tocopherol.

At the end of the study, ultrasound scans of the carotid artery demonstrated that none of the patients in the control group had

improved during the trial, while ten worsening of their condition (increased stenosis). In the tocotrienol group, however, atherosclerosis was reduced and blood flow to the brain improved in 7 of 25 patients, while the condition had worsened in only two patients. No adverse side effects were reported in either group.

Tocotrienols and statin drugs such as lovastatin both lower cholesterol by suppressing the activity of the enzyme HMG-CoA reductase, although through different mechanisms. The statins are thought to affect the enzyme through competitive inhibition, while the tocotrienols accelerate enzyme degradation and decrease the efficiency of mRNA translation of the enzyme.[18] This difference in mechanism is believed to be a reason for the absence of adverse side effects with tocotrienols, contrary to the common side effects of the statin drugs.

HMG-CoA reductase is the enzyme that permits the body to synthesize its own cholesterol from a precursor called mevalonate. The mevalonate pathway is also of great importance in regulating cell growth and proliferation. The ability of tocotrienols to inhibit this pathway, therefore, enables them to inhibit cancer growth (see more in the cancer section).



Some studies have demonstrated a significant reduction of both total and LDL cholesterol with tocotrienols administered to patients with high serum lipids. In a double blind, crossover study on 25 patients with high cholesterol levels, the patients in the treatment group were given 4 capsules daily of 50 mg tocotrienols mixed with palm oil, while the control group received only corn oil. At the end of the 8-week trial period, total cholesterol and LDL cholesterol had decreased significantly (15% and 8%) in the 15 subjects given the palm tocotrienols. There was no change in the control group.[19]

Total cholesterol and LDL-cholesterol were reduced even more (17 % and 24 % respectively) when tocotrienols were added to a low fat, low cholesterol diet and alcohol-free regimen in another double-blind, longer-lasting trial (12 weeks).[20] Other important cardiovascular risk factors were reduced by tocotrienols. Apoliipoprotein B and lipoprotein(a), strong predictors of cardiovascular disease[21-23], as well as thromboxane B2 and platelet factor 4 were all significantly lowered in the tocotrienol-treated group (15%, 17%, 31% and 14% respectively).

Thromboxane B2 contributes to cardiovascular disease through proinflammatory activities and platelet aggregation. It is formed from pro-inflammatory prostaglandins through the function of the enzyme cyclooxygenase (COX-2), which is known to be involved in the development of both inflammatory and neoplastic (cancerous) disease. The significant reduction (31%) of thromboxane B2 in this tocotrienol study is interesting, suggesting possible similarities with gamma-tocopherol, which is known to be a COX-2 inhibitor.[24]

While both alpha and gamma-tocopherol have been shown to reduce platelet aggregation and delay thrombus formation, gamma-tocopherol was shown to be significantly more potent in a study on rats.[25]

Tocotrienols were studied in combination with the statin drug lovastatin in another study. The 28 patients with elevated cholesterol levels in this double blind, cross-over clinical trial were placed on the American Heart Association Step-1 diet before beginning the treatment. After 35 days on the diet, they were given low doses of lovastatin, tocotrienols and alpha-tocopherol (and combinations of these agents) in stages of 35 days each, while staying on the diet. The combination of lovastatin (10mg) and palm tocotrienols (50mg) had a lipid-lowering effect of 20-25%, while tocotrienols or lovastatin alone in the same dosages reduced LDL-cholesterol 18% and 15% respectively. No side effects were reported during the study. It is important to note that dosages of cholesterol-lowering drugs should not be reduced on the basis of this preliminary study.[26]

Supplementation with gamma-tocotrienol alone, or in combination with alpha-tocopherol, to rats fed a diet rich in fat for 6 weeks, showed a significant reduction in total and LDL cholesterol, triglycerides and reactive oxidation products, particularly hydroperoxides.[27] The powerful antioxidant effects of tocotrienols will be discussed later in this article.

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