

REPORT

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.

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 phytol 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 life span 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 showed a 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. Apolipoprotein 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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Tocotrienols and breast cancer

Interestingly, human breast cancer cells have been shown to respond very well to treatment with tocotrienols.[38-44]

While most breast cancers are believed to be estrogen dependent, some tumors, particularly postmenopausal tumors, do not depend upon estrogen for their growth. Anti-estrogen drugs, such as the widely used tamoxifen, are most effective on hormone sensitive tumors. The use of tamoxifen is also limited by the development of resistance to this drug in many patients.[45] Tocotrienols provide growth inhibition of breast cancer cells in culture that is independent of estrogen sensitivity, and have great potential to be a significant aid in the prevention and treatment of breast cancer.

A number of in vitro studies have demonstrated the effectiveness of tocotrienols as inhibitors of both estrogen receptor-positive (estrogen responsive) and estrogen receptor-negative (non-estrogen responsive) cell proliferation.

Researchers tested the effect of palm tocotrienols on three different cell lines of estrogen responsive and estrogen non-responsive human breast cancer cells (MCF7, MDA-MB-231 and ZR-75-1). They found that tocotrienols inhibited cell growth strongly in both the presence and absence of estradiol, the major estrogen in the body. The researchers also demonstrated that tocotrienols enhanced the effect of tamoxifen. The gamma- and delta-fractions of tocotrienols were most effective at inhibiting cell growth, while alpha-tocopherol was ineffective in doing so.[38-40]

Among the tocotrienols, delta-tocotrienol was shown in another study to be the most potent inducer of apoptosis (programmed cell death) in both estrogen-responsive and estrogen non-responsive human breast cancer cells, followed by gamma and alpha-tocotrienol (beta-tocotrienol was not tested). Interestingly, delta-tocotrienol is more plentiful in palm tocotrienols than in tocotrienols derived from rice. Of the natural tocopherols, only delta-tocopherol showed any apoptosis-inducing effect, although it was less than a tenth of the effect of palm and rice delta-tocotrienol.[42]

Similar results were obtained when mammary cancer cells from mice were studied.[44] While tocopherols had no inhibitory effect on cancerous cell growth, alpha, gamma, and delta-tocotrienols effectively arrested the cell cycle and triggered cell death. Highly malignant cells were most sensitive to the anti-proliferative effects of tocotrienols, whereas less aggressive pre-cancerous cells were the least sensitive.

Tocotrienols were found to be far more effective than alpha-tocopherol in inhibiting breast cancer cell growth.[41] The tocotrienol concentration needed was less than 1/20 of alpha-tocopherol in estrogen responsive cells and less than 1/10 in cells unresponsive to estrogen. Tocotrienols in combination with tamoxifen were more inhibitory than either compound alone in both estrogen responsive and non-responsive breast cancer cells. The authors pointed out that the synergism between tamoxifen and tocotrienols may allow for the use of lower doses of tamoxifen, and reduce its risk of adverse side effects. It is important to note that further studies are needed before tocotrienols can be used safely in combination with any cancer therapy.

Gamma tocopherol and prostate cancer

While alpha-tocopherol has proven to be effective in inhibiting the growth of prostate cancer cells, gamma-tocopherol has been found to be more effective. In a study comparing the inhibitory effect of synthetic alpha-tocopherol and natural gamma-tocopherol on prostate cancer cell growth, it was demonstrated that gamma-tocopherol inhibited cell growth at concentrations 1,000 times lower than synthetic alpha-tocopherol.[46]

One recent study explored the association of alpha-tocopherol, gamma-tocopherol and selenium with prostate cancer. Blood samples were examined from 117 men who had developed prostate cancer and from 233 matched controls. Higher levels of gamma-tocopherol were associated with significantly lower prostate cancer risk. Men in the highest quintile of gamma-tocotrienol levels had

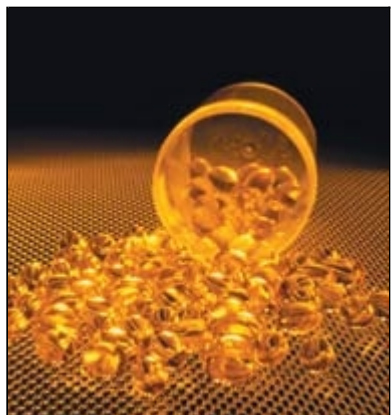


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a five-fold reduction in the risk of developing prostate cancer compared to men in the lowest quintile. Significant protection by high levels of selenium and alpha-tocopherol was observed only when gamma-tocopherol concentrations were high.[47]

The super antioxidant

Much of the broad involvement of vitamin E in human metabolism is due to its role as the body's primary lipid-soluble antioxidant. Tocopherols and tocotrienols are part of the body's highly effective defense system, without which life as we know it could not exist. This defense system consists of a network of antioxidants, interacting with and supporting each other. Antioxidants such as vitamin C, coenzyme Q10 and glutathione are needed for effective recycling of tocopherols and tocotrienols.



The unique power of both tocopherols and tocotrienols is their ability to break the chain reaction of lipid peroxidation by neutralizing peroxy radicals to prevent the spread of free radical damage in cell membranes. Tocotrienols are more potent scavengers of the peroxy radical than alpha-tocopherol and, as we shall see below, provide far better protection against lipid peroxidation. Peroxidation of fatty acids (lipids) in cell membranes has a great impact on both cellular structure and function. Peroxidation of LDL-cholesterol, for example, is known to be the first step in the development of atherosclerosis.[48-49]

Lipid peroxidation is destructive, because lipids are an essential part of cell membranes, hormones and nerve tissue. The damage itself initiates a chain reaction of free radical generation. Vulnerable polyunsaturated fatty acids generate peroxy radicals, which not only damage lipids, but also damage important proteins responsible for most daily functions in humans.

Much of the broad involvement of vitamin E in human metabolism is due to its role as the body's primary lipid-soluble antioxidant. Tocopherols and tocotrienols are part of the body's highly effective defense system, without which life as we know it could not exist.

The efficiency of the various vitamin E members is not equal, however. While gamma-tocopherol is a more effective antioxidant than alpha-tocopherol, particularly in reducing damage from nitrogen radicals[50-51], tocotrienols have proven to be even more powerful than tocopherols. The greater antioxidant effect of delta-tocotrienol compared to alpha-tocopherol is thought to be due to its molecular structure, more uniform distribution in cell membranes, greater recycling activity, and more effective collision with free radicals.[52]

In one study, the efficacy of alpha-tocotrienol was 40 times higher than alpha-tocopherol in protecting rat liver microsomal membranes against lipid peroxidation and 6.5 times higher in protecting cytochrome P-450 against oxidative damage.[53] Cytochrome P-450 is a system of enzymes that play a central role in the detoxification of both exogenous (such as drugs and pesticides) and endogenous (such as hormones) compounds and in the synthesis of steroid hormones and bile acids in the liver.

A follow-up study demonstrated that tocotrienols protect against injury from ischemia and reperfusion (interruption and resumption of blood flow) in isolated rat hearts[54]. A mixture of tocotrienols (55%) and tocopherols (45%) from palm oil was used in this study.

Following 40 minutes of ischemia, alpha-tocotrienol was more active in free radical scavenging than alpha-tocopherol and was preferentially consumed. The recycling efficiency of alpha-tocotrienol was also higher than alpha-tocopherol, which may be one reason for its significantly higher physiological activity under oxidative stress.

An in vitro rat brain study[55] confirmed the superiority of tocotrienols as inhibitors of lipid peroxidation. The study also demonstrated that tocotrienols at low dosage can inhibit protein oxidation in brain mitochondria. Palm tocotrienols were significantly more effective than alpha-tocopherol in this study. Gamma-tocotrienol had the strongest inhibitory effect, while alpha- and delta-tocotrienols were less effective. These results suggest that palm tocotrienols may be helpful in preventing neurodegenerative disorders caused by oxidative stress. Clinical studies are eagerly awaited.

Another study on rat liver microsomes demonstrated the ability of palm tocotrienols to protect cell membranes from oxidative damage. Gamma-tocotrienol again was the most effective. At the low concentration of 5 uM, palm tocotrienols significantly inhibited protein oxidation (37%) and lipid peroxidation (27-30%).[56]

Nitrogen radicals, originating from nitric oxide (NO), cause severe damage to the body. Nitric oxide is an important signaling molecule produced in many tissues, including the blood vessel lining (endothelium) and the brain. It regulates a diverse range of physiological processes. When superoxide and NO combine, however, one of the most toxic radicals in the human body, peroxynitrite, is formed.

Gamma-tocopherol and gamma-tocotrienol are the vitamin E isoforms that have been found most effective in reducing damage from nitrogen radicals. In contrast to alpha-tocopherol, gamma-tocopherol has the ability to scavenge nitrogen dioxide without forming

toxic nitrogen products, and was found to be a more effective inhibitor of cancerous transformation of cells.[57] Gamma-tocopherol is also significantly more effective than alpha-tocopherol in inhibiting peroxynitrite-induced lipid peroxidation. Another team of scientists demonstrated that gamma-tocopherol is required to remove peroxynitrite-derived toxic products, despite the antioxidant action of alpha-tocopherol.[51] This is an important discovery as peroxynitrite is one of the major damaging oxidants produced in humans. Its formation is particularly associated with ischemic injuries, inflammation and neurodegenerative disorders. The authors suggest that the presence of both tocopherols may be required in vivo for optimal protection against nitrogen radicals.

Indirect support for this argument can be found in a study showing that plasma levels of gamma-tocopherol (but not alpha-tocopherol) rapidly increase when long-term smokers stop smoking. This suggests that mainly gamma-tocopherol is consumed in combating free radicals produced by smoking. High doses of alpha-tocopherol have also been shown to displace gamma-tocopherol in plasma and other tissues.[58]

Tocotrienols and hypertension

An important factor in hypertension and congestive heart failure is the body's pool of extra-cellular fluid. Scientists have for decades searched for the hormone in the body that controls the release of excess water and thereby reduces high blood pressure. In 1996 a compound with this effect was isolated, LLU-alpha, which proved to be a metabolite of gamma-tocopherol.[59] Last year animal studies indicated that LLU-alpha also is produced from gamma-tocotrienol.[60-61]

Hypertension has also been associated with elevated lipid peroxide levels (see the antioxidant section) both in animals and humans. In a study of tocotrienols in spontaneously hypertensive rats[62], it was demonstrated that treatment with gamma-tocotrienol prevented the development of age-related hypertension by scavenging free radicals and enhancing the body's enzymatic antioxidant defense system. Tocotrienols reduced lipid peroxidation in blood vessels and significantly increased the activity of the antioxidant superoxide dismutase (SOD).

The radical scavenging effect of tocotrienols may affect blood pressure in other ways than through reduced lipid peroxidation. Earlier studies showed that free radicals can inactivate nitric oxide (NO) to impair vasodilatation, which leads to an increase of peripheral resistance and blood pressure. We look forward to further research in this area.

The need for full spectrum vitamin E

Vitamin E has an excellent safety record.[63-66] However, studies of alpha-tocopherol alone, without the mix of other tocopherols and tocotrienols, has shown pro-oxidant rather than antioxidant activity in people consuming high doses (over 1000 mg).[67]

We have seen that the various vitamin E forms have their unique role in the metabolism of the human body. Research strongly suggests that we need the full spectrum of vitamin E to maximize our chances of preventing and, possibly, treating many of the diseases of aging.

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What is a Free Radical?

Free radicals are the products of oxidative reactions in the body. They are highly reactive compounds that take electrons from other molecules to stabilize themselves. In this process of electron "theft", a new free radical is created, namely, the molecule from which the electron was taken. That new free radical then practices "theft" on another nearby molecule, and a chain-reaction cycle of cell destruction begins.

It is important to realize that oxidation is a normal part of life as are free radicals. Oxidation is what enables us to get and use energy from our food. When free radicals are produced in excess, however, they are so damaging that the body maintains a sophisticated antioxidant system to hold them in check.

However, when the body's prolonged exposure to oxidative factors causes an excessive output of free radicals that exceeds the body's ability to neutralize them (technically called "oxidative stress"), the body is put in an increasingly vulnerable position due to accelerated cell destruction.

Antioxidants are substances that neutralize free radicals.

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