

LE Magazine April 2006

REPORT

What Makes Gamma Tocopherol Superior to Alpha Tocopherol

By Lyle MacWilliam, MSc, FP



While the alpha tocopherol form of vitamin E has long been valued as a potent antioxidant, its little-known cousin, gamma tocopherol, may be equally important in promoting health and protecting against disease. Found in nuts, seeds, and vegetable oils, gamma tocopherol accounts for about 70% of the vitamin E in the North American diet.

Unlike alpha tocopherol, gamma tocopherol is a potent defender against disease-provoking compounds in the body known as reactive nitrogen oxides. Furthermore, gamma tocopherol has been found to reduce inflammation,¹ regulate factors that guard against certain cancers,²⁻⁵ and activate genes involved in protecting against Alzheimer's disease.^{6,7}

The latest research should compel all health-conscious adults to take a closer look at gamma tocopherol, a previously underestimated member of the vitamin E family.

BEYOND ALPHA TOCOPHEROL

Regular consumption of natural vitamin E has long been purported to lower the risk of degenerative disease. Laboratory evidence and data from epidemiological and retrospective studies show that abundant dietary intake of vitamin E can help ward off heart diseases⁸⁻¹¹ and keep several cancers at bay.¹²⁻¹⁴ While many published studies examine the effects of the alpha tocopherol form of vitamin E, scientists increasingly are turning their attention to gamma tocopherol.

Gamma tocopherol has distinctive chemical properties that differentiate it from alpha tocopherol and may explain the observed differences in the biological effects of these two forms of vitamin E. One of these differences makes gamma tocopherol a more effective trap for reactive nitrogen oxides,^{15,16} toxic compounds that must be removed from the body. As recent studies have shown, the accumulation of reactive nitrogen oxides in body tissues undoubtedly plays a central role in the etiology of several degenerative diseases.¹

TRAPPING REACTIVE NITROGEN OXIDES

Two particularly damaging free radicals are nitrogen dioxide and peroxynitrite. Nitrogen dioxide is a mutagenic metabolite and a major constituent of vehicle exhaust and cigarette smoke.¹⁷⁻¹⁹ Peroxynitrite is a dangerous oxidant created in activated phagocytes, which are a type of white blood cell.^{16,20,21} The formation of these toxic compounds is an integral part of the inflammation process, and their stable end products have been detected in both animals and humans with chronic inflammation.²² Inflammation induced by activated phagocytes is a major contributor to the development of cancer, cardiovascular disease, and several neurodegenerative disorders.^{23,24}

Gamma tocopherol plays a pivotal role in quenching this type of inflammation.²² In a landmark study at the University of California, Berkeley, researchers established that alpha tocopherol and gamma tocopherol exhibit dramatically different anti-inflammatory activities.¹⁶ Despite alpha tocopherol's superior antioxidant abilities, gamma tocopherol is required to remove peroxynitrite and other nitrogen-containing toxins that are responsible for initiating the inflammatory response. Acting through a mechanism unavailable to alpha tocopherol, gamma tocopherol reacts with and removes these harmful reactive nitrogen oxides, thereby helping to subdue the inflammatory cascade.

The Berkeley findings support previous studies that demonstrate gamma tocopherol's superior ability to neutralize reactive nitrogen oxides.^{25,26} This has led researchers to conclude that gamma tocopherol plays a vital complementary and synergistic role to its alpha counterpart in the prevention of inflammatory diseases.²² These findings also explain why studies using only high doses of alpha tocopherol often fail to produce significant clinical benefits.



INHIBITING OTHER INFLAMMATORY EVENTS

Gamma tocopherol and its major metabolite can also reduce inflammation by inhibiting the cyclooxygenase-2 enzyme. Cyclo-oxygenase-2 is central to inflammatory processes and associated diseases such as cancer and vascular disease. Gamma tocopherol's ability to block the production of this inflammatory mediator is not shared by alpha tocopherol.^{27,28}

Preliminary evidence shows that gamma tocopherol may help protect against the onset of type I diabetes. Gamma tocopherol is more effective than its alpha analog in protecting pancreatic cells from the damaging effects of interleukin 1-beta. This inflammation-signaling protein is secreted by macrophages (specialized white blood cells responsible for the destruction of pathogens) activated by exposure to reactive nitrogen oxides.²⁹

In a study of mammals, administration of gamma tocopherol reduced several powerful inflammatory mediators, including leukotriene B4 and tumor necrosis factor-alpha. The study investigators noted that this provides evidence that gamma tocopherol exerts anti-inflammatory activity in vivo (within the body) that may have important implications for human disease prevention and treatment.³⁰

COMPLEMENTARY ANTIOXIDANT EFFECTS

According to conventional wisdom concerning vitamin E, alpha tocopherol is the premier antioxidant in the tocopherol family. Recently, however, several investigators have reported that the relative antioxidant potentials of alpha and gamma tocopherol vary considerably.^{1,31}

Both forms of vitamin E are known to inhibit the formation of destructive superoxide radicals and reduce the oxidation of fats and low-density lipoproteins in the blood—all risk factors for cardiovascular disease. Surprisingly, researchers at the University of Uppsala in Sweden found that gamma tocopherol was even more effective than alpha tocopherol in reducing several pro-thrombotic (contributing to clot formation) events associated with such forms of oxidative stress.³²

THE EIGHT FORMS OF VITAMIN E



Discovered in 1922, vitamin E is not a single compound, but rather an entire family of compounds with eight structurally related forms, or isomers. The eight isomers are made up of four tocopherols (alpha, beta, gamma, and delta tocopherol) and four tocotrienols, also known by their alpha, beta, gamma, and delta forms. The distinct structures of these tocopherols and tocotrienols confer unique chemical characteristics to each of the eight forms of vitamin E. While all forms of vitamin E are potent membrane-soluble antioxidants, only two—alpha tocopherol and gamma tocopherol—are predominant in nature.

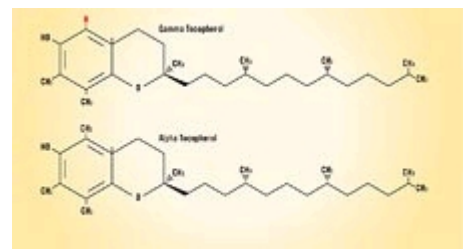
Humans and other animal species cannot synthesize their own vitamin E and therefore must acquire this nutrient from plants, which are the only organisms capable of manufacturing it.

Similarly, supplementation studies show that the combination of gamma tocopherol and alpha tocopherol can afford better protection against DNA damage than alpha tocopherol alone.³³ Moreover, University of Arkansas researchers discovered that a mixture of tocopherols is superior to alpha tocopherol in reducing oxidative damage in cultured muscle tissue. The authors propose that the lack of efficacy of commercial vitamin E supplements reported in clinical trials may reflect an absence of the gamma and delta tocopherol forms.³⁴

Finally, a European study reveals that both gamma tocopherol and the ratio of gamma tocopherol to alpha tocopherol are important nutritional markers related to the antioxidant and protective benefits of the traditional Mediterranean diet.¹³ The Mediterranean diet has been associated with greater longevity and a lower prevalence of many age-related diseases.

PROTECTING AGAINST CARDIOVASCULAR DISEASE

The alpha form of vitamin E decreases oxidative damage to the arterial lining, reduces dangerous aggregation and clumping of blood cells, delays clot formation,³² and enhances the activity of a known vascular dilator. It also inhibits smooth muscle proliferation (involved in the plaque-forming process),¹¹ improves the stability of fatty plaques, enhances the function of cells lining the arteries, regulates vascular tone, and fights inflammation.³⁵ Despite these impressive preliminary findings, however, clinical trials of alpha tocopherol alone have yielded mixed results concerning its cardioprotective effects.



Molecular Structure of Gamma Tocopherol and Alpha Tocopherol

The answer to this mystery may reside in the previously undiscovered benefits of gamma tocopherol and other forms of vitamin E. Since high-dose alpha tocopherol supplementation dramatically reduces gamma tocopherol levels, alpha tocopherol's benefits may be overshadowed by the adverse effects of diminished gamma tocopherol levels.³⁶⁻³⁸

Although less is known about gamma tocopherol than about alpha tocopherol, recent evidence suggests that the gamma form is an important weapon in defending against cardiovascular disease. Several investigations confirm that higher tissue concentrations of gamma tocopherol are associated with lower rates of illness and death due to cardiovascular events.²⁸

In fact, several studies show that patients with advanced cardiovascular disease exhibit normal plasma levels of alpha tocopherol but have substantially lower levels of gamma tocopherol.³⁹⁻⁴¹ In a seven-year follow-up study of more than 334,000 postmenopausal women with no previous heart disease, greater intake of dietary vitamin E—consisting predominantly of gamma tocopherol—was strongly associated with a lower risk of death from cardiovascular disease. The data did not appear to demonstrate a similarly protective role for supplemental alpha tocopherol.⁸

Numerous animal studies likewise suggest that gamma tocopherol may provide powerful protection for the heart. In laboratory rats, supplementation with gamma tocopherol reduced platelet aggregation and clot formation even more effectively than alpha tocopherol.³² In addition, gamma tocopherol at physiological doses was more effective than alpha tocopherol in enhancing the activity of superoxide dismutase (SOD), an antioxidant enzyme that may help reduce the risk of cardiac events.⁴²

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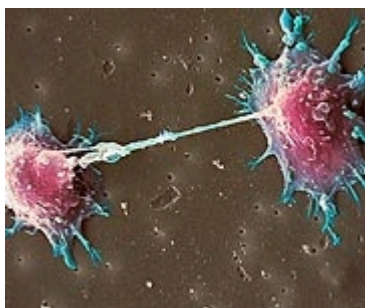
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GAMMA'S CANCER-PREVENTIVE PROPERTIES

While human and animal prevention trials are lacking, several studies support gamma tocopherol's potential role in cancer prevention, having demonstrated that it inhibits cancer cell growth even more effectively than alpha tocopherol.⁴³ Gamma tocopherol's actions appear multifactorial, and include the ability to:

- destroy reactive nitrogen species^{1,16}
- prevent the formation of mutagens (DNA-damaging agents) in the colon²
- induce apoptosis (programmed cell death) in cancerous cell lines^{4,5}
- regulate the expression of genetic factors that can influence cancerous growth.⁴⁴⁻⁴⁶

Colorectal cancer. As the second most common cause of cancer death in North America, colorectal cancer is a silent but deadly enemy. Gamma tocopherol may play an important role in arresting its development.



Prostate cancer cell division. Colored scanning electron micrograph of two prostate cancer cells in the final stage of cell division (cytokinesis).

While both gamma and alpha tocopherol appear to act as gene regulators,⁴⁴ recent epidemiological and experimental evidence suggests that gamma tocopherol may be a more potent chemopreventive agent than alpha tocopherol against this disease.⁴⁵ New evidence from tissue culture studies shows that both tocopherols, and gamma tocopherol in particular, can shield colon cells through a mechanism that enhances the expression of genetic factors that protect against cancerous growth. Scientists suggest that these findings hold relevance not only for cancer prevention, but also for the management of diabetes, inflammatory disorders, and cardiovascular disease.⁴⁶

The ratio of gamma tocopherol to alpha tocopherol appears higher in the bowel than in the blood,^{47,48} which may explain gamma tocopherol's protective effect against colorectal cancer. Gamma tocopherol may help prevent colon cancer by inhibiting the formation of mutagens arising from the oxidation of fecal lipids, as well as by diminishing oxidative stress in the cells lining the colon.^{24,45,49}

Prostate cancer. Both alpha tocopherol and gamma tocopherol may guard against prostate cancer.³⁻⁵ Gamma tocopherol effectively inhibits cell proliferation and DNA synthesis in colon and prostate cancer cells.⁵⁰ In one study, researchers found that gamma tocopherol—but not alpha tocopherol—induced apoptosis (programmed cell death) in both prostate and lung cancer cells.⁵⁰ Similar effects have been observed with gamma-tocopheryl quinone, a metabolite of gamma tocopherol that demonstrates powerful chemotherapeutic and cell-killing properties in human leukemia cells.⁵¹

One study revealed an intriguing association between prostate cancer and plasma and toenail concentrations of alpha tocopherol, gamma tocopherol, and selenium. Men with the highest concentrations of gamma tocopherol had a fivefold lower risk of developing prostate cancer than men with the lowest levels. Moreover, the protective effect observed for high levels of selenium and alpha tocopherol was observed only when gamma tocopherol levels were also high, leading the authors to recommend the use of mixed tocopherol supplements in future prevention trials.⁵²

Other cancers. Blood levels of both alpha tocopherol and gamma tocopherol appear to be substantially lower in women at risk for cervical cancer.⁵³ In addition, epidemiological evidence indicates that women who consume the most dietary vitamin E (which consists primarily of gamma tocopherol) have a 60% lower risk of breast cancer than women with low dietary vitamin E intake.¹² Finally, gamma tocopheryl quinone, the gamma tocopherol metabolite, has been found to kill leukemia and breast cancer cells in the laboratory.^{51,54}

GAMMA MAY GUARD AGAINST DEMENTIA

Some of the most promising protective benefits of gamma tocopherol involve Alzheimer's disease. Scientists believe that oxidative stress and inflammation are major contributing factors in the development of Alzheimer's, and that reactive nitrogen oxides play a role in the disease process. The results of one study suggest that gamma tocopherol offers greater protection than alpha tocopherol in subduing oxidative stress in the brain related to reactive nitrogen oxides, thus helping to protect the brain

GAMMA TOCOPHEROL EXCLUDED FROM DIETARY REFERENCE INTAKES

Until recently, scant attention has been paid to the biological importance of gamma tocopherol and the other tocopherol forms. In fact, they are not even included in the new dietary reference intakes recently established by the US Food and Nutrition Board.

Under the current dietary reference intake definition for vitamin E activity, the daily intake requirement can be met only with alpha tocopherol. This is not the case in the European Union, where gamma tocopherol is considered an integral component of the nutrient-based recommendations in many EU member countries.

The US Food and Nutrition Board's decision has failed to consider the cumulative results of more than three decades of research, which consistently point to a unique nutritional role for gamma tocopherol. This underestimated nutrient—the most prevalent form of vitamin E in nature—may contribute significantly to human health in ways yet fully recognized.

British researchers recently found that dietary vitamin E, mainly comprising gamma tocopherol, strongly affects the expression of an array of genes involved in the clearance of amyloid beta proteins.⁷ The accumulation of amyloid beta plaques is a hallmark of the oxidation and inflammation that occurs in the brains of Alzheimer's sufferers. Fighting beta amyloid tangles is believed to be essential in slowing the progression of this incapacitating disease.

Moreover, vitamin E appears to help regulate other genes associated with nerve growth, the transmission of nerve signals, and the clearance of advanced glycation end products, which are pro-inflammatory sugar-protein complexes that result from oxidative damage to biological molecules.⁷ Such evidence of vitamin E's role as a gene regulator indicates an important protective role for dietary vitamin E against the progression of Alzheimer's disease.

Alpha tocopherol, more so than gamma tocopherol, suppresses the degeneration of neurons caused by oxidative stress.⁵⁶ This has led some researchers to dismiss gamma tocopherol's importance in protecting against neurodegenerative decline. However, research conducted in 2005 provides strong evidence that gamma tocopherol may play just such a protective role. The study authors found that increased consumption of a mixture of tocopherols from food, rather than alpha tocopherol alone, was associated with a lower risk of Alzheimer's-related cognitive decline.⁶ Their findings are consistent with several other recent studies that validate vitamin E's importance in preventing the onset of Alzheimer's disease.^{7,57-59}

THE FUTURE OF VITAMIN E SUPPLEMENTATION

As recent investigations show, gamma tocopherol is quickly gaining recognition within the medical research community and is emerging as an important partner to alpha tocopherol in the science of preventive health.

While both forms of vitamin E have disease-preventive actions that reflect their individual chemistries, it is their combination that likely accounts for the powerful preventive effects observed in epidemiological, retrospective, and laboratory studies. Consequently, to highlight one form and exclude the other is to sell both forms short. We may soon find that the other tocopherol forms of vitamin E pack even more preventive punch in ways not yet revealed.

STUDY FLAWS FUEL VITAMIN E CONTROVERSY

Life Extension members and other health-conscious adults have expressed concern about recent headlines that question the safety and effectiveness of vitamin E supplements. In fact, findings from several clinical trials of alpha tocopherol have been ambiguous, failing to show consistent results due to the way the trials were structured and conducted.⁶⁰⁻⁶⁴

For example, a recent meta-analysis of seven clinical trials of antioxidant vitamins concluded that the data do not support the use of vitamin E supplements for preventing heart disease.⁶⁵ Likewise, a number of large prospective studies examining vitamin E's cancer-preventive effects have produced inconsistent results.¹⁴

Several plausible explanations may account for this ambiguity. At a recent conference on vitamin E and health sponsored by the New York Academy of Sciences, researchers noted that the various clinical trials of vitamin E differed markedly in ways that contribute to the inconsistent findings.¹⁴ For one thing, many of the studies focused on supplementation with vitamin E alone rather than with a broad spectrum of antioxidants. It is well known that nutrients work best when they work synergistically; consequently, the inconsistent findings may simply reflect the fact that no single nutrient is a "magic bullet."

In addition, many of the clinical studies involved elderly adults who were seriously ill, rather than healthy individuals. The results

of such studies would not, therefore, reflect the preventive nature of nutritional supplementation. Moreover, virtually all of the clinical trials used alpha tocopherol, the primary form of vitamin E in dietary supplements, and most used synthetic vitamin E—which is known to cause adverse effects at high dosage—rather than the mixed tocopherols found in natural dietary sources.⁴⁶ According to researchers at Johns Hopkins, the benefits of alpha tocopherol may in fact be compromised by a decrease in the levels of gamma and other tocopherols that is known to occur with high-dose alpha tocopherol supplementation.³⁶

To explain these inconsistencies, scientists are now looking beyond alpha tocopherol to other forms of vitamin E, particularly gamma tocopherol. To date, relatively few clinical studies have examined gamma tocopherol's role in the context of prevention. Those few, however, concur that gamma tocopherol may be every bit as important as alpha tocopherol in preventing chronic diseases.^{25,39} These findings may prelude a paradigm shift in scientific thinking on vitamin E.

Nevertheless, it is important to keep in mind that most research to date consists of laboratory studies and that further human clinical trials are needed to reveal the true powers of gamma tocopherol and other forms of vitamin E. Researchers have called for such trials to employ a mixture of tocopherols that better reflects the ratio found in the diet. Others urge a review of international dietary standards that to date have considered only the alpha tocopherol form.

Given the widespread popularity of vitamin E supplementation, the potential public health implications of using mixed tocopherols are immense. According to Dr. Kenneth Hensley of the Oklahoma Medical Research Foundation, recent findings may signal a major paradigm shift in free radical biology and medicine, and argue for a thorough reappraisal of the role of gamma tocopherol and other tocopherol forms, especially within the context of cardiovascular disease and cancer biology.⁶⁶

Dr. Stephan Christen of the University of California, Berkeley, contends that consumers taking vitamin E supplements containing an imbalance of the two principal forms of vitamin E are depriving themselves of the protective value afforded by a mixture of tocopherols. His views are based on joint investigations by US and Australian researchers that confirm previous findings—namely, that gamma tocopherol possesses distinctive and protective biochemical properties not seen in alpha tocopherol, and plays an equally important but complementary role in limiting cell damage and disarming toxic metabolites.²⁶ Accordingly, he and other scientists contend that vitamin E supplements should contain a ratio of alpha tocopherol to gamma tocopherol that is closer to what is found in nature.



In the meantime, consumers of dietary supplements committed to optimal nutrition should seriously consider the inclusion of mixed tocopherols in their daily regimens. Johns Hopkins scientists initially recommended that at least 20% of supplemental vitamin E be in the form of gamma tocopherol,⁵² while researchers at Berkeley just this year have proposed a 50-50 blend of alpha tocopherol and gamma tocopherol.⁶⁷ For optimal supplementation, it would appear logical to consume at least 200 mg of gamma tocopherol each day, in addition to around 400 IU of alpha tocopherol.

Editor's note: *Individuals who use the medication warfarin (Coumadin®) or have a history of bleeding disorder or hemorrhagic stroke should consult a physician before supplementing with vitamin E.*

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