

What's Wrong With Vitamin E?

Tocotrienols and Cancer

Tocotrienols possess the ability to stimulate the killing of cancer cells selectively through programmed cell death (apoptosis) in order to reduce cancer cell proliferation, while leaving normal cells unaffected.[28]

One of the mechanisms by which tocotrienols are thought to suppress cancer is related to the isoprenoid side chain that makes them different from tocopherols. Isoprenoids are plant compounds that have suppressed the initiation, growth and progression of many types of cancer in experimental studies.[29-31] They are common in fruits and vegetables, which may explain why diets rich in these foods have consistently been shown to reduce the incidence of cancer.[32-34]

The anti-proliferative effect of isoprenoids is thought to be due to suppression of the mevalonate pathway, through which mutated ras proteins transform healthy cells into cancer cells. Mutated ras is the most common cellular defect found in human cancers. The mevalonate pathway escapes regulatory control in tumor tissue, but remains highly sensitive to regulation by tocotrienols. Tocotrienols are at least 5 times more powerful than farnesol, the body's regulator of the mevalonate pathway.[33]

An early study demonstrated that long-term supplementation with palm-derived tocotrienols reduced the impact of carcinogens in rats.[35] After exposure to liver toxins, one group of rats was fed a diet supplemented with tocotrienols (30mg/kg food), while another group was given a standard diet. All 10 rats on the standard diet that were exposed to the liver toxins developed liver cancer during the 9-month-long study. In contrast, only one of the 6 rats supplemented with tocotrienols developed cancer nodules. Tocotrienol supplementation also significantly reduced the plasma level of GGT (gamma-glutamyl-transpeptidase), a marker enzyme for liver cancer.[35-36]

Another animal study demonstrated the effectiveness of tocotrienols in suppressing established tumors. When mice were given feed supplemented with gamma-tocotrienol (7umol/day), established melanoma tumors were significantly suppressed and the survival time of the hosts increased by 35%. Doubling of the dose did not further increase the duration of survival. Alpha-tocopherol had only a marginal effect.[37]

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 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.

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.



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

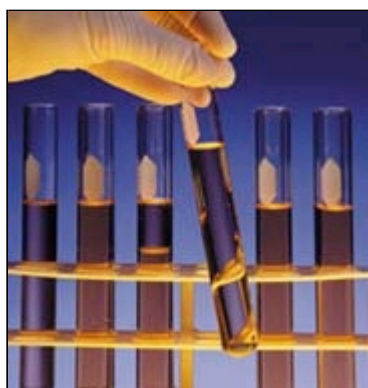
cycle of cell destruction begins.

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

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.

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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