ADVANCED ORTHOMOLECULAR RESEARCH

AOR CODE: AOR04309

Premium

Total E

$52.95 CAD

100% Natural Vitamin E with CoQ10

- Contains all 8 E-complex vitamers
- High in tocotrienols and gamma-tocopherol
- Powerful antioxidant, cardiovascular and cellular support
- Promotes healthy, youthful skin

Gluten Free Non-GMO Absorbables Heart Health

AOR Code	Variant	Price
AOR04309	60 SOFTGELS	$52.95

Details

Vitamin E is primarily an antioxidant and is one of five members of the body's antioxidant network. It is often used to help keep skin healthy and youthful, protecting it against UV damage and helping to heal wounds. Vitamin E also has many benefits for heart health. Vitamin E is not just one molecule, but a complex of eight different "vitamers" (four tocopherols and four tocotrienols). The benefits of all 8 members of the vitamin E family cannot be ignored. For example, gamma-tocopherol and gamma-tocotrienol may be involved in helping to regulate blood pressure. In addition, people with low gamma-tocopherol have been found to have a higher incidence of prostate problems and cognitive decline.

In 2001, AOR introduced Total E, the first complete, balanced E-complex to North America. It provides all four tocopherols and four tocotrienols in their natural ratios. The formula also includes Coenzyme Q10, because this nutrient plays a vital role in "recharging" E vitamins to their active antioxidant forms when they are deactivated in the battle against free radicals.

People who supplement with regular vitamin E that contains only alpha-tocopherol (or one of the synthetic variations) should consider switching to a natural, full-spectrum vitamin E. Those who need antioxidant, skin health and cholesterol support may benefit from taking Total E.

Label Info

Discussion

Total E™ is the first truly balanced, complete E-complex supplement that provides antioxidants for good health. Unlike other vitamin E supplements, Total E™ includes eight distinct vitamin E molecules: four tocopherols and four tocotrienols. Research shows that each of the different vitamin E molecules has a unique function.

Product Variation

Product Code	Size
AOR04309	60 SOFTGELS

Supplements Facts

Serving Size: 1 Softgel	Amount	% Daily
Mixed Tocopherols* (soy & palm)	365 mg	
Mixed Tocotrienols* (palm)	50 mg	
Coenzyme Q10	30 mg	

* Typical tocopherols : alpha – 65 mg, beta – 8 mg, gamma – 210 mg, delta – 82 mg

** Typical tocotrienols : alpha – 15 mg, beta – 0.6 mg, gamma – 28 mg, delta – 6.3 mg

olive and soybean oil. Softgel: gelatin, glycerin, caramel.

Guarantees

AOR™ guarantees that all ingredients have been declared on the label. Contains no wheat, gluten, corn, nuts, peanuts, sesame seeds, mustard, dairy, eggs, fish or shellfish.

Adult Dosage

Take 1 softgel daily with a fat-containing meal, or as directed by a qualified health care practitioner.

Cautions

Consult a health care practitioner prior to use if you are pregnant, breastfeeding, or taking blood pressure medication. Contains soy and sulphites. Do not use if you have a soy or sulphite allergy.

Source

Tocopherols – soy & palm

Tocotrienols – palm

CoQ10 - pharmaceutical synthesis

Main Application

Network antioxidant

Cardiovascular health

Cholesterol

Disclaimer

The information and product descriptions appearing on this website are for information purposes only, and are not intended to provide or replace medical advice to individuals from a qualified health care professional. Consult with your physician if you have any health concerns, and before initiating any new diet, exercise, supplement, or other lifestyle changes.

Research

Background

An 8-Member Family

Say “vitamin E” to most health-conscious people, and they immediately think of one molecule: alpha-tocopherol. But vitamin E is not just this one molecule, but a complex, like the B-complex. The E complex is an eight-member family, composed of eight closely related vitamin E molecules (or “vitamers”): four tocopherols and four tocotrienols. Each member of the vitamin E complex has its own unique strengths, and even unique properties not shared with other E vitamers. If your “vitamin E” contains only alpha-tocopherol – or alpha tocopherol with token quantities of “mixed tocopherols” – you’re missing out on the benefits of the “other” vitamin E molecules. But more than that: studies show that unbalanced alpha-tocopherol supplementation actually depletes the body of the other members of the family, and can negate many of their benefits!

Everyone Has a Role

Tocotrienols reduce cholesterol synthesis and are powerful antioxidants. Gamma tocopherol detoxifies free radicals that could contribute to Alzheimer’s disease, suppresses inflammation and may reduce the risk of prostate cancer. Other vitamin E molecules lower cholesterol and bloodpressure. As an extra boost, coenzyme Q10 is included to recharge vitamin E molecules when they are deactivated by oxidants.

Research

Balancing Gamma & Alpha-Tocopherol

After just one month of supplementing with 400 IU of alpha-tocopherol, peoples’ gamma-tocopherol levels are reduced by two-thirds. It may take as much as two years for the ratio of alpha- and gamma-tocopherol to normalize after unbalanced alpha-tocopherol supplementation is stopped! By contrast, gamma-tocopherol supplements actually raise alpha-tocopherol levels. Over the long term, tocotrienols may have a similar effect, as they are slowly converted to alpha-tocopherol over time.

Which “E” For the Heart?

Many studies (the HOPE, GISSI, CHAOS, Primary Prevention Project (PPP)) have now found that, despite all expectations, alpha-tocopherol does not give any protection against death from a heart attack or other heart hazards in people at high risk. Many objections have been raised against these trials, but the problem may have been that they had the wrong “vitamin E.”

When you consider all the heart-protective properties of the “other” E vitamins – cholesterol-lowering, anti-inflammatory, blood-pressure reduction, inhibition of adhesion molecules, and on and on – you might expect that alpha-tocopherol, alone, is not going to be the heart cure-all many people expect it to be. It’s interesting, therefore, that several studies have found that low plasma levels of gamma-tocopherol – but not alpha tocopherol – are found in patients with atherosclerosis. Three such studies have specifically found an unbalanced ratio of alpha- to gamma-tocopherol in such patients! A key step in the development of atherosclerosis is the invasion of injured blood vessel walls by immune cells called monocytes. A recent study found that alpha-tocotrienol actually inhibited the sticking of monocytes to the endothelial cell. Alpha-tocotrienol was much more potent than alpha-tocopherol.

Likewise, in two large epidemiological studies (one involving American women, and the other including Finnish people of both genders), it’s been found that vitamin E from food, but not from supplements, was protective against death from heart disease. Why would this be? Maybe the problem lies, again, in the form of vitamin E being used. Crucially, most of the vitamin E in the food we eat is gamma-tocopherol, while most “vitamin E” supplements are overbalanced with alpha.

Tocotrienols & Cholesterol

One of the key benefits of the tocotrienols is their ability to reduce cholesterol synthesis, by reducing the activity of HMG-CoA reductase, a key enzyme in this process. Alpha-tocopherol supplements have been shown to interfere with this action in animal experiments. Double-blind, placebo-controlled trials have shown that high-dose tocotrienol complex can help restore cholesterol balance in people whose levels are too high. In one such trial, tocotrienols actually reversed the thickening of the arteries leading into the brain in patients with advanced carotid stenosis.

The Gammas for Blood Pressure

Extracellular fluid pressure plays a key role in the regulation of blood pressure, and high extracellular fluid pressure puts you at risk of congestive heart failure, cardiac fibrosis, and liver cirrhosis. It was recently found that gamma-tocopherol and gamma-tocotrienol, but not alpha-tocopherol, help control extracellular fluid pressure through a key metabolite.

Healthy Prostate Cells

While one study (the ATBC trial) found that low-dose alpha-tocopherol promotes healthy cell activities in the prostate, two studies suggest that high-dose alpha-tocopherol may actually increase the risk of prostate problems. Some researchers think that the reason may be due to alpha-tocopherol's ability to deplete gamma-tocopherol, since (as discussed below) some studies have found that higher levels of gamma-tocopherol, but not alpha-tocopherol alone, reduce the risk of this problem. A recent study found that men who had the most gamma-tocopherol in their blood were an astounding five times less likely to develop prostate problems than men whose blood gamma-tocopherol levels were lowest. In the same study, alpha-tocopherol and selenium levels were only found to be protective in men whose gamma-tocopherol levels were also high!

Cell Suicide

Five studies have found that that delta-tocopherol, as well as all four tocotrienols, but not alpha-tocopherol, can cause unhealthy breast cells to commit "cellular suicide" in a test tube.

Tocotrienols Are Stronger Antioxidants

Alpha-tocopherol is a good antioxidant against many kinds of free radicals, but gamma-tocopherol is much more effective in detoxifying "reactive nitrogen species," the class of free radicals found in smog. In fact, alpha-tocopherol cannot effectively remove peroxynitrite (a key reactive nitrogen species) without gamma-tocopherol as a partner. The tocotrienols' unique chemical structures allow them to move around more freely in cell membranes. As a result, the tocotrienols are forty to sixty times more potent antioxidants than the tocopherols in biological membranes. Researchers recently reported that tocotrienols, but not alpha-tocopherol, extend the average lifespan of flatworms, and protected them against carbonylation, a kind of free radical damage to the body's proteins.

Gamma-Tocopherol for Inflammation

COX-2 is a key enzyme in the inflammatory process. It is targeted by "COX-2 inhibitor" drugs such as Celebrex® and Vioxx.® Researchers have recently reported that gamma-tocopherol, but not alpha-tocopherol, is an effective COX-2 inhibitor. The researchers also mention that "the current finding is consistent with our recent [unpublished] observation that gamma-tocopherol supplementation attenuated inflammation-induced damage in rats."

Alzheimer's Disease and Gamma-Tocopherol

There's been evidence for a long time that free radicals are important in the degenerative process of Alzheimer's disease. But until recently, it hasn't been clear which kinds of free radicals are perpetrating these acts of neurological terrorism. And without an understanding of which free radicals are doing the damage, you can't know which antioxidants are likely to be most effective in putting out the fires.

Recent research has begun to provide evidence that nitrogen-based free radicals, such as peroxynitrite, is especially virulent in the brains of people with Alzheimer's disease. As noted above, gamma-, but not alpha-tocopherol can detoxify nitrogen-based free radicals such as peroxynitrite. So researchers looked at levels of gamma- and alpha-tocopherol in the brains of people who had died with Alzheimer's disease. The results: victims of Alzheimer's disease were found to have a specific depletion of gamma-tocopherol in areas of the brain affected by the disease: alpha-tocopherol levels

were the same in the brains of the Alzheimer's casualties as in people without the disease, but gamma-tocopherol levels were found to be lower throughout the brains of people with the disease compared to the brains of those without.

These depleted levels of gamma-tocopherol corresponded with increased levels of a waste product left over when gamma-tocopherol is used up in fighting nitrogen-based free radicals. Crucially, the region-by-region pattern of used-up gamma-tocopherol followed the pattern of nitrogen-based free radical damage already established in earlier studies.

Finally, the same team showed that gamma-, but not alpha-tocopherol could significantly protect the enzyme alpha-ketoglutarate dehydrogenase from damage by peroxynitrite. Levels of this enzyme have been found to be reduced by 50 to 75% in the brains of people with Alzheimer's than it is in the brains of people not suffering with the disease. The researchers confirmed their suspicions: as much as 55% of the peroxynitrite damage to this Alzheimer's-sensitive enzyme was prevented by gamma-tocopherol, while alpha-tocopherol offered only a 15% reduction at the optimal concentration.

One large, double-blind, placebo-controlled study has already shown that alpha-tocopherol supplements can provide some limited support for people with Alzheimer's, slowing the progression of the disease. This new research suggests that gamma-tocopherol may provide far greater protection. In fact, these scientists suggest that, since "Dietary supplementation with alpha-tocopherol will decrease plasma levels of gamma-tocopherol …it is conceivable that the beneficial effect of alpha-tocopherol supplementation are confounded by a diminuition of gamma-tocopherol pools in [Alzheimer's disease] … A better clinical paradigm might entail co-supplementation with gamma-tocopherol."

Market Trends

Vitamin E is a popular supplement that is commonly taken as an antioxidant and for immunity, eye and skin health. Many people do not realize the importance of taking the full complex of vitamin E forms rather than solely alpha-tocopherol.

Since 2001 (see AOR Advantage), many E-complex products have appeared on the North American market. Many of these products contain mostly alpha-tocopherol with small amounts of tocotrienols and the rest of the tocopherols mixed in but at doses that are not therapeutic or natural. This is a cheaper route of production and a miserable trick to play on the consumer. A completely natural E-complex supplement should contain all four tocopherols and all four tocotrienols at the ratios present in AOR's Total E.

AOR Advantage

In 2001, AOR introduced the first complete E-complex to North America. Total E contains only natural ingredients and is not bolstered with synthetic alpha-tocopherol or unnatural ratios of each vitaminer. Total E is the first complete, full-spectrum, balanced E complex supplement in Canada, providing alpha-, beta-, gamma-, and delta-tocopherols and tocotrienols in a potency designed to create an excellent E-complex profile. The formula also includes Coenzyme Q10, because this nutrient plays a

vital role in “recharging” E vitamins to their active antioxidant form when they are deactivated in the battle against free radicals.

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Abstract

Review: Antiangiogenic and anticancer potential of unsaturated vitamin E (tocotrienol).

The Journal of Nutritional Biochemistry 2009, 20(2):79-86.

Teruo Miyazawa, Akira Shibata, Phumon Sookwong, Yuki Kawakami, Takahiro Eitsuka, Akira Asai, Shinichi Oikawa, Kiyotaka Nakagawa

Several lines of evidence support the beneficial effect of tocotrienol (T3; an unsaturated vitamin E) on inhibition of tumor development. Many factors, including decrease in oxidative stress and modulation of cell signaling pathways in tumor and endothelial cells, have been implicated in such anticancer action of T3, while the in vivo potency and exact intracellular mechanisms for the anticancer properties of T3 remain not fully understood. We have hypothesized that the inhibitory effect of T3 on cancer may be attributable to the antiangiogenic activity of T3, and we found that T3 acts as a potent regulator of growth-factor-dependent signaling in endothelial cells and as an antiangiogenic agent minimizing tumor growth. In this work, we review the history and biological action (i.e., anticancer) of vitamin E and describe current research on the antiangiogenic effects of T3 and its mechanisms.

Tocotrienol-rich fraction of palm oil exhibits anti-inflammatory property by suppressing the expression of inflammatory mediators in human monocytic cells.

Mol Nutr Food Res 2008, 52:921-929.

Shu-Jing Wu, Po-Len Liu, Lean-Teik Ng.

Tocotrienol-rich fraction (TRF – Tocomin®SupraBio™) of palm oil has been shown to possess potent antioxidant, anticancer, and cholesterol lowering activities. In this study, our aim was to examine the effects of TRF on LPS-induced inflammatory response through measuring the production of inflammatory mediators, namely nitric oxide (NO), prostaglandin E2 (PGE2), inducible nitric oxide synthase (iNOS), cytokines (TNF-a, IL-4, and IL-8), cyclooxygenase-1 and -2 (COX-1 and COX-2), and nuclear factor-jB (NFjB) in human monocytic (THP-1) cells. At concentrations 0.5–5.0 lg/mL, TRF dose-dependently protected against LPS-induced cell death. At same concentrations, TRF also showed potent anti-inflammatory activity as demonstrated by a dose-dependent inhibition of LPS (1 lg/mL)-induced release of NO and PGE2, and a significant decrease in the transcription of proinflammatory cytokines. TRF at 1.0 lg/mL significantly blocked the LPS induction of iNOS and COX-2 expression, but not COX-1. This anti-inflammatory activity was further supported by the inhibition of NF-jB expression. These results conclude that TRF possesses potent anti-inflammatory activity, and its mechanism of action could be through the inhibition of iNOS and COX-2 production, as well as NF-jB expression.

Arterial Compliance and Vitamin E Blood Levels with a Self Emulsifying Preparation of Tcotrienol Rich Vitamin E. Arch Pharm Res 2008, 31(9):1212-1217.

Aida Hanum Ghulam Rasool, Abd Rashid Abd Rahman, Kah Hay Yuen, Abdul Rahim Wong.

The tocotrienol vitamin E has potent antioxidant property, however absorption is low due to high lipid solubility. A self emulsifying preparation of tocotrienol rich vitamin E (SF-TRE – Tocomin®SupraBio™) had been reported to increase their bioavailability. This randomized, placebo controlled, blinded end point clinical study aimed to determine the effects of 50, 100 and 200 mg daily of SF-TRE and placebo for two months on arterial compliance and vitamin E blood levels. Assessment of arterial compliance by carotid femoral pulse wave velocity (PWV) and augmentation index (AI), plasma vitamin E, serum total cholesterol and low density lipoprotein cholesterol were taken before and after 2 months' treatment in 36 healthy males. Un-supplemented tocotrienol levels were low, after treatment, all SF-TRE treated groups had significantly higher plasma ?, ? and ? tocotrienol concentrations compared to placebo.

Augmentation index change from baseline to end of treatment for groups placebo, 50, 100, and 200 mg were 2.22±1.54, -6.59±2.84, -8.72±3.77, and -6.27±2.67% respectively (p=0.049, 0.049, and 0.047 respectively). Groups 100 and 200 mg showed significant improvement after treatment with pulse wave velocity reductions of 0.77 m/s and 0.65 m/s respectively (p=0.007 and p=0.002). There was no effect of SF-TRE on serum lipids. We conclude that there was a trend towards improvement in arterial compliance with 2 months' of SF-TRE.

Cardioprotection with palm oil tocotrienols: Comparison of different isomers.

Am J Physiol Heart Circ Physiol 2008, 294:H970-H978.

Samarjit Das, Istvan Lekli, Manika Das, Gergo Szabo, Judit Varadi, Bela Juhasz, Istvan Bak, Kalanity Nesaretnam, Arpad Tosaki, Saul R Powell, Dipak K Das

A recent study from our laboratory indicated the cardioprotective ability of the tocotrienol-rich fraction (TRF) from red palm oil. The present study compared cardioprotective abilities of different isomers of tocotrienol (Tocomin®) against TRF as recently tocotrienol has been found to function as a potent neuroprotective agent against stroke. Rats were randomly assigned to one of the following groups: animals were given, by gavage, either 0.35%, 1%, or 3.5% TRF for two different periods of time (2 or 4 wk) or 0.03, 0.3, and 3 mg/kg body wt of one of the isomers of tocotrienol (?, ?, or ?) for 4 wk; control animals were given, by gavage, vehicle only. After 2 or 4 wk, rats were killed, and their hearts were then subjected to 30 min of global ischemia followed by 2 h of reperfusion. Dose-response and time-response experiments revealed that the optimal concentration for TRF was 3.5% TRF and 0.3 mg/kg body wt of tocotrienol given for 4 wk. TRF as well as all the isomers of tocotrienol used in our study provided cardioprotection, as evidenced by their ability to improve postischemic ventricular function and reduce myocardial infarct size. The ?-isoform of tocotrienol was the most cardioprotective of all the isomers followed by the ?- and ?-isoforms. The molecular mechanisms of cardioprotection afforded by tocotrienol isoforms were probed by evaluating their respective abilities to stabilize the proteasome, allowing it to maintain a balance between prodeath and prosurvival signals. Our results demonstrated that tocotrienol isoforms reduced c-Src but increased the phosphorylation of Akt, thus generating a survival signal.

Caveolin and Proteasome in Tocotrienol Mediated Myocardial Protection.

Cell Physiol Biochem 2008, 22:287-294.

Manika Das, Samarjit Das, Ping Wang, Saul R Powell, Dipak K Das

The effect of different isomers of tocotrienol was tested on myocardial ischemia reperfusion injury. Although all of the tocotrienol isomers offered some degree of cardioprotection, gamma-tocotrienol was the most protective as evident from the result of myocardial apoptosis. To study the mechanism of tocotrienol mediated cardioprotection, we examined the interaction and/or translocation of different signalling components to caveolins and activity of proteasome. The results suggest that differential interaction of MAP kinases with caveolin 1/3 in conjuncture with proteasome stabilization play a unique role in tocotrienol mediated cardioprotection possibly by altering the availability of pro-survival and anti-survival proteins.

Heart disease and single-vitamin supplementation.

Am J Clin Nutr 2007, 85(suppl): 293S-9S.

Maret G Traber

Heart disease is the number one cause of death in the United States and has long been recognized to be multifactorial. A growing body of evidence suggests that not only free radical–mediated reactions but also inflammatory responses play major roles in atherogenesis. Vitamin E has both antioxidant and antiinflammatory properties and is the most widely studied vitamin in clinical trials and thus will be the primary example used in this review. Clinical trials of vitamin E efficacy, in hindsight, have been overly optimistic in their expectation that a vitamin could reverse poor dietary habits and a sedentary lifestyle as well as provide benefit beyond that of pharmaceutical agents in treating heart disease. However, it is also apparent that most Americans do not consume dietary amounts adequate to meet established vitamin E requirements. In response to oxidative stressors, vitamin E can decrease biomarkers of lipid peroxidation, is itself killed, and requires optimal vitamin C status to function most effectively. Thus, adequate vitamin E intakes are clearly needed, but what is adequate for what function has yet to be defined. It is noteworthy that in most trials, biomarkers were not used nor were oxidative stress and lipid peroxidation markers used or plasma vitamin E concentrations measured.

In Vivo Angiogenesis Is Suppressed by Unsaturated Vitamin E, Tocotrienol.

J Nutr 2007, 137:1938-1943.

Kiyotaka Nakagawa, Akira Shibata, Shinji Yamashita, Tsuyoshi Tsuzuki, Jun Kariya, Shinichi Oikawa, Teruo Miyazawaz

Antiangiogenic therapy using drugs and food components is a recognized strategy for the prevention of various angiogenesis-mediated disorders such as tumor growth, diabetic retinopathy, and rheumatoid arthritis. Our preliminary cell culture studies, using both bovine aortic endothelial cells and human umbilical vein endothelial cells (HUVEC) on screening for food-derived antiangiogenic compounds, showed tocotrienol (T3 – Tocomin®), an unsaturated version of vitamin E, to be a potential angiogenic inhibitor. We therefore investigated the in vivo antiangiogenic properties of T3 using 2 well characterized angiogenic models [mouse dorsal air sac (DAS) assay and the chick embryo chorioallantoic membrane (CAM) assay]. In the DAS assay, the increased neovascularization (angiogenesis index, 4.8 6 0.6) in tumor cell–implanted mice was suppressed (angiogenesis index, 2.7 6 0.6) by dietary supplementation of 10 mg T3-rich oil/d (equivalent to 4.4 mg T3/d). In the CAM assay, T3 (500–1000 mg/egg) inhibited new blood vessel formation on the growing CAM and increased the frequency of avascular zone (36–50%). To evaluate the antiangiogenic mechanism, we conducted cell culture studies and found that T3 significantly reduced fibroblast growth factor - induced proliferation, migration, and tube formation in HUVEC (P , 0.05), with d-T3 having the highest activity. Western blot analysis revealed that d-T3 suppressed the phosphorylation of phosophoinositide-dependent protein kinase (PDK) and Akt, and increased the phosphorylation of apoptosis signal-regulating kinase and p38 in fibroblast growth factor-treated HUVEC, indicating that the antiangiogenic effects of T3 are associated with changes in growth factor-dependent phosphatidylinositol-3 kinase /PDK/Akt signaling as well as induction of apoptosis in endothelial cells. Our findings suggest that T3 has potential as a therapeutic dietary supplement for preventing angiogenic disorders, and therefore future clinical study will be required to evaluate the efficacy and safety of T3.

Characterization of the potent neuroprotective properties of the natural vitamin E ?-tocotrienol.

J Neurochem 2006, 98(5):1474-1486.

Savita Khanna, Sashwati Roy, Narasimham L Parinandi, Mariah Maurer, Chandan K Sen

The natural vitamin E tocotrienols possess properties not shared by tocopherols. Nanomolar alphatocotrienol, not alpha-tocopherol, is potently neuroprotective (JBC 275:13049; 278:43508; Stroke 36:2258). On a concentration basis, this finding represents the most potent of all biological functions exhibited by any natural vitamin E molecule. We sought to dissect the antioxidant-independent and –dependent neuroprotective properties of alphatocotrienol by using two different triggers of neurotoxicity, homocysteic acid (HCA) and linoleic acid. Both HCA and linoleic acid caused neurotoxicity with comparable features such as increased GSSG/GSH, elevated [Ca2]i and compromised mitochondrial ?? . Mechanisms underlying HCA-induced neurodegeneration were comparable to the path implicated in glutamate-induced neurotoxicity. Inducible activation of c-Src and 12-lipoxygenase (12-Lox) represented early events in that pathway. Over-expression of active c-Src or 12-Lox sensitized cells to HCA-induced death. Nanomolar alpha-tocotrienol protected. Knock-down of c-Src or 12-Lox attenuated HCA-induced neurotoxicity. Oxidative stress represented a late event in HCA-induced death. The observation that micromolar, but not nanomolar, alpha-tocotrienol functions as an antioxidant was verified in the model involving linoleic acid induced oxidative stress and cell death. Oral supplementation of alpha-tocotrienol to humans results in a peak plasma concentration of 3 micromolar. Thus, oral alpha-tocotrienol may be neuroprotective by antioxidant-

independent as well as antioxidant-dependent mechanisms.

Tocotrienols: Vitamin E beyond tocopherols.

Life Sci. 2006 Feb 2;

Sen CK, Khanna S, Roy S.

Laboratory of Molecular Medicine, Department of Surgery, Davis Heart and Lung Research Institute, The Ohio State University Medical Center, Columbus, Ohio 43210, United States. 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.

Down-regulation of telomerase activity in DLD-1 human colorectal adenocarcinoma cells by tocotrienol.

Biochemical and biophysical Research Communications 2006, 348:170-175.

Takahiro Eitsuka, Kiyotaka Nakagawa, Teruo Miyazawa

As high telomerase activity is detected in most cancer cells, inhibition of telomerase by drug or dietary food components is a new strategy for cancer prevention. Here, we investigated the inhibitory effect of vitamin E, with particular emphasis on tocotrienol (unsaturated vitamin E), on human telomerase in cell-culture study. As results, tocotrienol inhibited telomerase activity of DLD-1 human colorectal adenocarcinoma cells in time- and dose-dependent manner, interestingly, with d-tocotrienol exhibiting the highest inhibitory activity. Tocotrienol inhibited protein kinase C activity, resulting in down-

regulation of c-myc and human telomerase reverse transcriptase (hTERT) expression, thereby reducing telomerase activity. In contrast to tocotrienol, tocopherol showed very weak telomerase inhibition. These results provide novel evidence for the first time indicating that tocotrienol acts as a potent candidate regulator of telomerase and supporting the anti-proliferative function of tocotrienol.

Neuroprotective properties of the natural vitamin E alpha-tocotrienol.

Stroke. 2005 Oct;36(10):2258-64.

Khanna S, Roy S, Slivka A, Craft TK, Chaki S, Rink C, Notestine MA, DeVries AC, Parinandi NL, Sen CK.

BACKGROUND AND PURPOSE: The current work is based on our previous finding that in neuronal cells, nmol/L concentrations of alpha-tocotrienol (TCT), but not alpha-tocopherol (TCP), blocked glutamate-induced death by suppressing early activation of c-Src kinase and 12-lipoxygenase.

METHODS: The single neuron microinjection technique was used to compare the neuroprotective effects of TCT with that of the more widely known TCP. Stroke-dependent brain tissue damage was studied in 12-Lox-deficient mice and spontaneously hypertensive rats orally supplemented with TCT.

RESULTS: Subattomole quantity of TCT, but not TCP, protected neurons from glutamate challenge. Pharmacological as well as genetic approaches revealed that 12-Lox is rapidly tyrosine phosphorylated in the glutamate-challenged neuron and that this phosphorylation is catalyzed by c-Src. 12-Lox-deficient mice were more resistant to stroke-induced brain injury than their wild-type controls. Oral supplementation of TCT to spontaneously hypertensive rats led to increased TCT levels in the brain. TCT-supplemented rats showed more protection against stroke-induced injury compared with matched controls. Such protection was associated with lower c-Src activation and 12-Lox phosphorylation at the stroke site.

CONCLUSIONS: The natural vitamin E, TCT, acts on key molecular checkpoints to protect against glutamate- and stroke-induced neurodegeneration.

The therapeutic impacts of tocotrienols in type 2 diabetic patients with hyperlipidemia.

Atherosclerosis 2005, 182:367-374.

Simant Baliarsingh, Zafarul H Beg, Jamal Ahmad

In type 2 diabetics, the progression of atherosclerosis is more rapid than the general population and 80% of these patients will die of an atherosclerotic event. Since in these patients hyperglycemia per se confers increased risk for cardiovascular disease (CVD), the presence of even borderline-high-risk LDL-C signals the need for more aggressive LDL-lowering therapy. Most of the lipid lowering agents, currently in use in the treatment of dyslipidemia in type 2 diabetics, have a host of side effects. In contrast, dietary tocotrienols are Vitamin E and have effective lipid lowering property in addition to their potent antioxidant activity. In this study, we have investigated the therapeutic impacts of tocotrienols on serum and lipoprotein lipid levels in type 2 diabetic patients. Based on known

tocotrienol rich fraction (TRF)-mediated decrease on elevated blood glucose and glycated hemoglobin A1C (HbA1C) in diabetic rats, we have also investigated the effect of TRF on these parameters. A randomized, double blind, placebo-controlled design involving 19 type 2 diabetic subjects with hyperlipidemia was used. After 60 days of TRF treatment, subjects showed an average decline of 23, 30, and 42% in serum total lipids, TC, and LDL-C, respectively. The goal in type 2 diabetics is to reduce LDL-C levels?100 mg/dl. In the present investigation tocotrienols mediated a reduction of LDL-C from an average of 179 mg/dl to 104 mg/dl. However, hypoglycemic effect of TRF was not observed in these patients because they were glycemically stable and their glucose and HbA1 levels were close to normal values. In conclusion, daily intake of dietary TRF by type 2 diabetics will be useful in the prevention and treatment of hyperlipidemia and atherogenesis.

Effects of tocotrienols on cell viability and apoptosis in normal murine liver cells (BNL CL.2) and liver cancer cells (BNL 1ME A.7R.1), in vitro.

Asia Pac J Clin Nutr 2005, 14(4):374-380. Chan Hooi Har, Chan Kok Keong

The effects of tocotrienols on murine liver cell viability and their apoptotic events were studied over a dose range of 0–32?g mL-1. Normal murine liver cells (BNL CL.2) and murine liver cancer cells (BNL 1ME A.7R.1) were treated with tocotrienols (T3 – Tocomin®), alpha tocopherol (?-T) and the chemo drug, Doxorubicin (Doxo, as a positive control). Cell viability assay showed that T3 significantly ($P < 0.05$) lowered the percentage of BNL 1ME A.7R.1 cell viability in a dose-responsive manner (8-16 ?g mL-1), whereas T did not show any significant ($P > 0.05$) inhibition in cell viability with increasing treatment doses of 0 – 16 ?g mL-1. The IC50 for tocotrienols were 9.8, 8.9, 8.1, 9.7, 8.1 and 9.3 ?g mL-1 at 12, 24, 36, 48, 60 and 72 hours respectively. Early apoptosis was detected 6 hours following T3 treatment of BNL 1ME A.7R.1 liver cancer cells, using Annexin V-FITC fluorescence microscopy assay for apoptosis, but none were observed for the non-treated liver cancer cells at the average IC50 of 8.98 ?g mL-1 tocotrienols for liver cancer cells. Several apoptotic bodies were detected in BNL 1ME A.7R.1 liver cancer cells at 6 hours post-treatment with tocotrienols (8.98?g mL-1) using Acridine Orange/Propidium Iodide fluorescence assay. However, only a couple of apoptotic bodies were seen in the non-treated liver cancer cells and the BNL CL.2 normal liver cells. Some mitotic bodies were also observed in the T3-treated BNL 1ME A.7R.1 liver cancer cells but were not seen in the untreated BNL 1ME A.7R.1 cells and the BNL CL.2 liver cells. Following T3-treatment (8.98?g mL-1) of the BNL 1ME A.7R.1 liver cancer cells, 24.62%, 25.53% and 44.90% of the cells showed elevated active caspase 3 activity at 9, 12 and 24 hours treatment period, respectively. DNA laddering studies indicated DNA fragmentation occurred in the T3-treated liver cancer cells, BNL 1ME A.7R.1 but not in non-treated liver cancer cells and the T3-treated and non-treated normal liver cells. These results suggest that tocotrienols were able to reduce the cell viability in the murine liver cancer cells at a dose of 8-32 ?g mL-1 and that this decrease in percentage cell viability may be due to apoptosis.

Cardioprotection with palm tocotrienol: antioxidant activity of tocotrienol is linked with its ability to stabilize proteasomes.

Am J Physio Heart Cirrc Physiol 2005, 289:H361-H367.

Samarjit Das, Saul R Powell, Ping Wang, Andras Divald, Kalanithi Nesaretnam, Arpad Tosaki, Gerald A Cordis, Nilanjana Maulik, Dipak K Das.

Tocotrienols, isomers of vitamin E, have been found to possess many health benefits. The present study was designed to determine whether tocotrienol has a direct cardioprotective role. Isolated rat hearts were perfused for 15 min with Krebs-Ringer bicarbonate buffer in the absence or presence of palm tocotrienol derived from the tocotrienol rich fraction (0.035%) of palm oil (TRF). In another group of studies, the hearts were preperfused for 15 min in the presence of a c-Src inhibitor, 4-amino-5-(4-methylphenyl)-7-(t-butyl)-pyrazolo-3,4-d-pyrimidine (PPI). The hearts were then subjected to 30 min of global ischemia followed by 2 h of reperfusion. As expected, ischemia/reperfusion caused ventricular dysfunction, electrical rhythm disturbances, and increased myocardial infarct size. PPI or TRF could reverse the ischemia-reperfusion-mediated cardiac dysfunction. Ischemia-reperfusion also pregulated c-Src expression and phosphorylation. Although TRF only minimally affected c-Src expression, it significantly inhibited the phosphorylation of c-Src. Ischemia-reperfusion reduced 20S and 26S proteasome activities, an effect prevented by TRF pretreatment. PPI exerted a cardioprotective effect that is not mediated by the proteasome but, rather, through direct inhibition of c-Src. The results of this study support a role for c-Src in postischemic cardiac injury and dysfunction and demonstrate direct cardioprotective effects of TRF. The cardioprotective properties of TRF appear to be due to inhibition of c-Src activation and proteasome stabilization.

Mixed tocopherols inhibit platelet aggregation in humans: potential mechanisms.

Am J Clin Nutr 2003 Mar; 77(3): 700-6.

Liu M, Wallmon A, Olsson-Mortlock C, Wallin R, Saldeen T.

BACKGROUND: Epidemiologic studies have shown an inverse correlation between acute coronary events and high intake of dietary vitamin E. Recent clinical studies, however, failed to show any beneficial effects of alpha-tocopherol on cardiovascular events. Absence of tocopherols other than alpha-tocopherol in the clinical studies may account for the conflicting results.

OBJECTIVE: This study compared the effect of a mixed tocopherol preparation rich in gamma-tocopherol [13% alpha-tocopherol, 62% gamma-tocopherol and 25% delta-tocopherol] with that of alpha-tocopherol on platelet aggregation in humans and addressed the potential mechanisms of the effect.

DESIGN: Forty-six subjects were randomly divided into 3 groups: alpha-tocopherol, mixed tocopherols, and control. ADP and phorbol 12-myristate 13-acetate-induced platelet aggregation, nitric oxide (NO) release, activation of endothelial constitutive nitric-oxide synthase (ecNOS; EC 1.14.13.39) and of protein kinase C (PKC), and ecNOS, superoxide dismutase (SOD; EC 1.15.1.1), and PKC protein content in platelets were measured before and after 8 wk of administration of tocopherols.

RESULTS: ADP-induced platelet aggregation decreased significantly in the mixed tocopherol group but not in the alpha-tocopherol and control groups. NO release, ecNOS activation, and SOD protein content in platelets increased in the tocopherol-treated groups. PKC activation in platelets was

markedly decreased in the tocopherol-treated groups. Mixed tocopherols were more potent than alpha-tocopherol alone in modulating NO release and ecNOS activation but not SOD protein content or PKC activation.

CONCLUSIONS: Mixed tocopherols were more potent in preventing platelet aggregation than was alpha-tocopherol alone. Effects of mixed tocopherols were associated with increased NO release, ecNOS activation, and SOD protein content in platelets, which may contribute to the effect on platelet aggregation.

The nitration product 5-nitro-gamma-tocopherol is increased in the Alzheimerbrain.

Nitric Oxide 2002 Mar; 6(2): 221-7.

Williamson KS, Gabbita SP, Mou S, West M, Pye QN, Markesbery WR, Cooney RV,Grammas P, Reimann-Philipp U, Floyd RA, Hensley K.

Oxidative stress and quasi-inflammatory processes recently have been recognized as contributing factors in the pathogenesis of Alzheimer's disease (AD). Reactive nitrating species have specifically been implicated in AD based on immunochemical and instrumental detection of nitrotyrosine in AD brain protein. The significance of lipid-phase nitration has not been investigated in AD. This study documents a significant two- to threefold increase in the lipid nitration product 5-nitro-gamma-tocopherol in affected regions of the AD brain asdetermined by high-performance liquid chromatography with electrochemical detection. In a bioassay to compare the relative potency of alpha-tocopherol and gamma-tocopherol against nitrative stress, rat brain mitochondria were exposed to the peroxynitrite-generating compound SIN-1. The oxidation-sensitive Kreb's cycle enzyme alpha-ketoglutarate dehydrogenase was inactivated by SIN-1, in a manner that could be significantly attenuated by gamma-tocopherol.

Tocotrienols-rich diet decreases advanced glycosylation end-products in non-diabetic rats and improves glycemic control in streptozotocin-induced diabetic rats.

Malaysian J Pathol 2002, 24(2):77-82.

WM Wan Nazaimoon, BAK Khalid

This study determined the effects of palm vitamin E (TRF) diet on the levels of blood glucose, glycated hemoglobin (gHb), serum advanced glycosylation end-products (AGE) and malondialdehyde (MDA) of diabetic Sprague-Dawley rats. The rats received either control (normal rat chow), TRF diet (normal chow fortified with TRF at lgkg) or Vitamin C diet (vitamin E-deficient but contained vitamin C at 45 gkg). The animals were maintained on the respective diet for 4 weeks, made diabetic with streptozotocin (STZ), then followed-up for a further 8 weeks. At week-4, mean serum AGE levels of rats given TRF diet (0.7f0.3 unitslml) were significantly lower than those of control or Vitamin C diet rats (~£0.03)T. he levels increased after STZ and became comparable to the other groups. At weekl2, blood glucose (20.9f6.9mM) and gHb (10.0f 1.6%) of rats on TRF diet remained significantly low compared to that of control or Vitamin C diet rats (~£0.03)M. DA however, was not affected and

remained comparable between groups throughout the study. This study showed that TRF may be a useful antioxidant; effectively prevented increase in AGE in normal rats, and caused decrease in blood glucose and gHb in diabetic rats. Further studies are needed to elucidate the mechanisms of action of TRF.

Does lack of tocopherols and tocotrienols put women at increased risk of breast cancer? J

Nutr Biochem 2002 Jan; 13(1): 2-20.

Schwenke DC.

Breast cancer is the leading site of new cancers in women and the second leading cause (after lung cancer) of cancer mortality in women. Observational studies that have collected data for dietary exposure to alpha-tocopherol with or without the other related tocopherols and tocotrienols have suggested that vitamin E from dietary sources may provide women with modest protection from breast cancer. However, there is no evidence that vitamin E supplements confer any protection whatever against breast cancer. Observational studies that have assessed exposure to vitamin E by plasma or adipose tissue concentrations of alpha-tocopherol have failed to provide consistent support for the idea that alpha-tocopherol provides any protection against breast cancer. In addition, evidence from studies in experimental animals suggest that alpha-tocopherol supplementation alone has little effect on mammary tumors. In contrast, studies in breast cancer cells indicate that alpha- gamma-, and delta-tocotrienol, and to a lesser extent delta-tocopherol, have potent antiproliferative and proapoptotic effects that would be expected to reduce risk of breast cancer. Many vegetable sources of alpha-tocopherol also contain other tocopherols or tocotrienols. Thus, it seems plausible that the modest protection from breast cancer associated with dietary vitamin E may be due to the effects of the other tocopherols and the tocotrienols in the diet. Additional studies will be required to determine whether this may be the case, and to identify the most active tocopherol/tocotrienol.

Molecular aspects of alpha-tocotrienol antioxidant action and cell signalling.

J Nutr 2001 Feb; 131(2): 369S-73S.

Packer L, Weber SU, Rimbach G.

Vitamin E, the most important lipid-soluble antioxidant, was discovered at the University of California at Berkeley in 1922 in the laboratory of Herbert M. Evans (Science 1922, 55: 650). At least eight vitamin E isoforms with biological activity have been isolated from plant sources. Since its discovery, mainly antioxidant and recently also cell signaling aspects of tocopherols and tocotrienols have been studied. Tocopherols and tocotrienols are part of an interlinking set of antioxidant cycles, which has been termed the antioxidant network. Although the antioxidant activity of tocotrienols is higher than that of tocopherols, tocotrienols have a lower bioavailability after oral ingestion. Tocotrienols penetrate rapidly through skin and efficiently combat oxidative stress induced by UV or ozone. Tocotrienols have beneficial effects in cardiovascular diseases both by inhibiting LDL oxidation and by down-regulating 3-hydroxyl-3-methylglutaryl-coenzyme A (HMG CoA) reductase, a key enzyme of the mevalonate pathway. Important novel antiproliferative and neuroprotective effects of tocotrienols,

which may be independent of their antioxidant activity, have also been described.

Gamma-tocopherol, the major form of vitamin E in the US diet, deserves more attention.

Am J Clin Nutr 2001 Dec; 74(6): 714-22.

Jiang Q, Christen S, Shigenaga MK, Ames BN.

Gamma-tocopherol is the major form of vitamin E in many plant seeds and in the US diet, but has drawn little attention compared with alpha-tocopherol, the predominant form of vitamin E in tissues and the primary form in supplements. However, recent studies indicate that gamma-tocopherol may be important to human health and that it possesses unique features that distinguish it from alpha-tocopherol. gamma-Tocopherol appears to be a more effective trap for lipophilic electrophiles than is alpha-tocopherol. gamma-Tocopherol is well absorbed and accumulates to a significant degree in some human tissues; it is metabolized, however, largely to 2,7,8-trimethyl-2-(beta-carboxyethyl)-6-hydroxychroman (gamma-CEHC), which is mainly excreted in the urine. gamma-CEHC, but not the corresponding metabolite derived from alpha-tocopherol, has natriuretic activity that may be of physiologic importance. Both gamma-tocopherol and gamma-CEHC, but not alpha-tocopherol, inhibit cyclooxygenase activity and, thus, possess antiinflammatory properties. Some human and animal studies indicate that plasma concentrations of gamma-tocopherol are inversely associated with the incidence of cardiovascular disease and prostate cancer. These distinguishing features of gamma-tocopherol and its metabolite suggest that gamma-tocopherol may contribute significantly to human health in ways not recognized previously. This possibility should be further evaluated, especially considering that high doses of alpha-tocopherol deplete plasma and tissue gamma-tocopherol, in contrast with supplementation with gamma-tocopherol, which increases both. We review current information on the bioavailability, metabolism, chemistry, and nonantioxidant activities of gamma-tocopherol and epidemiologic data concerning the relation between gamma-tocopherol and cardiovascular disease and cancer.

Association of serum antioxidant capacity with coronary artery disease in middle-aged men.

Jpn Heart J 2001 Nov; 42(6): 677-90.

Nojiri S, Daida H, Mokuno H, Iwama Y, Mae K, Ushio F, Ueki T.

The possible involvement of oxidative damage in the progression of atherosclerosis has been suggested. There is some evidence that antioxidant therapy may be beneficial for the prevention of coronary heart disease. In this study, we investigated the relationship between coronary artery disease (CAD) and serum antioxidative status by measuring the total antioxidant status (TAS). Other relevant antioxidants, such as retinol, alpha, gamma-tocopherol, ascorbic acid, alpha, beta-carotenoids, erythrocyte glutathione peroxidase (GSH-Px) and oxidative products, were also determined in 31 male CAD patients with angiographically defined CAD and 66 male controls, aged 40-70 years, in a case-control study. The TAS levels, ratio and the concentrations of retinol, albumin, total protein and HDL cholesterol were significantly lower in the CAD patients than in the controls (p

Association between alpha-tocopherol, gamma-tocopherol, selenium, and subsequent prostate cancer.

J Natl Cancer Inst 2000 Dec 20; 92(24): 2018-23.

Helzlsouer KJ, Huang HY, Alberg AJ, Hoffman S, Burke A, Norkus EP, Morris JS, Comstock GW.

BACKGROUND: Selenium and alpha-tocopherol, the major form of vitamin E in supplements, appear to have a protective effect against prostate cancer. However, little attention has been paid to the possible role of gamma-tocopherol, a major component of vitamin E in the U.S. diet and the second most common tocopherol in human serum. A nested case-control study was conducted to examine the associations of alpha-tocopherol, gamma-tocopherol, and selenium with incident prostate cancer.

METHODS: In 1989, a total of 10,456 male residents of Washington County, MD, donated blood for a specimen bank. A total of 117 of 145 men who developed prostate cancer and 233 matched control subjects had toenail and plasma samples available for assays of selenium, alpha-tocopherol, and gamma-tocopherol. The association between the micronutrient concentrations and the development of prostate cancer was assessed by conditional logistic regression analysis. All statistical tests were two-sided.

RESULTS: The risk of prostate cancer declined, but not linearly, with increasing concentrations of alpha-tocopherol (odds ratio (highest versus lowest fifth) = 0.65; 95% confidence interval = 0.32–1.32; P(trend) =.28). For gamma-tocopherol, men in the highest fifth of the distribution had a fivefold reduction in the risk of developing prostate cancer than men in the lowest fifth (P:(trend) =.002). The association between selenium and prostate cancer risk was in the protective direction with individuals in the top four fifths of the distribution having a reduced risk of prostate cancer compared with individuals in the bottom fifth (P(trend) =.27). Statistically significant protective associations for high levels of selenium and alpha-tocopherol were observed only when gamma-tocopherol concentrations were high.

CONCLUSIONS: The use of combined alpha- and gamma- tocopherol supplements should be considered in upcoming prostate cancer prevention trials, given the observed interaction between alpha-tocopherol, gamma-tocopherol, and selenium.

Lipophilic antioxidants in blood plasma as markers of atherosclerosis: the role of alpha-carotene and gamma-tocopherol.

Atherosclerosis 1999 May; 144(1): 117-22.

Kontush A, Spranger T, Reich A, Baum K, Beisiegel U.

Oxidative theory of atherosclerosis implies that plasma levels of lipophilic antioxidants might serve as indicators of lipoprotein oxidation in the arterial wall and as markers of the development of atherosclerosis. However, it is unknown whether the measurement of plasma antioxidants is able to

reflect atherogenesis or its risk. In order to assess whether the levels of lipophilic antioxidants in human plasma can discriminate between subjects with and without atherosclerosis, we measured the lipophilic antioxidants alpha-tocopherol, gamma-tocopherol, alpha-carotene, beta-carotene and ubiquinol-10 in plasma of 34 patients with coronary heart disease (CHD) and in 40 control subjects. We found that alpha-carotene and gamma-tocopherol were significantly lower in plasma of CHD patients compared to controls. This decrease was significantly independent of whether the antioxidants were expressed as its absolute amounts in plasma ($P < 0.001$ for alpha-carotene, and $P = 0.001$ for gamma-tocopherol) or normalized to plasma lipids ($P < 0.001$ for both). In contrast, beta-carotene was only lower in plasma of CHD patients in comparison to controls, when normalized to the lipids ($P = 0.02$). Independent contributions of different parameters to the variation in these plasma antioxidants were estimated using multiple regression approach. The analysis showed that both the decrease in alpha-carotene and the decrease in gamma-tocopherol were significantly associated only with the presence of CHD ($P < 0.001$ for each regression), while the decrease in beta-carotene was significantly related to the presence of hyperlipidaemia ($P < 0.001$). In striking contrast, no decrease in plasma alpha-tocopherol and ubiquinol-10 was detected in the patient group independently of how these antioxidants were expressed. These data suggest that plasma levels of alpha-carotene and gamma-tocopherol may represent markers of atherosclerosis in humans. Measuring these antioxidants may be of clinical importance as a practical approach to assess atherogenesis and/or its risk.

Effects of ?-Tocotrienol on ApoB Synthesis, Degradation and Secretion in HepG2 Cells.

Arterioscler Thromb Vasc Biol 1999, 19:704-712.

Andre Theriault, Qi Wang, Abdul Gapor, Khosrow Adeli.

g-Tocotrienol (g-T3), a naturally occurring analog of tocopherol (vitamin E), has been shown to have a hypocholesterolemic effect in animals and humans. Unlike tocopherol, it has also been shown to reduce plasma apoB levels in hypercholesterolemic subjects. The aim of this study was to define the mechanism of action of g-T3 on hepatic modulation of apoB production using cultured HepG2 cells as the model system. HepG2 cells preincubated with g-T3 were initially shown to inhibit the rate of incorporation of [14C]acetate into cholesterol in a concentration- and time-dependent manner, with a maximum 8663% inhibition at 50 mmol/L observed within 6 hours. g-T3, on the other hand, had no significant effect on the uptake of [14C]glycerol into pools of cellular triacylglycerol and phospholipid relative to untreated control. The rate of apoB synthesis and secretion was then studied by an [35S]methionine pulse-labeling experiment and quantified by immunoprecipitating apoB on chasing up to 3 hours. An average reduction of 2463% in labeled apoB in the media was apparent with g-T3 despite a 6062% increase in apoB synthesis. Fractionation of secreted apoB revealed a relatively denser lipoprotein particle, suggesting a less stable particle. Using a digitonin-permeabilized HepG2 cell system, the effects of g-T3 on apoB translocation and degradation in the endoplasmic reticulum were further investigated. The generation of a specific N-terminal 70-kDa proteolytic fragment proved to be a sensitive measure of the rate of apoB translocation and degradation. The abundance of this fragment increased significantly in g-T3-treated cells relative to untreated control cells (50621%) after 2 hours of chase. In addition, the presence of g-T3 resulted in an average decrease of 6468% in intact apoB. Taken together, the data suggest that g-T3 stimulates apoB degradation possibly as the result of decreased apoB translocation into the endoplasmic reticulum lumen. It is speculated that the

lack of cholesterol availability reduces the number of secreted apoB-containing lipoprotein particles by limiting translocation of apoB into the endoplasmic reticulum lumen.

Palm oil antioxidant effects in patients with hyperlipidaemia and carotid stenosis-2 year experience.

Asia Pacific J Clin Nutr 1997, 6(1):72-75.

DK Kooyenga, M Geller, TR Watkins, A Gapor, E Diakoumakis, ML Bierenbaum.

Antioxidants appear to play a role in the prevention of atherosclerosis. Here, we investigated the antioxidant properties of a ?-tocotrienol and ?-tocopherol enriched fraction of palm oil, in patients with carotid atherosclerosis. Serum lipids, fatty acid peroxides, platelet aggregation, and carotid artery stenosis were measured over a 24-month period in 50 patients with cerebrovascular disease. Change in stenosis was measured with bilateral duplex ultrasonography. These studies revealed apparent carotid atherosclerotic regression in eight and progression in two of the 25 antioxidant patients, while none of the control group exhibited regression and ten of 25 showed progression (P

Effects of palm olein tocopherol and tocotrienol on lipid peroxidation, lipid profiles and glycemic control in non-insulin diabetes mellitus patients.

Nutrition Research 1996, 16(11/12): 1901-1911.

WM Wan Nazaimoon, O Sakinah, A Gapor, BAK Khalid

Refined palm oil, palm olein contains very low amount of vitamin-E (0.01 %, w/w) as compared to its tocotrienol-rich extract, Palmvitee, which contains about 20 % (w/w) of vitamin E. The effects of palm olein intake on serum lipid peroxides or malondialdehyde (MDA) levels, lipid profiles and glycemic control of 32 non-insulin dependent diabetes mellitus patients were compared to those of Palmvitee using a double-blind study. Patients took six 300 mg capsules of Palmvitee or palm olein daily for 60 days, underwent a washout period of 60 days, crossed-over in treatments and continued for another 60 days. Subjects who consumed Palmvitee showed significant increase in tocopherol and tocotrienol (p=O.O04 and p=O.O2 respectively), while subjects who consumed palm olein showed increase only in tocopherol levels (p = 0.04). MDA levels on day 60 in patients given palm olein were inversely correlated with tocopherol levels (r=-0.644, p=O.O07). MDA (mean f SEM) declined significantly (p < 0.001) following pahn olein or Palmvitee intake, 1.33 f 0.1 versus 1.07 0.07 and 1.47 f 0.09 versus 1.13 f 0.06 nmol/l respectively. The decline continued to be significant (p < 0.001) during the washout period, then showed no further change thereafter. Neither palm olein nor Palmvitee hcaused significant changes in total cholesterol, HDL-chol, triglyceride, LDLchol and glycemic control of the patients. This study showed that the small amount of vitamin E present in palm olein, was sufficient to significantly reduce lipid peroxidation and that increased intake of the vitamin, as in Palmvitee, did not cause further reduction in the peroxide levels.

Dietary alpha-tocopherol attenuates the impact of gamma-tocotrienol on hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase activity in chickens.

J Nutr 1996 Feb; 126(2): 389-94.

Qureshi AA, Pearce BC, Nor RM, Gapor A, Peterson DM, Elson CE.

The concentration-dependent impact of gamma-tocotrienol on serum cholesterol can be traced to the posttranscriptional down-regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity. gamma-Tocotrienol also suppresses tumor growth. Palmvitee, the tocopherol and tocotrienol-rich fraction of palm oil, is the sole commercial source of gamma-tocotrienol. Contrary to the universal findings of the efficacy of gamma-tocotrienol there are conflicting reports of the impact of Palmvitee on 3-hydroxy-3-methylglutaryl coenzyme A reductase activity, serum cholesterol concentrations and tumor development. These conflicting reports led us to examine the impact of alpha-tocopherol on the cholesterol-suppressive action of gamma-tocotrienol. Control and experimental diets were fed to groups of White Leghorn chickens (n = 10) for 26 d. The control diet was supplemented with 21 nmol alpha-tocopherol/g. All experimental diets provided 141 nmol of blended tocols/g diet. The alpha-tocopherol and gamma-tocotrienol concentrations of the experimental diets ranged from 21 to 141 and 0 to 120 nmol/g, respectively. We now report that including alpha-tocopherol in tocol blends containing adequate gamma-tocotrienol to suppress 3-hydroxy-3-methylglutaryl coenzyme A reductase activity results in an attenuation of the tocotrienol action ($P < 0.001$). A summary of results from studies utilizing different Palmvitee preparations shows that effective preparations consist of 15-20% alpha-tocopherol and approximately 60% gamma- (and delta-) tocotrienol, whereas less effective preparations consist of > or = 30% alpha-tocopherol and 45% gamma- (and delta-) tocotrienol.

Gamma, but not alpha, tocopherol levels in serum are reduced in coronary heart disease patients.

J Intern Med 1996 Feb; 239(2): 111-7.

Ohrvall M, Sundlof G, Vessby B.

OBJECTIVES: Low concentrations of alpha tocopherol are claimed to be associated with an increased prevalence of coronary heart disease. This study was undertaken to see whether measurements of serum tocopherol concentrations can contribute to discrimination between subjects with and without coronary heart disease.

SETTING: All patients had been referred to the department of cardiology of the University Hospital in Uppsala, Sweden.

SUBJECTS: Male patients (n = 69) below 60 years of age with coronary heart disease (CHD) and healthy age-matched reference subjects (n = 138) were compared.

RESULTS: Lipid-corrected alpha tocopherol concentrations did not differ significantly between the groups, but the CHD group had a lower mean concentration of gamma tocopherol and a higher

alpha/gamma ratio. In a stepwise logistic regression analysis, the LDL/HDL ratio was the best independent discriminator between the groups, followed by the proportion of palmitic acid in the cholesterol esters and the alpha/gamma tocopherol ratio.

CONCLUSIONS: The lower gamma tocopherol concentration and the high ratio between alpha and gamma tocopherol in the CHD group indicate a difference in antioxidative status between CHD patients and healthy subjects. The lipid-lowering treatment of these CHD patients is far from optimal.

Antioxidant effects of tocotrienols in patients with hyperlipidemia and carotid stenosis. Lipids 1995 Dec; 30(12): 1179-83. Tomeo AC, Geller M, Watkins TR, Gapor A, Bierenbaum ML.

Antioxidants may have a role in the prevention of atherosclerosis. In the present trial, we investigated the antioxidant properties of Palm Vitee, a gamma-tocotrienol-, and alpha-tocopherol enriched fraction of palm oil, in patients with carotid atherosclerosis. Serum lipids, fatty acid peroxides, platelet aggregation and carotid artery stenosis were measured over an 18-month period in fifty patients with cerebrovascular disease. Change in stenosis was measured with duplex ultrasonography. Ultrasound scans were done at six months, twelve months, and yearly thereafter. Bilateral duplex ultrasonography revealed apparent carotid atherosclerotic regression in seven and progression in two of the 25 tocotrienol patients, while none of the control group exhibited regression and ten of 25 showed progression ($P < 0.002$). Serum thiobarbituric acid reactive substances, an ex vivo indicator of maximal platelet peroxidation, decreased in the treatment group from 1.08 /- 0.70 to 0.80 /- 0.55 microM/L ($P < 0.05$) after 12 mon, and in the placebo group, they increased nonsignificantly from 0.99 /- 0.80 to 1.26 /- 0.54 microM/L. Both tocotrienol and placebo groups displayed significantly attenuated collagen-induced platelet aggregation responses ($P < 0.05$) as compared with entry values. Serum total cholesterol, low density lipoprotein cholesterol, and triglyceride values remained unchanged in both groups, as did the plasma high density lipoprotein cholesterol values. These findings suggest that antioxidants, such as tocotrienols, may influence the course of carotid atherosclerosis.

Comparison of plasma alpha and gamma tocopherol levels following chronic oral administration of either all-rac-alpha-tocopheryl acetate or RRR-alpha-tocopheryl acetate in normal adult male subjects.

Am J Clin Nutr 1986 Mar; 43(3): 382-7.

Baker H, Handelman GJ, Short S, Machlin LJ, Bhagavan HN, Dratz EA, Frank O.

Vitamin E was administered orally (400 IU twice a day) to adult male humans for 28 days as either dl-alpha-tocopheryl acetate (all-rac-alpha-tocopheryl acetate) or d-alpha-tocopheryl acetate (RRR-alpha-tocopheryl acetate). Plasma alpha-tocopherol rose rapidly and fell at the same rate following cessation of supplementation with both forms of vitamin E. No significant differences in plasma alpha- or gamma-tocopherol levels were found between the two forms of vitamin E following their administration. The results confirm the currently accepted biopotencies of 1.0 IU/mg and 1.36 IU/mg, respectively for the two forms of vitamin E. Supplementation with either form of alpha-tocopheryl acetate resulted in depressing plasma gamma-tocopherol to less than 1/3 of initial levels; also the

gamma/alpha ratio was depressed to less than 1/7 of the initial value. The study suggests that the gamma/alpha vitamin E ratio might also serve as a sensitive index of alpha-tocopherol ingestion.