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Free radical recycling and intramembrane mobility in the

Title: **antioxidant properties of alpha-tocopherol and alpha-tocotrienol.**

Author: Serbinova, E : Kagan, V : Han, D : Packer, L

Citation: Free-Radic-Biol-Med. 1991; 10(5): 263-75

Abstract: d-Alpha-tocopherol (2R,4'R,8'R-Alpha-tocopherol) and d-alpha-tocotrienol are two vitamin E constituents having the same aromatic chromanol "head" but differing in their hydrocarbon "tail": tocopherol with a saturated and tocotrienol with an unsaturated isoprenoid chain. d-Alpha-tocopherol has the highest vitamin E activity, while d-alpha-tocotrienol manifests only about 30% of this activity. Since vitamin E is considered to be physiologically the most important lipid-soluble chain-breaking antioxidant of membranes, we studied alpha-tocotrienol as compared to alpha-tocopherol under conditions which are important for their antioxidant function. d-Alpha-tocotrienol possesses 40-60 times higher antioxidant activity against (Fe²⁺ + ascorbate)- and (Fe²⁺ + NADPH)-induced lipid peroxidation in rat liver microsomal membranes and 6.5 times better protection of cytochrome P-450 against oxidative damage than d-alpha-tocopherol. To clarify the mechanisms responsible for the much higher antioxidant potency of d-alpha-tocotrienol compared to d-alpha-tocopherol, ESR studies were performed of recycling efficiency of the chromanols from their chromanoxyl radicals. ¹H-NMR measurements of lipid molecular mobility in liposomes containing chromanols, and fluorescence measurements which reveal the uniformity of distribution (clusterizations) of chromanols in the lipid bilayer. From the results, we concluded that this higher antioxidant potency of d-alpha-tocotrienol is due to the combined effects of three properties exhibited by d-alpha-tocotrienol as compared to d-alpha-tocopherol: (i) its higher recycling efficiency from chromanoxyl radicals, (ii) its more uniform distribution in membrane bilayer, and (iii) its stronger disordering of membrane lipids which makes interaction of chromanols with lipid radicals more efficient. The

data presented show that there is a considerable discrepancy between the relative in vitro antioxidant activity of d-alpha-tocopherol and d-alpha-tocotrienol with the conventional bioassays of their vitamin activity.

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Title: **Lowering of serum cholesterol in hypercholesterolemic humans by tocotrienols (palmvitee).**

Author: Qureshi, A A : Qureshi, N : Wright, J J : Shen, Z : Kramer, G : Gapor, A : Chong, Y H : DeWitt, G : Ong, A : Peterson, D M : et al.

Citation: Am-J-Clin-Nutr. 1991 Apr; 53(4 Suppl): 1021S-1026S

Abstract: A double-blind, crossover, 8-wk study was conducted to compare effects of the tocotrienol-enriched fraction of palm oil (200 mg palmvitee capsules/day) with those of 300 mg corn oil/d on serum lipids of hypercholesterolemic human subjects (serum cholesterol 6.21-8.02 mmol/L). Concentrations of serum total cholesterol (-15%), LDL cholesterol (-8%), Apo B (-10%), thromboxane (-25%), platelet factor 4 (-16%), and glucose (-12%) decreased significantly only in the 15 subjects given palmvitee during the initial 4 wk. The crossover confirmed these actions of palmvitee. There was a carry over effect of palmvitee. Serum cholesterol concentrations of seven hypercholesterolemic subjects (greater than 7.84 mmol/L) decreased 31% during a 4-wk period in which they were given 200 mg gamma-tocotrienol/d. This indicates that gamma-tocotrienol may be the most potent cholesterol inhibitor in palmvitee capsules. The results of this pilot study are very encouraging.

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Title: **Dietary tocotrienols reduce concentrations of plasma cholesterol, apolipoprotein B, thromboxane B2, and platelet factor 4 in pigs with inherited hyperlipidemias.**

Author: Qureshi, A A : Qureshi, N : Hasler Rapacz, J O : Weber, F E : Chaudhary, V : Crenshaw, T D : Gapor, A : Ong, A S : Chong, Y H : Peterson, D : et al.

Citation: Am-J-Clin-Nutr. 1991 Apr; 53(4 Suppl): 1042S-1046S

Abstract: Normolipemic and genetically hypercholesterolemic pigs of defined lipoprotein genotype were fed a standard diet supplemented with 50 micrograms/g tocotrienol-rich fraction (TRF) isolated from palm oil. Hypercholesterolemic pigs fed the TRF supplement showed a 44% decrease in total serum cholesterol, a 60% decrease in low-density-lipoprotein (LDL)-cholesterol, and significant decreases in levels of apolipoprotein B (26%), thromboxane-B2 (41%), and platelet factor 4 (PF4; 29%). The declines in thromboxane B2 and PF4 suggest that TRF has a marked protective effect on the endothelium and platelet aggregation. The effect of the lipid-lowering diet persisted only in the hypercholesterolemic swine after 8 wk feeding of the control diet. These results support observations from previous studies on lowering plasma cholesterol in animals by tocotrienols, which are naturally occurring compounds in grain and palm oils and may have some effect on

lowering plasma cholesterol in humans.

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Title: The effect of vitamin E analogues and long hydrocarbon chain compounds on calcium-induced muscle damage. A novel role for alpha-tocopherol?

Author: Phoenix, J : Edwards, R H : Jackson, M J

Citation: Biochim-Biophys-Acta. 1991 Oct 21; 1097(3): 212-8

Abstract: Previous studies have demonstrated that supplemental alpha-tocopherol inhibited calcium-induced cytosolic enzyme efflux from normal rat skeletal muscles incubated in vitro and suggested that the protective action was mediated by the phytyl chain of alpha-tocopherol [1]. In order to investigate this further a number of hydrocarbon chain analogues of tocopherol (7,8-dimethyl tocol, 5,7-dimethyl tocol, tocol, alpha-tocotrienol, alpha-tocopherol [10], vitamin K1, vitamin K1 [10], vitamin K1 diacetate, vitamin K2 [20], phytyl ubiquinone and retinol) were tested for any ability to inhibit calcium ionophore, A23187, induced creatine kinase (CK) enzyme efflux. Some compounds were found to be very effective inhibitors and comparison of their structures and ability to inhibit TBARS production in muscle homogenates revealed that the effects did not appear related to antioxidant capacity or chromanol methyl groups, but rather the length and structure of the hydrocarbon chain was the important mediator of the effects seen.

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Title: Dietary alpha-tocopherol decreases alpha-tocotrienol but not gamma-tocotrienol concentration in rats.

Author: Ikeda, S : Tohyama, T : Yoshimura, H : Hamamura, K : Abe, K : Yamashita, K

Citation: J-Nutr. 2003 Feb; 133(2): 428-34

Abstract: We previously showed that alpha- and gamma-tocotrienols accumulate in adipose tissue and skin but not in plasma or other tissues of rats fed a tocotrienol-rich fraction extracted from palm oil containing alpha-tocopherol and alpha- and gamma-tocotrienols. To clarify the nature of tocotrienol metabolism, we studied the distribution of alpha- or gamma-tocotrienol in rats fed alpha- or gamma-tocotrienol without alpha-tocopherol, and the effect of alpha-tocopherol on their distribution. Wistar rats (4-wk-old) were fed a diet with 50 mg alpha-tocotrienol/kg alone or with 50 mg alpha-tocopherol/kg in expt. 1, and a diet with 50 mg gamma-tocotrienol/kg alone or with 50 mg alpha-tocopherol/kg in expt. 2, for 8 wk. alpha-Tocotrienol was detected in various tissues and plasma of the rats fed alpha-tocotrienol alone, and the alpha-tocotrienol concentrations in those tissues and plasma decreased (P less than 0.05) by the dietary alpha-tocopherol in the rats fed alpha-tocotrienol with alpha-tocopherol. However, gamma-tocotrienol preferentially accumulated in the adipose tissue and skin of the rats fed gamma-tocotrienol alone, and the dietary alpha-tocopherol failed either to decrease (P greater than/= 0.05) gamma-tocotrienol concentrations in the adipose tissue and skin or to increase (P greater than/= 0.05) in the urinary excretion of

2,7,8-trimethyl-2(2'-carboxymethyl)-6-hydroxycroman, a metabolite of gamma-tocotrienol, in the rats fed gamma-tocotrienol with alpha-tocopherol. These data suggest that alpha-tocopherol enhances the alpha-tocotrienol metabolism but not the gamma-tocotrienol metabolism in rats.

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Title: **Vitamin E isoforms alpha-tocotrienol and gamma-tocopherol prevent cerebral infarction in mice.**

Author: Mishima, K : Tanaka, T : Pu, F : Egashira, N : Iwasaki, K : Hidaka, R : Matsunaga, K : Takata, J : Karube, Y : Fujiwara, M

Citation: Neurosci-Lett. 2003 Jan 30; 337(1): 56-60

Abstract: Alpha-tocopherol and its derivatives have been shown to be effective in reducing cerebral ischemia-induced brain damage. However, the effects of other vitamin E isoforms have not been characterized. In the present study, we investigated the effects of six different isoforms of vitamin E on the ischemic brain damage in the mice middle cerebral artery (MCA) occlusion model. All vitamin E isoforms were injected i.v., twice, immediately before and 3 h after the occlusion. Alpha-tocopherol (2 mM), alpha-tocotrienol (0.2 and 2 mM) and gamma-tocopherol (0.2 and 2 mM) significantly decreased the size of the cerebral infarcts 1 day after the MCA occlusion, while gamma-tocotrienol, delta-tocopherol and delta-tocotrienol showed no effect on the cerebral infarcts. These results suggest that alpha-tocotrienol and gamma-tocopherol are potent and effective agents for preventing cerebral infarction induced by MCA occlusion.

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Title: **Tocotrienol is the most effective vitamin E for reducing endothelial expression of adhesion molecules and adhesion to monocytes.**

Author: Theriault, Andre : Chao, Jun Tzo : Gapor, Abeli

Citation: Atherosclerosis. 2002 Jan; 160(1): 21-30

Abstract: Alpha-tocopherol and its esterified derivatives have been shown to be effective in reducing monocytic-endothelial cell adhesion. However, the effect of alpha-tocotrienol (alpha-T3) has not been characterized. In the present study, using human umbilical vein endothelial cells (HUVEC) as the model system, we examined the relative inhibitory effects of alpha-T3 and other vitamin E derivatives on cell surface adhesion molecule expression under TNF-alpha stimulation. Using enzyme-linked immunosorbent assay, we demonstrated that alpha-T3 markedly inhibited the surface expression of vascular cell adhesion molecule-1 in TNF-alpha activated HUVEC in a dose- and time-dependent manner. The optimal inhibition was observed at 25 micromol/l alpha-T3 within 24 h (77+/-5%) without cytotoxicity. In addition, the surface expression of intercellular adhesion molecule-1 and E-selectin were also reduced by 40+/-7 and 42+/-5%, respectively. In order to further evaluate the effects of alpha-T3 on the vascular endothelium, we investigated the ability of monocytes to adhere to endothelial cells. Interestingly, a 63+/-3% decrease in monocytic cell

adherence was observed. Compared to alpha-tocopherol and alpha-tocopheryl succinate, alpha-T3 displayed a more profound inhibitory effect on adhesion molecule expression and monocytic cell adherence. This inhibitory action by alpha-T3 on TNF-alpha-induced monocyte adhesion was shown to be NF-kappaB dependent and was interestingly reversed with co-incubation with farnesol and geranylgeraniol, suggesting a role for prenylated proteins in the regulation of adhesion molecule expression. In summary, the above results suggest that alpha-T3 is a potent and effective agent in the reduction of cellular adhesion molecule expression and monocytic cell adherence.

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Title: **Protective effect of alpha-tocotrienol against free radical-induced impairment of erythrocyte deformability.**

Author: Begum, A N : Terao, J

Citation: Biosci-Biotechnol-Biochem. 2002 Feb; 66(2): 398-403

Abstract: Alpha-tocotrienol (alpha-T3) has been suggested to protect cellular membranes against free radical damage. This study was done to estimate the effect of alpha-T3 on free radical-induced impairment of erythrocyte deformability by comparing it to alpha-tocopherol (alpha-T). An erythrocyte suspension containing 2,2'-azobis (2-amidinopropane) dihydrochloride (AAPH) was forced to flow through microchannels with an equivalent diameter of 7 microm for measuring erythrocyte deformability. A higher concentration of AAPH caused a marked decrease in erythrocyte deformability with concomitant increase of membranous lipid peroxidation. Treatment of erythrocytes with alpha-T or alpha-T3 suppressed the impairment of erythrocyte deformability as well as membranous lipid peroxidation and they also increased erythrocyte deformability even in the absence of AAPH. In these cases, the protecting effect of alpha-T3 was significantly higher than that of alpha-T. We emphasize that higher incorporating activity of alpha-T3 into erythrocyte membranes seems to be the most important reason for higher protection against erythrocyte oxidation and impairment its deformability.

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Title: **Supplementation with 3 compositionally different tocotrienol supplements does not improve cardiovascular disease risk factors in men and women with hypercholesterolemia.**

Author: Mustad, V A : Smith, C A : Ruey, P P : Edens, N K : DeMichele, S J

Citation: Am-J-Clin-Nutr. 2002 Dec; 76(6): 1237-43

BACKGROUND: Tocotrienols have been reported to lower LDL-cholesterol and fasting glucose concentrations and to have potent antioxidant effects, but the results are contradictory. OBJECTIVE: The objective was to study the relative effect of tocotrienol supplements of different compositions (mixed alpha- plus gamma-, high gamma-, or P25-complex tocotrienol) on blood lipids, fasting blood glucose, and the excretion of 8-iso-prostaglandin F(2alpha), a measure of oxidative stress, in

healthy hypercholesterolemic men and women. DESIGN: This was a double-blind, randomized, parallel-design study in which subjects (n = 67 men and women) consumed 1 of 3 commercially available tocotrienol supplements or a safflower oil placebo for 28 d. Blood and urine samples were obtained before and after the 28-d supplementation phase for analysis of fasting blood lipids, glucose, tocotrienols and tocopherols, and 8-iso-prostaglandin F(2alpha). RESULTS: Overall, serum tocotrienols were increased in subjects who consumed tocotrienols, which showed that the putatively active components were absorbed. No significant differences in mean lipid or glucose concentrations were observed among the 4 treatment groups at the end of the 28-d supplementation phase. Abstract: However, when the values were expressed as a percentage change from the concentrations during the presupplementation run-in phase, LDL cholesterol increased slightly (7 +/- 2%) but significantly (P less than 0.05) in the group consuming the mixed alpha- plus gamma-tocotrienol supplement when compared with LDL cholesterol in the group consuming the P25-complex tocotrienol. Neither mean concentrations nor the percentage change in 8-iso-prostaglandin F(2alpha) differed significantly among treatments. CONCLUSION: Supplementation with 200 mg tocotrienols/d from 3 commercially available sources has no beneficial effect on key cardiovascular disease risk factors in highly compliant adults with elevated blood lipid concentrations.

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Dose-dependent suppression of serum cholesterol by tocotrienol-rich fraction (TRF25) of rice bran in hypercholesterolemic humans.

Title: **tocotrienol-rich fraction (TRF25) of rice bran in hypercholesterolemic humans.**

Author: Qureshi, Asaf A : Sami, Saeed A : Salser, Winston A : Khan, Farooq A

Citation: Atherosclerosis. 2002 Mar; 161(1): 199-207

Tocotrienols are effective in lowering serum total and LDL-cholesterol levels by inhibiting the hepatic enzymic activity of beta-hydroxy-beta-methylglutaryl coenzymeA (HMG-CoA) reductase through the post-transcriptional mechanism. alpha-Tocopherol, however, has an opposite effect (induces) on this enzyme activity. Since tocotrienols are also converted to tocopherols in vivo, it is necessary not to exceed a certain dose, as this would be counter-productive. The present study demonstrates the effects of various doses of a tocotrienol-rich fraction (TRF25) of stabilized and heated rice bran in hypercholesterolemic human subjects on serum lipid parameters. Ninety (18/group) hypercholesterolemic human subjects participated in this study, which comprised three phases of 35 days each. The subjects were initially placed on the American Heart Association (AHA) Step-1 diet and the effects noted. They were then administered 25, 50, 100, and 200 mg/day of TRF25 while on the restricted (AHA) diet. The results show that a dose of 100 mg/day of TRF25 produce maximum decreases of 20, 25, 14 (Pless than 0.05) and 12%, respectively, in serum total cholesterol, LDL-cholesterol, Abstract:

apolipoprotein B and triglycerides compared with the baseline values, suggesting that a dose of 100 mg/day TRF25 plus AHA Step-1 diet may be the optimal dose for controlling the risk of coronary heart disease in hypercholesterolemic human subjects.

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Title: **Effect of either gamma-tocotrienol or a tocotrienol mixture on the plasma lipid profile in hamsters.**

Author: Raederstorff, D : Elste, V : Aebischer, C : Weber, P

Citation: Ann-Nutr-Metab. 2002; 46(1): 17-23

Abstract: BACKGROUND/AIMS: Tocotrienols has been shown to inhibit the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity; however, the published animal and human studies yield conflicting results. We investigated the effects of a 4-week dietary supplement of either gamma-tocotrienol (86% gamma-T3) or a mixture of tocotrienols (29.5% alpha-T3, 3.3% beta-T3, 41.4% gamma-T3, 0.1% delta-T3: mix-T3) on the plasma lipid profile in hamsters receiving a high fat diet. METHODS: The hamsters were randomized into 7 groups: no treatment, 16 mg/day/kg BW simvastatin, 23, 58, 263 mg/day/kg BW gamma-tocotrienol, and 39 or 263 mg/day/kg BW for the mixture of tocotrienols. Plasma lipid levels were measured after 2 and 4 weeks of treatment. RESULTS: In all groups treated with tocotrienol total cholesterol levels were decreased, ranging from 7 to 23% after 2 weeks of treatment and from 7 to 15% after 4 weeks. Low-density lipoprotein plasma levels changed accordingly: a decline of 6-37% after 2 weeks and of 12-32% at the end of the study was observed. After 4 weeks of treatment, total cholesterol and low-density lipoprotein plasma levels were significantly reduced in the 263 mg/day/kg BW mixed tocotrienols and the 58 mg/day/kg BW and 263 mg/day/kg BW gamma-tocotrienol groups when compared to the no treatment group. Plasma triglycerides and high-density lipoprotein levels did not change significantly. CONCLUSION: This study provides further evidence that tocotrienols lower total cholesterol and low density lipoprotein plasma levels in hamsters and that gamma-tocotrienol is a more potent agent than a mixture of tocotrienols. Copyright 2002 S. Karger AG, Basel

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Title: **Does lack of tocopherols and tocotrienols put women at increased risk of breast cancer.**

Author: Schwenke,-D.C.

Citation: J-nutr-biochem. New York, N.Y. : Elsevier Science Inc. Jan 2002. v. 13 (1) p. 2-20.

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. SP\$ISSN: 0955-2863 SP\$VOLUME: 13 SP\$ISSUE: 1 SP\$PAGE1: 2

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Title: **Oral toxicity of a tocotrienol preparation in rats.**

Author: Nakamura, H : Furukawa, F : Nishikawa, A : Miyauchi, M : Son, H Y : Imazawa, T : Hirose, M

Citation: Food-Chem-Toxicol. 2001 Aug; 39(8): 799-805

Tocotrienols are added as antioxidants to food. As there have been no reports of toxicological evaluation, a 13-week oral toxicity study was performed in Fischer 344 rats of both sexes at dose levels of 0 (group 1), 0.19 (group 2), 0.75 (group 3) and 3% (group 4) of a preparation in powdered diet. Suppression of body weight gain was observed in group 4 males. On hematological examination, significant decrease in mean corpuscular volume (MCV) was observed in all treated males. Platelets were significantly reduced in group 3 and 4 males. Hemoglobin concentration, MCV, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration were significantly decreased in group 3 and 4 females and hematocrit in group 4 females. On serum biochemical examination, increase in the albumin/globulin ratio (A/G) and alkaline phosphatase in all treated males, elevated alanine transaminase in group 4 of both sexes and increases in asparagine transaminase and gamma-glutamyl transaminase in group 4 females were observed. With regard to relative organ weights, liver weights in group 4 of both sexes and adrenal weights in all treated males demonstrated an increase, and ovary and uterus weights in group 4 females were reduced. Histopathologically, slight hepatocellular hypertrophy in group 3 and 4 males, and reduction of cytoplasmic vacuolation in the adrenal cortical region in group 4 males were observed. Because of pathological changes in male liver and hematological changes in females, the no-observed-adverse-effect level (NOAEL) was concluded to be 0.19% in the diet (120 mg/kg body weight/day for male rats and 130 mg/kg body

weight/day for female rats). As a decrease in MCV, an increase in the A/G, elevation of alkaline phosphatase and increase in adrenal weight were observed in all treated males, a no-observed-effect level (NOEL) could not be determined in this examination.

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Title: **The combined effects of novel tocotrienols and lovastatin on lipid metabolism in chickens.**

Author: Qureshi, A A : Peterson, D M

Citation: Atherosclerosis. 2001 May; 156(1): 39-47

Both lovastatin (a fungal product) and a tocotrienol rich fraction (TRF(25), a mixture of tocopherols isolated from stabilized and heated rice bran containing desmethyl [d-P(21)-T3] and didesmethyl [d-P(25)-T3] tocotrienols) are potent hypocholesterolemic agents, although they suppress cholesterol biosynthesis by different mechanisms. To determine additive and/or synergistic effects of both agents, chickens were fed diets supplemented with 50 ppm TRF(25) or d-P(25)-T3 in combination with 50 ppm lovastatin for 4 weeks. Combinations of d-P(25)-T3 with lovastatin were found most effective in reducing serum total cholesterol and low-density lipoprotein (LDL) cholesterol compared to the control diet or individual supplements. The mixture of TRF(25)+lovastatin inhibited the activity of beta-hydroxy-beta-methylglutaryl coenzyme A

Abstract: reductase (21%) compared to lovastatin alone, which did not change its activity. Cholesterol 7alpha-hydroxylase activity was increased by lovastatin (11%) and by lovastatin plus TRF(25) (19%). TRF(25)+lovastatin decreased levels of serum total cholesterol (22%), LDL cholesterol (42%), apolipoprotein B (13-38%), triglycerides (19%), thromboxane B(2) (34%) and platelet factor 4 (26%), although high-density lipoprotein (HDL) cholesterol, and apolipoprotein A1 levels were unaffected. The mixture of TRF(25)+lovastatin showed greater effects than did the individual treatments alone, reflecting possible additive pharmacological actions. The effects, however, of the d-P(25)-T3/lovastatin combination were no greater than that of d-P(25)-T3 alone, possibly indicating that d-P(25)-T3 produced a maximum cholesterol lowering effect at the concentration used.

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Title: **Novel tocotrienols of rice bran suppress cholesterogenesis in hereditary hypercholesterolemic swine.**

Author: Qureshi, A A : Peterson, D M : Hasler Rapacz, J O : Rapacz, J

Citation: J-Nutr. 2001 Feb; 131(2): 223-30

A tocotrienol-rich fraction (TRF(25)) and novel tocotrienols (d-P(21)-T3 and d-P(25)-T3) of rice bran significantly lowered serum and low density lipoprotein cholesterol levels in chickens. The present study evaluated the effects of novel tocotrienols on lipid metabolism in swine expressing hereditary hypercholesterolemia. Fifteen 4-mo-old genetically hypercholesterolemic swine were divided into five groups (n = 3). Four groups were fed a corn-soybean control diet,

supplemented with 50 microg of either TRF(25), gamma-tocotrienol, d-P(21)-T3 or d-P(25)-T3 per g for 6 wk. Group 5 was fed the control diet for 6 wk and served as a control. After 6 wk, serum total cholesterol was reduced 32-38%, low density lipoprotein cholesterol was reduced 35-43%, apolipoprotein B was reduced 20-28%, platelet factor 4 was reduced 12-24%, thromboxane B(2) was reduced 11-18%, glucose was reduced 22-25% (Pless than 0.01), triglycerides were reduced 15-19% and glucagon was reduced 11-17% (Pless than 0.05) in the treatment groups relative to the control. Insulin was 100% greater (Pless than 0.01) in the treatment groups than in the control group. Preliminary data (n = 1) indicated that hepatic activity of the 3-hydroxy-3-methylglutaryl-coenzyme A reductase was lower in the treatment groups, and cholesterol 7alpha-hydroxylase activity was unaffected. Cholesterol and fatty acid levels in various tissues were lower in the treatment groups than in control. After being fed the tocotrienol-supplemented diets, two swine in each group were transferred to the control diet for 10 wk. The lower concentrations of serum lipids in these four treatment groups persisted for 10 wk. This persistent effect may have resulted from the high tocotrienol levels in blood of the treatment groups, suggesting that the conversion of tocotrienols to tocopherols may not be as rapid as was reported in chickens and humans.

Abstract:

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

Author: Packer, L : Weber, S U : Rimbach, G

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

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.

Abstract: 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.

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Title: **Novel tocotrienols of rice bran inhibit atherosclerotic lesions in C57BL/6 ApoE-deficient mice.**

Author: Qureshi, A A : Salser, W A : Parmar, R : Emeson, E E

Citation: J-Nutr. 2001 Oct; 131(10): 2606-18

We are studying novel tocotrienols, which have a number of activities that might interfere with the formation of atherosclerotic plaques, including hypocholesterolemic, antioxidant, anti-inflammatory and antiproliferation effects. This study compared the effects of alpha-tocopherol, the tocotrienol-rich fraction (TRF(25)) and didesmethyl tocotrienol (d-P(25)-T3) of rice bran on the pathogenesis of atherosclerotic lesions in C57BL/6 apolipoprotein (apo)E-deficient (-/-) mice. These mice are an excellent model because they become hyperlipidemic even when they consume a low fat diet and they develop complex atherosclerotic lesions similar to those of humans. These compounds were also tested in wild-type C57BL/6 apoE (+/+) and (+/-) mice fed low or high fat diets. When a high fat diet was supplemented with alpha-tocopherol, TRF(25) or d-P(25)-T3 and fed to mice (+/+) for 24 wk, atherosclerotic lesion size was reduced 23% (P = 0.33), 36% (P = 0.14) and 57% (P less than 0.02), respectively, and in mice (+/-) fed for 18 wk, lesions were reduced by 19% (P = 0.15), 28% (P less than 0.01) and 33% (P less than 0.005), respectively, compared with mice fed a control diet. A low fat diet did not cause atherosclerotic lesions in these mice. The low fat diet supplemented with TRF(25) or d-P(25)-T3 fed to apoE-deficient (-/-) mice for 14 wk decreased atherosclerotic lesion size by 42% (P less than 0.04) and 47% (P less than 0.01), respectively, whereas alpha-tocopherol supplementation resulted in only an 11% (P = 0.62) reduction. These results demonstrate the superior efficacy of tocotrienols compared with alpha-tocopherol. Although tocotrienols decreased serum triglycerides, total and LDL cholesterol levels, the decreases in atherosclerotic lesions seem to be due to the other activities. Serum tocol concentrations in various groups are also described. This is the first report of a significant reduction in the atherosclerotic lesion size in all three genotypes of apoE mice fed a novel tocotrienol (d-P(25)-T3) of rice bran. Dietary tocotrienol supplements may provide a unique approach to promoting cardiovascular health.

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Dietary Sesame Seeds Elevate alpha- and gamma-Tocotrienol Concentrations in Skin and Adipose Tissue of Rats Fed the Tocotrienol-Rich Fraction Extracted from Palm Oil.

Author: Ikeda, S : Toyoshima, K : Yamashita, K

Citation: J-Nutr. 2001 Nov; 131(11): 2892-7

The metabolism of tocotrienol remains unclear. We studied the distribution of tocotrienol in rats fed the tocotrienol-rich fraction extracted from palm oil. We have previously shown that dietary sesame seeds markedly elevate the tocopherol concentration in rats. In this study, we also examined the effect of dietary sesame seeds on the tocotrienol concentration. In experiment 1, rats (4-wk-old) were fed the diet with alpha-tocopherol alone or with alpha- and gamma-tocotrienols. In experiment 2, the effect of dietary sesame seeds on tocopherol

and tocotrienol concentrations in rats fed the diet with tocopherol and tocotrienol was studied. The rats were fed the experimental diet for 8 wk in both experiments. alpha- and gamma-Tocotrienols accumulated in the adipose tissue and skin, but not in plasma or other tissues, of the rats fed tocotrienols. Dietary sesame seeds elevated (P less than 0.05) tocotrienol concentrations in the adipose tissue and skin, but did not affect their concentrations in other tissues or in plasma. The gamma-tocopherol concentration in all tissues and plasma of rats fed gamma-tocopherol was extremely low but was elevated (P less than 0.05) in many tissues by feeding sesame seeds. These data suggest that the transport and tissue uptake of vitamin E isoforms are different. Dietary sesame seeds elevate the concentrations of both tocopherols and tocotrienols.

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Synergistic effect of tocotrienol-rich fraction (TRF25) of rice bran and lovastatin on lipid parameters in hypercholesterolemic humans.

Title: **rice bran and lovastatin on lipid parameters in hypercholesterolemic humans.**

Author: Qureshi, A.A. : Sami, S.A. : Salser, W.A. : Khan, F.A.

Citation: J-nutr-biochem. New York, N.Y. : Elsevier Science Inc. June 2001. v. 12 (6) p. 318-329.

Tocotrienols exert hypocholesterolemic action in humans and animals. Lovastatin is widely used for that purpose. Both agents work by suppressing the activity of beta-hydroxy-beta-methylglutaryl coenzyme A reductase through different mechanisms, post-transcriptional vs competitive inhibition. A human study with 28 hypercholesterolemic subjects was carried out in 5 phases of 35 days each, to check the efficacy of tocotrienol-rich fraction (TRF25) of rice bran alone and in combination with lovastatin. After placing subjects on the American Heart Association (AHA) Step-1 diet (phase II), the subjects were divided into two groups, A and B. The AHA Step-1 diet was continued in combination with other treatments during phases III to V. Group A subjects were given 10 mg lovastatin, 10 mg lovastatin plus 50 mg TRF25, 10 mg lovastatin plus 50 mg alpha-tocopherol per day, in the third, fourth, and fifth phases, respectively. Group B subjects were treated exactly to the same protocol except that in the third phase, they were given 50 mg TRF25 instead of lovastatin. The TRF25 or lovastatin plus AHA Step-1 diet effectively lower serum total cholesterol (14%, 13%) and LDL-cholesterol (18%, 15% P less than 0.001), respectively, in hypercholesterolemic subjects. The combination of TRF25 and lovastatin plus AHA Step-1 diet significantly reduces of these lipid parameters of 20% and 25% (P less than 0.001) in these subjects. Substitution of TRF25 with alpha-tocopherol produces insignificant changes when given with lovastatin. Especially significant is the increase in the HDL/LDL ratio to 46% in group (A) and 53% (P less than 0.002) in group (B). These results are consistent with the synergistic effect of. these two agents. None of the subjects reported any side-effects throughout the study of 25-weeks. In the present study, the increased effectiveness of low doses of tocotrienols (TRF25) as hypocholesterolemic agents might be

due to a minimum conversion to alpha-tocopherol. The report also describes in vivo the conversion of gamma-[4-(3)H]-, and [(14)C]-desmethyl (d-P21-T3) tocotrienols to alpha-tocopherol.SP\$ISSN: 0955-2863SP\$VOLUME: 12SP\$ISSUE: 6SP\$PAGE1: 318

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Title: **Palm tocotrienols protect ApoE +/- mice from diet-induced atheroma formation.**

Author: Black, T M : Wang, P : Maeda, N : Coleman, R A

Citation: J-Nutr. 2000 Oct; 130(10): 2420-6

Abstract: We evaluated the effects of vitamin E and beta-carotene on apolipoprotein (apo)E +/- female mice, which develop atherosclerosis only when fed diets high in triglyceride and cholesterol. Mice were fed a nonpurified control diet (5.3 g/100 g triglyceride, 0.2 g/100 g cholesterol), an atherogenic diet alone (15.8 g/100 g triglyceride, 1.25 g/100 g cholesterol, 0.5 g/100 g Na cholate) or the atherogenic diet supplemented with either 0.5 g/100 g (+)-alpha-tocopherol (mixed isomers); 0.5 g/100 g palm tocopherols (palm-E; 33% alpha-tocopherol, 16.1% alpha-tocotrienol, 2.3% beta-tocotrienol, 32.2% gamma-tocotrienol, 16.1% delta-tocotrienol); 1.5 g/100 g palm-E; or 0.01 g/100 g palm-carotenoids (58% beta-carotene, 33% alpha-carotene, 9% other carotenoids). Compared with mice fed the control diet, plasma cholesterol was fourfold greater in mice fed the atherogenic diet. Mice fed the 1.5 g/100 g palm-E supplement had 60% lower plasma cholesterol than groups fed the other atherogenic diets. Mice fed the atherogenic diet had markedly higher VLDL, intermediate density lipoprotein (IDL) and LDL cholesterol and markedly lower HDL cholesterol than the controls. Lipoprotein patterns in mice supplemented with alpha-tocopherol or palm carotenoids were similar to those of the mice fed the atherogenic diet alone, but the pattern in mice supplemented with 1.5 g/100 g palm-E was similar to that of mice fed the control diet. In mice fed the atherogenic diet, the hepatic cholesterol plus cholesterol ester concentration was 4.4-fold greater than in mice fed the control diet. Supplementing with 1.5 g/100 g palm-E lowered hepatic cholesterol plus cholesterol ester concentration 66% compared with the atherogenic diet alone. Mice fed the atherogenic diet had large atherosclerotic lesions at the level of the aortic valve. With supplements of 0.5 g/100 g palm-E or 1.5 g/100 g palm-E, the size of the lesions was 92 or 98% smaller, respectively. The 0.5 g/100 g alpha-tocopherol and palm carotenoid supplements had no effect. Supplements did not alter mRNA abundance for apolipoproteins A1, E, and C3. The beneficial effect of tocotrienols on atherogenesis, the plasma lipoprotein profile and accumulation of hepatic cholesterol esters cannot be attributed to their antioxidant properties.

[Detail](#) [Delete](#)

Title: **Vitamin E and beta-carotene affect natural killer cell function.**

Author: Ashfaq, M K : Zuberi, H S : Anwar Waqar, M

Citation: Int-J-Food-Sci-Nutr. 2000; 51 SupplS13-20

Vitamin E supplementation has been shown to contribute in immunoregulation, antibody production, and resistance to implanted tumors. Similarly beta-carotene has been shown to down-regulate growth factors which contribute towards proliferation of pre-malignant cells. We embarked upon a study to evaluate the effect of vitamin E and beta-carotene on natural killer (NK) cells, which perform tumor surveillance role in the mammalian body. Mouse splenocytes or human peripheral blood lymphocytes were used as NK cells with murine YAC-1 lymphoma or human K-562 lymphoma cells, respectively, as target cells. The NK cells were treated with vitamin E or beta-carotene while target cells were labeled with sodium 51chromate. Both cell types were then reacted for 4 hours. The NK cell tumorolytic activity was measured by the chromium release assay. Oral administration of alpha-tocopherol at a dose of 100 mg/d in mice showed a significant increase in NK cell

Abstract: activity. Similarly, treatment of NK cells with alpha-tocopherol in vitro at doses 0.5 mg/ml, 1-0 mg/ml, and 2.0 mg/ml increased the tumorolytic activity of NK cells. Tocotrienol showed a similar response at ten times lower dose. When NK cells were treated with varying concentrations of palm vitee (mixture of alpha-tocopherol and tocotrienol), maximum effect was observed at the dose mixture of 12 micrograms and 24 micrograms alpha-tocopherol and tocotrienol, respectively. When murine NK cells were treated in vitro with beta-carotene at doses ranging from 2 ng/mg to 200 ng/ml, a decrease in tumorolytic effect was observed. However, human NK cells after treatment with beta-carotene at doses ranging from 0.1 microgram/ml to 10 micrograms/ml showed a significant increase in tumorolytic function. NK cells were also obtained from mice that had been parenterally administered beta-carotene and alpha-tocopherol. These experiments showed no significant increase in the NK cell function.

[Detail](#) [Delete](#)

Title: **Vitamin E and factors affecting atherosclerosis in rabbits fed a cholesterol-rich diet.**

Author: Ismail, N M : Abdul Ghafar, N : Jaarin, K : Khine, J H : Top, G M

Citation: Int-J-Food-Sci-Nutr. 2000; 51 SupplS79-94

The present study aims to examine the effects of a palm-oil-derived vitamin E mixture containing tocotrienol (approximately 70%) and tocopherol (approximately 30%) on plasma lipids and on the formation of atherosclerotic plaques in rabbits given a 2% cholesterol diet. Eighteen New Zealand White rabbits (2.2-2.8 kg) were divided into three groups; group 1 (control) was fed a normal diet, group 2 (AT) was fed a 2% cholesterol diet and group 3 (PV) was fed a 2% cholesterol diet with oral palm vitamin E (60 mg/kg body weight) given daily for 10 weeks. There were no differences in the total cholesterol and triacylglycerol levels between the AT and PV groups. The PV group had a significantly higher concentrations of HDL-c and a lower TC/HDL-c ratio compared to the AT

Abstract:

group (P less than 0.003). The aortic tissue content of cholesterol and atherosclerotic lesions were comparable in both the AT and PV groups. However, the PV group had a lower content of plasma and aortic tissue malondialdehyde (P less than 0.005). Our findings suggest that despite a highly atherogenic diet, palm vitamin E improved some important plasma lipid parameters, reduced lipid peroxidation but did not have an effect on the atherosclerotic plaque formation.

[Detail](#) [Delete](#)

Title: **Tocotrienols inhibit growth of ZR-75-1 breast cancer cells.**

Author: Nesaretnam, K : Dorasamy, S : Darbre, P D

Citation: Int-J-Food-Sci-Nutr. 2000; 51 SupplS95-103

Abstract: The vitamin E component of palm oil provides a rich source of tocotrienols which have been shown previously to be growth inhibitory to two human breast cancer cell lines: responsive MCF7 cells and unresponsive MDA-MB-231 cells. Data presented here shows that the tocotrienol-rich fraction (TRF) of palm oil and individual fractions (alpha, gamma and delta) can also inhibit the growth of another responsive human breast cancer cell line, ZR-75-1. At low concentrations in the absence of oestrogen tocotrienols stimulated growth of the ZR-75-1 cells, but at higher concentrations in the presence as well as in the absence of oestradiol, tocotrienols inhibited cell growth strongly. As for MCF7 cells, alpha-tocopherol had no effect on growth of the ZR-75-1 cells in either the absence or presence of oestradiol. In studying the effects of tocotrienols in combination with antioestrogens, it was found that TRF could further inhibit growth of ZR-75-1 cells in the presence of tamoxifen (10(-7) M and 10(-8) M). Individual tocotrienol fractions (alpha, gamma, delta) could inhibit growth of ZR-75-1 cells in the presence of 10(-8) M oestradiol and 10(-8) M pure antioestrogen ICI 164,384. The immature mouse uterine weight bioassay confirmed that TRF could not exert oestrogen antagonist action in vivo. These results provide evidence of wider growth-inhibitory effects of tocotrienols beyond MCF7 and MDA-MB-231 cells, and with an oestrogen-independent mechanism of action, suggest a possible clinical advantage in combining administration of tocotrienols with antioestrogen therapy.

[Detail](#) [Delete](#)

Title: **Antiproliferative and apoptotic effects of tocopherols and tocotrienols on normal mouse mammary epithelial cells.**

Author: McIntyre, B S : Briski, K P : Tirmenstein, M A : Fariss, M W : Gapor, A : Sylvester, P W

Citation: Lipids. 2000 Feb; 35(2): 171-80

Studies were conducted to determine the comparative effects of tocopherols and tocotrienols on normal mammary epithelial cell growth and viability. Cells isolated from midpregnant BALB/c mice were grown within collagen gels and maintained on serum-free media. Treatment with 0-120 microM alpha- and gamma-tocopherol had no effect, whereas 12.5-100m microM tocotrienol-rich fraction of palm oil (TRF), 100-120 microM delta-tocopherol, 50-60 microM alpha-tocotrienol, and 8-14

microM gamma- or delta-tocotrienol significantly inhibited cell growth in a dose-responsive manner. In acute studies, 24-h exposure to 0-250 microM alpha-, gamma-, and delta-tocopherol had no effect, whereas similar treatment with 100-250 microM TRF, 140-250 microM alpha-, 25-100 microM gamma- or delta-tocotrienol significantly reduced cell viability. Growth-inhibitory doses of TRF, delta-tocopherol, and alpha-, gamma-, and delta-tocotrienol were shown to induce apoptosis in these cells, as indicated by DNA fragmentation. Results also showed that mammary epithelial cells more easily or preferentially took up tocotrienols as compared to tocopherols, suggesting that at least part of the reason tocotrienols display greater biopotency than tocopherols is because of greater cellular accumulation. In summary, these findings suggest that the highly biopotent gamma- and delta-tocotrienol isoforms may play a physiological role in modulating normal mammary gland growth, function, and remodeling.

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Molecular basis of vitamin E action. Tocotrienol potently inhibits glutamate-induced pp60(c-Src) kinase activation and death of HT4 neuronal cells.

Author: Sen, C K : Khanna, S : Roy, S : Packer, L

Citation: J-Biol-Chem. 2000 Apr 28; 275(17): 13049-55

HT4 hippocampal neuronal cells were studied to compare the efficacy of tocopherols and tocotrienol to protect against glutamate-induced death. Tocotrienols were more effective than alpha-tocopherol in preventing glutamate-induced death. Uptake of tocotrienols from the culture medium was more efficient compared with that of alpha-tocopherol. Vitamin E molecules have potent antioxidant properties. Results show that at low concentrations, tocotrienols may have protected cells by an antioxidant-independent mechanism. Examination of signal transduction pathways revealed that protein tyrosine phosphorylation processes played a central role in the execution of death. Activation of pp60(c-Src) kinase and phosphorylation of ERK were observed in response to glutamate treatment.

Abstract: Nanomolar amounts of alpha-tocotrienol, but not alpha-tocopherol, blocked glutamate-induced death by suppressing glutamate-induced early activation of c-Src kinase. Overexpression of kinase-active c-Src sensitized cells to glutamate-induced death. Tocotrienol treatment prevented death of Src-overexpressing cells treated with glutamate. alpha-Tocotrienol did not influence activity of recombinant c-Src kinase suggesting that its mechanism of action may include regulation of SH domains. This study provides first evidence describing the molecular basis of tocotrienol action. At a concentration 4-10-fold lower than levels detected in plasma of supplemented humans, tocotrienol regulated unique signal transduction processes that were not sensitive to comparable concentrations of tocopherol.

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Antiproliferative and apoptotic effects of tocopherols and tocotrienols on preneoplastic and neoplastic mouse

mammary epithelial cells.

Author: McIntyre, B S : Briski, K P : Gapor, A : Sylvester, P W

Citation: Proc-Soc-Exp-Biol-Med. 2000 Sep; 224(4): 292-301

Studies were conducted to determine the comparative effects of tocopherols and tocotrienols on preneoplastic (CL-S1), neoplastic (-SA), and highly malignant (+SA) mouse mammary epithelial cell growth and viability in vitro. Over a 5-day culture period, treatment with 0-120 microM alpha- and gamma-tocopherol had no effect on cell proliferation, whereas growth was inhibited 50% (IC50) as compared with controls by treatment with the following: 13, 7, and 6 microM tocotrienol-rich-fraction of palm oil (TRF); 55, 47, and 23 microM delta-tocopherol; 12, 7, and 5 microM alpha-tocotrienol; 8, 5, and 4 microM gamma-tocotrienol; or 7, 4, and 3 microM delta-tocotrienol in CL-S1, -SA and +SA cells, respectively. Acute 24-hr exposure to 0-250 microM alpha- or gamma-tocopherol (CL-S1, -SA, and +SA) or 0-250 microM delta-tocopherol (CL-S1) had no effect on cell viability, whereas cell viability was reduced 50% (LD50) as compared with controls by treatment

Abstract: with 166 or 125 microM delta-tocopherol in -SA and +SA cells, respectively. Additional LD50 doses were determined as the following: 50, 43, and 38 microM TRF; 27, 28, and 23 microM alpha-tocotrienol; 19, 17, and 14 microM gamma-tocotrienol; or 16, 15, or 12 microM delta-tocotrienol in CL-S1, -SA, and +SA cells, respectively. Treatment-induced cell death resulted from activation of apoptosis, as indicated by DNA fragmentation. Results also showed that CL-S1, -SA, and +SA cells preferentially accumulate tocotrienols as compared with tocopherols, and this may partially explain why tocotrienols display greater biopotency than tocopherols. These data also showed that highly malignant +SA cells were the most sensitive, whereas the preneoplastic CL-S1 cells were the least sensitive to the antiproliferative and apoptotic effects of tocotrienols, and suggest that tocotrienols may have potential health benefits in preventing and/or reducing the risk of breast cancer in women.

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Isolation and identification of novel tocotrienols from rice

Title: **bran with hypocholesterolemic, antioxidant, and antitumor properties.**

Author: Qureshi, A A : Mo, H : Packer, L : Peterson, D M

Citation: J-Agric-Food-Chem. 2000 Aug; 48(8): 3130-40

Two novel tocotrienols were isolated from stabilized and heated rice bran, apart from the known alpha-, beta-, gamma-, and delta-tocopherols and tocotrienols. These new tocotrienols were separated by HPLC, using a normal phase silica column. Their structures were determined by ultraviolet, infrared, nuclear

Abstract: magnetic resonance, circular dichroism, and high-resolution mass spectroscopies and established as desmethyl tocotrienol [3, 4-dihydro-2-methyl-2-(4,8,12-trimethyltrideca-3'(E),7'(E), 11'-trienyl)-2H-1-benzopyran-6-ol] and didesmethyl tocotrienol [3, 4-dihydro-2-(4,8,12-trimethyltrideca-3'(E),7'(E), 11'-trienyl)-2H-1-benzopyran-6-ol]. These tocotrienols significantly

lowered serum total and LDL cholesterol levels and inhibited HMG-CoA reductase activity in chickens. They had much greater in vitro antioxidant activities and greater suppression of B16 melanoma cell proliferation than alpha-tocopherol and known tocotrienols. Results indicated that the number and position of methyl substituents in tocotrienols affect their hypocholesterolemic, antioxidant, and antitumor properties.

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A vitamin E concentrate rich in tocotrienols had no effect on serum lipids, lipoproteins, or platelet function in men with mildly elevated serum lipid concentrations.

Author: Mensink, R P : van Houwelingen, A C : Kromhout, D : Hornstra, G

Citation: Am-J-Clin-Nutr. 1999 Feb; 69(2): 213-9

BACKGROUND: Tocotrienols, lipid-soluble antioxidants with vitamin E activity, have been reported to lower LDL-cholesterol concentrations and platelet aggregation in men, but results are contradictory. **OBJECTIVE:** To examine in detail the effects of a vitamin E concentrate rich in tocotrienols on serum lipoproteins and on platelet function in men at risk for cardiovascular disease. **DESIGN:** In this randomized, double-blind, placebo-controlled parallel trial, 20 men received daily for 6 wk 4 capsules, each containing 35 mg tocotrienols and 20 mg alpha-tocopherol; 20 other men received 4 capsules daily, each providing 20 mg alpha-tocopherol. All men had concentrations of serum total cholesterol between 6.5 and 8.0 mmol/L or lipoprotein(a) concentrations greater than 150 mg/L. **RESULTS:** Compliance was confirmed by changes in serum tocopherol and tocotrienol concentrations. Serum LDL

Abstract: cholesterol in the tocotrienol group was 4.80 mmol/L before and 4.79 mmol/L after intervention, and increased from 4.70 to 4.86 mmol/L in the placebo group (95% CI for the difference: -0.54, 0.19 mmol/L; P = 0.333). Also, changes in HDL cholesterol, triacylglycerol, lipoprotein(a), and lipid peroxide concentrations did not differ between the groups. After adjustment for differences in initial values, no effects were found on collagen-induced platelet aggregation velocity, maximum aggregation, or thromboxane B2 formation in citrated whole blood. ATP release, however, was lower in the tocotrienol group. Urinary thromboxane B2 and 11-keto-thromboxane B2 concentrations and coagulation and fibrinolytic measures did not change. **CONCLUSION:** The tocotrienol supplements used had no marked favorable effects on the serum lipoprotein profile or on platelet function in men with slightly elevated lipid concentrations.

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Effect of gamma-tocotrienol on blood pressure, lipid

Title: peroxidation and total antioxidant status in spontaneously hypertensive rats (SHR).

Author: Newaz, M A : Nawal, N N

Citation: Clin-Exp-Hypertens. 1999 Nov; 21(8): 1297-313

The aim of this study was to determine the effects of gamma

tocotrienol on lipid peroxidation and total antioxidant status of spontaneously hypertensive rats (SHR), comparing them with normal Wistar Kyoto (WKY) rats. SHR were divided into three groups and treated with different doses of gamma tocotrienol (gamma1, 15 mg/kg diet; gamma2, 30 mg/kg diet and gamma3, 150 mg/kg diet). Normal WKY and untreated SHR were used as normal (N) and hypertensive control (HC). Blood pressure were recorded every fortnightly for three months. At the end of the trial, animals were killed and measurement of plasma total antioxidant status, plasma superoxide dismutase (SOD) activity and lipid peroxide levels in plasma and blood vessels were carried out following well established methods. Study shows that lipid peroxides were significantly higher in hypertensive plasma and blood vessels compared to that of normal rats (Plasma- N: 0.06+/-0.01, HC: 0.13+/-0.008; pless than 0.001, B1. Vessels - N: 0.47+/-0.17, HC: 0.96+/-0.37; pless than 0.001). SOD activity was significantly lower in hypertensive than normal rats (N = 148.58+/-29.56 U/ml, HC = 110.08+/-14.36 U/ml; p = 0.014). After three months of antioxidant trial with gamma-tocotrienol, it was found that all the treated groups have reduced plasma lipid peroxides concentration but was only significant for group gamma1 (gamma1: 0.109+/-0.026, HC: 0.132+/-0.008; p = 0.034). On the other hand, lipid peroxides in blood vessels reduced significantly in all treated groups (gamma1; pless than 0.05, gamma2; pless than 0.001, gamma3; pless than 0.005). All the three treated groups showed improve total antioxidant status (pless than 0.001) significantly. SOD activity also showed significant improvement in all groups (gamma1: pless than 0.001, gamma2: pless than 0.05, gamma3: pless than 0.001). Correlation studies showed that, total antioxidant status (TAS) and SOD were significantly negatively correlated with blood pressure in normal rats (p = 0.007; p = 0.008) but not in SHR control. This correlation regained in all three groups SHR's after treatment with tocotrienol. Lipid peroxides in blood vessel and plasma showed a positive correlation with blood pressure in normal and SHR control. This correlation also remains in treated groups significantly except that in gamma3 where positive correlation with plasma lipid peroxide was not significant. In conclusion it was found that antioxidant supplement of gamma-tocotrienol may prevent development of increased blood pressure, reduce lipid peroxides in plasma and blood vessels and enhanced total antioxidant status including SOD activity.

Abstract:

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Title: **Tocotrienol: a review of its therapeutic potential.**

Author: Theriault, A : Chao, J T : Wang, Q : Gapor, A : Adeli, K

Citation: Clin-Biochem. 1999 Jul; 32(5): 309-19

OBJECTIVES: To summarize new knowledge surrounding the physiological activity of tocotrienol, a natural analogue of tocopherol. RESULTS: The biological activity of vitamin E has generally been associated with its well-defined antioxidant property, specifically against lipid peroxidation in biological membranes. In the vitamin E group, alpha-tocopherol is

considered to be the most active form. However, recent research has suggested tocotrienol to be a better antioxidant. Moreover, tocotrienol has been shown to possess novel hypocholesterolemic effects together with an ability to reduce the atherogenic apolipoprotein B and lipoprotein(a) plasma levels. In addition, tocotrienol has been suggested to have an anti-thrombotic and anti-tumor effect indicating that tocotrienol may serve as an effective agent in the prevention and/or treatment of cardiovascular disease and cancer.

Abstract: **CONCLUSION:** The physiological activities of tocotrienol suggest it to be superior than alpha-tocopherol in many situations. Hence, the role of tocotrienol in the prevention of cardiovascular disease and cancer may have significant clinical implications. Additional studies on its mechanism of action, as well as, long-term intervention studies, are needed to clarify its function. From the pharmacological point-of-view, the current formulation of vitamin E supplements, which is comprised mainly of alpha-tocopherol, may be questionable.

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Title: **Apoptosis and cell-cycle arrest in human and murine tumor cells are initiated by isoprenoids.**

Author: Mo, H : Elson, C E

Citation: J-Nutr. 1999 Apr; 129(4): 804-13

Diverse classes of phytochemicals initiate biological responses that effectively lower cancer risk. One class of phytochemicals, broadly defined as pure and mixed isoprenoids, encompasses an estimated 22,000 individual components. A representative mixed isoprenoid, gamma-tocotrienol, suppresses the growth of murine B16(F10) melanoma cells, and with greater potency, the growth of human breast adenocarcinoma (MCF-7) and human leukemic (HL-60) cells. beta-Ionone, a pure isoprenoid, suppresses the growth of B16 cells and with greater potency, the growth of MCF-7, HL-60 and human colon adenocarcinoma (Caco-2) cells. Results obtained with diverse cell lines differing in ras and p53 status showed that the isoprenoid-mediated suppression of growth is independent of mutated ras and p53 functions. beta-Ionone suppressed the growth of human colon fibroblasts (CCD-18Co) but only when present at three-fold the concentration required to suppress the growth of Caco-2 cells. The isoprenoids initiated apoptosis and, concomitantly arrested cells in the G1 phase of the cell cycle. Both suppress 3-hydroxy-3-methylglutaryl CoA reductase activity. beta-Ionone and lovastatin interfered with the posttranslational processing of lamin B, an activity essential to assembly of daughter nuclei. This interference, we postulate, renders neosynthesized DNA available to the endonuclease activities leading to apoptotic cell death. Lovastatin-imposed mevalonate starvation suppressed the glycosylation and translocation of growth factor receptors to the cell surface. As a consequence, cells were arrested in the G1 phase of the cell cycle. This rationale may apply to the isoprenoid-mediated G1-phase arrest of tumor cells. The additive and potentially synergistic actions of these isoprenoids in the suppression of tumor cell proliferation and initiation of

apoptosis coupled with the mass action of the diverse isoprenoid constituents of plant products may explain, in part, the impact of fruit, vegetable and grain consumption on cancer risk.

[Detail](#) [Delete](#)

Title: **Effects of gamma-tocotrienol on ApoB synthesis, degradation, and secretion in HepG2 cells.**

Author: Theriault, A : Wang, Q : Gapor, A : Adeli, K

Citation: *Arterioscler-Thromb-Vasc-Biol.* 1999 Mar; 19(3): 704-12

gamma-Tocotrienol (gamma-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 gamma-T3 on hepatic modulation of apoB production using cultured HepG2 cells as the model system. HepG2 cells preincubated with gamma-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 86+/-3% inhibition at 50 micromol/L observed within 6 hours. gamma-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 24+/-3% in labeled apoB in the

Abstract: media was apparent with gamma-T3 despite a 60+/-2% 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 gamma-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 gamma-T3-treated cells relative to untreated control cells (50+/-21%) after 2 hours of chase. In addition, the presence of gamma-T3 resulted in an average decrease of 64+/-8% in intact apoB. Taken together, the data suggest that gamma-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.

[Detail](#) [Delete](#)

Title: **Tocotrienols inhibit the growth of human breast cancer cells irrespective of estrogen receptor status.**

Author: Nesaretnam, K : Stephen, R : Dils, R : Darbre, P

Citation: *Lipids.* 1998 May; 33(5): 461-9

Potential antiproliferative effects of tocotrienols, the major

vitamin E component in palm oil, were investigated on the growth of both estrogen-responsive (ER+) MCF7 human breast cancer cells and estrogen-unresponsive (ER-) MDA-MB-231 human breast cancer cells, and effects were compared with those of alpha-tocopherol (alphaT). The tocotrienol-rich fraction (TRF) of palm oil inhibited growth of MCF7 cells in both the presence and absence of estradiol with a nonlinear dose-response but such that complete suppression of growth was achieved at 8 microg/mL. MDA-MB-231 cells were also inhibited by TRF but with a linear dose-response such that 20 microg/mL TRF was needed for complete growth suppression. Separation of the TRF into individual tocotrienols revealed that all fractions could inhibit growth of both ER+ and ER- cells and of ER+ cells in both the presence and absence of estradiol. However, the gamma- and delta-fractions were the most inhibitory. Complete inhibition of MCF7 cell growth was achieved at 6 microg/mL of gamma-tocotrienol/delta-tocotrienol (gammaT3/deltaT3) in the absence of estradiol and 10 microg/mL of deltaT3 in the presence of estradiol, whereas complete suppression of MDA-MB-231 cell growth was not achieved even at concentrations of 10 microg/mL of deltaT3. By contrast to these inhibitory effects of tocotrienols, alphaT had no inhibitory effect on MCF7 cell growth in either the presence or the absence of estradiol, nor on MDA-MB-231 cell growth. These results confirm studies using other sublimes of human breast cancer cells and demonstrate that tocotrienols can exert direct inhibitory effects on the growth of breast cancer cells. In searching for the mechanism of inhibition, studies of the effects of TRF on estrogen-regulated pS2 gene expression in MCF7 cells showed that tocotrienols do not act via an estrogen receptor-mediated pathway and must therefore act differently from estrogen antagonists. Furthermore, tocotrienols did not increase levels of growth-inhibitory insulin-like growth factor binding proteins (IGFBP) in MCF7 cells, implying also a different mechanism from that proposed for retinoic acid inhibition of estrogen-responsive breast cancer cell growth. Inhibition of the growth of breast cancer cells by tocotrienols could have important clinical implications not only because tocotrienols are able to inhibit the growth of both ER+ and ER- phenotypes but also because ER+ cells could be growth-inhibited in the presence as well as in the absence of estradiol. Future clinical applications of TRF could come from potential growth suppression of ER+ breast cancer cells otherwise resistant to growth inhibition by antiestrogens and retinoic acid.

Abstract:

[Detail](#) [Delete](#)

Title: **Penetration and distribution of alpha-tocopherol, alpha- or gamma-tocotrienols applied individually onto murine skin.**

Author: Traber, M G : Rallis, M : Podda, M : Weber, C : Maibach, H I : Packer, L

Citation: Lipids. 1998 Jan; 33(1): 87-91

To evaluate skin penetration of various vitamin E homologs, a 5% solution of either alpha-tocopherol, alpha-tocotrienol, or gamma-tocotrienol in polyethylene glycol was topically applied

to SKH-1 hairless mice. After 0.5, 1, 2, or 4 h (n = four per time point and four per vitamin E homolog), the skin was washed, the animals killed, the skin rapidly removed, frozen on dry ice, and a biopsy taken and sectioned: stratum corneum (two uppermost, 5-micron sections--SC1 and SC2), epidermis (next two 10-micron sections--E1 and E2), papillary dermis (next 100 microns, PD), dermis (next 400 microns, D), and subcutaneous fat (next 100 microns, SF). SC1 contained the highest vitamin E concentrations per mu thickness. To compare the distribution of the various vitamin E forms into the skin layers, the percentage

Abstract: of each form was expressed per its respective total. Most surprising was that the largest fraction of skin vitamin E following topical application was found in the deeper subcutaneous layers--the lowest layers, PD (40 +/- 15%) and D (36 +/- 15%), contained the major portion of the applied vitamin E forms. Although PD only represents about 16% of the total skin thickness, it contains sebaceous glands--lipid secretory organs, and, thus, may account for the vitamin E affinity for this layer. Hence, applied vitamin E penetrates rapidly through the skin, but the highest concentrations are found in the uppermost 5 microns.

[Detail](#) [Delete](#)

Title: **Inhibition of proliferation of estrogen receptor-negative MDA-MB-435 and -positive MCF-7 human breast cancer cells by palm oil tocotrienols and tamoxifen, alone and in combination.**

Author: Guthrie, N : Gapor, A : Chambers, A F : Carroll, K K

Citation: J-Nutr. 1997 Mar; 127(3): 544S-548S

Abstract: Tocotrienols are a form of vitamin E, having an unsaturated isoprenoid side-chain rather than the saturated side-chain of tocopherols. The tocotrienol-rich fraction (TRF) from palm oil contains alpha-tocopherol and a mixture of alpha-, gamma- and delta-tocotrienols. Earlier studies have shown that tocotrienols display anticancer activity. We previously reported that TRF, alpha-, gamma- and delta-tocotrienols inhibited proliferation of estrogen receptor-negative MDA-MB-435 human breast cancer cells with 50% inhibitory concentrations (IC50) of 180, 90, 30 and 90 microg/mL, respectively, whereas alpha-tocopherol had no effect at concentrations up to 500 microg/mL. Further experiments with estrogen receptor-positive MCF-7 cells showed that tocotrienols also inhibited their proliferation, as measured by [3H] thymidine incorporation. The IC50s for TRF, alpha-tocopherol, alpha-, gamma- and delta-tocotrienols were 4, 125, 6, 2 and 2 microg/mL, respectively. Tamoxifen, a widely used synthetic antiestrogen inhibits the growth of MCF-7 cells with an IC50 of 0.04 microg/mL. We tested 1:1 combinations of TRF, alpha-tocopherol and the individual tocotrienols with tamoxifen in both cell lines. In the MDA-MB-435 cells, all of the combinations were found to be synergistic. In the MCF-7 cells, only 1:1 combinations of gamma- or delta-tocotrienol with tamoxifen showed a synergistic inhibitory effect on the proliferative rate and growth of the cells. The inhibition by tocotrienols was not overcome by addition of excess estradiol to

the medium. These results suggest that tocotrienols are effective inhibitors of both estrogen receptor-negative and -positive cells and that combinations with tamoxifen should be considered as a possible improvement in breast cancer therapy.

[Detail](#) [Delete](#)

Title: **Tocotrienols from palm oil as effective inhibitors of protein oxidation and lipid peroxidation in rat liver microsomes.**

Author: Kamat, J P : Sarma, H D : Devasagayam, T P : Nesaretnam, K : Basiron, Y

Citation: Mol-Cell-Biochem. 1997 May; 170(1-2): 131-7

Abstract: Tocotrienols from palm oil showed significant ability to inhibit oxidative damage induced by ascorbate-Fe²⁺ and photosensitization, involving different mechanisms, in rat liver microsomes. The tocotrienol-rich fraction from palm oil (TRF), being tried as a more economical and efficient substitute for alpha-tocopherol, showed time- and concentration-dependent inhibition of protein oxidation as well as lipid peroxidation. It was more effective against protein oxidation. The extent of inhibition by TRF varied with different peroxidation products such as conjugated dienes, lipid hydroperoxides and thiobarbituric acid reactive substances (TBARS). Among the constituents of TRF, gamma-tocotrienol was the most effective followed by its alpha- and delta-isomers. In general, at a low concentration of 5 microM, TRF was able to prevent oxidative damage to significant extent (37% inhibition of protein oxidation and 27-30% of lipid peroxidation at 1 h of incubation). The protective ability of TRF (30.1% at 5 microM with TBARS formation) was significantly higher than that of the dominant form of vitamin E, alpha-tocopherol (16.5% under same conditions). Hence our studies indicate that this fraction from palm oil can be considered as an effective natural antioxidant supplement capable of protecting cellular membranes against oxidative damage.

[Detail](#) [Delete](#)

Title: **Different starting times of alpha-tocopherol and gamma-tocotrienol supplementation and tumor marker enzyme activities in the rat chemically induced with cancer.**

Author: Makpol, S : Shamaan, N A : Jarien, Z : Top, A G : Khalid, B A : Wan Ngah, W Z

Citation: Gen-Pharmacol. 1997 Apr; 28(4): 589-92

Abstract: 1. alpha-Tocopherol (alpha-T) and gamma-tocotrienol (gamma-T) were supplemented continuously for 8 weeks in the diets of normal rats and rats chemically induced with cancer using diethylnitrosamine (DEN), 2-acetylaminofluorene (AAF) and partial hepatectomy. Hepatocarcinogenesis was followed by determining the plasma gamma-glutamyl-transpeptidase (GGT) and alkaline phosphatase (ALP) activities as well as placental glutathione S-transferase (PGST) and GGT activities histochemically, at 4-week intervals. 2. Male Rattus norvegicus were supplemented alpha-T and gamma-T at two different doses of 30 and 300 mg/kg diet. The supplementation was started at three different times: simultaneously with DEN

administration; 4 weeks; and 8 weeks after DEN administration. 3. Elevation of plasma GGT activities and formation of PGST and GGT positive foci were attenuated significantly (P less than 0.05) when alpha-T and gamma-T were supplemented simultaneously with cancer induction. Supplementation begun 4 and 8 weeks after cancer induction did not affect plasma enzyme activities and formation of enzyme-positive foci. 4. alpha-T was more effective than gamma-T, and a lower dose of 30 mg/kg was found to be more effective in reducing the severity of hepatocarcinogenesis.

[Detail](#) [Delete](#)

Title: **Isoprenoids suppress the growth of murine B16 melanomas in vitro and in vivo.**

Author: He, L : Mo, H : Hadisusilo, S : Qureshi, A A : Elson, C E

Citation: J-Nutr. 1997 May; 127(5): 668-74

Sundry mevalonate-derived constituents (isoprenoids) of fruits, vegetables and cereal grains suppress the growth of tumors. This study estimated the concentrations of structurally diverse isoprenoids required to inhibit the increase in a population of murine B16(F10) melanoma cells during a 48-h incubation by 50% (IC50 value). The IC50 values for d-limonene and perillyl alcohol, the monoterpenes in Phase I trials, were 450 and 250 micromol/L, respectively; related cyclic monoterpenes (perillaldehyde, carvacrol and thymol), an acyclic monoterpene (geraniol) and the end ring analog of beta-carotene (beta-ionone) had IC50 values in the range of 120-150 micromol/L. The IC50 value estimated for farnesol, the side-chain analog of the tocotrienols (50 micromol/L) fell midway between that of alpha-tocotrienol (110 micromol/L) and those estimated for gamma- (20 micromol/L) and delta- (10 micromol/L) tocotrienol. A novel tocotrienol lacking methyl groups on the tocol ring proved to be extremely potent (IC50, 0.9

Abstract: micromol/L). In the first of two diet studies, experimental diets were fed to weanling C57BL female mice for 10 d prior to and 28 d following the implantation of the aggressively growing and highly metastatic B16(F10) melanoma. The isomolar (116 micromol/kg diet) and the Vitamin E-equivalent (928 micromol/kg diet) substitution of d-gamma-tocotrienol for dl-alpha-tocopherol in the AIN-76A diet produced 36 and 50% retardations, respectively, in tumor growth (P less than 0.05). In the second study, melanomas were established before mice were fed experimental diets formulated with 2 mmol/kg d-gamma-tocotrienol, beta-ionone individually and in combination. Each treatment increased (P less than 0.03) the duration of host survival. Our finding that the effects of individual isoprenoids were additive suggests the possibility that one component of the anticarcinogenic action of plant-based diets is the tumor growth-suppressive action of the diverse isoprenoid constituents of fruits, vegetables and cereal grains.

[Detail](#) [Delete](#)

Title: **Interactions between vitamin E homologues and ascorbate free radicals in murine skin homogenates irradiated with**

ultraviolet light.

Author: Kitazawa, M : Podda, M : Thiele, J : Traber, M G : Iwasaki, K : Sakamoto, K : Packer, L

Citation: Photochem-Photobiol. 1997 Feb; 65(2): 355-65

The mechanism of oxidation of ascorbic acid in mouse skin homogenates by UV light was investigated by measuring ascorbate free radical formation using electron spin resonance signal formation. Addition of vitamin E (alpha-tocopherol or alpha-tocotrienol) had no effect, whereas short-chain homologues (2,5,7,8-tetramethyl-6-hydroxychroman-2-carboxylic acid [Trolox] and 2,2,5,7,8-pentamethyl-6-hydroxychromane [PMC]) accelerated ascorbate oxidation. The similar hydrophilicity of ascorbate, Trolox and PMC increased their interaction, thus rapidly depleting ascorbate. When dihydrolipoic acid was added simultaneously with the vitamin E homologues, the accelerated ascorbate oxidation was prevented. This was due to the regeneration of ascorbate and PMC from their free radicals by a recycling mechanism between ascorbate, vitamin E homologues and dihydrolipoic acid. Potentiation of antioxidant recycling may be protective against UV irradiation-induced damage. The rate of ascorbate oxidation in the presence of vitamin E homologues was enhanced by a photosensitizer (riboflavin) but was not influenced by reactive oxygen radical quenchers, superoxide dismutase or 5,5-dimethyl-1-pyrroline-N-oxide. These experimental results suggest that the UV irradiation-induced ascorbate oxidation in murine skin homogenates is caused by photoactivated reactions rather than reactive oxygen radical reactions.

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Efficacy of topically applied tocopherols and tocotrienols in protection of murine skin from oxidative damage induced by UV-irradiation.

Title: **protection of murine skin from oxidative damage induced by UV-irradiation.**

Author: Weber, C : Podda, M : Rallis, M : Thiele, J J : Traber, M G : Packer, L

Citation: Free-Radic-Biol-Med. 1997; 22(5): 761-9

To assess the efficacy of various forms of vitamin E in protection of skin from UV-light-induced oxidative stress, vitamin E (tocotrienol-rich fraction of palm oil, TRF) was applied to mouse skin and the contents of antioxidants before and after exposure to UV-light were measured. Four polypropylene plastic rings (1 cm²) were glued onto the animals' backs, and 20 microliters 5% TRF in polyethylene glycol-400 (PEG) was applied to the skin circumscribed by two rings and 20 microliters PEG to the other two rings. After 2 h, the skin was washed and half of the sites were exposed to UV-irradiation (2.8 mW/cm² for 29 min: 3 MED). TRF treatment (n = 19 mice) increased mouse skin alpha-tocopherol 28 +/- 16-fold, alpha-tocotrienol 80 +/- 50-fold, gamma-tocopherol 130 +/- 108-fold, and gamma-tocotrienol 51 +/- 36-fold. A significantly higher percentage of alpha-tocopherol was present in the skin as compared with that in the applied TRF. After UV-irradiation, all vitamin E forms decreased significantly (p less than .01), while a larger proportion of the vitamin E remained

in PEG-treated (approximately 80%) compared with TRF-treated (approximately 40%) skin. Nonetheless, vitamin E concentrations in irradiated TRF-treated skin were significantly higher than in the nonirradiated PEG-treated (control) skin (p less than .01). Thus, UV-irradiation of skin destroys its antioxidants: however, prior application of TRF to mouse skin results in preservation of vitamin E.

[Detail](#) [Delete](#)

Title: **Inhibition of proliferation fo estrogen receptor-negative MDA-MB-435 and -positive MCF-7 human breast cancer cells by palm oil tocotrienols and tamoxifen, alone and in combination.**

Author: Guthrie, N. : Gapor, A. : Chambers, A.F. : Carroll, K.K.

Citation: J-nutr. Bethesda : American Society for Nutritional Sciences. Mar 1997. v. 127 (3) p. 544S-548S.

Tocotrienols are a form of vitamin E, having an unsaturated isoprenoid side-chain rather than the saturated side-chain of tocopherols. The tocotrienol-rich fraction (TRF) from palm oil contains alpha-tocopherol and a mixture of alpha-, gamma and delta-tocotrienols. Earlier studies have shown that tocotrienols display anticancer activity. We previously reported that TRF, alpha, gamma- and delta-tocotrienols inhibited proliferation of estrogen receptor-negative MDA-MB-435 human breast cancer cells with 50% inhibitory concentrations (IC₅₀) of 180, 90, 30 and 90 micrograms/mL, respectively, whereas alpha-tocopherol had no effect at concentrations up to 500 micrograms/mL.

Abstract: Further experiments with estrogen receptor-positive MCF-7 cells showed that tocotrienols also inhibited their proliferation, as measured by [3H] thymidine incorporation. The IC₅₀s for TRF, alpha-tocopherol, alpha-, gamma- and delta-tocotrienols were 4, 125, 6, 2 and 2 micrograms/mL, respectively. Tamoxifen, a widely used synthetic antiestrogen inhibits the growth of MCF-7 cells with an IC₅₀ of 0.04 micrograms/mL. We tested 1:1 combinations of TRF, alpha-tocopherol and the individual tocotrienols with tamoxifen in both cell lines. In the MDA-MB-435 cells, all of the combinations were found to be synergistic. In the MCF-7 cells, only 1:1 combinations of gamma- or delta-tocotrienol with tamoxifen showed a synergistic inhibitory effect on the proliferative rate and growth of the cells. The inhibition by tocotrienols was not overcome by addition of excess estradiol to the medium. These results suggest that tocotrienols are effective inhibitors of both estrogen receptor-negative and -positive cells and that combinations with tamoxifen should be considered as a possible improvement in breast cancer therapy.SP\$ISSN: 0022-3166SP\$VOLUME: 127SP\$ISSUE: 3SP\$PAGE1: 544

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Title: **Novel tocotrienols of rice bran modulate cardiovascular disease risk parameters of hypercholesterolemic humans.**

Author: Qureshi, A.A. : Bradlow, B.A. : Salser, W.A. : Brace, L.D.

Citation: J-nutr-biochem. New York, N.Y. : Elsevier Science Inc. May 1997. v. 8 (5) p. 290-298.

Tocotrienols inhibit cholesterol synthesis by post-transcriptionally suppressing beta-hydroxy-beta-methylglutarylcoenzyme A reductase activity. A double blind, 12-week study was performed to investigate the effect of a novel tocotrienol-rich fraction (TRF25; obtained by molecular distillation from specially processed rice bran oil) on cardiovascular disease risk factors of hypercholesterolemic human subjects (serum total cholesterol greater than 5.69 mmol/L). After acclimation to an alcohol-free regimen (baseline) participants were assigned to the National Cholesterol Education Program (NCEP) Step-1 diet (saturated fat less than 19%, total fat less than 30% of total calories and cholesterol less than 7.76 mmol/L). The participants were evaluated after 4 weeks of exposure to the NCEP Step-1 diet; one group of 21 participants was continued on the NCEP Step-1 diet for 4 weeks receiving an additional 1.2 gm corn oil (placebo group) and a second group of 20 received 200 mg TRF25 dissolved in 1.0 gm corn oil (TRF25 group). Serum total cholesterol and LDL-cholesterol levels of all the participants, stable during the baseline phase of the study, decreased 5% and 8%, respectively, during the 4-week NCEP Step-1 diet. Placebo continuing on the NCEP Step-1 diet for an additional 4 weeks experienced additional but modest decreases in serum total cholesterol (2%) and LDL-cholesterol (3%), yielding significant (P less than 0.05) decreases when compared with the baseline values. These responses confirm the cholesterol-lowering action of a low fat, low cholesterol diet. Participants receiving TRF25 had 12% and 16% reductions (P less than 0.05) in total cholesterol and LDL-cholesterol levels during the 4-week experimental phase; during the two phases. (NCEP Step-1 diet plus treatment) the serum total cholesterol and LDL-cholesterol levels of these participants were decreased (P less than 0.05) by 17% and 24%, respectively. TRF25-mediated decreases in Apo B, Lp(a), platelet factor 4 and thromboxane B2 (15%, 17%, 14%, and 31%, respectively) were significant (P less than 0.05). There was no change in the levels of HDL-cholesterol and apolipoprotein A-1 by this treatment. The treatments also resulted in remarkable increases in the levels of LDL-bound antioxidants, especially tocotrienols, which have substantially greater antioxidant activity than vitamin E. SP\$ISSN: 0955-2863 SP\$VOLUME: 8 SP\$ISSUE: 5 SP\$PAGE1: 290

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Effects of palm olein tocopherol and tocotrienol on lipid

Title: peroxidation, lipid profiles and glycemic control in non-insulin diabetes mellitus patients.

Author: Wan Nazaimoon, W.M. : Sakinah, O. : Gapor, A. : Khalid, B.A.K.

Citation: Nutr-res. Tarrytown, N.Y. : Elsevier Science Inc. Nov/Dec 1996. v. 16 (11/12) p. 1901-1911.

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 ($p=0.004$ and $p=0.02$ 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 ($r=-0.644$, $p=0.007$). MDA (mean \pm SEM) declined significantly (p less than 0.001) following palm olein or Palmvitee intake, 1.33 ± 0.1 versus 1.07 ± 0.07 and 1.47 ± 0.09 versus 1.13 ± 0.06 nmol/l respectively. The decline continued to be significant (p less than 0.001) during the washout period, then showed no further change thereafter. Neither palm olein nor Palmvitee caused significant changes in total cholesterol, HDL-chol, triglyceride, LDL-chol 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.

[Detail](#) [Delete](#)

Title: Response of hypercholesterolemic subjects to administration of tocotrienols.

Author: Qureshi, A A : Bradlow, B A : Brace, L : Manganello, J : Peterson, D M : Pearce, B C : Wright, J J : Gapor, A : Elson, C E

Citation: Lipids. 1995 Dec; 30(12): 1171-7

The cholesterol-suppressive actions of Palmvitee and gamma-tocotrienol were assessed in hypercholesterolemic subjects after acclimation to the American Heart Association Step 1 dietary regimen for four and eight weeks, respectively. The four-week dietary regimen alone elicited a 5% decrease (P less than 0.05) in the cholesterol level of the 36 subjects. Subjects continuing on the dietary regimen for a second four-week period experienced an additional 2% decrease in their cholesterol levels. Dietary assessments based on unanticipated recalls of 24-h food intake records suggest that significant reductions in energy and fat, predominantly in saturated fat, intakes are responsible. The subjects experienced significant Palmvitee- and gamma-tocotrienol-mediated decreases in cholesterol. The group of subjects acclimated to the dietary regimen for four weeks responded to Palmvitee (a blend of tocols providing 40 mg alpha-tocopherol, 48 mg alpha-tocotrienol, 112 mg gamma-tocotrienol, and 60 mg delta-to-cotrienol/day for four weeks) with a 10% decrease in cholesterol (P less than 0.05). Dietary assessments showed no further change in energy and fat intakes. alpha-Tocopherol attenuated the cholesterol-suppressive action of the tocotrienols. The second group of

subjects, acclimated to the dietary regimen for eight weeks, received 200 mg gamma-tocotrienol/d for four weeks. The cholesterol-suppressive potency of this alpha-tocopherol-free preparation was calculated to be equivalent to that of the mixture of tocotrienols (220 mg) used in the prior study. Cholesterol levels of the 16 subjects in the second group decreased 13% (P less than 0.05) during the four-week trial. Plasma apolipoprotein B and ex vivo generation of thromboxane B2 were similarly responsive to the tocotrienol preparations, whereas neither preparation had an impact on high density lipoprotein cholesterol and apolipoprotein A-1 levels.

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Tocotrienols from palm oil as potent inhibitors of lipid

Title: **peroxidation and protein oxidation in rat brain mitochondria.**

Author: Kamat, J P : Devasagayam, T P

Citation: Neurosci-Lett. 1995 Aug 11; 195(3): 179-82

Abstract: The tocotrienol-rich-fraction (TRF) from palm oil, being tried as a more economical and efficient substitute for alpha-tocopherol, significantly inhibited oxidative damage in vitro to both lipids and proteins in rat brain mitochondria induced by ascorbate-Fe²⁺, the free radical initiator azobis(2-amidopropane)dihydrochloride (AAPH) and photosensitisation. The observed inhibitory effect was both time- and concentration-dependent. At a low concentration of 5 microM, TRF can significantly inhibit oxidative damage to both lipids and proteins. The inhibitory effect of TRF seems to be mainly due to gamma-tocotrienol and to a lesser extent alpha- and delta-tocotrienols. TRF was significantly more effective than alpha-tocopherol. This fraction from palm oil can be considered a natural antioxidant supplement capable of protecting the brain against oxidative damage and thereby from the ensuing adverse alterations.

[Detail](#) [Delete](#)

Title: **Effect of tocotrienols on the growth of a human breast cancer cell line in culture.**

Author: Nesaretnam, K : Guthrie, N : Chambers, A F : Carroll, K K

Citation: Lipids. 1995 Dec; 30(12): 1139-43

Abstract: The tocotrienol-rich fraction (TRF) of palm oil consists of tocotrienols and some alpha-tocopherol (alpha-T). Tocotrienols are a form of vitamin E having an unsaturated side-chain, rather than the saturated side-chain of the more common tocopherols. Because palm oil has been shown not to promote chemically-induced mammary carcinogenesis, we tested effects of TRF and alpha-T on the proliferation, growth, and plating efficiency (PE) of the MDA-MB-435 estrogen-receptor-negative human breast cancer cells. TRF inhibited the proliferation of these cells with a concentration required to inhibit cell proliferation by 50% of 180 microgram/mL whereas alpha-T had no effect at concentrations up to 1000 microgram/mL as measured by incorporation of [3H]thymidine. The effects of TRF and alpha-T also were tested in longer-term growth experiments, using

concentrations of 180 and 500 microgram/mL. We found that TRF inhibited the growth of these cells by 50%, whereas alpha-T did not. Their effect on the ability of these cells to form colonies also was studied, and it was found that TRF inhibited PE, whereas alpha T had no effect. These results suggest that the inhibition is due to the presence of tocotrienols in TRF rather than alpha T.

[Detail](#) [Delete](#)

Title: **Antioxidant effects of tocotrienols in patients with hyperlipidemia and carotid stenosis.**

Author: Tomeo, A C : Geller, M : Watkins, T R : Gapor, A : Bierenbaum, M L

Citation: Lipids. 1995 Dec; 30(12): 1179-83

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 less than 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 less than 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 less than 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.

Abstract:

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Title: **Human atherosclerotic plaque contains both oxidized lipids and relatively large amounts of alpha-tocopherol and ascorbate.**

Author: Suarna, C : Dean, R T : May, J : Stocker, R

Citation: Arterioscler-Thromb-Vasc-Biol. 199 : 5 Oct; 15(10): 1616-24

We assessed the antioxidant status and contents of unoxidized and oxidized lipids in freshly obtained, homogenized samples of both normal human iliac arteries and carotid and femoral atherosclerotic plaque. Optimal sample preparation involved homogenization of human atherosclerotic plaque for 5 minutes, which resulted in recovery of most of the unoxidized and

oxidized lipids without substantial destruction of endogenous vitamins C and E and 87% and 43% recoveries of added standards of alpha-tocotrienol and isoascorbate, respectively. The total protein, lipid, and antioxidant levels obtained from human plaque varied among donors, although the reproducibility of replicates from a single sample was within 3%, except for ubiquinone-10 and ascorbate, which varied by 20% and 25%, respectively. Plaque samples contained significantly more ascorbate and urate than control arteries, with no discernible difference in the vitamin C redox status between plaque and control materials. The concentrations of alpha-tocopherol and ubiquinone-10 were comparable in plaque samples and control arteries. However, approximately 9 mol percent of plaque alpha-tocopherol was present as alpha-tocopherylquinone, whereas this oxidation product of vitamin E was not detectable in control arteries. Coenzyme Q10 in plaque and control arteries was only detected in the oxidized form ubiquinone-10, although coenzyme Q10 oxidation may have occurred during processing. The most abundant of all studied lipids in plaque samples was free cholesterol, followed by cholesteryl oleate and cholesteryl linoleate (Ch18:2). Approximately 30% of plaque Ch18:2 was oxidized, with 17%, 12%, and 1% present as fatty acyl hydroxides, ketones, and hydroperoxides, respectively. (ABSTRACT TRUNCATED AT 250 WORDS)

[Detail](#) [Delete](#)

Title: Inhibition of tumour promotion by various palm-oil tocotrienols.

Author: Goh, S H : Hew, N F : Norhanom, A W : Yadav, M

Citation: Int-J-Cancer. 1994 May 15; 57(4): 529-31

Inhibition of tumour promotion by various vitamin E compounds (tocopherols and tocotrienols) and some of their dimers was examined by an in vitro assay utilizing the activation of Epstein-Barr virus (EBV) early antigen (EA) expression in EBV-genome-carrying human lymphoblastoid cells. The results reveal that gamma- and delta-tocotrienols derived from palm oil exhibit a strong activity against tumour promotion by inhibiting EBV EA expression in Raji cells induced by 12-O-tetradecanoylphorbol-13-acetate (TPA). However, alpha- and gamma-tocopherols and dimers of gamma-tocotrienol or gamma-tocopherol lack this activity.

[Detail](#) [Delete](#)

Title: The chemoprevention of cancer by mevalonate-derived constituents of fruits and vegetables.

Author: Elson, C E : Yu, S G

Citation: J-Nutr. 1994 May; 124(5): 607-14

Anutritive isoprenoid constituents of fruits, vegetables, cereal grains and essential oils exhibit a spectrum of anticarcinogenic activities. The induction of hepatic Phase II detoxifying activities by dietary isoprenoids appears to underlie their blocking action. The second anticarcinogenic action of the dietary isoprenoids, suppression of the growth of chemically

initiated and transplanted tumors is, we suggest, secondary to the inhibition of mevalonate pathway activities. Mevinolin, a competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase activity, depletes cells of the intermediate products of the pathway that are required for the posttranslational modification of proteins, a process giving the proteins lipophilic anchors that bind to membranes. As a consequence, nuclear lamins and ras oncoproteins remain in nascent states, and cells do not proliferate. gamma-Tocotrienol, perillyl alcohol, geraniol and d-limonene suppress hepatic HMG-CoA reductase activity, a rate-limiting step in cholesterol synthesis, and modestly lower serum-cholesterol levels of animals. These isoprenoids also suppress tumor growth. The HMG-CoA reductase of neoplastic tissues differs from that of sterologenic tissues in being markedly resistant to sterol feedback inhibition. Our review suggests that the mevalonate pathway of tumor tissues is uniquely sensitive to the inhibitory actions of the dietary isoprenoids.

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Comparative antioxidant activity of tocotrienols and other natural lipid-soluble antioxidants in a homogeneous system, and in rat and human lipoproteins.

Author: Suarna, C : Hood, R L : Dean, R T : Stocker, R

Citation: Biochim-Biophys-Acta. 1993 Feb 24; 1166(2-3): 163-70

The antioxidant activity of tocotrienols toward peroxy radicals was compared with that of other natural lipid-soluble antioxidants in three different systems by measuring the temporal disappearance of antioxidants and the formation of lipid hydroperoxides. In homogeneous solution, the initial rates of consumption of the various antioxidants, assessed by competition experiments between pairs of antioxidants for radicals, decreased in the order: ubiquinol-10 approximately ubiquinol-9 greater than alpha-tocopherol approximately alpha-tocotrienol greater than beta-carotene approximately lycopene greater than gamma-tocopherol approximately gamma-tocotrienol. Following in vitro incubation of human plasma with alpha-tocotrienol, this form of vitamin E was present in all classes of lipoproteins isolated from the supplemented plasma.

Abstract: Dietary supplementation of rats and humans with a tocotrienol-rich preparation resulted in a dose-dependent appearance of alpha- and gamma-tocotrienols in plasma and all circulating lipoproteins, respectively. Exposure of such enriched rat plasma to aqueous peroxy radicals resulted in simultaneous consumption of the alpha- and then gamma-isomers of vitamin E. The sequence of radical-induced consumption of antioxidants in freshly isolated, in vitro and in vivo tocotrienol-enriched low density lipoprotein (LDL) was again ubiquinol-10 greater than alpha-tocotrienol approximately alpha-tocopherol greater than carotenoids greater than gamma-tocopherol approximately gamma-tocotrienol. Under conditions where radicals were generated at constant rates, the rate of lipid hydroperoxide formation in LDL was not constant. It proceeded in at least three stages separated by the phase of ubiquinol-10

consumption and, subsequently, that of alpha-tocopherol/alpha-tocotrienol. Our results show that dietary tocotrienols become incorporated into circulating human lipoproteins where they react with peroxy radicals as efficiently as the corresponding tocopherol isomers.

[Detail](#) [Delete](#)

Title: **Tocotrienol and fatty acid composition of barley oil and their effects on lipid metabolism.**

Author: Wang, L : Newman, R K : Newman, C W : Jackson, L L : Hofer, P J

Citation: Plant-Foods-Hum-Nutr. 1993 Jan; 43(1): 9-17

Abstract: Barley oil was extracted with hexane from the grain of a high oil waxy hull-less barley. Twelve male broiler chicks were fed corn-based diets with either 10% barley oil, 10% corn oil or 10% margarine ad libitum for ten days. Total plasma cholesterol concentration of the chicks fed barley oil was 34% lower (p less than 0.05) than that of the chicks fed margarine. Plasma low density lipoprotein cholesterol concentration of chicks fed barley oil was 53% and 59% lower (p less than 0.05) than those of chicks fed corn oil and margarine, respectively. Plasma high density lipoprotein cholesterol and triglyceride concentration of the barley oil group were similar to those of the margarine but higher (p less than 0.05) than those of the corn oil group. Chicks fed the barley oil gained more (p less than 0.05) body weight than those fed the corn oil and margarine. Barley oil had an effect in suppression of TC and LDLC in chicks compared to margarine. Barley oil suppressed LDLC but not HDLC in chicks compared to corn oil. A greater weight gain of the chicks fed barley oil suggested that these chicks had normally functioning digestion and absorption. alpha-Tocotrienol and gamma-tocotrienol content of the barley oil were 24 and 17 times greater, respectively, than those observed in the corn oil, while the same fractions were not detectable in the margarine. Polyunsaturated fatty acid content of the barley oil was more than threefold that of margarine. These data suggest that alpha-tocotrienol and polyunsaturated fatty acids are hypocholesterolemic components in barley oil.

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Title: **Influence of palm oil or its tocotrienol-rich fraction on the lipid peroxidation potential of rat liver mitochondria and microsomes.**

Author: Nesaretnam, K : Devasagayam, T P : Singh, B B : Basiron, Y

Citation: Biochem-Mol-Biol-Int. 1993 May; 30(1): 159-67

The effect of palm oil, a widely used vegetable oil, rich in tocotrienols, on peroxidation potential of rat liver was examined. Long-term feeding of rats with palm oil as one of the dietary components significantly reduced the peroxidation potential of hepatic mitochondria and microsomes. As compared to hepatic mitochondria isolated from rats fed control or corn oil-rich diet, those from palm oil-fed group showed significantly less susceptibility to peroxidation induced by ascorbate and NADPH. However, in microsomes, only

Abstract: NADPH-induced lipid peroxidation was significantly reduced in rats fed palm oil rich-diet. Though the accumulation of thiobarbituric acid reactive substances during ascorbate-induced lipid peroxidation in mitochondria from rats fed corn oil-rich diet supplemented with tocotrienol-rich fraction (TRF) of palm oil was similar to that of control rats, the initial rate of peroxidation was much slower than those from control or corn oil fed diets. Our in vitro studies as well as analyses of co-factors related to peroxidation potential indicated that the observed decrease in palm oil-fed rats may be due to increased amount of antioxidants in terms of tocotrienol as well as decrease in the availability of substrates for peroxidation.

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Structural and dynamic membrane properties of alpha-

Title: **tocopherol and alpha-tocotrienol: implication to the molecular mechanism of their antioxidant potency.**

Author: Suzuki, Y J : Tsuchiya, M : Wassall, S R : Choo, Y M : Govil, G : Kagan, V E : Packer, L

Citation: Biochemistry. 1993 Oct 12; 32(40): 10692-9

Abstract: d-alpha-Tocopherol and d-alpha-tocotrienol are two vitamin E constituents having the same aromatic chromanol "head" but different hydrocarbon "tails". alpha-Tocotrienol has been shown to be more potent in protecting against free radical-induced oxidative stress than alpha-tocopherol. Simple models of phospholipid membrane systems were used to investigate the mechanism of the antioxidant potency of alpha-tocotrienol in terms of its effects on membrane order and reorientation dynamics. Chemiluminescence and fluorescence measurements demonstrated that alpha-tocotrienol exhibits significantly greater peroxy radical scavenging potency than alpha-tocopherol in phosphatidylcholine liposomes, whereas both antioxidants have identical activity in hexane. This suggests that the antioxidant potency of alpha-tocotrienol requires the membrane environment. When alpha-tocopherol and alpha-tocotrienol were examined for their effects on phospholipid molecular order using conventional ESR spin labeling with 5- and 16-position-labeled doxylstearic acid, although both vitamin E constituents disordered the gel phase and stabilized the liquid-crystalline phase, no differences were observed between the effects of the two compounds. A slightly greater increase (19% vs 15%) in ordering of the liquid-crystalline state due to alpha-tocopherol, however, was discerned in noninvasive ²H NMR experiments. The difference is most noticeable near C10-C13 positions of the phospholipid chain, possibly suggesting alpha-tocotrienol is located closer to the membrane surface. Saturation-transfer ESR, furthermore, revealed that on the time scale $\tau_c = 10^{-7}$ - 10^{-3} s the rates of rotation about the long molecular axis and of the wobbling motion of the axis are modified to differing extents by the two forms of the vitamin E. (ABSTRACT TRUNCATED AT 250 WORDS)

[Detail](#) [Delete](#)

Title: **Long-term administration of tocotrienols and tumor-marker enzyme activities during hepatocarcinogenesis in**

rats.

Author: Rahmat, A : Ngah, W Z : Shamaan, N A : Gapor, A : Abdul Kadir, K

Citation: Nutrition. 1993 May-Jun; 9(3): 229-32

The effects of long-term administration of tocotrienol on hepatocarcinogenesis in rats induced by diethylnitrosamine (DEN) and 2-acetylaminofluorene (AAF) were investigated by determining the activities of gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), glutathione S-transferases (GSTs), and glutathione (GSH) levels in blood and liver. Twenty-eight male 7- to 8-wk-old *Rattus norvegicus* rats, weighing 120-160 g, were used in this study. The rats were divided into four treatment groups: a control group on a basal diet, a group fed a basal diet supplemented with tocotrienol (30 mg/kg food), a group treated with DEN/AAF, and a group treated with DEN/AAF and fed a diet supplemented with tocotrienol (30 mg/kg food). Blood was collected monthly, and GGT, ALP, and GSH levels were determined. The rats were killed after 9 mo, and the livers were examined morphologically. Grayish white nodules (2/liver) were found in all the DEN/AAF-treated rats (n = 10), but only one of the rats treated with DEN/AAF and supplemented with tocotrienol (n = 6) had liver nodules. A significant increase in the level of blood and liver GSH, ALP, and GGT activities was observed in the DEN/AAF-treated rats. Liver GSTs were similarly increased with DEN/AAF treatment. Tocotrienol supplementation attenuated the impact of the carcinogens in the rats.

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Tocotrienols regulate cholesterol production in mammalian cells by post-transcriptional suppression of 3-hydroxy-3-methylglutaryl-coenzyme A reductase.

Title:

Author: Parker, R A : Pearce, B C : Clark, R W : Gordon, D A : Wright, J J

Citation: J-Biol-Chem. 1993 May 25; 268(15): 11230-8

Tocotrienols are natural farnesylated analogues of tocopherols which decrease hepatic cholesterol production and reduce plasma cholesterol levels in animals. For several cultured cell types, incubation with gamma-tocotrienol inhibited the rate of [¹⁴C]acetate but not [³H] mevalonate incorporation into cholesterol in a concentration- and time-dependent manner, with 50% inhibition at approximately 2 microM and maximum approximately 80% inhibition observed within 6 h in HepG2 cells. 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase total activity and protein levels assayed by Western blot were reduced concomitantly with the decrease in cholesterol synthesis. In HepG2 cells, gamma-tocotrienol suppressed reductase despite strong blockade by inhibitors at several steps in the pathway, suggesting that isoprenoid flux is not required for the regulatory effect. HMG-CoA reductase protein synthesis rate was moderately diminished (57% of control), while the degradation rate was increased 2.4-fold versus control (t_{1/2} declined from 3.73 to 1.59 h) as judged by [³⁵S]methionine pulse-chase/immunoprecipitation analysis of

HepG2 cells treated with 10 microM gamma-tocotrienol. Under these conditions, the decrease in reductase protein levels greatly exceeded the minor decrease in mRNA (23 versus 76% of control, respectively), and the low density lipoprotein receptor protein was augmented. In contrast, 25-hydroxycholesterol strongly cosuppressed HMG-CoA reductase protein and mRNA levels and the low density lipoprotein receptor protein. Thus, tocotrienols influence the mevalonate pathway in mammalian cells by post-transcriptional suppression of HMG-CoA reductase, and appear to specifically modulate the intracellular mechanism for controlled degradation of the reductase protein, an activity that mirrors the actions of the putative non-sterol isoprenoid regulators derived from mevalonate.

[Detail](#) [Delete](#)

Title: **gamma-Tocotrienol as a hypocholesterolemic and antioxidant agent in rats fed atherogenic diets.**

Author: Watkins, T : Lenz, P : Gapor, A : Struck, M : Tomeo, A : Bierenbaum, M

Citation: Lipids. 1993 Dec; 28(12): 1113-8

Abstract: This study was designed to determine whether incorporation of gamma-tocotrienol or alpha-tocopherol in an atherogenic diet would reduce the concentration of plasma cholesterol, triglycerides and fatty acid peroxides, and attenuate platelet aggregability in rats. For six weeks, male Wistar rats (n = 90) were fed AIN76A semisynthetic test diets containing cholesterol (2% by weight), providing fat as partially hydrogenated soybean oil (20% by weight), menhaden oil (20%) or corn oil (2%). Feeding the ration with menhaden oil resulted in the highest concentrations of plasma cholesterol, low and very low density lipoprotein cholesterol, triglycerides, thiobarbituric acid reactive substances and fatty acid hydroperoxides. Consumption of the ration containing gamma-tocotrienol (50 mg/kg) and alpha-tocopherol (500 mg/kg) for six weeks led to decreased plasma lipid concentrations. Plasma cholesterol, low and very low density lipoprotein cholesterol, and triglycerides each decreased significantly (P less than 0.001). Plasma thiobarbituric acid reactive substances decreased significantly (P less than 0.01), as did the fatty acid hydroperoxides (P less than 0.05), when the diet contained both chromanols. Supplementation with gamma-tocotrienol resulted in similar, though quantitatively smaller, decrements in these plasma values. Plasma alpha-tocopherol concentrations were lowest in rats fed menhaden oil without either chromanol. Though plasma alpha-tocopherol did not rise with gamma-tocotrienol supplementation at 50 mg/kg, gamma-tocotrienol at 100 mg/kg of ration spared plasma alpha-tocopherol, which rose from 0.60 +/- 0.2 to 1.34 +/- 0.4 mg/dL (P less than 0.05). The highest concentration of alpha-tocopherol was measured in plasma of animals fed a ration supplemented with alpha-tocopherol at 500 mg/kg.(ABSTRACT TRUNCATED AT 250 WORDS)

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Vitamin E inhibits protein oxidation in skeletal muscle of

Title: **resting and exercised rats.**

Author: Reznick, A Z : Witt, E : Matsumoto, M : Packer, L

Citation: Biochem-Biophys-Res-Commun. 1992 Dec 15; 189(2): 801-6

It is well known that exercise induces lipid peroxidation in skeletal muscle and that vitamin E prevents exercise-induced lipid damage. In this study we show for the first time, an increase in protein oxidation in skeletal muscle after a single bout of exercise, related to an exercise-induced decrease in lipophilic antioxidants, and substantial protection against both resting and exercise-induced protein oxidation by supplementation with various isomers (alpha-tocopherol, alpha-tocotrienol) of vitamin E.

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Effects of alpha-tocopherol and tocotrienols on blood

Title: **pressure and linoleic acid metabolism in the spontaneously hypertensive rat (SHR).**

Author: Koba, K : Abe, K : Ikeda, I : Sugano, M

Citation: Biosci-Biotechnol-Biochem. 1992 Sep; 56(9): 1420-3

Both alpha-tocopherol and a 1:1.7 mixture of alpha-tocopherol and tocotrienols at a 0.2% dietary level significantly depressed the age-related increase in the systolic blood pressure of spontaneously hypertensive rats (SHRs) after 3 weeks of feeding. The aortic production of prostacyclin was increased 1.5 times both by alpha-tocopherol and a tocotrienol mixture, suggesting a possible relevance to their hypotensive effect.

Abstract: These vitamins did not influence the delta 6- and delta 5-desaturase activities of liver microsomes, but fatty acid profiles of the liver phospholipids predicted a reduction of linoleic acid desaturation. These effects were in general more clear with tocotrienols than with alpha-tocopherol. Platelet aggregation by 5 microM ADP remained uninfluenced. Thus, tocotrienols may have effects on various lipid parameters somewhat different from those of alpha-tocopherol.

[Detail](#) [Delete](#)

Title: **Hypocholesterolemic activity of synthetic and natural tocotrienols.**

Author: Pearce, B C : Parker, R A : Deason, M E : Qureshi, A A : Wright, J J

Citation: J-Med-Chem. 1992 Oct 2; 35(20): 3595-606

Tocotrienols are farnesylated benzopyran natural products that exhibit hypocholesterolemic activity in vitro and in vivo. The mechanism of their hypolipidemic action involves posttranscriptional suppression of HMG-CoA reductase by a process distinct from other known inhibitors of cholesterol biosynthesis. An efficient synthetic route to tocotrienols and their isolation from palm oil distillate using an improved procedure is presented. gamma-Tocotrienol exhibits a 30-fold greater activity toward cholesterol biosynthesis inhibition compared to alpha-tocotrienol in HepG2 cells in vitro. The synthetic (racemic) and natural (chiral) tocotrienols exhibit nearly identical cholesterol biosynthesis inhibition and HMG-

CoA reductase suppression properties as demonstrated in vitro and in vivo.

[Detail](#) [Delete](#)

Title: **Effect of palm oil on lipid and lipoprotein metabolism and eicosanoid production in rats.**

Author: Sugano, M : Imaizumi, K

Citation: Am-J-Clin-Nutr. 1991 Apr; 53(4 Suppl): 1034S-1038S

Palm oil (PA), which is very rich in palmitic acid, influenced the serum cholesterol concentration and tissue eicosanoid profile of rats characteristically. It increased the serum cholesterol concentration compared with safflower oil (SA), but the degree of the elevation was moderate compared with that of olive oil (OL). The proportion of arachidonic acid in tissue lipids was by no means lower on a PA diet than on an SA diet.

Abstract: The ratio of prostacyclin produced by the aorta to thromboxane A₂ in plasma was not simply predicted by the dietary level of saturated fatty acid. PA tended to facilitate the utilization of arachidonate for prostacyclin in vitro in peritoneal macrophages compared with SA. Fatty acid profiles of PA rather than the glyceride structure or the tocotrienol appeared to be the major determinant for the specific features of lipid metabolism observed in rats fed PA.

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Free radical recycling and intramembrane mobility in the antioxidant properties of alpha-tocopherol and alpha-tocotrienol.

Author: Serbinova, E : Kagan, V : Han, D : Packer, L

Citation: Free-Radic-Biol-Med. 1991; 10(5): 263-75

d-Alpha-tocopherol (2R,4'R,8'R-Alpha-tocopherol) and d-alpha-tocotrienol are two vitamin E constituents having the same aromatic chromanol "head" but differing in their hydrocarbon "tail": tocopherol with a saturated and tocotrienol with an unsaturated isoprenoid chain. d-Alpha-tocopherol has the highest vitamin E activity, while d-alpha-tocotrienol manifests only about 30% of this activity. Since vitamin E is considered to be physiologically the most important lipid-soluble chain-breaking antioxidant of membranes, we studied alpha-tocotrienol as compared to alpha-tocopherol under conditions which are important for their antioxidant function. d-

Abstract: Alpha-tocotrienol possesses 40-60 times higher antioxidant activity against (Fe²⁺ + ascorbate)- and (Fe²⁺ + NADPH)-induced lipid peroxidation in rat liver microsomal membranes and 6.5 times better protection of cytochrome P-450 against oxidative damage than d-alpha-tocopherol. To clarify the mechanisms responsible for the much higher antioxidant potency of d-alpha-tocotrienol compared to d-alpha-tocopherol, ESR studies were performed of recycling efficiency of the chromanols from their chromanoxyl radicals. ¹H-NMR measurements of lipid molecular mobility in liposomes containing chromanols, and fluorescence measurements which reveal the uniformity of distribution (clusterizations) of chromanols in the lipid bilayer. From the results, we concluded

that this higher antioxidant potency of d-alpha-tocotrienol is due to the combined effects of three properties exhibited by d-alpha-tocotrienol as compared to d-alpha-tocopherol: (i) its higher recycling efficiency from chromanoxyl radicals, (ii) its more uniform distribution in membrane bilayer, and (iii) its stronger disordering of membrane lipids which makes interaction of chromanols with lipid radicals more efficient. The data presented show that there is a considerable discrepancy between the relative in vitro antioxidant activity of d-alpha-tocopherol and d-alpha-tocotrienol with the conventional bioassays of their vitamin activity.

[Detail](#) [Delete](#)

Title: **Lowering of serum cholesterol in hypercholesterolemic humans by tocotrienols (palmvitee).**

Author: Qureshi, A A : Qureshi, N : Wright, J J : Shen, Z : Kramer, G : Gapor, A : Chong, Y H : DeWitt, G : Ong, A : Peterson, D M : et al.

Citation: Am-J-Clin-Nutr. 1991 Apr; 53(4 Suppl): 1021S-1026S

A double-blind, crossover, 8-wk study was conducted to compare effects of the tocotrienol-enriched fraction of palm oil (200 mg palmvitee capsules/day) with those of 300 mg corn oil/d on serum lipids of hypercholesterolemic human subjects (serum cholesterol 6.21-8.02 mmol/L). Concentrations of serum total cholesterol (-15%), LDL cholesterol (-8%), Apo B (-10%), thromboxane (-25%), platelet factor 4 (-16%), and glucose (-12%) decreased significantly only in the 15 subjects given

Abstract: palmvitee during the initial 4 wk. The crossover confirmed these actions of palmvitee. There was a carry over effect of palmvitee. Serum cholesterol concentrations of seven hypercholesterolemic subjects (greater than 7.84 mmol/L) decreased 31% during a 4-wk period in which they were given 200 mg gamma-tocotrienol/d. This indicates that gamma-tocotrienol may be the most potent cholesterol inhibitor in palmvitee capsules. The results of this pilot study are very encouraging.

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Title: **Dietary tocotrienols reduce concentrations of plasma cholesterol, apolipoprotein B, thromboxane B2, and platelet factor 4 in pigs with inherited hyperlipidemias.**

Author: Qureshi, A A : Qureshi, N : Hasler Rapacz, J O : Weber, F E : Chaudhary, V : Crenshaw, T D : Gapor, A : Ong, A S : Chong, Y H : Peterson, D : et al.

Citation: Am-J-Clin-Nutr. 1991 Apr; 53(4 Suppl): 1042S-1046S

Abstract: Normolipemic and genetically hypercholesterolemic pigs of defined lipoprotein genotype were fed a standard diet supplemented with 50 micrograms/g tocotrienol-rich fraction (TRF) isolated from palm oil. Hypercholesterolemic pigs fed the TRF supplement showed a 44% decrease in total serum cholesterol, a 60% decrease in low-density-lipoprotein (LDL)-cholesterol, and significant decreases in levels of apolipoprotein B (26%), thromboxane-B2 (41%), and platelet factor 4 (PF4; 29%). The declines in thromboxane B2 and PF4 suggest that

TRF has a marked protective effect on the endothelium and platelet aggregation. The effect of the lipid-lowering diet persisted only in the hypercholesterolemic swine after 8 wk feeding of the control diet. These results support observations from previous studies on lowering plasma cholesterol in animals by tocotrienols, which are naturally occurring compounds in grain and palm oils and may have some effect on lowering plasma cholesterol in humans.

[Detail](#) [Delete](#)

Title: The effect of vitamin E analogues and long hydrocarbon chain compounds on calcium-induced muscle damage. A novel role for alpha-tocopherol?

Author: Phoenix, J : Edwards, R H : Jackson, M J

Citation: Biochim-Biophys-Acta. 1991 Oct 21; 1097(3): 212-8

Previous studies have demonstrated that supplemental alpha-tocopherol inhibited calcium-induced cytosolic enzyme efflux from normal rat skeletal muscles incubated in vitro and suggested that the protective action was mediated by the phytyl chain of alpha-tocopherol [1]. In order to investigate this further a number of hydrocarbon chain analogues of tocopherol (7,8-dimethyl tocol, 5,7-dimethyl tocol, tocol, alpha-tocotrienol, alpha-tocopherol [10], vitamin K1, vitamin K1 [10], vitamin K1 Abstract: diacetate, vitamin K2 [20], phytyl ubiquinone and retinol) were tested for any ability to inhibit calcium ionophore, A23187, induced creatine kinase (CK) enzyme efflux. Some compounds were found to be very effective inhibitors and comparison of their structures and ability to inhibit TBARS production in muscle homogenates revealed that the effects did not appear related to antioxidant capacity or chromanol methyl groups, but rather the length and structure of the hydrocarbon chain was the important mediator of the effects seen.

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Title: A comparison of tocopherol and tocotrienol for the chemoprevention of chemically induced rat mammary tumors.

Author: Gould, M N : Haag, J D : Kennan, W S : Tanner, M A : Elson, C E

Citation: Am-J-Clin-Nutr. 1991 Apr; 53(4 Suppl): 1068S-1070S

Two forms of vitamin E, tocopherol and tocotrienol, were tested for chemopreventive activity in two chemically induced rat mammary-tumor models. When mammary tumors were induced by 7,12-dimethylbenz(a)anthracene (DMBA, 50 mg/kg), only the tocotrienol group had a statistically significant increase in tumor latency. There was no effect of either compound on tumor multiplicity. When tumors were induced by N-nitrosomethylurea (NMU, 30 mg/kg), neither analogue of vitamin E modified latency, whereas tocotrienol increased tumor multiplicity. In summary, neither vitamin analog had a major impact on mammary-tumor development after tumor induction with either DMBA or NMU.

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Effect of sampling site on retinol, carotenoid, tocopherol,

Title: **and tocotrienol concentration of adipose tissue of human breast with cancer.**

Author: Rautalahti, M : Albanes, D : Hyvonen, L : Piironen, V :
Heinonen, M

Citation: Ann-Nutr-Metab. 1990; 34(1): 37-41

The effect of sampling site and closeness of malignant tumor on the retinoid, carotenoid, tocopherol, and tocotrienol concentration of adipose tissue of human breast was studied in 10 cases of breast cancer. The four anatomic quadrants of breast did not differ from each other statistically significantly in

Abstract: relation to adipose tissue concentrations of the vitamins studied. Proximity of malignant tumor did not affect the vitamin concentrations when compared to the more distant sampling sites. Representative sample of breast adipose tissue for vitamin concentration analysis can be obtained from tissue adjacent to the tumor.

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