Vitamin E: Tocotrienols

The Science Behind Tocotrienols

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Tocotrienols are novel components of the vitamin E family. The vitamin E family consists of two subgroups: tocotrienols (T3) and tocopherols (T). Tocotrienols are naturally derived from several sources, including rice bran, palm, and annatto. This paper will discuss and document the benefits and superior function of annatto-derived delta- and gamma-tocotrienols, including their role in cholesterol reduction and cardiovascular disease, influence on metabolic syndrome and diabetes, and potential in cancer and chemoprevention.

History and Discovery of Tocotrienols

Although vitamin E (in the form of alpha-tocopherol) was discovered in the 1920s [1], it was not until the 1960s that tocotrienols were assessed to be part of the vitamin E family tree [2]. Vitamin E is known as a "vitamin" because it is essential for reproduction, and sometimes dubbed as the "birth vitamin". Its antioxidant activity was discovered earlier (1930s) [3].

Tocotrienols from current sources (rice, palm and annatto) were first developed and brought to the market by Dr. Barrie Tan, inventor of numerous tocotrienol extraction processes from natural sources. These discoveries include tocotrienols from palm (1992), then rice (1998), and finally annatto (2002).

The first ever tocopherol-free tocotrienol product derived from annatto beans appeared about 2005. The annatto plant originates from the Amazon rainforest and has been used since ancient times. Its Latin name, Bixa orellana, is derived from Spanish conquistador Francesco de Orellana, who led several scientific expeditions to the Peruvian and Brazilian jungles and discovered the plant in the 16th century. Annatto as a natural colorant was introduced into the US about 160 years ago, and today it is used in the food industry worldwide.

The "tocopherol-free" aspect of annatto tocotrienol is important, since research has shown that alpha-tocopherol interferes with the benefits of tocotrienol. Contrary to annatto, both palm and rice contain a significant amount of alpha-tocopherol (25-50% of total vitamin E), which confers interference with tocotrienol functions (Figure 1). For the purpose of this discussion, the definition of "tocopherol-free" is the amount found to be below the measurable limit of alpha-tocopherol by high performance liquid chromatography (HPLC), which is *less than* 0.1%. Typically, the alpha-tocopherol found in rice and palm is much more than 200x that found in annatto. Annatto remains the first and only true source of nature-derived vitamin E that supplies tocotrienol only.

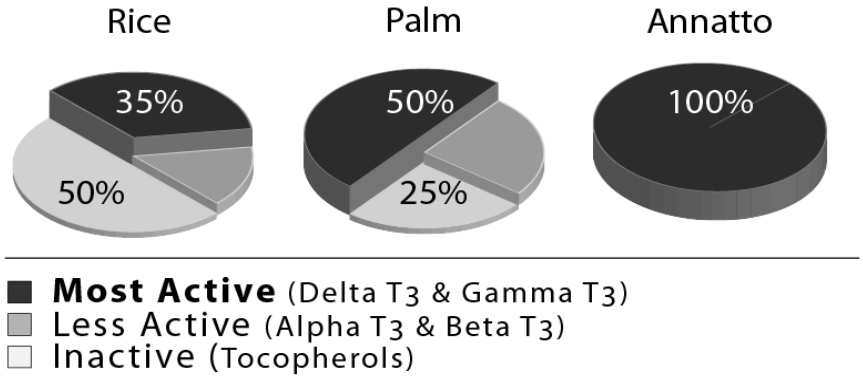

Figure 1. Typical Compositions of Vitamin E in Natural Tocotrienol Sources.

Structures of Tocotrienol, Tocopherol, and Isomers

Tocotrienol and tocopherol both have a chromanol nucleus, which is the site of antioxidant activities. Tocotrienol and tocopherol differ in the tail region of the molecule. Tocotrienol has a farnesylated tail, allowing it to downregulate 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase – an essential enzyme for cholesterol synthesis – whereas tocopherol has a longer phytyl tail without double bonds, disallowing a similar function. The downregulation of HMG-CoA reductase has been shown to decrease total and LDL cholesterol levels, and is considered a critical pathway that involves tocotrienol in the inhibition of several cancers.

Alpha, beta, gamma, and delta are among the isomers of tocotrienol as well as tocopherol. The potency of cholesterol inhibition as well as impact on cancer treatment by these tocotrienol isomers is as follows: delta > gamma > alpha > beta. Tocopherols are inactive in lowering cholesterol or cancer.

Desmethyl tocotrienols is a collective term for reduced methyl substituents on the vitamin E molecule, and primarily refers to delta- and gamma-tocotrienol. Desmethyl tocotrienols are more potent, especially in the absence of a methyl group at the C5 position on the chromanol ring system. Delta-tocotrienol is monomethylated at the C8 position of the chromanol ring system, making it the least substituted, and therefore the most potent isomer of the four tocotrienol compounds. The majority of vitamin E dietary supplements contain mostly tocopherols, of which alpha-tocopherol is the most common. Typically, only traces of tocotrienol are found, which is due to its scarcity in plants from which vitamin E is extracted.

While tocopherols have high antioxidant value, they lack the ability to regulate aberrant cells (e.g. cancer) or cholesterol synthesis (hypercholesterolemia). Large clinical studies on their benefits to treat cardiovascular or other diseases have been equivocal or without effect [4], and possibly harmful [5, 6].

Tocotrienol Mechanism

The mechanism of tocotrienol's hypolipidemic action involves posttranscriptional suppression of HMG-CoA reductase via controlled degradation of the reductase protein [7, 8]. Recently it has been reported that only gamma- and delta-tocotrienol stimulate the degradation of the HMG-CoA reductase, and block processing of sterol regulatory element-binding protein (SREBP). Blocking SREBP processing has implications on the triglyceride synthesis (or reduction) with importance in prediabetic and diabetic conditions. Therefore, the mechanism for cholesterol reduction by tocotrienol shown 20 years ago was revalidated some 15 years later. This study came from the Michael Brown and Joseph Goldstein research group that discovered the cholesterol receptor, hence explaining how cholesterol is regulated. Brown and Goldstein were awarded the 1985 Nobel prize for this work [9].

Other forms of vitamin E (all four tocopherols and alpha- and beta-tocotrienols) do not degrade, downregulate, nor block SREBP processing [8]. Delta-tocotrienol was also found to have the greatest antioxidant properties among the tocotrienol isomers [10], which is due to the decreased methylation on the chromanol ring that allows the molecule to be more easily incorporated into cell membranes [11]. A comparative in vitro study showed that gamma- and delta-tocotrienol was 4-fold more efficient as scavenger of peroxyl radicals than other tocotrienol isomers [12].

The Problem with Alpha-Tocopherol

Tocopherols do not have the cholesterol-lowering ability that tocotrienols do [7]. In fact, the opposite is true. Alpha-tocopherol has been repeatedly shown to attenuate or interfere with the cholesterol-lowering action of tocotrienols [13]. Preparations *effective* in cholesterol-lowering consist of 15% (or less) alpha-tocopherol and 60% (or more) gamma- and delta-tocotrienol, whereas *ineffective* preparations consist of 20% (or more) alpha-tocopherol and 45% (or less) of gamma- and delta-tocotrienol. This has been supported by clinical studies in which supplements with high alpha-tocopherol content did not contribute to the lowering of cholesterol [14, 15], whereas supplementation containing low amounts of alpha-

tocopherol and high amounts of gamma- and delta-tocotrienol led to a significant decrease in total and LDL cholesterol [16-18].

In addition, tocotrienols absorbed better in the body than tocopherols, and tocopherols have even been shown to prevent absorption and organ/tissue delivery of tocotrienols [19-21]. To summarize, alpha-tocopherol is thought to interfere with tocotrienol benefits directly by:

- compromising cholesterol reduction [13]
- attenuating cancer cell inhibition [22]
- blocking absorption [19, 21]
- inducing tocotrienol catabolism (or break-down) [23]

By itself, alpha-tocopherol may lead to other predicaments, potentially:

- causing the premature catabolism (or break-down) of prescription drugs [24]
- increasing cholesterol and blood pressure [13, 25-28]
- increasing prostate cancer risk in humans [5, 29]

Tocotrienol Absorption and Bioavailability

As part of the vitamin E family, tocotrienols are fat-soluble, and are hence absorbed in a similar fashion as fats from food in the gut. Tocotrienols are bioavailable, and have been shown to deposit in lipid-rich organs, including the liver, brain, spleen, lung, kidney, and heart [30]. They peak in the blood at approximately 4 hours following ingestion, and are known to absorb more readily when taken along with meals [31].

Daily Recommended Dosage

Clinical studies determined that the optimal dose of tocotrienol for cholesterol and triglyceride reduction is 100mg/day [17]. The safe dose of various tocotrienols for human consumption is estimated to be 200-1,000mg/day [32]. The supplement is best taken with a meal to increase absorption in the gut [31]. Due to possible interference, it is recommended for tocotrienols to be taken approximately six hours apart from tocopherol-containing supplements.

Tocotrienol's Antioxidant Properties

The antioxidant efficiency of tocotrienols was evaluated as the ability of the compounds to inhibit lipid peroxidation, reactive oxygen species (ROS) production, and heat shock protein expression. Delta-tocotrienol was found to have the greatest antioxidant properties among the tocotrienol isomers [33], which is due to the decreased methylation of the chromanol ring that allows the molecule to be more easily incorporated into cell membranes [34]. A comparative in vitro study showed that gamma- and delta-tocotrienol was 4-fold more efficient as a scavenger of peroxyl radicals than other tocotrienol isomers [35]. In lipid ORAC studies, delta- and gamma-tocotrienols had the highest antioxidant value of all vitamin E isomers at 5.5x and 3x the potency of alpha-tocopherol, respectively. Interestingly, delta- and gamma-tocopherol were also strong antioxidants [10]. In vitamin E mixtures containing both tocotrienols and tocopherols, a higher concentration of alpha-tocopherol was associated with lower antioxidant activity [35].

Cardiovascular Benefits of Tocotrienols

Regulation of Cholesterol Synthesis in Animal and Clinical Studies: Approximately one in every six adults in the US has high total cholesterol (240 mg/dL and above) [36]. Recently, animal studies supported results found in earlier cell line studies. Animals whose diet was supplemented with gamma- and delta-tocotrienols showed the greatest decrease in cholesterol levels (32% total and 66% LDL cholesterol), whereas alpha- tocopherol had no effect on cholesterol-lowering. In this study, HDL/LDL

cholesterol ratios were improved by 123-150% in chickens, which more closely reflect the lipogenic activity and cholesterol levels of humans.

In two open clinical studies, fasting blood lipids were measured before and after 2 months of annatto tocotrienol (75mg/day) supplementation [18]. In both groups, total cholesterol levels dropped 13%, whereas LDL cholesterol dropped 9-15% and HDL cholesterol increased by 4-7%. Considering that tocotrienols are naturally occurring compounds, these numbers are very encouraging. It is well documented that prescription drugs may lower LDL cholesterol by 15-30% with no effect on HDL cholesterol levels. Furthermore, tocotrienols do not have any of the potential side effects of prescription drugs.

The LDL/HDL ratio was reduced by 12-21%. In the same study, an additional benefit of delta-tocotrienol was found to promote metabolic health, where triglyceride levels dropped 20-30%.
Another study conducted by Bristol-Myers Squibb found that after 4-week supplementation with gamma- and delta-tocotrienol (100mg/day) total cholesterol was reduced by 15-22%, and LDL cholesterol was decreased by 10-20% [37].

Tocotrienol and Monocyte-Endothelial Cell Adhesion and Platelet Aggregation: Studies have shown that tocotrienols positively affect monocyte-endothelial cell adhesion and platelet aggregation. In other words, tocotrienols may prevent the artery walls from getting narrower and clots from forming, important elements for optimal heart and artery health. One of the first steps of atherogenesis is fatty streak formation in arteries, which begins with the adherence of circulating monocytes to the endothelium. Tocotrienols have been shown to reduce cellular adhesion molecule expression and monocytic cell adherence [38, 39].

In particular, delta-tocotrienol showed the most profound inhibitory effect on monocytic cell adherence as compared to tocopherols and other tocotrienol isomers. Delta- and gamma-tocotrienol were 60x and 30x more potent than alpha-tocopherol, respectively [40]. It has been suggested that this phenomenon occurs via inhibition of VCAM-1 expression by delta- tocotrienol [40]. Essentially, delta-tocotrienol dramatically reduces the “Velcro-effect” of circulating monocytes on the arterial wall, a process known to initiate plaque formation [41].

Tocotrienol and Hypertension: Approximately 33% of American adults have hypertension, and 25% have pre-hypertension [42]. Recent animal studies showed that tocotrienols lower blood pressure, reduce plasma and blood vessel lipid peroxides, and improve total antioxidant status [43]. Gamma-tocotrienol was shown to reduce systolic blood pressure significantly, and improved nitric oxide synthase activity (NOS), both of which play a critical role in the pathogenesis of essential hypertension [44]. In humans, tocotrienols have been shown to increase arterial compliance and reduce blood pressure [45, 46].

Tocotrienol and Atheroma Formation: Before turning 35, two out of three Americans will have some degree of plaque build-up in their arteries [47]. This may be variously termed coronary, carotid, or peripheral atherosclerosis and/or stenosis. The effects of tocotrienols on atheroma formation have been compared in vivo. Comparison studies on animals investigated the impact of tocotrienol supplementation vis-à-vis tocopherol or non-supplementation. Results to date indicate that animals on an atherogenic diet and given desmethyl tocotrienols had 60% lower plasma cholesterol than the control group, and the size of atherosclerotic lesions was reduced 10-fold. Alpha-tocopherol, on the other hand, had no effect [48]. This finding was further corroborated in a similar independent study, where desmethyl tocotrienols inhibited atherosclerotic lesions in hyperlipidemic mice. Atherosclerotic lesion size in mice supplemented with desmethyl tocotrienols was decreased by 42%, whereas with alpha-tocopherol, lesion size was only decreased by 11% [49]. Fully methylated tocotrienols and tocopherols – namely alpha- and beta-isomers – do not have the cardiovascular benefits characteristic of desmethyl tocotrienols.

Tocotrienol and Carotid Arteriosclerosis: A 4-year study on patients with carotid arteriosclerosis showed that tocotrienol-tocopherol supplementation caused regression of the disease. In 88% of patients that took the supplement, carotid artery stenosis was regressed or stabilized. Of the control group

receiving a placebo, 60% deteriorated, and only 8% improved [50, 51]. Interestingly, total cholesterol in the supplemented group decreased 14% and LDL cholesterol fell 21% in the fourth year of the study [52].

Cardiometabolic Benefits of Tocotrienols

The leading statement of the 2011 Cardiometabolic Health Congress warns that "the firestorm of diabetes and metabolic syndrome continues to spread, with the increasing incidence of hypertension and hypercholesterolemia acting like gasoline to further fuel the flames and contribute to higher CV morbidity and mortality" [53]. Besides 24 million diabetics and perhaps as many as 60 million prediabetics, an estimated 36% of US adults, 74 million, have metabolic syndrome [54-57]. The occurrence of metabolic disorders mirrors the US obesity pandemic, with two in three adults being overweight [58, 59]. Some of the AHA and NIH defining hallmarks of metabolic syndrome include [60, 61]:

- Increased serum triglycerides (above 150mg/dL)
- Elevated blood pressure (above 130/85mmHg)
- Elevated serum glucose (100mg/dL and higher)
- Decreased good HDL (under 40mg/dL for males and under 50mg/dL for females)
- Increased waist circumference (above 40in. for males and above 35in. for females)

Clinical Studies: In several clinical studies with metabolic syndrome and diabetes patients, tocotrienol was shown to reduce the symptoms associated with the disease. Rice bran water solubles (270ppm of >90% tocotrienols) reduced hyperglycemia, glycosylated hemoglobin, and increased insulin levels, while rice bran fiber (30ppm of >90% tocotrienols) reduced hyperlipidemia in both type 1 and type 2 diabetics [62]. In another large clinical study, vitamin E intake from diet was associated with reduced risk of type 2 diabetes [63]. In patients with type 2 diabetes, progression of atherosclerosis is more rapid, and 80% of patients die of atherosclerotic events. In addition, LDL-lowering therapies normally prescribed for patients with diabetes have many side-effects, creating a need for alternative treatment. Tocotrienols, which have no known side-effects, were shown to decrease serum total lipids by 23%, total cholesterol by 30%, and LDL-cholesterol by 42% (from 179mg/dL to 104mg/dL) within 60 days in type 2 diabetics [64]. In two open studies [18], fasting blood lipids were measured before and after 2 months of annatto tocotrienol (75mg/day) supplementation. In both groups, total cholesterol levels dropped 13%, whereas LDL cholesterol dropped 9-15% and HDL cholesterol increased by 4-7%. The LDL/HDL ratio was reduced by 12-21%. Important to metabolic health promotion, triglyceride levels dropped 20-30%.

Tocotrienols Under Investigation for Cancer Chemoprevention and Treatment

In addition to its superior antioxidant, hypocholesterolemic, and anti-thrombotic activities, tocotrienol has shown consistent anti-tumor benefits. Some researchers attribute these anti-cancer effects to tocotrienol's antioxidant activity [65], HMG-CoA reductase downregulation and/or degradation [8, 66], caspase-3 apoptotic pathways [67], and vascular endothelial growth factor (VEGF) inhibition [68, 69]. The fact remains that there are many possible modes of action for cancer prevention/therapy by tocotrienols. Tocotrienols – but not tocopherols and in particular not alpha-tocopherol – have repeatedly been shown to inhibit proliferation and induce cancer cell death, and cells with the greatest degree of malignancy are most sensitive to the apoptotic action of tocotrienol [67, 70, 71]. In all cases -- independent of mechanism -- delta- and gamma-tocotrienol were the two most potent vitamin E isomers.

Breast Cancer: Breast cancer is the leading cancer among white and African American women, with an approximate 275,000 new cases and estimated 41,000 deaths each year in the United States. Tocotrienol-rich fractions (TRF) containing 43% desmethyl tocotrienols inhibited the proliferation of human breast cancer cells, whereas alpha-tocopherol had no effect [72]. Another study found that tocotrienols inhibit breast cancer irrespective of estrogen receptor status, with gamma- and delta-tocotrienol being the most potent inhibitors [73]. Since gamma- and delta-tocotrienol were reproducibly shown to be the strongest inhibitors of cancer, it may be of great advantage to use desmethyl tocotrienols in their purest form during treatment. A breast cancer clinical trial currently using a tocopherol-tocotrienol mixture will be replaced with pure gamma-tocotrienol, presumably to avoid tocopherol interference issues

[74]. Unfortunately, *dietary* vitamin E only contains a very small amount of desmethyl tocotrienols (<10%), and a large amount of tocopherols (>90%), which have no effect in the treatment of cancer. For breast cancer, the safety of tocotrienols has been reported in a recent study where no or only low levels of apoptosis occurred in immortalized non-tumorigenic breast epithelial cells [75].

Pancreatic Cancer: Pancreatic cancer remains the most lethal of all cancers. Anti-tumorigenic effects of delta-tocotrienol on human pancreatic cancer were shown in vitro and in vivo (xenografts in mice). Here, delta-tocotrienol inhibited pancreatic tumor growth, blocked malignant transformation, induced apoptosis in vitro, and accumulated in the pancreas 10x more than in the liver and tumor. The preferred composition was a preparation containing delta-tocotrienol and/or gamma-tocotrienol, and free of alpha-tocotrienol, beta-tocotrienol and other tocopherols [76]. A phase I dose-escalation trial on delta-tocotrienol in patients with resectable pancreatic exocrine neoplasia is underway and so far shows no adverse effects up to 800mg/day, while apoptosis of cancer cells in patients was observed at the lowest dosage of 200mg/day [77]. Further dose escalation up to 3,200mg/day and a phase II trial are planned. Other cell line and animal studies undertaken by independent research groups clearly underscore and lend unambiguous support to tocotrienol's effect on pancreatic cancer [78-80].

Prostate Cancer: Prostate cancer is the cause of ~30,000 deaths per year in the United States [81], and is, after lung cancer, the leading cause of cancer deaths in males. Tocotrienols, delta- and gamma-tocotrienol in particular, were shown to have inhibitory effects on several types of prostate cancer cell lines. Delta-tocotrienol most effectively induced cell death of prostate cancer cell lines, and activated caspase-independent programmed cell death and disrupted NFkB signaling [29, 82].

Lung Adenocarcinoma, Liver and Lung Carcinogenesis: Without doubt, the single leading cause of cancer deaths in both sexes is lung cancer. Non-small cell lung cancer accounts for 80% of lung cancers. Delta-tocotrienol treatment of non-small lung cancer cells resulted in a dose- and time-dependent inhibition of cell growth, and was associated with downregulation of the Notch-1 via NFkB inhibition [83]. Additionally, an alpha-tocotrienol analogue decreased human lung adenocarcinoma by suppression of Ras and RhoA prenylation [71].

A recent in vivo and in vitro study showed suppression of liver and lung carcinogenesis in mice. Delta-tocotrienol potently induced apoptosis and S phase arrest while increasing CYPIAI gene, a phase I enzyme [70].

Colon Carcinoma: Excluding skin cancers, colorectal cancer is the third most common cancer diagnosed in both sexes in the United States. The American Cancer Society's most recent estimates for the number of colorectal cancer cases in the United States are 101,340 new cases of colon cancer and 39,870 new cases of rectal cancer in 2011 [84]. Delta-tocotrienol was shown to induce paraptosis-like cell death in SW620 colon carcinoma cells, and was associated with suppression of the Wnt signaling pathway [85]. Likewise, gamma-tocotrienol induced apoptosis in HT-29 colon carcinoma cells and human gastric cancer cells accompanied by activation of caspase-3 [86, 87]. Inflammatory bowel diseases such as Crohn's disease and ulcerative colitis have been linked to an almost 20-fold increase in the risk of colon cancer [88], and tocotrienols may inhibit the excessive fibroblast expansion associated with these diseases [89].

Tocotrienol's Protective Effect on Skin: Vitamin E, and in particular delta- and gamma-tocotrienol and tocotrienol-rich fractions (TRF), have been shown to be superior protectors against environmental stressors such as UV-irradiation of the skin [90]. TRF has significantly higher potency than alpha-tocopherol, and is effective against protein oxidation and lipid peroxidation at low concentrations [91, 92]. Normally, UV-irradiation destroys the antioxidants of the skin, but prior application of TRF to mouse skin preserved the vitamin E [93]. Also, the largest fraction of vitamin E was found in the subcutaneous layer of the skin, which shows that applied vitamin E penetrates rapidly through the skin [94], and therefore combats oxidative stress induced by UV or ozone efficiently [95]. In addition, delta- and gamma-tocotrienol have been shown to reduce inflammation [96-98], and are potent skin whitening agents via reduction of tyrosinase activity, while also blocking UV-induced melanogenesis [99]. Delta-tocotrienol has the greatest sun protection factor (SPF) of the tocotrienol isomers at SPF 5.5 [99].

Melanoma: Gamma- and delta-tocotrienol inhibited melanoma cells in vitro and produced tumor retardation in mice with highly metastatic melanoma. Tocotrienol-treated animals also experienced prolonged survival rates [100]. Gamma- and delta-tocotrienol in combination with lovastatin are yet more potent in melanoma inhibition in vitro and in vivo [101].

Angiogenesis Inhibition: Recent studies showed that tocotrienols but not tocopherols inhibit abnormal angiogenesis, an indispensable step in tumor growth or progression beyond 1mm. Vascular endothelial growth factor (VEGF) regulates angiogenesis by binding to VEGF receptor (VEGFR) in endothelial cells. Tocotrienol downregulates VEGFR, therefore blocking intracellular signaling of VEGF and inhibiting angiogenesis [69]. In addition, tocotrienol inhibits the proliferation and formation of tubes by bovine aortic endothelial cells, where delta-tocotrienol had the strongest inhibitory activity [102]. Since angiogenesis is essential to tumor growth and this kind of angiogenesis is abnormal or aberrant, its inhibition likely stunts tumor growth and prevents cancer metastasis.

Tocotrienol may well work on dual antitumor mechanisms that include the removal of the vital nutrient-to-tumor lifeline (via inhibiting angiogenesis) and the targeting of tumor cells via signals [67, 103].

Tocotrienol Emerging Benefits

Inflammation: Tocotrienols were shown to have potent anti-inflammatory properties. New research focused on the effect of tocotrienols in reducing inflammation in experimental mice [96]. They demonstrated that alpha-, gamma- and delta-tocotrienols strongly inhibited the inflammatory response using such markers as chymotrypsin, trypsin and tumor necrosis factor-a (TNF-a), with delta-tocotrienol being the most effective. The results of this study demonstrated that the use of tocotrienols can function as a powerful proteasome modulator, while increasing the immune system's ability to fight inflammation. At the same time, tocotrienols induce a hormone that produces an anti-inflammatory steroid to block inflammation directly.

Radiation Countermeasures: In the past six years, the Armed Forces Radiobiology Research Institute (AFRRI, Bethesda, MD) has performed extensive research on tocotrienol as a radiation countermeasure agent [104]. Of the tocotrienol isomers, delta- and gamma-tocotrienol are among the most effective radioactive countermeasure agents [105, 106]. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are the primary source of radiation-induced damage, and tocotrienols – as potent antioxidants – are effective radioprotectors, supporting the hypothesis that "strong antioxidants make strong radioprotectors" [107]. However, amelioration of radiation lethality – which is acute and severe – goes beyond tocotrienol's antioxidant properties. The first line of insult by radiation to the human body is the bone marrow that produces blood. Delta- and gamma-tocotrienol display an unambiguous stimulatory effect on hematopoietic (blood-forming) tissue [105, 108], with delta-tocotrienol performing equal to or better than gamma-tocotrienol, restoring the fresh blood supply damaged by radiation insults.

Following total body irradiation of mice, both delta- and gamma-tocotrienol regenerated blood-borne cells by increasing the total white blood cell count; in addition, only delta-tocotrienol regenerated lymphocytes. Tocotrienols almost fully restored bone marrow cellularity to normal levels following radiation, while overall cellularity in untreated controls remained depleted [105, 106]. In both cases, prophylactic treatment 24 hours pre-radiation *was more effective* than post-radiation treatment. These results suggest that tocotrienols, especially of the delta- and gamma-isoforms, could be used as powerful radioprotectors in first responders to nuclear fallout areas, radiation workers, and cancer radiotherapy patients.

Annatto tocotrienol is the only source containing exclusively delta-tocotrienol (90%) and gamma-tocotrienol (10%) that may be useful for radiation countermeasures [18].

Eye Health: Tocotrienols may have application in improving eye conditions, especially those of angiogenic nature. In macular degeneration, central vision loss occurs due to abnormal neovascularization in the retina beneath the macula, and leaking blood vessels push up the retina. Similarly, diabetic retinopathy is caused by damage to blood vessels of the retina, and is the leading cause of adult blindness in the West. In both cases, angiogenesis – the aberrant growth of new blood

vessels – is to blame. Recent studies found tocotrienol to be a superb anti-angiogenic agent, with delta-tocotrienol being the most potent in reducing angiogenesis dose-dependently [109, 110].

It is estimated that over 4 million Americans have glaucoma [111], a condition where patients present with raised intraocular pressure that may lead to permanent damage of the optic nerve and can cause blindness. Tocotrienols reduce scarring of the Tenon's fibroblast that occurs during glaucoma filtration surgery [112], and - as a potent antioxidant - accumulate in the eye to combat cataract development [113], one of the most common eye problems of the aging population.

Other Emerging Benefits: Tocotrienols are currently under investigation for promoting bone formation [114], treating trauma-induced stroke [115], reducing the side effects of diabetic neuropathy [116] and autonomic nerve disorders [117, 118], and counteracting gastric injury [119].

Summary

Most studies published to date, especially in the last decade, point clearly to delta-tocotrienol and gamma-tocotrienol as the key isomers of vitamin E for positive health benefits. This has been shown for cholesterol (cardiovascular disease) [7, 8, 18], triglycerides (diabetes/prediabetes) [18, 32, 120], blood hypercoagulation/chemotaxis (arteriosclerosis) [40, 49, 52] and numerous cancers [101, 109, 121] besides tocotrienol's known power as lipid-soluble antioxidant [33, 95].

The discovery of annatto tocotrienols with only the most potent delta- and gamma-isomers was an important milestone, a composition never before seen.

Annatto is the only known source of tocotrienol that is naturally free of tocopherol and provides the highest content of the powerful delta-tocotrienol.

Compared to other major sources of tocotrienol, annatto has a distinct advantage in lowering cholesterol and enhancing cellular health without the interferences that would be expected from alpha-tocopherol. With all these positive reports, annatto tocotrienol is an excellent candidate for chronic and degenerative disease prevention

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