White Paper

The Science Behind Vitamin E Tocotrienols

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. Numerous studies uncovered 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, novel function for bone health, 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 soon after (1930s) [3].

Tocotrienols from current sources (rice, palm and annatto) were first developed and brought to the dietary supplement 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 – DeltaGold – derived from annatto seeds became available around 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 in the 16th century. Annatto as a natural colorant was introduced into the US during the 17th century, and today it is used in the food industry worldwide.

The "tocopherol-free" aspect of annatto tocotrienol is important, since research has shown alpha-tocopherol to interfere with tocotrienol functions and benefits. Contrary to annatto, both palm and rice contain a significant amount of alpha-tocopherol (25-50% of total vitamin E) (Figure 1). Annatto remains the first and only true source of nature-derived vitamin E that supplies tocotrienol only.

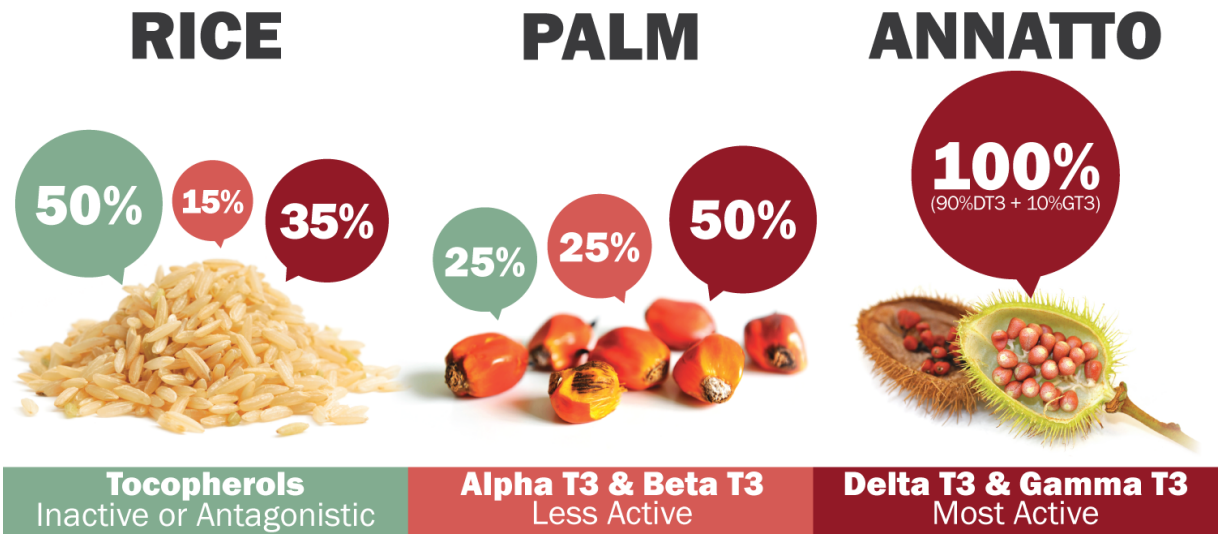

Figure 1. Typical Compositions of Vitamin E in Natural Tocotrienol Sources.

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 [4].

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 delta > gamma > alpha > beta. Tocopherols are inactive in lowering cholesterol [5].

Desmethyl tocotrienol 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), cholesterol synthesis (hypercholesterolemia) and triglyceride synthesis/transport (hypertriglyceridemia). Large clinical studies on alpha-tocopherol benefits to treat cardiovascular or other diseases have been equivocal or without effect [6], and possibly harmful [7, 8].

Tocotrienol Mechanism

The mechanism of tocotrienol's hypolipidemic action involves posttranscriptional suppression of HMG-CoA reductase via controlled degradation of the reductase protein [9, 10]. 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 (and 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 LDL cholesterol receptor, hence explaining how cholesterol is regulated. Brown and Goldstein were awarded the 1985 Nobel prize for this work [11]. These tocotrienol mechanisms of cholesterol and triglyceride synthesis – collectively controlling lipidemia – have manifested into clinical significance of CVD, such as hypercholesterolemia [12], chronic inflammation [13], atherosclerosis [14], and obesity and liver function associated with NAFLD [15].

Other forms of vitamin E (all four tocopherols and alpha- and beta-tocotrienols) do not degrade, downregulate, nor block SREBP processing [10]. Delta-tocotrienol was also found to have the greatest antioxidant properties among the tocotrienol isomers

[16], which is due to the decreased methylation on the chromanol ring that allows the molecule to be more easily incorporated into cell membranes [17]. 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 [18].

The Problem with Alpha-Tocopherol

Tocopherols do not have the cholesterol-lowering ability that tocotrienols do [9]. In fact, the opposite is true. Alpha-tocopherol has been repeatedly shown to attenuate or interfere with the cholesterol-lowering action of tocotrienols [19]. Combinations *effective* in cholesterol-lowering consist of 15% (or less) alpha-tocopherol and 60% (or more) gamma- and delta-tocotrienol, whereas *ineffective* formulations consist of 20% (or more) alpha-tocopherol and 45% (or less) of gamma- and delta-tocotrienol. Substantiating these formulating guidelines are clinical studies in which supplements with high alpha-tocopherol content did not contribute to the lowering of cholesterol [20-22], whereas supplements containing low amounts of alpha-tocopherol and high amounts of gamma- and delta-tocotrienol led to a significant decrease in total and LDL cholesterol [13, 23-25].

While tocotrienols absorbed better in the body than tocopherols, tocopherols have been shown to prevent absorption and organ/tissue delivery of tocotrienols [26-30]. To summarize, alpha-tocopherol is thought to interfere with tocotrienol benefits directly by:

- compromising cholesterol and triglyceride reduction [19, 30, 31]
- lowering antioxidant capacity [32]
- attenuating cancer cell inhibition [33, 34]

- blocking absorption [26-29]
- inducing tocotrienol catabolism (break-down) [35]
- preventing adipose and liver storage [30]

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

- causing the premature catabolism (or break-down) of prescription drugs [36]
- interfering with chemotherapy drug action [34, 37, 38]
- increasing cholesterol and blood pressure [19, 31, 39-41]
- increasing prostate cancer and glioblastoma risk in humans [7, 42, 43]
- exacerbating stroke injury [44]
- decreasing bone mass [45]
- increasing LDL oxidation [46]

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, aided by bile salts. These vitamin Es are mixed into large emulsified particles (1,000um) called chylomicrons that absorb through the gut. These particles that carry both tocopherols and tocotrienols travel in the lymph and blood. Along the way, the particles become smaller and denser, variously named VLDL (~65um), IDL (~45um), and LDL (~25um). The larger particles mainly contain tocotrienols. The IDL sheds the denser HDL (~10um) that enter the cells and organs, and the less dense LDL that stay in the blood and return to the liver. Therefore, lipoproteins are "fat shuttles" transporting cholesterol and lipid nutrients alike to organs including the liver. At this stage, the path of lipid vitamin E tocopherols and tocotrienols part way (this is a preferential picture, not an absolute

one). Tocotrienols progressively deposit into cells as larger lipoproteins move to smaller ones. Alpha-tocopherol progressively remains in the LDL and returns to the liver or gets repackaged into LDL in the liver. Therefore, tocotrienols are particularly bioavailable, and have been shown to deposit in lipid-rich organs, including the brain, spleen, lung, kidney, and heart [27, 47], with particular preference in the adipose, skin, and heart [48] prior to hepatic circulation. Conversely, alpha-tocopherol is particularly bioavailable to the liver and blood [48] after hepatic circulation.

An alpha-tocopherol transport protein (ATTP) exists and adds to the complexity. When vitamin E is returned to the liver (entero-hepatic circulation), ATTP preferentially repackages alpha-tocopherol into LDL without (or little) recognition of the other tocopherols and tocotrienols. Hence, the blood alpha-tocopherol level remains high (≥10-fold that of tocotrienol), providing the perception that alpha-tocopherol is more bioavailable. It means only that alpha-tocopherol is conserved in the blood, and not destructed in the liver. Since tocotrienols have been shown to be present in many organ tissues – and in some cases at levels comparable to alpha-tocopherol – tocotrienols are deported to cells and organs prior to entero-hepatic circulation, thereby not destructed in the liver. Tocotrienol's rapid drop in the blood after ~4 hours (whereas alpha-tocopherol remains in the blood for longer) attests to the fast absorption of tocotrienols into organs rather than the presumption that tocotrienols are excreted.

It is now generally accepted that all vitamin E molecules absorb through the intestines equally via triglyceride-rich chylomicrons (TRC) into the lymphatic blood system [49]. All tocotrienols are higher in TRC and HDL (particularly delta-tocotrienol)

[50], allowing for rapid absorption while alpha-tocopherol retains preferentially in the LDL, whose main task is to return to the liver.

Two studies on DeltaGold confirmed the bioavailability of tocopherol-free annatto tocotrienol [51, 52]. An open-label randomized trial involved 125, 250, 500, 750, and 1000 mg/day dosage groups. Many pharmacokinetic parameters were studied in healthy subjects to ascertain that delta- and gamma-tocotrienol were absorbed. When taken with a meal, both tocotrienols were absorbed and are bioavailable. A trial is now underway to ascertain tocotrienol's biovavailability in adipose tissue, considered the main depot for tocotrienol.

Daily Recommended Dosage and Safety

Clinical studies determined that the optimal dose of DeltaGold tocotrienol for cholesterol and triglyceride reduction is 250mg/day [13]. In clinical studies, DeltaGold tocotrienols have been safely consumed at dosages ranging from 125-750mg/day without adverse events. DeltaGold is also generally recognized as safe (GRAS) by the FDA. The supplement is best taken with a meal to increase absorption in the gut [53]. Due to possible interference, it is recommended for tocotrienols to be taken approximately six hours apart from tocopherol-containing supplements**.** The dietary source of alpha-tocopherol (typically 10-15 mg/d) is inconsequential to interfere with tocotrienol function.

Tocotrienol's Antioxidant Properties

Well-known antioxidants include astaxanthin, lutein, lycopene, and CoQ10. While all of these are helpful in protecting the body's cells, vitamin E is uniquely shaped to

reside within the lipid cell membrane to protect its integrity. Few, however, are aware that vitamin E is a family of molecules that include tocopherols and tocotrienols. Of the two, tocotrienol is and emerging antioxidant ingredient. Aside from protecting cell membranes (tocotrienols were shown to be ~50x more potent as an antioxidant compared to tocopherols [54]), tocotrienols also protect lipids such as omega-3s in softgel products and foods and beverages [55]. The antioxidant efficiency of tocotrienols was evaluated as the ability of the compounds to inhibit lipid peroxidation and reactive oxygen species (ROS) production. Delta-tocotrienol was found to have the greatest antioxidant properties among the tocotrienol isomers [56], which is due to the decreased methylation of the chromanol ring that allows the molecule to be more easily incorporated into cell membranes [57]. 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 [16]. In vitamin E mixtures containing both tocotrienols and tocopherols, a higher concentration of alpha-tocopherol was associated with lower antioxidant activity [32].

Lipid oxidation of foods is a major concern due to their increased fortification with polyunsaturated fatty acids for added health benefits. When oxidation of these healthy fats in food products occurs, the results can range from undesirable flavors to decreased nutritional quality and safety. Antioxidants, such as vitamin E (traditionally tocopherol), are applied to prevent food lipid oxidation.

In one study, researchers tested the antioxidant effects of annatto tocotrienol in comparison to palm tocotrienol, alpha-tocopherol, delta-tocotrienol and delta-tocopherol in fish oil and infant formula for 28 days [55]. Concentrations of study

compounds used were 0.02% and 0.05%. Results in fish oil showed that alpha-tocopherol increased hydroperoxide formation, while palm tocotrienol acted as a prooxidant, and no effect was seen with annatto tocotrienol on primary oxidation products. In the infant formula oil-in-water emulsion, annatto tocotrienol and delta-tocotrienol fared significantly better in decreasing hydroperoxide formation compared to alpha-tocopherol, palm tocotrienol, and delta-tocopherol. After 28 days, delta-tocotrienol and annatto tocotrienol at 0.05% still showed an antioxidant effect, as opposed to a prooxidant effect noted for both concentrations of alpha-tocopherol, palm tocotrienol, and delta-tocopherol.

Annatto tocotrienols were also assessed for their antioxidant activity and stability during frying and in fried tortilla chips [58]. In this study, sunflower oil used for frying tortilla chips was infused with DeltaGold. Upon frying, tocotrienol was absorbed into the chips along with the oil, and was shown to slow the degradation of alpha-tocopherol during frying. Tocotrienols reduced the painty and rancid flavor of fried aging chips, which correlated to a reduction in hexanal (a volatile byproduct of lipid oxidation). These results suggest that tocotrienols can be conveniently enriched into fried snack foods, while also enhancing their shelf life.

For practical applications, it is recommended that tocotrienols are added to fats in foods at quantities of 500-1,000ppm to convey antioxidant and shelf life-extending properties.

Cardiovascular Benefits of Tocotrienols

Regulation of Cholesterol Synthesis in Animal and Clinical Studies:

Approximately one in every three adults in the US has high total cholesterol (240

mg/dL and above) [59]. Recently, animal studies supported the earliest studies first conducted by University of Wisconsin, Madison researchers in the early 1980s [60]. Mechanisms of cholesterol reduction were elucidated then and confirmed today by University of Texas researchers [10]. 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 [5].

In a recent clinical trial, researchers tested the dose-dependent effects of annatto tocotrienols ranging from 125 – 750mg per day on hypercholesterolemic individuals [13]. Results showed that after only 4 weeks, the optimum daily dose of 250mg decreased total cholesterol by 15%, LDL cholesterol by 18%, and triglycerides by 14%.

Furthermore, cytokines associated with cardiovascular disease and their gene expression, including TNF-alpha, IL-2, IL-4, IL-6, and IL-8, were down-regulated 39-64%. Selected microRNAs that are typically down-regulated in hypercholesterolemic individuals were up-regulated by tocotrienol treatment, suggesting a beneficial effect on these biomarkers.

Anti-Inflammation: The traditional view of cardiovascular disease combines the clogging of arteries with elevated cholesterol. Surprisingly, however, half of the patients presenting with heart attacks have normal cholesterol levels. Today, it is well-known that inflammation is cholesterol's aid in furthering cardiovascular disease progression, recruiting white blood cells to arterial walls, causing them to stick and

initiate plaque buildup. Tocotrienols were shown to have potent anti-inflammatory properties. New research focused on the effect of tocotrienols in reducing inflammation in experimental mice [61]. 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.

One tocotrienol clinical study underscores the supplement's impressive anti-inflammatory benefits [12]. Among the most notable biomarkers to be affected by a 250mg tocotrienol dosage were C-reactive protein (CRP; a predictor for chronic inflammation), nitric oxide (NO), and malondialdehyde, with decreases of 40%, 40%, and 34%, respectively. Total antioxidant status, on the other hand, increased 22%. Several inflammatory cytokines and microRNAs were found to be modulated by tocotrienol treatment, suggesting more favorable outcomes in cardiovascular and aging diseases with supplement use.

When combined with other anti-inflammatory ingredients, tocotrienols showed synergistic efficacy. Two clinical studies show that delta-tocotrienol in combination with antioxidant polyphenols curb inflammation and manage dyslipidemia [62, 63]. One of the placebo-controlled study was conducted in two groups of elderly subjects, one with normal and the other with elevated lipid levels. The product formulation was composed of delta-tocotrienol from annatto (as found in DeltaGold®), along with a B-vitamin (niacin) and polyphenols. In both groups,

supplementation led to a significant drop in CRP and γ-glutamyl-transferase (a predictor for non-fatal myocardial infarction and fatal coronary heart disease), while increasing total antioxidant status, a measure of the body's capacity to counteract reactive oxygen species. In the hypercholesterolemic group, LDL cholesterol (20-28%) and triglycerides (11-18%) also dropped. C-reactive protein dropped in healthy elderly (21-29%) as well as lipidemic elderly (31-48%), as did γ-glutamyl-transferase (14-20%). Notably, there were no adverse effects associated with the 6-week supplementation period.

Tocotrienol and Monocyte-Endothelial Cell Adhesion and Platelet Aggregation:

The ability of "activated" cells in the blood to adhere to artery walls is not a good thing. It is a stressed condition prompted by inflammation; it is an attempt to remove chemicals and particles out of circulation. This process of arterial adhesion is termed chemotaxis. Tocotrienol's role is anti-chemotactic.

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 [64, 65].

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 [66]. It has been suggested that this phenomenon occurs via inhibition of VCAM-1 expression by delta- tocotrienol [66]. Essentially, delta-tocotrienol dramatically reduces the "Velcro-effect" of circulating monocytes on the arterial wall, a process known to initiate plaque formation [67].

LDL is a risk factor to CVD, especially atherosclerosis. It is generally understood that oxidized LDLs – not LDL particles – are atherogenic [68]. In a clinical trial where all four tocotrienols were studied, delta-tocotrienol alone reduced oxidized LDL, a significant indicator to reduced atherosclerosis. Contrary to this, alpha-tocotrienol can potentially pro-oxidize LDL to oxidized LDL [46].

Tocotrienol and Hypertension: Approximately 32% of American adults have hypertension, and 25% have pre-hypertension [69]. Animal studies showed that tocotrienols lower blood pressure, reduce plasma and blood vessel lipid peroxides, and improve total antioxidant status [70]. 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 [71]. In humans, tocotrienols have been shown to increase arterial compliance and reduce blood pressure [72, 73].

Tocotrienol and Atheroma Formation: Before turning 35, two out of three Americans will have some degree of plaque build-up in their arteries [74]. 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 [75]. 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% [76]. Fully methylated tocotrienols and tocopherols – namely alpha- and beta-isomers – do not have the cardiovascular benefits characteristic of desmethyl tocotrienols.

Later studies with advanced designs pinned this concept down even further. Tocotrienols, especially delta- and gamma-tocotrienols, significantly reduced plaque scores, plaque stabilization, and inflammation, three of the pillars responsible for overall atherosclerosis [77, 78].

Tocotrienol and Carotid Arteriosclerosis: A 4-year study on patients taking a 240 mg/day dosage 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 [79, 80]. Interestingly, total cholesterol in the supplemented group decreased 14% and LDL cholesterol fell 21% in the fourth year of the study [14]**.**

Cardiometabolic Benefits of Tocotrienols

According to the American Diabetes Association, 30 million Americans had diabetes, with an additional 85 million Americans having been diagnosed with prediabetes, representing more than one-third of all Americans. Furthermore, metabolic syndrome – defined by a cluster of distinct abnormal cardiovascular measurements – is on the rise and mirrors the US obesity pandemic, with two in three adults being overweight or obese [81]. Some of the AHA and NIH defining hallmarks of metabolic syndrome include [82, 83]:

- 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)

MetS Animal Studies: In one study, researchers gave rats a high carb high fat diet to induce obesity with accompanying cardiac remodeling, insulin resistance, hypertension, and fatty liver [84]. Animals then received oral alpha-tocopherol, alpha-, gamma-, or delta-tocotrienol at 85mg/kg/day, corresponding to a 60kg human dose of ~800mg/day. Results showed that, while all isomers reduced collagen deposition and inflammatory cell infiltrates in the heart, only delta- and gamma-tocotrienol improved cardiovascular function and systolic blood pressure. Delta-tocotrienol normalized eccentric hypertrophy shown by lower left ventricular internal diameter (during diastole), stroke volume and cardiac output. Furthermore, only delta-tocotrienol affected important markers of metabolic syndrome and diabetes by

enhancing glucose metabolism and improving insulin sensitivity, while reducing lipids and abdominal adiposity. The mechanism of action appears to be reduction in organ inflammation, especially of the heart, liver, and abdominal fat.

A similar study confirmed this anti-inflammatory mechanism in a high-fat-fed mouse model, which examined the effects of tocotrienol on obesity-related adipocyte hypertrophy, inflammation, and hepatic steatosis [85]. The approximate human equivalent of tocotrienol given to the mice was 160-640mg/day for 14 weeks, at which point improvements in glucose tolerance along with reduced hepatic steatosis and triglycerides were observed. In addition, adipocyte size and macrophage infiltration into the liver were reduced, with the results of an overall improved metabolic profile.

Two closely related researchers further added to this MetS construct using tocotrienols. One group separately looked at delta-T3 and gamma-T3, and these tocotrienols attenuated "nascent flames" – called inflammasomes – of macrophages that protected chronic metabolic diseases [86-88]. The other research group looked at the impact of tocotrienols with alpha-tocopherol removed [30]. They found that tocopherol-free rice bran tocotrienol (RBT3) had anti-lipidemic effects, reducing cholesterol (15%↓) and triglycerides (28%↓) simultaneously. Further, tocotrienol upregulated both carnitine palmitoyltransferase by 67% (responsible for triglyceride drop) and cytochrome P450 by 47% (responsible for cholesterol drop). When alpha-tocopherol was added to the tocotrienols, the coadministration abrogated tocotrienol anti-lipidemic effects and decreased the presence of all tocotrienols in the liver by about 2.5-fold. Alpha-tocopherol on its own had almost no anti-lipidemic effects.

MetS 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 [89]. In another large clinical study, vitamin E intake from diet was associated with reduced risk of type 2 diabetes [90]. 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 [91]. Clinical studies have shown that tocotrienols – when taken apart from alpha-tocopherol (due to interference issues [25]) – lower total cholesterol, LDL, and triglyceride levels between 15-20% [13]. Further, an optimum daily dose of 250mg tocotrienols (without tocopherols) lowered C-reactive protein and other inflammation markers between 35-60% [12]. Combinations with other anti-inflammatory ingredients, such as quercetin, resveratrol, and B-vitamins can synergize with tocotrienol's cardiometabolic benefits, as was shown in clinical trials [62, 63].

However, in patients with MetS on tocopherol-tocotrienol mixtures, cardiometabolic benefits were not observed [22] nor was the chemotaxis/platelet aggregation reduced [92].

Non-Alcoholic Fatty Liver Disease (NAFLD): An ailment closely associated with obesity and metabolic syndrome is NAFLD, which occurs when excess fat is stored in the liver. Based on findings by the National Institute of Health, NAFLD affects 30-40% of US adults, without a selection of treatment options other than diet and exercise. To examine the effects of tocotrienol on fatty liver disease, a 12-week randomized, double-blind, placebo-controlled study was conducted in 71 NAFLD patients [15]. Significant improvements in liver biomarkers indicative of hepatic stress reduction were evident after 12 weeks, with decreases of 15-16% in ALT, AST. Furthermore, significant decreases in triglycerides (11%), MDA (14%), and hs-CRP (18%) were indicative of reduced inflammation and are consistent with results of previous clinical trials conducted with DeltaGold® in hypercholesterolemic subjects. Notably, the fatty liver index (FLI) score decreased a significant 11%, suggesting intrahepatic fat reduction. During the 12-week treatment period, patients in the tocotrienol-supplemented group lost an average of 9.7 pounds.

Tocotrienol Bone Health Benefits

One exciting area of research for the vitamin is on the subject of bone health, where we may soon see tocotrienols on the shelves among staple ingredients such as vitamin D and calcium. Many pre-clinical studies have already shown promise in this area [93-97], while a clinical double-blind placebo-controlled trial has just been published. In this important study, post-menopausal women with osteopenia were given tocopherol-free tocotrienols over the course of 12 weeks [98], administered at two dosages (300 and 600mg/day), both of which led to decreased bone resorption and improved bone turnover rate. This was compared to an independent and

blinded control group that was given a placebo. All subjects, including the placebo group, were also given a daily 400IU vitamin D and 500mg calcium supplement.

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 [99], HMG-CoA reductase downregulation and/or degradation [10, 100], caspase-3 apoptotic pathways [101], and vascular endothelial growth factor (VEGF) inhibition [102, 103]. 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 [101, 104, 105]. 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 [106]. Another study found that tocotrienols inhibit breast cancer irrespective of estrogen receptor status, with gamma- and delta-tocotrienol being the most potent inhibitors [107]. 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 [108]. 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 [109].

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 [110]. A phase I dose-escalation trial on delta-tocotrienol in patients with resectable pancreatic exocrine neoplasia was completed and showed no adverse effects up to 3,200mg/day, while apoptosis of cancer cells in patients was observed at the lowest dosage of 200mg/day [111]. The greatest biological effect response was reached at doses of 400-800mg/day, with delta-tocotrienol's apoptotic effects increasing with tumor malignancy. No apoptosis occurred in normal cells, indicating tocotrienol's safety in this trial. Other cell line and animal studies undertaken by independent research groups clearly underscore and lend unambiguous support to tocotrienol's effect on pancreatic cancer [112-116].

Prostate Cancer: Prostate cancer is the cause of ~30,000 deaths per year in the United States [117], 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 [42, 118].

Further complicating the disease is the transition from an androgen-dependent to an androgen-independent state of prostate cancer, which has a poorer prognosis, limited treatment options, and reduced survival [119]. One study showed that annatto tocotrienol effectively reduced androgen-independent prostate cancer cells, while also lowering PSA levels by 40% [119]. The mechanism involved reduction of a nonreceptor tyrosine kinase called Src, along with reduction of signal transducer and activator of transcription 3 (Stat3), which is closely associated with malignancy in several cancers. Another study found an additive effect when delta-tocotrienol was used in combination with gamma-tocopherol in the suppression of androgen-dependent prostate cancer cells [119]. Perhaps more astounding is the finding that delta-tocotrienol demonstrated a cytotoxic effect on prostate cancer stem-like cells under hypoxia, one of the main features correlated with poor prognosis in cancer patients [120].

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 [121-123].

Additionally, a redox-silent alpha-tocotrienol analogue decreased human lung adenocarcinoma by suppression of Ras and RhoA prenylation [105], indicating that cancer kill is not dependent on tocotrienol's antioxidant property.

An 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 [104]. When combined with the chemotherapy agent epirubicin in an animal study, tocotrienols improved the drug's antitumor activity against liver carcinoma, and also reduced the cardiotoxivity that is frequently associated with treatment [124]. In a clinical trial with DeltaGold tocotrienol, delta-tocotrienol reduced the severity on hepatitis C patients, suggesting DeltaGold to be a potential intervention for Hep C-induced liver carcinoma [125].

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 97,220 new cases of colon cancer and 43,030 new cases of rectal cancer in 2018 [126]. Delta-tocotrienol has been found to suppress colon cancer in both *in vivo* and *in vitro* models. One study tested tocotrienol's effect in both colon epithelial and stromal cells, and found that of all isomers, delta-tocotrienol had the most potent antiproliferative and apoptotic effects [127]. In the same study, delta-tocotrienol was also effective in preventing colorectal cancer in mice with induced colorectal cancer. A similar study showed inhibition of tumor growth in mice treated with tocotrienol, while adding that delta-tocotrienol halted proliferation of colorectal adenocarcinoma under both normoxic and hypoxic conditions [128]. Another study showed that delta-tocotrienol could induce paraptosis-like cell death in SW620 colon

carcinoma cells, and was associated with suppression of the Wnt signaling pathway [129]. Likewise, gamma-tocotrienol induced apoptosis in HT-29 colon carcinoma cells and human gastric cancer cells accompanied by activation of caspase-3 [130, 131]. 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 [132], and tocotrienols may inhibit the excessive fibroblast expansion associated with these diseases [133].

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 [134]. Gamma- and delta-tocotrienol in combination with lovastatin are yet more potent in melanoma inhibition in vitro and in vivo [135]. In another in vivo study on melanoma, delta-tocotrienol reduced tumor volume and tumor mass in mice, and significantly delayed tumor progression [136]. The probability of melanoma development was 3.3-fold higher in the control without delta-tocotrienol. The compound's proapoptotic activity through endoplasmic reticulum-stressed pathways was confirmed in human melanoma cell lines, where it did not affect the viability of normal human melanocytes. The same research group also examined delta-tocotrienol's role in targeting melanoma stem cells, which may play a crucial role in metastatic melanoma with poor prognosis [137].

Effect on Cancer Stem Cells (CSCs): Originally identified in leukemia [138], cancer stem cells display high self-reneal and tumorigenicity [139]. CSCs have since been identified in a variety of solid tumors, including breast [140], prostate [141], and brain [142] among others. Constituting only 0.5-1% of tumor cells within a tumor mass [143], research suggests that these cells are the primary mediators of tumor initiation, progression, recurrence, metastasis, and resistance to treatment [139, 144]. Since

CSCs are able to survive standard chemo- and radiotherapy, the development of new intervention strategies is the focus of intense research studies. Remarkably, tocotrienol was shown to suppress CSCs in a number of studies.

In a prostate cancer stem cell-like population, gamma-tocotrienol downregulated expression of prostate CSC markers (CD133/CD44) in androgen-independent cells [145]. Although CD133-enriched prostate cancer cells were resistant to standard chemotherapy treatment, they were sensitive to treatment with gamma-tocotrienol. Another study added that delta-tocotrienol's cytotoxic effect on prostate cancer stem-like cells was dose-dependent and particularly active under hypoxic conditions [120].

In breast cancer stem-like cells, a combination of gamma-tocotrienol and simvastatin was shown to eliminate enriched CSCs, while suppressing the expression of Stat3, a signaling mediator that is typically elevated in these cells [146]. Gamma-tocotrienol alone or in combination with DHA also reduced triple-negative breast cancer cells with aldehyde dehydrogenase activity, a marker of CSCs [147].

In a study examining pancreatic cancer metastasis, delta-tocotrienol was shown to selectively inhibit pancreatic ductal adenocarcinoma stem-like cells (PDAC) by suppressing viability, survival, self-renewal, and expression of transcription factors present in these cells [116]. Furthermore, delta-tocotrienol inhibited processes critical for tumor metastasis, including migration, invasion, and biomarkers of epithelial-to-mesenchymal transitions and angiogenesis in PDAC cells and tumors. In the in vivo component of the study, delta-tocotrienol inhibited tumor volume, and tumor weight by 60%. Liver metastasis was suppressed by 90%, and lung metastasis by 80%. Delta-tocotrienol's effect was more significant in terms of reducing tumor volume, weight, and metastasis score than the standard gemcitabine chemotherapy treatment.

Combining gemcitabine and delta-tocotrienol yielded the most astounding results, almost entirely abolishing metastasis score by ≥95%.

Another study showed delta-tocotrienol to be a viable target for melanoma stem cells, where tocotrienol reduced the cells' ability to form melanospheres while also impairing their growth [137]. Thus, tocotrienol's effect on CSCs may aid in overcoming chemoresistance, and improve the therapeutic options for highly aggressive tumors.

Targeting CSCs in aggressive cancers is a growing field of research aiming to go after the ~1% rogue cancers activated by aberrant DNA, referred to by scientists as "stemness" of cancer. Little research has been done in this field and, for that, tocotrienol's effect on CSCs is all the more dramatic. To date, tocotrienols – especially delta- and gamma-tocotrienol (the two components of DeltaGold) – specifically target CSCs of the pancreas, breast, skin, and prostate. It is likely that more targets will be indicated in the future.

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 [103]. In addition, tocotrienol inhibits the proliferation and formation of tubes by bovine aortic endothelial cells [148]. Of the tocotrienol isomers, delta-tocotrienol is the most potent in reducing neovascularization, whereas alpha-tocopherol has no anti-angiogenic activity [149]. In contrast, alpha-tocopherol has been shown to interfere with the anti-angiogenic properties of tocotrienol [29, 150].

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) preventing its mobility to other sites, and the targeting of tumor cells via signals [101, 151].

Clinical Study Outlook: There are currently five clinical trials underway in patients with advanced stage ovarian, breast, lung, and colorectal cancer [152]. These studies are designed to examine the effect tocotrienols have on survival and reduction of chemotherapy side effects. Results from these trials shall be forthcoming in 2019 and 2020.

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 [153]. TRF has significantly higher potency than alpha-tocopherol, and is effective against protein oxidation and lipid peroxidation at low concentrations [154, 155]. Normally, UV-irradiation destroys the antioxidants of the skin, but prior application of TRF to mouse skin preserved the vitamin E [156]. 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 [157], and therefore combats oxidative stress induced by UV or ozone efficiently

[158]. In addition, delta- and gamma-tocotrienol have been shown to reduce inflammation [61, 159, 160], and are potent skin whitening agents via reduction of tyrosinase activity, while also blocking UV-induced melanogenesis [161-163].Delta-tocotrienol has the greatest sun protection factor (SPF) of the tocotrienol isomers at SPF 5.5 [163].

Methicillin-resistant Staphylococcus aureus (MRSA) is a bacterium responsible for several difficult-to-treat infections in humans, and also a common reason for skin and soft-tissue infections worldwide. This is a particular concern in hospice institutions and hospital settings. For the first time, a study in animals showed that DeltaGold tocotrienol can be an immunomodulator to help fend off infections and improve wound repair [164]. In the prevention model, the MRSA-infected animals were administered tocotrienol, antibiotics, tocotrienol+antibiotics, and compared to infected control (no treatment). Tocotrienol was given orally to animals eight days before wound infection and antibiotics were given intraperitoneally two days following infection. Other conditions were the same for all groups. The results showed that tocotrienol reduced bacterial load by a factor of 10, antibiotics by 1,000 times, and tocotrienols in combination with the antibiotic by 10,000. This suggests that, while antibiotics work to kill bacteria as expected, tocotrienol potentiated the antibiotics' bacterial kill by reducing bacterial load in animals. Responsible for potentiating the antibiotic properties, at least in part, was tocotrienol's effect on natural killer cells. Although the number of natural killer cells remained unchanged throughout the treatments, their activity was dramatically improved in parallel to decreased bacterial load with a ranking order of:

tocotrienol + antibiotics > antibiotics >> tocotrienol > control.

In addition to being a potent immune adjuvant to antibiotics, tocotrienol had dramatic wound healing effects. Compared with antibiotics, which showed adverse effects in wound healing, tocotrienol was 2-6 times more effective in improving wound healing biomarkers, indicating efficacy in wound healing in the order of:

tocotrienol > tocotrienol + antibiotics >> control > antibiotics.

The authors of the study speculated that DeltaGold could work to reduce bacterial load and improve wound healing due to a local protection and regenerative action because of its accumulation in the skin.

Tocotrienol Emerging Benefits

Radiation Countermeasures: In the past decade, the Armed Forces Radiobiology Research Institute (AFRRI, Bethesda, MD) has performed extensive research on tocotrienol as a radiation countermeasure agent [165]. Of the tocotrienol isomers, delta- and gamma-tocotrienol are among the most effective radioactive countermeasure agents [166, 167]. 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" [168]. 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 [166, 169], with delta-tocotrienol performing equal to or better than gamma-tocotrienol, restoring fresh blood supply damaged by ionizing radiation.

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 [166, 167]. In both cases, prophylactic treatment 24 hours pre-radiation *was more effective* than post-radiation treatment. Besides blood protection, tocotrienol also helped to reduce gastro-intestinal damage [170]. More recently, gamma-tocotrienol was administered to non-human primates, causing metabolic changes such as increased bioavailability of antioxidants that would benefit the treatment of radiation injury [171]. When non-human primates were irradiated, those treated with gamma-tocotrienol showed reduced fluctuations in serum metabolite levels, implying tocotrienol's radioprotective effect [172]. 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 [173].

Eye Health: Vitamin E has long been regarded as a beneficial nutrient to support eye health, and was included in the original Age-Related Eye Disease Study (AREDS), as well as in AREDS2, which also examined addition of lutein, zeaxanthin, DHA and EPA. Vitamin E has since become a staple ingredient in standard AREDS as well as other eye health formulations. However, few are aware that vitamin E includes tocotrienols. While the AREDS study investigated only the alpha-tocopherol form of vitamin E, new

studies suggest that it is tocotrienol that deserves a closer look. 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 [150, 174].

The Glaucoma Research Foundation estimates that over 3 million Americans have glaucoma, 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 [175]. As a potent antioxidant, tocotrienol accumulates in the eye to combat cataract development [176], one of the most common eye problems of the aging population.

A Malaysian study tested the effect of tocotrienols from annatto (DeltaGold) on cataract formation in galactosemic rats [177]. In the study, topically applied tocotrienol at 0.01-0.05% delayed the onset and progression of cataract by reducing lenticular oxidative and nitrosative stress. In a follow-up study on diabetic rats, tocotrienols were applied topically via eye drops at a low concentration of 300ppm [178]. Diabetic rats that did not receive tocotrienols quickly progressed to stage 3 and 4 cataracts, whereas for those receiving the tocotrienols progression was arrested. Notably, tocotrienol restored lens transparency to normal. The anti-cataract

effect of tocotrienol may in part be attributed to the vitamin's anti-inflammatory action and ability to reduce oxidative stress, while mitochondrial function was improved.

Other Emerging Benefits: Tocotrienols are currently under investigation for treating trauma-induced stroke [179], reducing the side effects of diabetic neuropathy [180] and autonomic nerve disorders [181, 182], and counteracting gastric injury [183, 184].

Summary

Most studies published to date, especially in the last decade, point clearly to delta-tocotrienol and gamma-tocotrienol as the key isomers for vitamin E health benefits in reversing chronic conditions or aging maladies. This has been shown for cholesterol (cardiovascular disease) [9, 10, 173], triglycerides (diabetes/prediabetes) [5, 173, 185], blood hypercoagulation/chemotaxis (arteriosclerosis) [14, 66, 76], liver and hepatitis C [15, 30, 84, 85, 88, 125] bone and numerous cancers [135, 174, 186] besides tocotrienol's known power as lipid-soluble antioxidant [56, 158].

The discovery of annatto tocotrienols with only the most potent delta- and gamma-isomers was an important milestone, a composition never before seen. Annatto-derived DeltaGold® 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 lipids (cholesterol and triglycerides) 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 addressing chronic conditions, particularly those associated with aging. Delta-tocotrienol is considered to be the 21st Century Vitamin E.

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