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The Science Behind Vitamin E Tocotrienols

WHITE PAPER ABSTRACT

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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 have 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 support for eye and skin health. Additionally, the substantial potential for tocotrienols as adjuncts to conventional cancer therapies has been addressed in a previous paper.[120]

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.[2] Vitamin E is known as a "vitamin" because it is essential for reproduction, and has been dubbed 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 derived from annatto seeds—DeltaGold®—became available around 2005. 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.

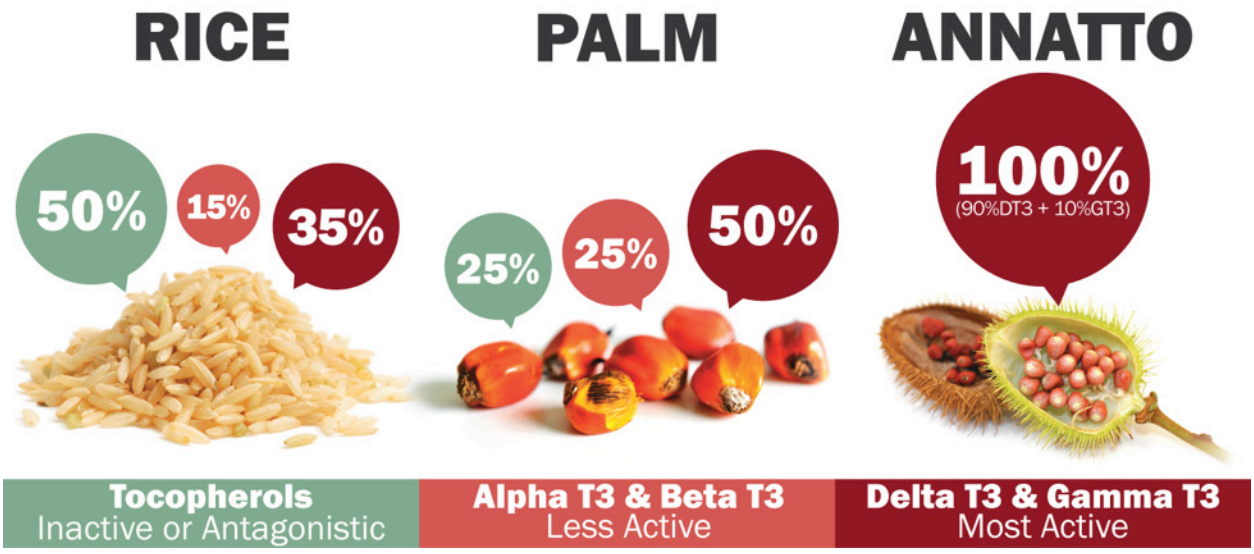

Figure 1. Typical compositions of vitamin E in natural tocotrienol sources.

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 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 have shown alpha-tocopherol to possibly be 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 HMG-CoA reductase, and block processing of sterol regulatory element-binding protein (SREBP). Blocking SREBP processing has implications for triglyceride synthesis (and reduction), with importance in diabetes and prediabetes. Therefore, the mechanism for cholesterol reduction by tocotrienol shown 20 years ago was revalidated some 15 years later. This study came from the Brown and Goldstein research group that discovered the LDL cholesterol receptor, 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 hyperlipidemia—have manifested into clinical significance for cardiovascular disease (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-tocotrienols were 4-fold more efficient as scavengers 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 are absorbed better 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[35]
- Preventing adipose and liver storage[30]

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

- Causing the premature catabolism 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 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 (1,000µm) 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 (~65µm), IDL (~45µm), and LDL (~25µm). The larger particles mainly contain tocotrienols. The IDL sheds the denser HDL (~10µm) 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 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 exported 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 remains preferentially in the LDL, the main task of which 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 1000mg/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 were bioavailable. A trial is now underway to ascertain tocotrienol's bioavailability in adipose tissue, considered the main depot for tocotrienol.

TOCOTRIENOL'S ANTIOXIDANT PROPERTIES

Vitamin E is uniquely shaped to reside within cell membranes to protect against oxidation. 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]

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 later 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 in chickens, there was a 123-150% improvement in HDL/LDL cholesterol ratios, which more closely reflect the.[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 upregulated 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 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-α (TNF-α), 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 compound'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 studies 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 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 hyperlipidemic elderly (31-48%), as did γ-glutamyl-transferase (14-20%). There were no adverse effects associated with the 6-week supplementation period.

Tocotrienol and Monocyte-Endothelial Cell Adhesion and Platelet Aggregation: The adhering of "activated" cells in the blood to artery walls is undesirable. It is a stressed condition prompted by inflammation and an attempt to remove harmful compounds 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 artery walls from getting narrower and clots from forming, important elements for cardiovascular 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 monocyte adherence.[64, 65]

In particular, delta-tocotrienol showed the most profound inhibitory effect on monocyte adherence 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]

Elevated LDL is a risk factor for CVD, especially atherosclerosis. It is generally understood that it is oxidized LDL particles, not non-oxidized particles, that 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 improve nitric oxide synthase activity, 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 buildup 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 240mg/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 have diabetes, with an additional 85 million Americans 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 HDL (under 40mg/dL for males; under 50mg/dL for females)
- Increased waist circumference (above 40in. for males; 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 result being an overall improved metabolic profile.

Closely related research 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 had anti-lipidemic effects, simultaneously reducing cholesterol by 15% and triglycerides by 28%. 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 the tocotrienols' 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 treatments. 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, a daily dose of 250mg tocotrienols (without tocopherols) lowered C-reactive protein and other inflammatory markers between 35-60%.[12] Combinations with other anti-inflammatory ingredients, such as quercetin, resveratrol, and B-vitamins, can synergize with tocotrienols' 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 MetS is NAFLD, which occurs when excess fat is stored in the liver. Based on findings by the National Institutes of Health, NAFLD affects 30-40% of US adults, and treatment is limited to diet and exercise. To examine the effects of tocotrienol on fatty liver disease, a 12-week randomized, double-blind, placebo-controlled study was conducted with 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 and 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'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.[94] TRF have significantly higher potency than alpha-tocopherol, and are effective against protein oxidation and lipid peroxidation at low concentrations.[95,96] Normally, UV-irradiation destroys the antioxidants in the skin, but prior application of TRF to mouse skin preserved the vitamin E.[97] 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,[98] and therefore combats oxidative stress induced by UV or ozone.[99] In addition, delta- and gamma-tocotrienol have been shown to reduce inflammation,[61, 100, 101] and are potent skin whitening agents via reduction of tyrosinase activity, while also blocking UV-induced melanogenesis.[102-104] Delta-tocotrienol has the greatest sun protection factor (SPF) of the tocotrienol isomers at SPF 5.5.[104]

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 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.[105] In the prevention model, the MRSA-infected animals were administered tocotrienol, antibiotics, or tocotrienol plus antibiotics, and compared to infected controls (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 were effective 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.

EYE HEALTH

Vitamin E has long been regarded as a beneficial nutrient to support eye health. It 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 the standard AREDS formula as well as other eye health formulations. While the AREDS study investigated only the alpha-tocopherol form of vitamin E, new studies suggest tocotrienol 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.[93, 107]

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.[108] As a potent antioxidant, tocotrienol accumulates in the eye to combat cataract development,[109] 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.[110] 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.[111] 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.

BONE HEALTH

Vitamin E tocotrienols are being explored for applications beyond their more traditional uses for lipid management, cardiovascular health and antioxidant status. Bone health is one such exciting area, with many pre-clinical studies already having shown promise for supporting stronger bones.[121-125] A double-blind placebo-controlled trial showed that, among post-menopausal women with osteopenia, compared to placebo, tocopherol-free tocotrienols administered at two different dosages (300 and 600mg/day) for 12 weeks resulted in decreased bone resorption and improved bone turnover rate.[126] Osteoporosis is not solely a women's issue. Men are not immune to bone loss as they age, and bone loss may also be an undesirable side-effect of androgen deprivation therapies. Rodent models of this scenario show that supplementation with annatto tocotrienols resulted in significantly higher bone volume, calcium content, trabecular thickness, and improved biomechanical strength of the femur.[127, 128]

Other osteopenic rat models show that tocotrienols improve osteoblast number, bone formation, mineral deposition, and bone microarchitecture.[124] Metabolic syndrome and type 2 diabetes increase risk for osteoporosis, likely owing to systemic hormonal alterations and inflammatory processes. A rodent model showed that supplementation with annatto tocotrienols (60 and 100mg/kg) improved bone strength and trabecular bone microstructure and increased osteoclast number in male rats with metabolic syndrome induced by a high-carb, high-fat diet.[129] Along with these improvements in bone health, annatto tocotrienol supplementation also resulted in improvements in several metabolic syndrome parameters, including decreased triglycerides, blood pressure, and fasting glucose. A separate rodent model had similar findings: in male mice with diet-induced type 2 diabetes, supplementation with annatto tocotrienols (400 and 1600mg/kg) for 14 weeks resulted in increased trabecular bone volume and cortical thickness, with increased markers of bone formation and decreased markers of bone resorption.[130] Additionally, the tocotrienol supplemented mice also had lower area under the curve for glucose and insulin. Notably, these improvements were greater than those seen in a separate group of diabetic mice treated with metformin (200mg/kg). It is believed that tocotrienols may upregulate antioxidant defenses in osteoclasts and "indirectly act against free radical signaling essential in osteoclastogenesis".[131] It is worth noting that alpha-tocopherol, the most common vitamin E subfraction in conventional supplements, may have adverse effects on bone formation, partly due to interference with the "anabolic effect" of gamma-tocopherol on bone, as was shown for a cohort of postmenopausal women in an analysis of NHANES data.[132]

SUMMARY

Most studies published to date, especially in the last decade, point clearly to delta- and gamma-tocotrienol as the key isomers for vitamin E health benefits in reversing chronic conditions or aging maladies. This has been shown for reducing cholesterol and triglycerides, with implications for CVD[9, 10, 107] and diabetes,[5, 107, 118] and blood hypercoagulation/chemotaxis, with implications for arteriosclerosis.[14, 66, 76] These effects are in addition to tocotrienol's known power as lipid-soluble antioxidant.[56, 99]

Compared to other major sources of tocotrienol, annatto has a distinct advantage in lowering lipids 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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