ANNATTO™ 150 & ANNATTO™ 300

SOURCE OF ANTIOXIDANTS

ANNATTO-E™ 150 | 30 SOFTGELS | NPN80093334 | ANT150-CN
ANNATTO-E™ 300 | 30 SOFTGELS | NPN80096032 | ANT300-CN

Vitamin E research has come a long way in recent decades. Vitamin E is not a single nutrient, but rather a complex comprising 4 tocopherols and 4 tocotrienols. Each of these components has a different molecular weight and slightly different chemical structure, which impart distinct properties that influence their biochemical functions. Commercial supplements are typically rich in tocopherols—alpha-tocopherol, in particular—but the tocotrienol fractions have unique effects across a variety of tissues that make them desirable to supplement alone, without tocopherols.

Rich sources of vitamin E include whole grains, such as wheat (especially the germ), rice, barley, oats and corn, as well as palm fruit and annatto. Most of these foods, however, are higher in tocopherols than in tocotrienols (T3). The vitamin E in rice, for example, is comprised of 50% tocopherols, 35% delta- and gamma-T3, and 15% alpha- and beta-T3, which are less potent than the delta and gamma forms. Palm is a bit higher in tocotrienols: 25% tocopherols, 25% alpha- and beta-T3, and 50% delta- and gamma-T3. But the richest known source of naturally occurring tocotrienols is annatto, which is virtually free of tocopherols and contains 100% tocotrienols (90% delta and 10% gamma).

The tocotrienols in Annatto-E™ are sourced from annatto, so they're exclusively tocotrienols. This was a deliberate choice by Designs for Health, because research indicates that tocopherols—especially alpha-tocopherol—interfere with key effects of tocotrienols, so it may be best to dose tocotrienols alone, or with 6 hours between tocotrienols and products containing alpha-tocopherol. (See "Why No Tocopherols?" below.) The tocotrienols in this product are provided as Delta Gold®, a patented tocotrienol formula from American River Nutrition. It is manufactured in the US and has GRAS status from the FDA.

ROLES FOR ANNATTO-E

Cardiovascular Health

Tocotrienols enhance the degradation of HMG-CoA reductase, a key enzyme in the mevalonate pathway, by which cholesterol is synthesized.[9,10] Animal studies indicate the potency of inhibition of cholesterol synthesis by tocotrienols is: delta > gamma > alpha > beta. Tocopherols are inactive in lowering cholesterol.[5]

Alpha-tocopherol has been repeatedly shown to attenuate or interfere with the mevalonate pathway action of tocotrienols.[19] Combinations shown to have an effect in cholesterol-lowering consist of 15% or less alpha-tocopherol and 60% or more gamma- and delta-T3, whereas formulas consisting of 20% or more alpha-tocopherol and 45% or less gamma- and delta-T3 have been shown to be ineffective. 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]

A clinical trial tested the dose-dependent effects of annatto tocotrienols ranging from 125-750 mg per day on hypercholesterolemic individuals.[13] Results showed that after only 4 weeks, a daily dose of 250 mg decreased total cholesterol by 15%, LDL cholesterol by 18%, and triglycerides by 14%. Additionally, cytokines associated with cardiovascular disease and their gene expression (TNF-α, IL-2, IL-4, IL-6, and IL-8), were downregulated 39-64%.

Inflammation is increasingly recognized as a major driver of cardiovascular disease. In a clinical trial of supplementation with delta-T3 in hypercholesterolemic subjects, 250 mg of delta-T3 decreased C-reactive protein (CRP) and malondialdehyde (MDA) by 40% and 34%, respectively, with a 22% increase in total antioxidant status.12 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-T3 showed the most profound inhibitory effect compared to tocopherols and other tocotrienol isomers. Delta- and gamma-tocotrienol were 60 and 30 times more potent than alpha-tocopherol, respectively.[66]

There may be a role for tocotrienols in hypertension. In hypertensive rats, gamma-T3 was shown to reduce systolic blood pressure 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]

Antioxidant Capacity
Antioxidants are abundant in the food supply, but vitamin E is uniquely shaped to reside within cell membranes to protect the integrity of the structural lipids. In this regard, tocotrienols were shown to be about 50 times more potent than tocopherols.[54] The antioxidant efficiency of tocotrienols was evaluated as the ability of the compounds to inhibit lipid peroxidation and reactive oxygen species production. Delta-tocotrienol was found to have the greatest antioxidant properties among the tocotrienol isomers.[56] In lipid ORAC studies, delta- and gamma-tocotrienols had the highest antioxidant value of all vitamin E isomers at 5.5 and 3 times the potency of alpha-tocopherol, respectively.[16]

Metabolic Syndrome
Rodent models of metabolic syndrome show that tocotrienol supplementation helps improve insulin sensitivity and reduces triglycerides, adipocyte size, abdominal adiposity, and liver fat deposition.[84, 85] Human studies employing rice bran extracts (>90% tocotrienols) reduced hyperglycemia, glycosylated hemoglobin, and hyperlipidemia in subjects with both type 1 and type 2 diabetes.[89] Within 60 days, tocotrienol supplementation was shown to decrease total and LDL cholesterol by 30% and 42%, respectively.[91] When taken apart from alpha-tocopherol, tocotrienols were shown to lower total cholesterol, LDL, and triglycerides 15-20%.[13] Moreover, tocotrienols also lowered CRP and other inflammatory markers 35-60%.[12]

Skin and Eye Health
Emerging research indicates that tocotrienols may help reduce the adverse effects of UV-irradiation of the skin and UV-induced melanogenesis.[153, 161-163] Tocotrienols may also have a role in improving wound healing and fending off skin infections. In MRSA-infected mice, given alone, tocotrienol reduced bacterial load by a factor of 10, and antibiotics alone by 1000 times. In combination, however, tocotrienols and daptomycin reduced bacterial load by 10,000 times, suggesting a highly synergistic effect between the two.[164]

Regarding eye health, isomers have long been regarded as a beneficial nutrient to support eye health and was included in the original Age-Related Eye Disease Study (AREDS) and in AREDS2, which also examined other antioxidants such as lutein and zeaxanthin. AREDS investigated only alpha-tocopherol, but newer studies suggest that tocotrienols warrant dedicated research. Owing to inhibition of angiogenesis, tocotrienols may have application in improving ocular conditions related to abnormal neovascularization, such as macular degeneration and diabetic retinopathy. Tocotrienol may be a potent anti-angiogenic agent, with delta-tocotrienol being the most effective.[150, 174]

As a powerful antioxidant, tocotrienol accumulates in the eye to combat cataract development, among the most common eye problems in the aging population.[176] Rodent models show that tocotrienol administration delayed the onset and progression of cataract by reducing lenticular oxidative and nitrosative stress,[177] and in diabetic rats, tocotrienol application arrested cataract progression and restored lens transparency to normal.[178] (It should be noted, however, that these studies employed topically applied tocotrienols, via eye drops.)

Bone Health
Tocotrienols are being explored for applications beyond their more traditional uses for cardiovascular health and antioxidant status. Bone health is one of these new areas, with many pre-clinical studies already having shown promise for supporting stronger bones.[93-97] 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 600 mg/day) for 12 weeks resulted in decreased bone resorption and improved bone turnover rate.[98] 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.[187-188]

Other osteopenic rat models show that tocotrienols improve osteoblast number, bone formation, mineral deposition, and bone microarchitecture.[96] 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 100 mg/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.[189] 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 1600 mg/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.190 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 (200 mg/kg). It is believed that tocotrienols may upregulate antioxidant defenses in osteoclasts and "indirectly act against free radical signaling essential in osteoclastogenesis".[191] 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.[192]

Why No Tocopherols?
Alpha-tocopherol compromises several of the potential effects of tocotrienols. For example, it has been shown to attenuate their cholesterol and triglyceride reducing effects,[19, 30, 31] lowers their antioxidant capacity,[32] attenuates potential cancer cell inhibition,[33, 34] blocks absorption of tocotrienols and induces their catabolism,[26-29, 35] and prevents adipose and liver storage of tocotrienols.[30]

Annatto 150™ Medicinal Ingredients (per softgel):
Tocotrienols (delta-tocotrienol 90%, gamma-tocotrienol 10%) (*Bixa orellana*-Seed) ..... 150 mg
Annatto 300™ Medicinal Ingredients (per softgel):
Tocotrienols (delta-tocotrienol 90%, gamma-tocotrienol 10%) (*Bixa orellana*-Seed) ..... 300 mg
Non-Medicinal Ingredients: Gelatin, purified water, glycerine. **Recommended Dose:** Adults: Take one softgel per day, or as directed by your health care practitioner.

REFERENCES
For a list of references cited in this document, please visit: http://catalog.designsforhealth.com/assets/itemresources/Annatto-E_References.pdf