Tocotrienols for cardiovascular health.

When most people think of vitamin E, more often than not they think of tocopherols—the most prominent being alpha-tocopherol. However, vitamin E refers to a family of eight distinct compounds: four tocopherols and four tocotrienols. While most people are familiar with alpha-tocopherol, other tocopherol forms include beta-, gamma-, and delta-. Similarly, the vitamin E family includes alpha-, beta-, gamma-, and delta-tocotrienols (the designations represent their structural makeup).

While vitamin E is generally renowned for its antioxidant properties, recent research suggests that tocotrienols may possess more potent antioxidant benefits than tocopherols do. Also, because of their difference in chemical structure, tocotrienols may be able to more efficiently penetrate cell membranes. Studies also indicate that tocotrienols have the potential to play a major role in down-regulating inflammatory pathways, with evidence pointing to these benefits in the realm of cancer prevention and other areas of health. Alongside their potent anti-inflammatory and antioxidant effects, tocotrienols also have the ability to act on enzymes responsible for cholesterol and lipid metabolism.

Given the multipronged effect of tocotrienols, these nutrients are excellent candidates for cardioprotection. Highlighted below is research detailing the significant and unique role tocotrienols play in cardiovascular health.

**Antioxidant Effects**

Free radical damage is a major contributor to poor health overall and is of primary concern in the development of cardiovascular disease. A major factor in atherosclerosis is a process known as lipid peroxidation, which results from free radical damage to lipid molecules and, specifically, to low-density lipoprotein (LDL) cholesterol. Once LDL molecules are damaged as a result of free radicals, macrophages circulating in the bloodstream engulf them, leading to the formation of foam cells and their deposition into atherosclerotic lesions.

Antioxidants can protect the integrity of lipid and cholesterol molecules by preventing free radical damage to their cell membranes. The vitamin E family is widely considered the most effective group of lipophilic antioxidants, operating efficiently to protect cholesterol cell membranes.

Within the vitamin E family, it is well known that tocotrienols exert the most potent antioxidant activity, whether measured *in vitro* or *in vivo*. Several studies conducted since the early 1990s show that tocotrienols are effective “chain-breaking” antioxidants, breaking the chain reaction of events that lead to lipid peroxidation by neutralizing highly unstable—and therefore damaging—free radicals, such as peroxyl radicals, to more-stable phenoxyl radicals.

A recent study conducted at Universiti Kebangsaan in Malaysia published in 2009 assessed the effects of oral administration of a tocotrienol-rich fraction of palm oil to diabetic rats. Several parameters of antioxidant function were included in this eight-week study. The induction of diabetes led to a decrease in superoxide dismutase (SOD) activity and vitamin C levels in the rats’ plasma and aorta. Rats fed the tocotrienol-rich palm oil showed significantly higher plasma SOD activity and levels of vitamin C. Malondialdehyde (MDA) and 4-hydroxynonenal (HNE) are important measures of oxidative stress. These measures were increased in diabetic rats; however, treatment with the tocotrienol-rich palm oil was found to normalize both MDA and HNE levels, indicating a significant reduction in oxidative stress.

The reductions in free radical activity seen in this study with the consumption of tocotrienols indicate tocotrienols’s potential to significantly benefit cardiovascular and overall health.

**Anti-Inflammatory Effects**

Inflammatory processes are intimately involved in the progression of poor cardiovascular health outcomes. Inflammation is an important contributor to circulatory issues, blood pressure concerns,
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atherosclerosis, heart attack, and stroke. Through interactions with multiple inflammatory pathways, tocotrienols likely play important roles in managing and regulating the body’s inflammatory response.

Earlier studies have shown that the administration of tocotrienols to animals lowers arachidonic acid levels in various tissues, which ultimately leads to a reduction in pro-inflammatory prostaglandins and leukotrienes, and a subsequent reduction in interleukin-1. Interleukin-1 is a promoter of the inflammatory response and, among other effects, has been shown to stimulate the synthesis of cyclo-oxygenase (COX) and the eicosanoid PGE2. Both of these play a role in perpetuating the inflammatory response.

Studies in mice further show that pretreatment with tocotrienols serves to attenuate the induction of tumor necrosis factor (TNF), a potentially key mechanism whereby tocotrienols may prevent atherosclerosis. In 2007, Mariarosaria Napolitano and colleagues from the Istituto Superiore di Sanità in Rome found that tocotrienols reduced the accumulation of cholesterol molecules in human macrophages in a dose-dependent manner. Cholesterol accumulation in macrophages sets the stage for inflammatory effects in the walls of blood vessels, leading to the development of atherosclerosis.

Recent studies have highlighted the significant role of nuclear factor-kappa beta (NF-kB) in cardiovascular health and disease. According to a 2010 review by Kim van der Heiden and colleagues from Imperial College London, NF-kB is a major transcription factor that influences processes, including immunity, inflammation, and cell survival, and regulates cellular responses to stress, hypoxia, and ischemia. Due to these far-reaching effects, it has been shown to influence the development and progression of several cardiovascular diseases, including atherosclerosis, ischemia/reperfusion injury, cardiac hypertrophy, and heart failure. Controlling the effects of NF-kB can, therefore, have a profound influence on cardiovascular health.

Tocotrienols possess the ability to modulate the effects of NF-kB in a manner conducive to decreased overall inflammation. In a study published in 2009, Anurag Kuhad and Kanwaljit Chopra from Panjab University in India showed that experimentally induced diabetic rats had an increase in an NF-kB–dependent protein in their kidneys. In this eight-week study, diabetic animals subsequently administered tocotrienols from weeks five to eight showed reduced expression of this NF-kB–dependent protein. An earlier study (2007) by Kwang Seok Ahn and colleagues also investigated the effects of tocotrienols on apoptosis, or the normal process of programmed cell death, and found significant influences of tocotrienols on the NF-kB pathway. These results indicate the multiple mechanisms through which tocotrienols can inhibit an overactive inflammatory response and promote cardiovascular wellness.

Lipid-Lowering Effects

Researchers investigating the cardioprotective effects of tocotrienols believe that the greatest potential benefits of these vitamin E compounds lie in their ability to block the enzyme HMG-CoA reductase, the rate-limiting step in cholesterol biosynthesis and also a target of statin drugs. In fact, this action of tocotrienols contrasts with that of tocopherols. Research has shown that tocopherol forms of vitamin E, when administered concurrently, may interfere with the inhibition of this enzyme by tocotrienols.

In a study that illustrates the direct lipid-lowering potential of tocotrienols, researchers at the University of Rochester Medical Center fed rats an atherogenic diet for three weeks to induce hyperlipidemia. Significant increases in triglycerides, total cholesterol, and LDL cholesterol were noted, while a decrease in HMG-CoA reductase activity was seen as a result of an abundance of cholesterol from dietary sources. Rats were then supplemented with a tocotrienol-rich fraction of rice bran oil for one week. Tocotrienol supplementation decreased the elevated lipids in a dose-dependent manner, with the optimal effects seen with a dose of 8 mg per kg of body weight.

HMG-CoA reductase activity, which rebounded after the withdrawal of the atherogenic diet, remained suppressed with tocotrienol administration, indicating the lipid-lowering effects of tocotrienols. Furthermore, a Singaporean study published in October 2010 investigated the lipid-modifying effects of a combination of gamma- and delta-tocotrienols in a three-tiered study involving research in a human liver cell line, in LDL receptor–deficient mice, and in human study subjects with borderline high cholesterol.

The in vitro study showed that the tocotrienol combination suppressed multiple regulators of lipid production—including HMG-CoA reductase—leading to decreased production of triglycerides, cholesterol, and VLDL (very-low-density lipoprotein) cholesterol molecules in the liver cell line. In the mice study, administration of the tocotrienol mixture resulted in significant decreases in total cholesterol (28%) and triglyceride levels (19%), while high-density lipoprotein (HDL) cholesterol
remained essentially the same. In the human study, administration of 120 mg of the gamma- and delta-tocotrienol mixture daily for eight weeks caused a decrease in plasma triglycerides of 28% and a subsequent decrease in VLDL cholesterol. However, no other lipid parameters were affected. The authors suggest that the contrasting results from the animal and human trials may be explained by the differential rates of metabolism post-absorption in humans versus other animal species. Earlier studies in humans have also shown inconsistent effects. Some studies have found tocotrienol supplementation to reduce various lipid parameters, while other studies have not. This may be a factor of determining optimal dosage for this benefit in humans. It also may require the development of unique formulations that overcome the metabolic challenges encountered with oral administration of tocotrienol-based formulations. What seems clear, however, is that oral administration of tocotrienols holds significant potential for beneficial cardiovascular effects in humans when it comes to lowering triglyceride levels. It’s likely that investigating optimal dosing will yield greater benefits.

**Tocotrienols Tomorrow**

Tocotrienols are unique forms of vitamin E conferring significant cardioprotective benefits. Working on multiple complementary pathways, these nutrients may decrease overall inflammation, raise antioxidant capacity, and favorably modify blood levels of cholesterol and other lipids to reduce cardiovascular risk. They also may confer significant benefits in other areas of health, including cancer prevention.

The initial research on these vitamin E compounds is compelling, and further research in humans will serve to sort out some of the challenges related to optimal dosing and bioavailability. While the tocopherols also contribute to many crucial metabolic functions, it’s increasingly clear that neglecting the “forgotten” vitamin E—tocotrienols—is something we do at the peril of our health and wellness.


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