

# REPORT

## The Little-Known Benefits Of Tocotrienols

By Thomas Rosenthal

If your vitamin E supplement contains only **tocopherol** forms, you may not be getting all of the benefits this nutrient has to offer. While tocopherols are very important, they lack many of the synergistic benefits offered by their cousins, the **tocotrienols**.

Few people realize that vitamin E is composed of eight different compounds. Half of these are called **tocopherols**, which is the most common form of vitamin E. The other half are known as **tocotrienols**.

Scientists are discovering that **tocotrienols** provide valuable therapeutic and preventive options for the diseases of aging that tocopherols alone may not provide.

For example, researchers found that tocotrienols given to mice with pancreatic cancer significantly improved their survival. Only **10%** of animals in the control group survived for the study period while **70%** of those taking **tocotrienols** survived!<sup>1</sup> Pancreatic cancer is a particularly fast-moving and lethal form of cancer, and this study presents a promising new treatment option.

Beyond cancer, research is showing that **tocotrienols** have a place in reducing important risk factors for some of the most lethal chronic diseases. For example, tocotrienols have been found to promote new artery formation after a stroke, lower homocysteine levels, improve insulin sensitivity, protect vital brain circuitry, and even prevent bone loss.<sup>2-5</sup>

In addition, tocotrienols have powerful lipid-lowering, anticancer, and neuroprotective properties that tocopherols lack.<sup>6,7</sup>

These recent investigations into this overlooked form of vitamin E are providing new strategies to fend off multiple risk factors to ensure optimal health.

### Tocotrienols And Cancer

For many years, studies of vitamin E produced inconsistent results regarding its effect on cancer. It is now thought that this inconsistency was likely due to the widespread use of *alpha*-tocopherol alone in such studies.<sup>8</sup> We now know that alpha-tocopherol has weak anticancer activity, while tocotrienols are more potent cancer-preventive agents.<sup>8-10</sup>

In a recent finding that stunned researchers, tocotrienol supplementation was found to dramatically extend the life span of mice with pancreatic cancer.<sup>8</sup> Pancreatic cancer is among the most aggressive and deadly human cancers, with survival times typically counted only in months.<sup>11,12</sup> The **2013** study showed that after 16 weeks of treatment, just **10%** of placebo-treated mice remained alive, while **30%** survived in a group treated with *gemcitabine*, a standard chemotherapy drug. However, a remarkable **70%** of mice had survived in the tocotrienol group. Combination treatment with *gemcitabine* and **tocotrienols** produced a remarkable **90%** survival rate.<sup>1</sup>

Tocotrienols are the ultimate multi-targeting nutrient when it comes to cancer. Their actions affect virtually every step in the progression of cancer.<sup>13</sup> They share antioxidant effects with tocopherols, but there seems to be a considerable amount of anticancer action that is unrelated to antioxidant actions.<sup>13,14</sup>

## PROPOSED MECHANISMS OF TOCOTRIENOLS IN CANCER PREVENTION<sup>13</sup>

Effect	Result
Apoptosis (programmed cell death)	Tumor-cell death
Cell cycle arrest	Slows tumor growth
Inhibit new blood vessel growth (angiogenesis)	Starves tumor of nutrients and oxygen
Inhibit HMG-CoA reductase enzyme	Inhibits metastasis <sup>65</sup>
Decreases expression of cancer causing genes	Prevents initiation of cancer
Increases the expression of genes that suppress cancer	Prevents initiation and progression of cancer

## Proposed Mechanisms Of Tocotrienols In Cancer Prevention

Tocotrienols impact several factors that tumors need for their development and growth.

Tocotrienols have been shown to inhibit the growth of new blood vessels to rapidly growing tumors and inhibit growth and proliferation of cancer cells.<sup>9,15</sup> Tocotrienols also sensitize cancer cells to the effects of standard chemotherapy, and astonishingly, appear capable of combating **cancer stem cells**, which are highly resistant to standard chemotherapy and contribute to cancer recurrences.<sup>9</sup> They also blunt the impact of chemical carcinogens in animal studies.<sup>16</sup>

Tocotrienols also trigger **apoptosis**, which is the programmed cancer cell death that can prevent a tumor from ever getting a toe-hold in the body. Apoptosis is also vital in shrinking existing tumors, a factor that may account for the growing use of tocotrienols (alone or with conventional chemotherapy drugs) in patients with existing cancers.<sup>14,17</sup>

Tocotrienols have another rather unusual mechanism for fighting cancer. They appear to block an enzyme that cancer cells need for invasion and metastasis. This enzyme, called *HMG-CoA reductase*, is the same enzyme blocked by statin drugs.<sup>2</sup> In fact, the combination of tocotrienols with the statin drug *atorvastatin* (**Lipitor**<sup>®</sup>) was recently shown to greatly increase inhibition of cancer cell growth.<sup>18</sup>

## WHAT YOU NEED TO KNOW

### Breakthrough Research On Tocotrienols

- Typical vitamin E supplements contain only alpha-tocopherol, the best known member of the eight-member vitamin E family.
- But tocopherols, while important nutrients, lack some of the additional benefits offered by their cousins, the tocotrienols.
- By virtue of small but important structural differences, tocotrienols can get more involved in profound biological processes, such as modulating gene expressions and regulating vital enzyme functions.
- Tocotrienols have potent anticancer and anti-diabetes abilities, as well as cardio-, neuro-, liver-, and bone-protective actions based on their unique functions in the body.
- It is now apparent that studies showing little or no effect from vitamin E supplementation failed in part because they used only alpha-tocopherol, rather than also including other tocopherols and tocotrienols.

## Tocotrienols For Cardiovascular Disease And Stroke

Tocotrienols offer many important complementary benefits to the tocopherol form of vitamin E, such as:

### 1. Improving Lipid Profiles

Tocotrienols help lower plasma cholesterol levels by blocking *HMG-CoA reductase*. This enzyme is a rate-limiting step in producing cholesterol, so blocking it is an effective means of lowering cholesterol levels. In fact, the common statin drugs used for lowering lipid levels also operate by inhibiting HMG-CoA reductase, although they do so by a different mechanism.<sup>4,19-21</sup>

Human research shows that tocotrienol supplementation can lower total serum lipids by up to **23%**, total cholesterol by **30%**, and LDL (bad) cholesterol by **42%**. Not all human studies show this dramatic reduction in LDL and cholesterol.<sup>22</sup> And animal studies demonstrate significant reductions in lipids, with the added benefit of reducing lipid oxidation; a precursor to the arterial damage that leads to stroke and heart attacks.<sup>23</sup>

Tocotrienols also can lower dangerous forms of *apolipoproteins*, which are lipid-carrying proteins that can increase cardiovascular risk.<sup>24</sup> Alpha tocopherol has no effect on serum lipids.<sup>25</sup>

## 2. Reducing Homocysteine

Tocotrienols have also been found to reduce blood levels of *homocysteine*, another important contributor to cardiovascular disease.

When scientists used a tocotrienol-rich fraction in a rat study to reduce plasma homocysteine and heart oxidative stress, they discovered that it proved more powerful than folate, the standard homocysteine-reducing vitamin.<sup>2</sup>

And in rabbits, tocotrienol supplementation after a high-fat diet significantly lowered a host of markers of both inflammation and heart muscle damage.<sup>26</sup>

## 3. Protecting Against Ischemia

If a vessel does become blocked, tocotrienols offer potent resistance to the loss of blood flow known as *ischemia*, which is generally involved in the development of heart attack or stroke.<sup>26</sup> This was powerfully demonstrated in a study of rabbits, in which supplementation not only lowered their lipids, but also protected their heart muscle from damage by ischemia induced in the laboratory. This was especially true of the alpha- and gamma-tocotrienol, which reduced the area of heart muscle damage significantly.<sup>26</sup>

## 4. Guarding Against Stroke-Related Brain Damage

Acute ischemic stroke (reduced blood flow to an area of the brain) remains a leading cause of death and disability worldwide.<sup>27</sup> Oral tocotrienols have been shown to protect against and minimize stroke-related brain damage in animal models.<sup>3,6,27,28</sup> This protection is the result of several independent mechanisms. Tocotrienols work by:

- Slowing the conversion of *arachidonic acid* (the most abundant brain fatty acid) into pro-inflammatory molecules, thereby reducing the inflammation that arises after an acute stroke.<sup>28,29</sup>
- Reducing the effects of specific oxidant damage-inducing molecules in brain tissue.<sup>3</sup>
- Increasing the recruitment of arterioles to rapidly restore blood flow to areas injured by stroke.<sup>4</sup>

## 5. Improving Metabolic Syndrome

In an exciting look ahead at what the future may hold in human studies, preclinical research has shown that tocotrienols can reverse many changes seen in metabolic syndrome, including improving lipid profiles, reducing atherosclerotic lesions, lowering blood glucose and markers of *glycation*, normalizing blood pressure, and inhibiting new fat deposits.<sup>30,31</sup> At the functional level, tocotrienols improve heart muscle function, improve glucose and insulin tolerance, and reduce infiltration of inflammatory cells into heart muscle.<sup>30</sup>

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### Tocotrienols And Diabetes

Diabetes accelerates aging through a variety of mechanisms. In fact, **80%** of diabetic patients will die of an atherosclerotic event such as a heart attack or a stroke, making it especially important to address the factors involved in diabetes.<sup>22</sup> Fortunately, a number of animal studies demonstrate that tocotrienols offer hope for patients suffering from this disease.

Tocotrienols have been found to improve blood sugar and kidney function in diabetic animals.<sup>32</sup> This effect has been attributed to their sugar- and lipid-lowering effects, and to their ability to modulate specific growth factors that prevent fibrous proteins from being deposited in kidney tissue.<sup>33</sup>

Other studies have shown that tocotrienols improve insulin sensitivity and whole-body sugar utilization in a similar way as some expensive diabetes drugs (through activation of the metabolic sensors known as *peroxisome proliferator-activated receptors* or PPARs).<sup>34</sup>

And a tocotrienol-rich diet reduced the attack of sugar on tissues (*glycation*), even in non-diabetic rats. In diabetic rats, it improved blood sugar control as well as glycation.<sup>35</sup>

Because diabetes also attacks the nerves, it eventually produces neuropathy, a potentially painful condition that has resisted many attempts to treat it with drugs. In diabetic rats with neuropathy, tocotrienol supplementation substantially reduced pain

behaviors and biochemical changes seen in neuropathy.<sup>36</sup>

## Tocotrienols And Liver Disease

In addition to growing indications that tocotrienols are effective against liver cancer,<sup>17</sup> there is compelling evidence of their effectiveness in treating non-alcoholic fatty liver disease (NAFLD). In NAFLD, fat is deposited in the liver and can lead to hepatitis, liver failure, or even cancer.<sup>37</sup>

In a randomized clinical trial, 87 adults with high cholesterol and NAFLD received either mixed tocotrienols (**200 mg** twice daily) or placebo.<sup>38</sup>

After one year, supplemented patients had a significantly greater rate of normalization of their liver tissue on ultrasound than did control patients. The rate of remission was also significantly higher in treated patients than in control patients, while NAFLD worsened in two controls but didn't worsen in any of the supplemented patients. This is the first clinical study ever to show liver protective effects in NAFLD patients using tocotrienols.<sup>38</sup>

Another study showed that oral tocotrienols delayed progression of end-stage liver disease in **50%** of liver transplant patients, compared with just **20%** in a group treated with alpha-tocopherol.<sup>39</sup> The study also demonstrated good tissue penetration of oral tocotrienols in humans, countering previous reports of poor bioavailability.

### MEET THE VITAMIN E FAMILY

Vitamin E was first discovered in 1938 as a "fertility factor."<sup>61</sup> During the ensuing years, it was discovered that vitamin E was an antioxidant with value in many different body systems.

Vitamin E can be divided into two groups: *tocopherols*, which is the most well-known form of vitamin E, and the lesser-known *tocotrienols*.<sup>6,7</sup>

The tocopherol group has received the most attention since the vitamin's discovery. This group contains members called alpha-, beta-, gamma-, and delta-tocopherol.<sup>7</sup> They are all important nutrients.

The second group in the vitamin E family is the tocotrienols, which until recently received little scientific attention. Even today, less than **1%** of the literature on vitamin E is devoted to tocotrienols. The family resemblance is still close: Tocotrienols exist in the same four configurations (alpha, beta, gamma, and delta), and differ from their respective tocopherol cousins only by a few chemical bonds.<sup>62</sup> But those small differences make for differences in function.

Tocotrienols and tocopherols are both antioxidants, but the antioxidant activity of tocotrienols is several times more than tocopherol.<sup>62,63</sup> Beyond that, tocotrienols modify gene expression, inhibit various enzymes, and carry out functions that tocopherols can't perform.

Tocotrienols have potent anticancer and anti-diabetes abilities, as well as cardio-, neuro-, liver-, and bone-protective actions based on their unique functions in the body.

## Tocotrienols For Neuroprotection

Oxidation, inflammation, and toxicity resulting from normal brain cell activity are all involved in the terrifying progression of cognitive decline. That's why there has been so much interest in vitamin E in general, with its antioxidant effect, and more recently in tocotrienols, with their ability to regulate a wide variety of genes and signaling molecules.

Patients with Alzheimer's disease and those with mild cognitive impairment are more likely than healthy people to have low blood tocopherol and tocotrienol levels.<sup>40</sup> Conversely, very old people with higher levels of tocotrienols in their blood have a **64%** reduced risk of having Alzheimer's.<sup>41</sup> Tocotrienols are incredibly effective at protecting vital brain circuitry in these conditions.

Animal studies demonstrate the remarkable neuroprotection offered by tocotrienols. A tocotrienol-rich fraction not only protected rats from free-radical-induced brain cell death, but it also reduced DNA damage in brain cells, and improved the animals' performance on various cognitive tests such as mazes and swimming challenges.<sup>42</sup>

Alpha-tocotrienol is the most potent neuroprotective form of natural vitamin E.<sup>3</sup> It is so incredibly potent that concentrations in the nanomole to attomole range (one-billionth to one-billion-billionth of a mole) block brain cell death caused by prolonged excitatory stimulation by the neurotransmitter *glutamate*.<sup>43-45</sup> Oral supplementation in humans results in tocotrienol plasma concentrations of **3 micromolar**; that's billions of times higher than the concentrations needed in the lab.<sup>46</sup>

Tiny concentrations of tocotrienols, when administered before neurotoxins, led to a sharp reduction in brain cell damage, restoring their normal growth and viability in the laboratory.<sup>43,47</sup> Most importantly, tocotrienol treatment of cultured brain cells under oxidative stress restores *neurites*, which are tiny projections off the cell that allow for normal cell-to-cell communication.<sup>48,49</sup>

Tocotrienols modulate many different cardioprotective mechanisms. They have been shown to:<sup>25</sup>

1. Reduce plasma levels of *C-reactive protein* (CRP), which is both a marker of and a cause in the inflammatory response that damages heart and blood vessels.
2. Reduce other inflammatory mediators such as *cytokines*.
3. Reduce *advanced glycation end products* (AGEs) arising from elevated blood sugar that damage vessels and tissues.
4. Reduce expression of adhesion molecules that cause platelets and white blood cells to stick to vessel walls, potentially blocking them.
5. Suppress expression of *matrix metalloproteinases* (MMPs) involved in the spread of certain cancers.
6. Reduce risk factors for destabilizing atherosclerotic plaques (such plaques, when unstable, readily burst, often blocking the artery and producing heart attack or stroke).
7. Reduce ischemia/perfusion injury to brain and heart muscle; this kind of injury subjects already vulnerable tissues to a blast of oxygen radicals, just when the tissue was beginning to heal.<sup>64</sup>
8. Suppress, regress, and slow the progression of atherosclerosis.

## Tocotrienols For Bone Health

Tocotrienols are rapidly emerging as major contributors to greater bone density and major inhibitors of bone loss.

Postmenopausal women are the leading sufferers of osteoporosis, though older men develop some degree of abnormal bone loss as well.<sup>50</sup> Long-term anti-inflammatory corticosteroid treatment is an increasingly common cause of bone loss. In addition, research suggests bone loss may be triggered by elevated cortisol levels from stress or smoking.<sup>51,52</sup>

A host of studies has now established that tocotrienols can prevent, and even reverse, bone loss and promote fracture healing in animal models of osteoporosis from many different causes, including menopause and steroid treatment.<sup>53-55</sup> The mechanisms are surprisingly well-understood.

Tocotrienols are potent antioxidants, which appear to reduce the oxidant-induced inflammation that contributes to bone loss.<sup>56-58</sup> Tocotrienols also upregulate genes related to new bone formation, while suppressing inflammatory signaling that generates bone destruction; this activity is not shared by tocopherols.<sup>59</sup>

As we mentioned earlier, tocotrienols inhibit the enzyme HMG-CoA reductase, which is associated with cholesterol production.<sup>20</sup> HMG-CoA reductase is also profoundly involved in osteoporosis, favoring bone-resorbing cells over bone-forming ones. By inhibiting HMG-CoA reductase, tocotrienols prevent excessive bone resorption (bone breakdown) and promote new bone formation.<sup>50,59,60</sup>

Since statins are also powerful HMG-CoA reductase inhibitors, combining statins with tocotrienols has been found to be especially beneficial for bone health. Animal studies have found that combining statins with tocotrienols potentially reduces the statin dose needed—therefore limiting the potential side effects of statins as well.<sup>50,60</sup>

Basic laboratory and animal studies have long supported a role for *tocotrienols* in protecting brain cells and tissue from the ravages of aging.<sup>66</sup> In these studies, tocotrienols have been closely linked to neuroprotection through their potent antioxidant properties, as well as their ability to redirect the production of inflammatory molecules to non- or even anti-inflammatory actions.<sup>67,68</sup>

Now, for the first time, these pre-clinical studies have been compellingly validated in a human study of a pervasive form of brain aging known as *leukoaraiosis*, or white matter lesions.<sup>1</sup> In this condition, damage to the endothelial lining of small arteries in the brain is thought to produce tiny areas of poor blood flow, resulting in the condition known as vascular cognitive impairment.<sup>69,70</sup> If it progresses, stroke, cognitive impairment, gait disturbances, and other conditions may follow.<sup>69-71</sup>

In a study released in April of 2014, researchers randomly assigned a group of volunteers with known cardiovascular risk factors and confirmed white matter lesions in their brains to receive either placebo or a twice-daily dose of **200 mg** mixed tocotrienols.<sup>66</sup> The study lasted two years.

In the placebo group, as expected, the mean volume of the white matter lesions increased over the two-year study period. But in the tocotrienol group, the volume of lesions remained unchanged, and the differences between the groups was statistically significant.<sup>66</sup> No adverse effects, including changes in blood chemistry, were observed.

This study is a “first-ever,” then, for two reasons. It is not only the first time that tocotrienol supplementation has been confirmed to be neuroprotective in living human patients, it is also the first demonstration that a simple nutritional therapy can slow progression of the white matter lesions, which many neurologists suspect lies at the root of the tragic and progressive loss of cognition suffered by so many aging adults.

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#### Summary

Tocotrienols are potent gene regulators and modulators of many enzymes involved in human health, helping to quash the inflammation, glycation, and other processes that contribute to age-related diseases.

Tocotrienols are increasingly being recognized for their potential roles in protecting against cancer, heart disease, stroke, diabetes, liver disease, neurodegenerative diseases, and even osteoporosis.

If you have any questions on the scientific content of this article, please call a **Life Extension**® Wellness Specialist at 1-866-864-3027.

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