

ANNATTO TOCOTRIENOLS

An Extensive Overview

INTRODUCTION

Vitamin E is a powerful, essential nutrient to the human diet. This potent fat-soluble antioxidant is necessary for life; without it, the human reproductive cycle comes to a halt. Relatively common in nature, the benefits of this nutrient stem from its ability to act as a powerful protectant against free radicals. As it is fat-soluble, it is able to penetrate into cellular membranes and readily react with harmful oxidizing agents, using its weak hydrogen bonds to neutralize potential oxidative damage.

Found in a variety of foods, vitamin E is common to many fatty plant sources including wheat germ oil, almond oil, grapeseed oil, and canola oil. As it is already a component in many foods, vitamin E retains a high tolerable upper intake level set at 1,000mg by the U.S. Food and Nutrition Board. In addition, it is a common nutrient used in prepared or stored foods to help improve shelf life stability due to its antioxidant nature.

Although the benefits of vitamin E have been well documented over the last century, research efforts have focused primarily on one half of this common antioxidant family, alpha-tocopherol. Despite this vast field of research, newer studies have shown that alpha-tocopherol fails to be the most powerful isoform of the nutrient. Instead, researchers have shifted toward studying the *tocotrienol* isoform, that expresses a more versatile reactivity with improved benefits. It has been from this exciting new perspective that annatto tocotrienols have come to light – with the intention to improve upon the benefits of vitamin E supplements by shifting the current paradigm of vitamin E therapy to focus instead on the impressive potential of tocotrienols.

The “Birth” of Vitamin E

The early 1900’s saw the rapid discovery of individual molecules deemed essential for life. The nutrients that were first discovered in nature were isolated, synthesized, and reproduced in the laboratory for experimentation and commercialization. The first identified isomer of vitamin E, alpha-tocopherol, was deemed essential for childbirth. The word tocopherol is a compounding of the Greek words for *birth* and *to carry*¹.

With further research, it was determined that, like many natural compounds, vitamin E comes in several forms. The vitamin E family has two sister compounds: tocopherols and tocotrienols - they each have four isomers acknowledged by a corresponding Greek letter; α (alpha), β (beta), γ (gamma), and δ (delta). Although identical in their main structure, these isoforms show slight molecular differences in composition, creating variations in their functioning, performance and bioavailability.

While vitamin E has been studied for nearly 100 years, all eight of its isoforms have only been identified in the last 60 years, with numerous groundbreaking developments and studies in the last 20 years. Many are related to how readily the different forms can enter the body and factor in health and wellbeing. The slight differences in molecular structure have been shown to have dramatic differences of effect among the sister compounds.

Tocotrienols, although less commonly consumed, are naturally found in many sources including rice bran, palm, and annatto. The superior benefits of tocotrienols over tocopherols have been supported by numerous studies. In fact, studies have illustrated tocotrienol’s

ability to help reduce the risks associated with cardiovascular disease^{2,3}, metabolic syndrome^{4,5}, diabetes⁶, bone injuries⁷⁻¹⁰, and cancer^{11,12} — as well as promote skin health¹³⁻¹⁵.

Because alpha-tocopherol has proven to be the most common form of vitamin E, the majority of research efforts have concentrated on alpha-tocopherol treatment. However, it was the discovery of tocotrienols in the 1960s that further established the antioxidant potential of vitamin E^{16,17}. The first tocotrienol supplements were brought to market by Dr. Barrie Tan, the inventor of several tocotrienol extraction processes. Dr. Tan derived his tocotrienols from rice, palm, and annatto sources. Tocotrienols from palm were the first to be commercialized in 1992, followed by the introduction of rice tocotrienols in 1996, and culminating in the 2002 development of the finest tocotrienol ingredient yet, sourced from annatto. 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 U.S. during the 17th century, and today it is used in the coloring of butter, cheeses, snacks, fruit fillings, and many other foods in the industry worldwide.



Benefits of Tocotrienols

Since its discovery, annatto tocotrienol has been praised for the absence of tocopherols in its make-up as many studies have shown they interfere with the functions and benefits of tocotrienols. By definition, “tocopherol-free” is the amount found to be below the measurable limit of alpha-tocopherol by high performance liquid chromatography (HPLC) methods, which is less than 0.1%. Both palm and rice sources have high tocotrienol and tocopherol composition; however, only the annatto plant boasts a pure naturally derived source of vitamin E tocotrienols. Thus, annatto tocotrienol is the only known source of tocotrienol that is not synthetically curated to be free of tocopherol and provides the highest natural content of the powerful delta-tocotrienol isoform. Compared to other major sources, annatto-originated tocotrienols have a distinct advantage in lowering cholesterol and enhancing cellular health without the interference of alpha-tocopherol¹⁸.

Various clinical studies have supported that the most effective dose of annatto tocotrienols to reduce cholesterol is 250mg/day, though significantly higher doses have been documented without adverse effects¹⁹. To optimize absorption, it is recommended that the supplement be taken with a meal²⁰. Due to possible interference, it is also recommended that tocotrienols be taken approximately six hours apart from tocopherol-containing supplements. It is important to note that normal dietary consumption of alpha-tocopherol from food is too small to disrupt tocotrienol supplementation.



Tocotrienol is 50x more potent than tocopherol as an antioxidant

Annatto Tocotrienol's Superior Antioxidant Properties

Many antioxidants exist in nature, including lycopene, CoQ10, and lutein. However, vitamin E has proven to be highly effective and uniquely equipped to penetrate and reside within the cell membrane, unlike many other water-soluble antioxidants. Aside from being 50 times more effective than tocopherols at protecting cell membranes, tocotrienols can safeguard the composition of essential fats found in foods and supplements like omega-3s^{21,22}. Above all isomers, gamma- and delta-tocotrienol were found to have the greatest antioxidant properties^{23,24}. Their antioxidant attributes are determined by their ability to limit fat oxidation and combat radical oxygen species production. Interestingly, in vitamin E mixtures containing both tocotrienols and tocopherols, a higher concentration of alpha-tocopherol was associated with lower antioxidant activity²⁵.

In food production, limiting the oxidation of fats can greatly improve and retain their flavor and reinforce the reach of their health benefits. Increasing the fortification of polyunsaturated fatty acids is a major concern of the food industry. Historically, antioxidants like vitamin E (predominantly tocopherol) are applied to increase shelf life by preventing flavor degradation and preserving the nutritional quality and safety of the product. Studies have shown that the antioxidant effects of annatto tocotrienols in fish oil and infant formula were more potent in preservation than palm tocotrienol, alpha-tocopherol, delta-tocotrienol, and delta-tocopherol over 28 days²². Moreover, alpha-tocopherol and delta-tocopherol actually exhibited a prooxidant effect.

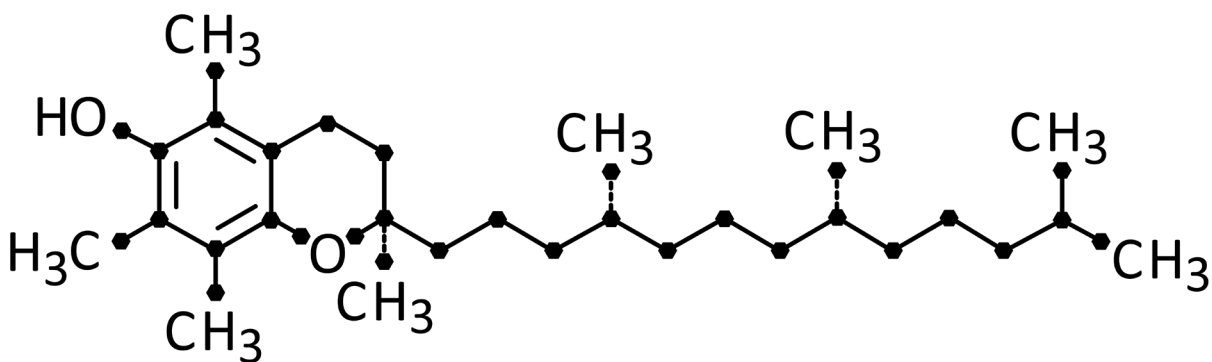
In a study exploring the effects of annatto tocotrienol-infused sunflower oil, fried tortilla chips had reduced rancid flavor from lipid oxidation that occurs at high temperatures²⁶. Furthermore, tocotrienols were absorbed into the chip and prevented the degradation of alpha-tocopherols. These results suggest that tocotrienols can be conveniently enriched into fried snack foods, while also enhancing their shelf life.

The Structure of Tocotrienol and Tocopherol

As mentioned, the sister compounds of vitamin E vary only slightly in molecular structure. Both contain a chromanol nucleus responsible for their potent antioxidant characteristics. Tocopherols contain a phytyl tail without double bonds. Tocotrienols, however, share the same chemical composition as tocopherols up until the tail, shifting their composition to a farnesylated tail which can impact cholesterol formation. The unique tail of tocotrienols allows them to slow down the synthesis of cholesterol by a negative feedback mechanism with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. This enzyme is essential for cholesterol formation and can be a critical element in managing cholesterol levels and the development of several cancers²⁷. This function remains elusive for tocopherols, which lack the necessary structures to regulate cholesterol synthesis²⁸.

Both tocopherols and tocotrienols contain four isomers named alpha, beta, gamma, and delta. The majority of tocotrienol benefits stem from the desmethyl tocotrienol group, referring to delta- and gamma-tocotrienols. The desmethyl tocotrienols include fewer methyl groups and maintain the highest potency, with the delta substituent being the most potent of all.

The majority of dietary vitamin E supplements contain primarily tocopherols due to the scarce selection of sources used for vitamin E extraction. These sources consist of common plant-based oils such as canola, soybean, and corn oils. Sources with high concentrations of tocotrienols can be found in less widely-used sources known for their high antioxidant values like palm and rice bran oils, as well as the annatto plant¹⁵⁻¹⁷. While tocopherols retain a strong antioxidant capacity, they lack the promising anticarcinogenic properties and the ability to regulate cholesterol synthesis.



Tocotrienol Mechanisms

In 1985, the Nobel prize was awarded to the Michael Brown and Joseph Goldstein research group for discovering the LDL cholesterol receptor and explaining how cholesterol is regulated through HMG-CoA reductase²⁹. The significance of this work was soon realized by the profound impact it had on cardiovascular disease research, improving the clinical understanding of hypercholesterolemia,

chronic inflammation, atherosclerosis, and non-alcoholic fatty liver disease.

One of the imperial benefits of tocotrienols is their molecular ability to interact with HMG-CoA reductase through a controlled degradation of the reductase protein^{30,31}. Gamma- and delta-tocotrienols stimulate this mechanism and further block the processing of the sterol regulatory element-binding protein (SREBP), a key component in triglyceride synthesis. This move prevents the synthesis of cholesterol and slows down the storage of lipids, aiding in diabetic and obesity outcomes. Based on their structure, tocopherols lack the ability to interact with cholesterol – unlike tocotrienols – and have even been shown to worsen circulating cholesterol levels³².

In fact, tocopherols are unable to degrade, downregulate, or block these processes²⁴ and retain only partial antioxidant potency in comparison to tocotrienols³³. This is in part due to the increased ability of tocotrienols to be absorbed into cell membranes from their desmethyl substituents. Additionally, gamma- and delta-tocotrienols have been found to be four times more effective at scavenging free radicals than any of the other vitamin E counterparts³³.

Tocotrienol Absorption and Bioavailability

As part of the vitamin E family, tocotrienols are fat-soluble and require the co-consumption of dietary lipids for proper absorption. During digestion, they form with other nutrients into emulsified particles called chylomicrons that enable them to be transported through the gut and into the bloodstream toward the liver. Afterward, the liver repackages them into small particles called lipoproteins that function to transport cholesterol and lipids to peripheral tissues. These lipoproteins act as “fat shuttles” to disperse tocotrienols and tocopherols as needed. In general, tocopherols remain attached to the lipoproteins and remain in circulation as they travel through the blood and back to the liver. Tocotrienols, however, have been shown to separate from their lipoprotein shuttles and deposit in several organs including the brain, spleen, lungs, kidneys, and heart^{34,35}, with particular preference to fat tissue, skin, and heart³⁶. This quality exemplifies their impressive bioavailability, assuring tocotrienols leave circulation and effectively penetrate into various tissues for optimal results.

Until recently, alpha-tocopherol was widely regarded as the most bioavailable form of vitamin E. The complexity of this issue stems from a unique protein called alpha-tocopherol transport protein, or ATP, which preferentially repackages alpha-tocopherol into the LDL cholesterol transport vehicle. This allows alpha-tocopherol to travel through circulation at much higher levels, conserved in the blood by its carrier. Tocotrienols, on the other hand, attach to HDL cholesterol, causing their levels to rapidly drop in the blood. This is due to their fast absorption into surrounding tissues before completing their hepatic circulation back to the liver^{37,38}.

Two studies were able to confirm the ability of annatto tocotrienols to rapidly enter the bloodstream through a clinical trial involving varying doses of the supplement. When taken with a meal, the tocotrienols were properly absorbed and peaked in the blood between 2-5 hours, expressing their uniquely effective uptake^{39,40}. Already, additional trials are underway to explore the extent of their bioavailability and impact in various other tissues, such as fat.

Tocopherol Interferes with Tocotrienol

As discussed, tocopherols fail to improve cholesterol levels and in some cases worsen them³². Studies have repeatedly shown that when co-administered, tocopherols interfere with the cholesterol-lowering action of tocotrienols, limiting their benefits⁴¹. Several studies suggest that anything more than a 15% content of tocopherols can prevent the cholesterol-lowering effects of tocotrienols^{32,42,43}. Various clinical studies confirm these guidelines, since high alpha-tocopherol concentrations likely contributed to their failure in reaching desired outcomes⁴⁴⁻⁴⁶. Supplements with higher concentrations of alpha-tocopherol were not found to lower the risk of cardiovascular events⁴⁴⁻⁴⁶. Moreover, tocopherols prevented the absorption and penetration of tocotrienols in several organs^{34,47,48}, interfering with tocotrienol benefits directly by:

- compromising cholesterol and triglyceride reduction^{32,49-51}
- lowering antioxidant capacity²⁵
- preventing anti-carcinogenic activity^{49,52,53}
- blocking tocotrienol absorption^{47,48}
- causing tocotrienol break-down⁵⁴
- preventing adipose storage of tocotrienols⁵⁰

Additionally, some studies have found tremendous negative effects of alpha-tocopherol supplementation when combined with certain pharmaceuticals. These studies have reported interaction and degradation of certain prescription drugs, including interfering with chemotherapy medications^{53,55,56}. Alpha-tocopherols have also been found to increase blood pressure and serum cholesterol levels, including oxidized LDL cholesterol^{32,51,57-60}. Moreover, the risk of certain ailments has been shown to heighten due to alpha-tocopherol supplementation, including prostate cancer and glioblastoma, as well as exacerbation of stroke injuries⁶⁰⁻⁶².



Cardiovascular Benefits of Annatto Tocotrienol

Previously, alpha-tocopherol had been widely studied for its efficacy in combating free radicals associated with aging and disease. Although the tocopherol family has been widely accepted for their healthy attributes, new and innovative research has highlighted the potential of tocotrienols as more dominant promoters of overall wellbeing. Already, studies have illuminated the numerous health benefits associated with tocotrienol supplementation, including natural boosts to bone, skin, metabolic, cellular, and even cardiovascular health.

Unfortunately, the lack of nutrition associated with the American diet has increased the prevalence of pharmaceutical strategies to combat growing incidences of disease. The rising trend of adverse health effects associated with these drugs has leading health specialists investigating opportunities to incorporate more natural remedies. Identifying a strong contender to more traditional methods has been at the forefront of therapeutic and preventative medicine for years. Recent studies have shown supplementation with high-quality tocotrienols may be the missing link in supporting improvements for ailments associated with the heart and blood vessels.



High Cholesterol

Approximately one in every three adults in the US has at one point been diagnosed with high cholesterol, increasing their risk of heart disease⁶³. Initial studies in the 1980s supported by the University of Wisconsin, Madison brought to light that tocotrienols were different from tocopherols: they were able to lower cholesterol⁶⁴. Building on this research, studies from the University of Texas sought to evaluate the mechanisms involved in tocotrienol's effect on cholesterol regulation³¹. It was shown that great variances between tocopherol and tocotrienol family members exist, noting both gamma- and delta-tocotrienol most effectively lowered LDL cholesterol levels up to 66%²⁸.

However, the ability to translate animal studies to clinical relevance continues to plague many research efforts. Thus, determining a human dose equivalent remains a primary focus in investigatory studies. In an effort to examine human relevancy, researchers isolated tocotrienols from the annatto plant and introduced them in varying doses to individuals with high cholesterol¹⁹. Results showed that after only 4 weeks, a dose of 250mg decreased total cholesterol by 15%, LDL cholesterol by 18%, and triglycerides by 14%. These studies suggest tocotrienol supplementation could effectively improve cholesterol even at low doses.

After only 4 weeks, a dose of 250mg tocotrienols decreased

Total Cholesterol



LDL Cholesterol



Triglycerides



Inflammation

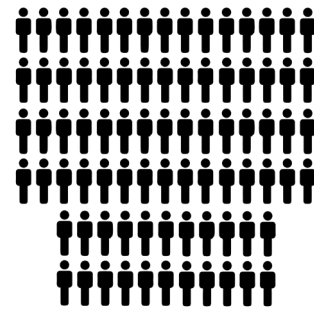
Cardiovascular disease is normally associated with high cholesterol due to its interaction with the arterial walls and plaque formation. Surprisingly, half of patients presenting with heart attacks have normal cholesterol levels. For these individuals, inflammation plays a role in furthering cardiovascular disease progression by recruiting white blood cells to stick to arterial walls and initiating plaque buildup. In addition to their potent antioxidant effects, tocotrienols have strong anti-inflammatory properties. New research has demonstrated the ability of alpha-, gamma-, and delta-tocotrienols to strongly inhibit the inflammatory response in mice, with delta-tocotrienol being the most effective⁶⁵⁻⁶⁷. In this context, tocotrienols can promote the function of certain cells that degrade damaged tissue and increase the immune system's ability to fight inflammation. At the same time, tocotrienols can induce a specific hormone that produces an anti-inflammatory steroid, directly blocking inflammatory pathways. Additional studies have found evidence that tocotrienols reduce inflammatory cell production and improve a number of biomarkers.

Clinical studies investigating this effect have supported claims of tocotrienol's impressive anti-inflammatory benefits. The most notable biomarker for inflammation is high-sensitivity C-reactive

protein (hsCRP). hsCRP has been clinically used to determine the presence and severity of inflammation in many patients across a multitude of conditions. Numerous studies have found remarkable reductions of this inflammatory marker by up to 40% in hypercholesterolemic patients using tocotrienol supplementation^{4,68,69}. Furthermore, when combined with other anti-inflammatory ingredients, tocotrienol exhibited a synergistic effect, rapidly decreasing inflammation. In a study combining annatto tocotrienol with niacin, vitamin B3, in elderly adults, significant reduction of CRP and γ -glutamyl-transferase (a predictor for non-fatal myocardial infarction and fatal coronary heart disease) was noted, while increasing the body's natural antioxidant capacity^{68,70}. This study also showed significant reduction in LDL cholesterol levels and improvement of dyslipidemia symptoms. Most notably, there were no adverse effects associated with the 6-week supplementation period, counter to many pharmaceutical methods.

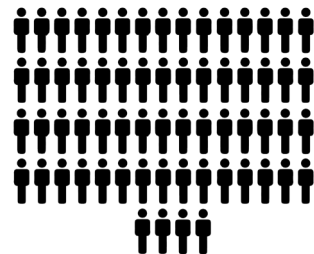
Risk Factors of Heart Disease

The development of heart disease is often associated with an individual's risk of high cholesterol, inflammation, and hypertension. Additionally, hypertension can be caused by the accrual of plaque and "adhesion" cells that restrict the lining of the arteries and block blood flow to the brain. Most traditional pharmaceutical methods address the symptoms of heart disease by alleviating the body's response to these factors. The risks associated with these medications are numerous and do little to counteract the actual cause. The use of natural bioagents instead focuses treatment at the core of the issue by supporting the body's natural defenses against the development of the condition. Resolving the source of the issue rather than alleviating the symptoms exemplifies how tocotrienols impart benefits for a healthy heart. Research has supported the use of tocotrienols to address many of these risk factors.



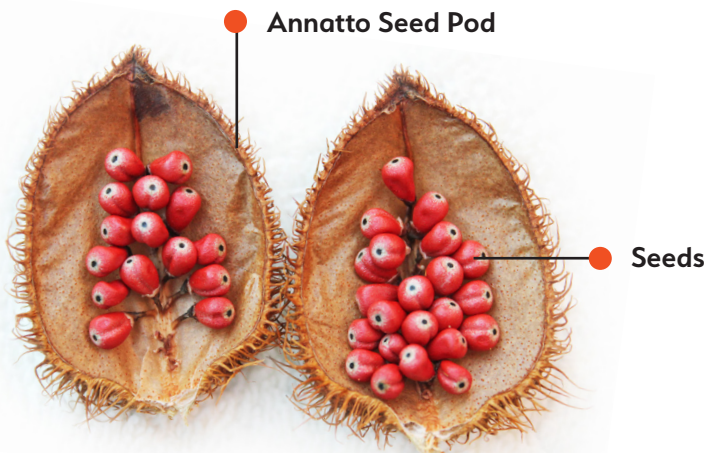
82 million+

American adults have hypertension



64 million+

American adults have pre-hypertension



Hypertension



Hypertension is known as a silent killer because a person can live years without any symptoms. Approximately 32% of American adults have hypertension, and 25% have pre-hypertension, supporting the necessity of blood pressure-lowering therapies⁷¹. Animal studies have shown that tocotrienols effectively decrease blood pressure, with the strongest evidence in support of gamma-tocotrienol^{72,73}. In human studies, tocotrienols have been shown to improve arterial function by reducing blood pressure as well^{74,75}.

Narrowing of the Arteries



Carotid arteriosclerosis is a condition defined by the narrowing of arteries in response to plaque buildup, reducing blood flow. In a 4-year study on patients with carotid arteriosclerosis, a 240 mg/day dosage of tocotrienol-tocopherol supplementation caused regression of the disease in 88% of the treatment group. The control group receiving a placebo deteriorated by 60% with very little improvement. Moreover, the patients treated with tocotrienol found that their total cholesterol decreased 14%, and LDL cholesterol fell 21% by the fourth year of the study⁷⁶.

Plaque Buildup



Before turning 35, two out of three Americans will have some degree of plaque buildup in their arteries⁷⁷. Some of the most profound evidence in support of the effects of tocotrienol on cardiovascular health comes from the plethora of studies evidencing a strong impact on plaque reduction. Comprehensive studies on animals investigated the impact of tocotrienol supplementation in comparison to tocopherol or non-supplementation. Several studies have established tocotrienols, especially delta- and gamma-tocotrienols, significantly reduced plaque scores, plaque stabilization and inflammation, three of the pillars responsible for overall atherosclerosis^{78,79}. Results to date indicate that animals on a westernized diet and given mixed tocotrienols had 60% lower serum cholesterol levels and reduced atherosclerotic lesions by 10-fold⁸⁰. Similar studies have supported these findings, determining tocotrienols as 30% more effective than tocopherols at reducing lesion size⁸¹.

Inflammation levels also promote the development of arterial adhesion, a process where cells aggregate and stick together, forming clotted substances and reducing arterial blood flow. Studies have shown that tocotrienols positively affect this cell adhesion process, preventing the steps involved in atherosclerosis and plaque formation^{82,83}. In examining the differences between tocotrienol and tocopherol therapies, delta- and gamma-tocotrienol were 60x and 30x more potent than alpha-tocopherol, respectively⁸⁴.

Metabolic Health Benefits of Annatto Tocotrienol

The obesity epidemic has affected the lives of more than two-thirds of Americans⁸⁵. With increased weight gain comes an accolade of metabolic disorders, often leading to more serious outcomes. Many of the diseases associated with obesity occur from unnatural changes in a person's metabolism, sometimes leading to dysregulated fasting blood glucose, systemic inflammation, and dyslipidemia.

The best way to reduce the risk of these ailments is by improving a person's health through diet and exercise. Many studies have shown the effectiveness of lifestyle changes. However, in more severe cases, determining faster ways to improve risk factors of metabolic disorders continues to be a top priority. Modern medicine has introduced numerous effective pharmaceutical agents, although many of these drugs have adverse health effects. Additionally, pharmaceuticals are employed to alleviate symptoms — whereas more natural remedies can actually help address the cause.

Health scientists have applied experimental studies to many of these natural agents to determine their therapeutic potential. Tocotrienols have been shown to be more powerful than their more infamous counterparts: tocopherols. As tocotrienols have been established to have a strong anti-inflammatory effect, research evaluating their impact on metabolic health has produced encouraging results for ailments such as metabolic syndrome, diabetes, dyslipidemia, and non-alcoholic fatty liver disease (NAFLD).

Dyslipidemia and Cholesterol

Metabolic syndrome – by way of diabetes – has also been linked to cardiovascular health, with statistics showing 70% of patients with diabetes die from cardiovascular events⁸⁶. As tocotrienols have been shown to improve cholesterol and lipid levels, they can then play a pivotal role in extending the lives of many diabetic and non-diabetic patients alike. Patients with diabetes prescribed LDL-lowering therapies normally experience many side effects, creating a need for alternative treatment. Several studies exploring the effects of tocotrienols have shown significant reductions in lipid and cholesterol levels. In one study, diabetic patients who supplemented with mixed-tocotrienols experienced decreased lipid levels by 23%, total cholesterol by 30%, and LDL-cholesterol by 42% within 60 days⁶.

Further yet, mice studies found that tocotrienols have the ability to promote fat oxidation and reduce cholesterol within the blood⁵. Burning fat stores and reducing cholesterol can help relieve symptoms of metabolic syndrome and diabetes and improve heart health. Surprisingly, these studies also determined that alpha-tocopherol did not show similar effects. In fact, when administered together, alpha-tocopherol prevented the benefits of tocotrienols. Similar to animal studies, alpha-tocopherol was shown to interfere with outcomes in humans when taken in conjunction with tocotrienols, negating any health benefits⁵. Clinical trials that removed alpha-tocopherol and supplemented tocotrienols alone were shown to drastically increase their effectiveness at lowering total cholesterol, LDL, and triglyceride levels between 15-20%¹⁹.

Non-Alcoholic Fatty Liver Disease

Many metabolic disorders promote high levels of inflammation that can induce cardiovascular and liver damage. The research supporting tocotrienols as a powerful natural anti-inflammatory agent suggest it can do more than help alleviate inflammation related to dyslipidemia. These studies determined that delta- and gamma-tocotrienol specifically have an ability to decrease the activity of the inflammatory cells responsible for the damaging effects of many chronic metabolic diseases^{87,88}. Non-alcoholic fatty liver disease (NAFLD) is a life-threatening condition caused by excessive fat deposits on the liver that inflame the organ and cause cirrhosis.

Delta-Tocotrienol Improves Fatty Liver in NAFLD Patients

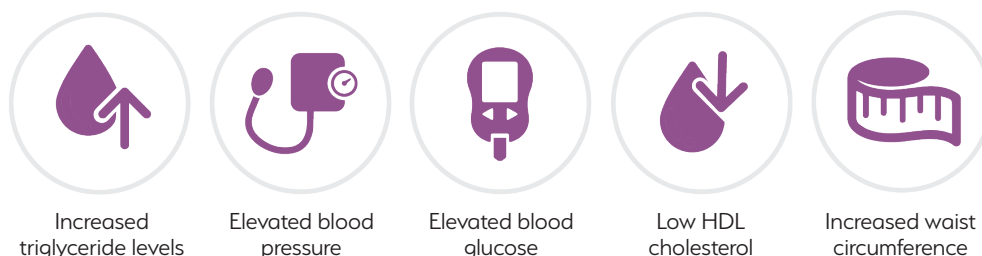
Study Parameters	Results
Weight Loss	9.7 lbs
BMI	30.7 ► 29.2
Weight Circumference	100.2 ► 97.98
Triglycerides	9.9% ▼
ALT & AST	15.6 ▼ & 14.6% ▼
hsCRP	18.0% ▼
FLI (steatosis)	11.1% ▼

The National Institute of Health has determined that NAFLD affects 30-40% of US adults, making it a serious concern⁸⁹. Many studies have confirmed tocotrienols' ability to relieve inflammation and burn fat stores, improving the prognosis for NAFLD patients.

In one animal study, the effects of tocotrienol therapy on obesity-related inflammation and fatty liver disease were evaluated⁹⁰. Over 14 weeks, obese mice showed incredible reductions to their circulating lipid levels, fasting blood glucose, and inflammation levels. Additionally, inflammation and fat accumulation within the liver decreased. Similar results can be seen in human clinical trials with patients at risk for NAFLD^{4,19}. One such study exhibited a 15-16% decrease in biomarkers for liver damage associated with the disease. Moreover, significant reductions in circulating lipid levels and inflammation were reported while using annatto tocotrienol in hypercholesterolemic subjects¹. Notably, patients in the tocotrienol-supplemented group lost an average of 9.7 pounds, improving their fatty liver index score by 11%.

Metabolic Syndrome and Diabetes

Metabolic syndrome, an ailment closely associated with obesity, is defined as a collection of risk factors that can increase a person's probability of developing heart disease, diabetes, or stroke, including^{91,92}:



As metabolic syndrome is closely related to the development of type 2 diabetes, therapies improving symptoms for one can often improve risk factors of the other. Patients with diabetes suffer from uncontrolled changes in their blood glucose that can have harmful effects on their immune system. According to the American Diabetes Association, 30 million Americans have diabetes with an additional 85 million Americans having been diagnosed with prediabetes, representing more than one-third of all Americans.

Animal studies experimenting with tocotrienols have reported substantial evidence of their anti-inflammatory and anti-diabetic properties in relation to metabolic syndrome. These studies found that tocotrienols were able to regulate metabolism by improving fasting blood glucose, an indicator of diabetes. Additionally, they had a profound effect on relieving inflammation levels in obese mice and reducing fat storage levels in such diseases associated with metabolic syndrome. In one study, researchers determined that several forms of tocotrienols were significantly more effective at reducing cardiac inflammation than alpha-tocopherol⁵. At a human dose equivalent of 800 mg/day, delta- and gamma-tocotrienol improved cardiovascular function and blood pressure levels, while delta-tocotrienol specifically helped normalize glucose levels associated with diabetes.

Excitingly, human studies have supported similar findings. Often, translatability of animal research must overcome many hurdles to find common ground among human clinical trials. However, several studies with tocotrienol therapies have shown significant reduction of symptoms in patients with metabolic syndrome and diabetes. For example, rice bran water (a tocotrienol supplement) was shown to reduce high blood glucose and boost insulin levels⁹³.

As many other phytonutrients like tocotrienols that are found in nature can have similar anti-inflammatory and anti-diabetic mechanisms, finding natural agents that can work together to increase their efficacy shows exciting promise in disease research. In some clinical trials, these bioactive ingredients formed complex synergistic relationships with tocotrienols, such as quercetin, resveratrol, and B-vitamins, increasing their effectiveness^{68,70}. Although this thrilling field of research is still in its early stages, new studies have continued to unveil the healing potential of mother nature.

Bone Health Benefits of Annatto Tocotrienol

Thanks to modern medicine, the average life expectancy has greatly increased over the last 100 years. However, as we witness longer life spans, our bodies have begun to exhibit more serious ailments associated with aging. For example, as we age our normal bone strengthening ability deteriorates, making it harder to maintain proper bone health. This initiates the development of osteoporosis, a silent bone disease that contributes heavily to elderly mortality in both women and men⁸. Osteoporotic fractures can do more harm than just limit the mobility of elderly adults; they can also drastically lower their quality of life and even cause death. Taking steps to improve bone health early on can slow down symptoms of bone frailty and lower the risk of fractures in aging adults. Typical methods to improve bone density include mineralization and drug therapies that come with a range of undesirable side effects. Consequently, the search for alternative therapies has sparked researchers to consider other compounds found in nature.

As a well-established natural antioxidant that can combat oxidative stress and inflammation, vitamin E has been used in many research studies. Despite the health benefits associated with alpha-tocopherol, tocotrienols were shown to be the competitive treatment alternative⁹⁴.

In osteoporotic studies, alpha-tocopherol supplements have shown limited potential in improving bone health⁹⁵. Recent efforts using tocotrienols instead have shown that they are incredible preventative agents. Their benefits stem from their profound ability to combat oxidative stress, strongly regulate inflammatory

pathways and support normal bone remodeling processes.

In preclinical studies, tocotrienols have been tested in a wide variety of bone loss models. The most frequently used models include those of estrogen deficiency⁹⁶⁻⁹⁸, representing women ages 45+ entering menopause, and those of testosterone deficiency^{7,8}, corresponding to men ages 70+ with age-related bone loss. Other preclinical models used nicotine to induce oxidative stress-related osteoporosis, as well as chronic steroid medications that carry bone loss as a severe complication of drug therapy⁹⁹. In all of these studies, tocotrienols were able to prevent bone loss by reducing high bone turnover rate, increasing bone formation (even at a genetic level), and maintaining bone strength. Combinations with lovastatin were also explored^{98,100}, and tocotrienol action was either additive or synergistic for bone support, indicating that it could be a valuable supplement for patients taking statins. One research group studied the direct application of tocotrienol with lovastatin to a fracture site, and found the combination to significantly improve fracture healing⁹⁸.



Reducing Inflammation and Oxidative Stress

Some specialists suggest the development of osteoporosis shares a strong relationship with the rising levels of systemic inflammation and free radicals associated with aging. As we age, the body's ability to heal itself slows down. Normally, cells go through a natural cycle of growth and decay, often resulting in cell replication to continue the line. This normal process deteriorates with age, increasing a cell's exposure to damaging oxidative stress and causing systemic inflammation. Chronic and systemic inflammation remain a hallmark for bone loss; thus, improving these parameters can have a profound effect on bone health. In animal studies, tocotrienols from annatto dramatically lowered inflammation and improved mechanical bone strength and bone cell health¹⁰¹. One of the primary ways inflammation affects bones is by interfering with bone remodeling processes and increasing bone resorption activity. Therefore, studies that reported the reduction of inflammatory signals from tocotrienol interventions successfully prevented bone loss⁹.

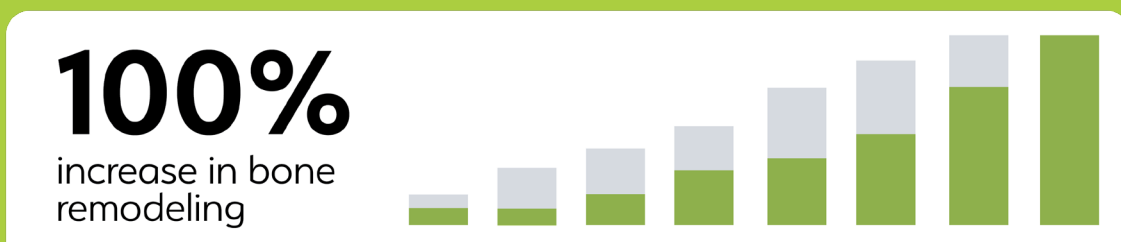


Promoting Bone Density

Regulating the effects of hormone activity related to serum calcium levels has proven to be an effective way of managing osteoporosis¹⁰². In cases of depleted vitamin D, levels of the parathyroid hormone rise and stimulate the release of calcium from the bones and into circulation. Removal of calcium leads to mineral gaps and decreases the stability of bones, leading to osteoporosis¹⁰³. Fortunately, some studies have determined a relationship between tocotrienol supplementation and bone mineral retention. In one animal study, tocotrienols not only restored bone calcium levels, but prevented the development of osteoporosis¹⁰⁴. Additionally, tocotrienols reduce the proliferation of specific bone cells that regulate resorption of bone¹⁶. By decreasing turnover rates, the bone retains its biomechanical strength and maintains its density. Furthermore, this research has extended to clinical trials that effectively suppressed bone resorption and expressed osteoprotective effects⁹.

In a 12-week study of 87 postmenopausal women, annatto tocotrienol was administered at dosages of 300 and 600 mg/day¹. Both doses led to decreased bone resorption and improved bone buildup. One bone biomarker, the BALP/NTX ratio, which is a measure of bone remodeling, increased 100% after 12 weeks. In addition, the RANKL/OPG ratio that indicates bone resorption is high was reduced 13-24% after 12 weeks, whereas this ratio increased 21-36% in the placebo group.

What causes tocotrienol to work so powerfully to protect the bone? Researchers believe that tocotrienol's ability to reduce oxidative stress, which dropped by an astonishing 49% in tocotrienol-supplemented individuals, is responsible for its osteoprotective effect¹⁰⁵.



In a 12-week study of 87 postmenopausal women, annatto tocotrienol led to decreased bone resorption and improved bone buildup.

Improving Calcium and Vitamin D Efficacy

The development of osteoporosis is often associated with decline of certain hormone stimulators that signal the growth and maintenance of bone. In aging adults, this decline is typical and well-evidenced among both genders¹⁰⁶. To counter these effects, health specialists recommend supplementing with vitamins and minerals to prevent bone degradation¹⁰⁷. In more serious circumstances, estrogen replacement therapy may additionally be prescribed. In one clinical trial, tocotrienols in conjunction with calcium and vitamin D supplementation were shown to recuperate and prevent bone loss, showing that supplementation with annatto tocotrienols may improve traditional staple therapies on the shelves at your local grocery store[†].



Annatto Tocotrienol's Potential Anticarcinogenic Effects

When the body is at its healthiest, our cells go through natural phases of growth and decay. These phases are part of the cell's cycle, which dictates when a cell grows, proliferates, and dies. In healthy cells, this cycle progresses naturally without any hitches; however, in cancer, this cycle becomes dysregulated, and the cell becomes stuck in its proliferation stage. As the cells continue to replicate, the potential for cancerous mutations increases. Without the cell's ability to shift into its programmed stage of death, mutations accrue and increase the likelihood of a cancerous tumor.

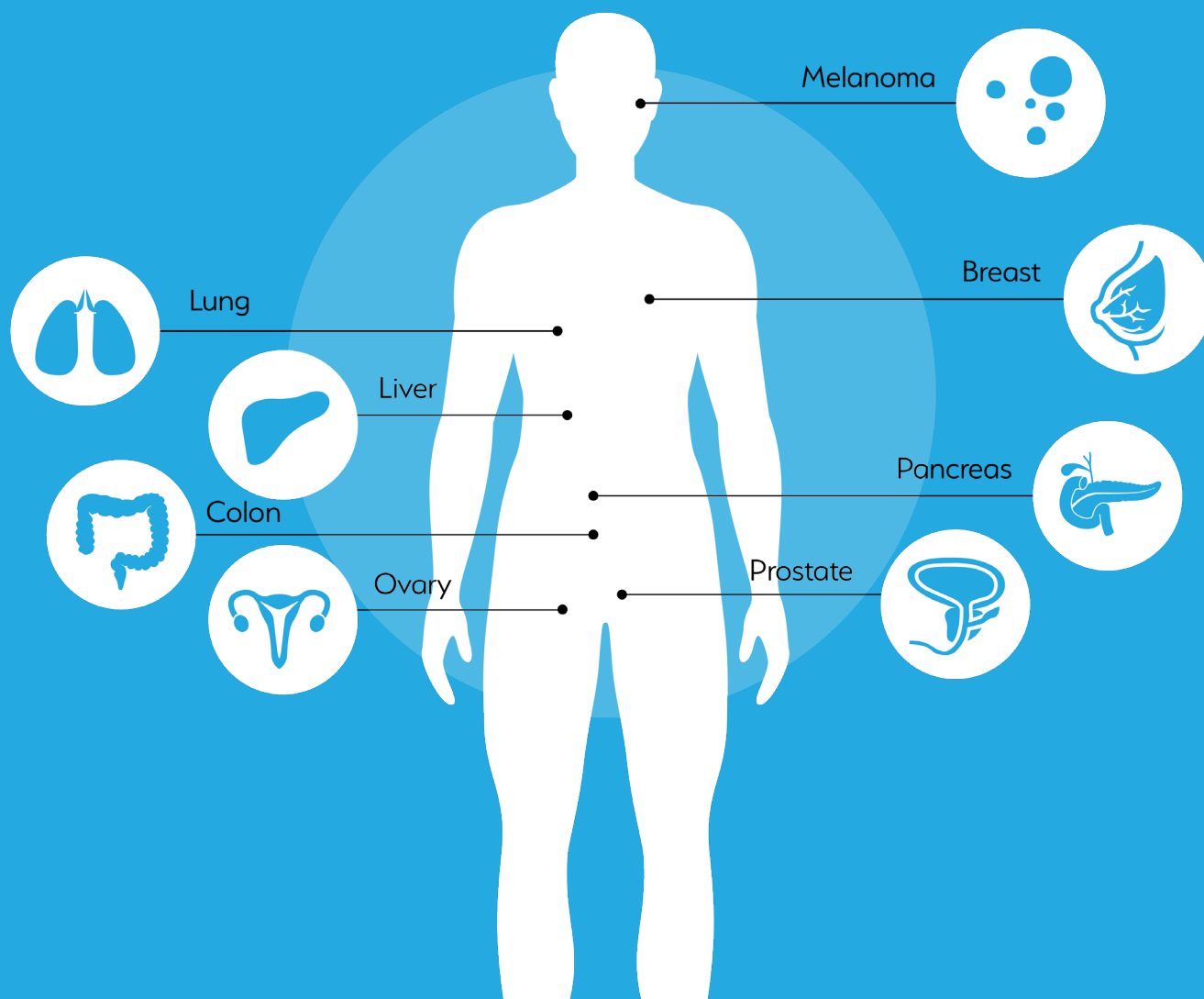
Researchers hypothesize that finding mechanisms to help recover the flow of this cycle in cancer cells may aid in the development of a solution. Many natural bioactive ingredients have been found to initiate this programmed cell death. Several studies determined that certain forms of vitamin E, such as tocotrienols, may help induce cancer cell death and help reduce cancer prevalence¹⁰⁸⁻¹¹⁰. Many of these studies found that alpha-tocopherol did not exhibit any anticarcinogenic potential and suggested tocotrienols were uniquely equipped. Tocotrienols, alone, retain the ability to return the cancer cell to its natural cycle and further improve prognosis through its antioxidant and anti-inflammatory properties^{111,112}.

A multitude of studies have linked tocotrienols to better outcomes in cancer. Scientific literature has shown tocotrienols to be effective modulators in many cancers, including breast, prostate, colon, lung, pancreas, liver, melanoma and ovary cancers. Moreover, tocotrienols specifically can prevent the development of cancer stem cells and decrease blood vessels that grow to support tumorigenesis, limiting the transport of nutrients essential for growth^{113,114}.

Tocotrienol's Effects on Eight Cancer Types

Breast

Breast cancer is the leading cancer among white and African American women, causing 41,000 deaths each year in the United States. In breast cancer studies, tocotrienols were able to penetrate cancer colonies and reduce populations, whereas alpha-tocopherol supplementation failed¹¹⁵. In fact, some studies have noted that tocopherol therapy may interfere with the beneficial effects of tocotrienols, leading some clinical trials to remove it completely from treatment protocols¹¹⁶. Additionally, large doses of tocotrienols were found safe when exposed to normal, healthy cells, suggesting limited negative effects outside of cancer treatment¹¹⁷.



Prostate

Prostate cancer is responsible for the deaths of nearly 30,000 men in the United States and is the second leading cause of cancer deaths in males. The progression of this cancer to its androgen hormone-independent form reduces survival and greatly limits treatment options¹¹⁸. Tocotrienols induced cancer cell death in multiple prostate cancer cell lines and slowed down the progression of cancer-related inflammation^{119,120}. These effects extended to androgen-independent prostate cancer lines and lowered prostate-specific antigen (PSA) levels, a marker for pancreatic cancer risk, by 40%¹¹⁸. Furthermore, tocotrienols were able to heighten cancer cell death in hypoxic conditions – a main feature that correlates with poor prognosis in cancer patients¹²¹.

Colon

Colorectal cancer is the third most prevalent cancer that affects both males and females. Tocotrienols have been found to suppress colon cancer in both animal and human studies. In colorectal cancer-induced mice, tocotrienols successfully prevented cancer development¹²². Additional studies support tocotrienol's ability to help kill cancer cells and repress their proliferation, even in hypoxic conditions¹²³. In patients with inflammatory bowel disease or ulcerative colitis, the risk of developing colorectal cancer increases 20-fold¹²⁴. However, tocotrienols have been shown to reduce inflammation and the development of fibrosis closely associated with this disease¹²⁵.

Lung

Lung cancer accounts for nearly as many breast, prostate, and colon cancer deaths combined and remains the leading cause of cancer deaths in America. More than 80% of these cases are considered non-small cell lung cancer, with a survival rate of just 15% after five years. Tocotrienols have been shown to reduce inflammation levels and reduce cell growth in lung cancer cells¹²⁶⁻¹²⁸. Further research on tocotrienol's ability to help battle cancer cells has shown that tocotrienols may benefit lung cancer patients by more than just their antioxidant properties, such as silencing certain oncogene mutations and by working in conjunction with chemotherapy to reduce treatment toxicity¹¹⁰.

Pancreas

Pancreatic cancer is a lethal and often silent killer, known for its difficulty to diagnose. Many diagnosed with pancreatic cancer are in the late stages of the disease and face a grim prognosis. Animal studies have found tocotrienols to be effective at killing pancreatic cancer cells and blocking malignant formation¹²⁹⁻¹³³. Clinical trials for early stage pancreatic cancer patients found up to 3,200mg of tocotrienols to be effective at halting cancer cell proliferation without adverse effects, though doses between 400-800mg have proven to be the most biologically effective treatment¹³⁴. These studies further establish the success of tocotrienol supplementation by their reasonable and attainable doses, lending to their credibility as being an effective cancer therapy.

Liver

Although rare, liver cancer is difficult to diagnose until later stages. One animal study found that tocotrienol therapy improved cancer outcomes when used in conjunction with epirubicin, a commonly used chemotherapy agent. This study determined tocotrienols reduced the toxicity of the drug and improved its anti-tumor activity¹³⁵.

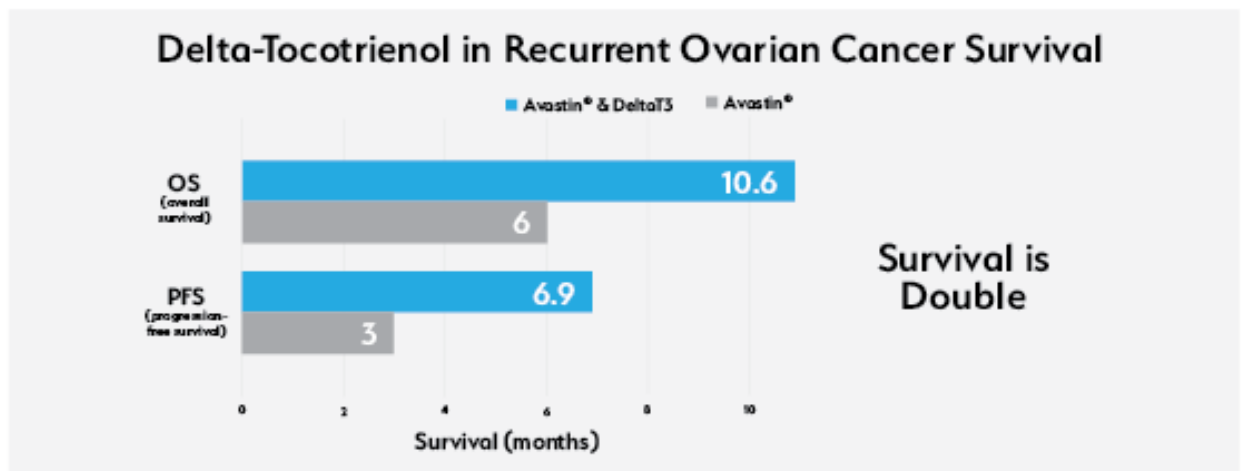
Melanoma

In cases of highly metastatic melanoma, tocotrienols were found to halt tumor development and

increase survival rates among mice¹³⁶. Other studies have noted drastic changes in tumor size and tumor progression in mice with tocotrienol supplementation¹⁴. In fact, without tocotrienols, the probability of these mice developing melanoma was increased three-fold.

Ovary

In the US, ovarian cancer is the 5th most common cause of cancer death among women. Advanced-stage ovarian cancer patients frequently experience a recurrence of the disease following primary treatment, and while further treatments are available, chemotherapy-resistance is common. Tocotrienols, especially delta, have shown advances for these patients. A study conducted at Denmark's Vejle Hospital revealed that a combination of delta-tocotrienol and bevacizumab had beneficial effects in chemotherapy for ovarian cancer, with a 70% disease stabilization and an increased survival rate that came very close to doubling¹².



Mechanisms of Tocotrienol Against Cancer Stem Cells

Cancer studies have revealed that a limited number of cancer cells act as stem cells that work to reproduce and sustain cancer development. Targeting cancer stem cells is a growing field of research with promising results in many cancer studies. Studies exploring tocotrienol supplementation with cancer stem cells has illuminated the profound impact tocotrienol supplementation may have. To date, gamma- and delta-tocotrienols specifically target cancer stem cells of the pancreas, breast, skin, and prostate.

Originally identified in leukemia, these cells work to increase tumorigenicity and display rapid proliferation and metastatic ability¹³⁷⁻¹³⁹. These cells have been identified in many forms of cancer including breast, prostate, and brain, and are highly resistant to treatment¹³⁹⁻¹⁴². Since cancer stem cells are able to survive standard chemotherapy and radiotherapy, the development of new intervention strategies is at the heart of intense research studies. Remarkably, tocotrienols were shown to suppress their growth in a number of trials^{121,131,143-145}.

Tocotrienol Mechanisms

According to research, tocotrienols can:



Prevent the development of cancer stem cells



Decrease blood vessels that grow to support tumorigenesis, limiting the transport of nutrients essential for growth



Slow the progression of cancer-related inflammation

Angiogenesis

One of the crucial steps in tumor growth is the development of blood vessels that transport nutrients essential for rapid growth. This is termed angiogenesis, and is a key factor in tumorigenesis¹⁰⁸. Tocotrienols have been found to downregulate factors that promote angiogenesis and prevent the growth and eventual metastasis of tumors¹¹⁴. Several studies have supported the results of tocotrienols in angiogenesis prevention, yet research has shown alpha-tocopherol does not share this effect. Tocotrienols alone contain the ability to cut off the nutrient-to-tumor lifeline^{49,113,114}.



Annatto Tocotrienol's Positive Effects on Skin Health

The skin is the largest organ of the body and acts as the first line of defense against pathogens and environmental toxins. Oftentimes, consumers turn to conventional skincare products to protect and nurture their skin. As new research continues to shed light on these ingredients, it's becoming increasingly apparent they may be doing more harm than good. Luckily, natural ingredients may offer safe, effective alternatives.

For over 50 years, vitamin E has been a staple in dermatological treatments. Many of these therapies taut the healing properties of vitamin E tocopherols, though few products have incorporated tocotrienols⁹⁴. Recently, the benefits of tocotrienols have received more attention as they possess antioxidant properties that differ from the properties of tocopherols⁹⁴. Additionally, support for tocotrienols has been found for their aptitude in skin care as studies have continued to expand on their protective nature. Research has shown a clear connection between tocotrienol supplementation and reduced signs of aging, decreased sun damage, and an improved ability to fight skin infection.



Signs of Aging and Sun Damage



Cosmetic companies across the globe recognize vitamin E for its anti-aging attributes, often in conjunction with its ability to reduce sun damage — as well as fight oxidative stress¹⁴⁶. Radical oxygen species have long been considered the culprit of aging mechanisms. These energy byproducts are created from normal metabolic processes that increase over time, causing cell death and tissue damage. Strong antioxidants can reduce and slow down this process by neutralizing the toxic effects that accrue over time. The unsaturated side chain that differentiates tocotrienols from tocopherols increases its ability to be absorbed into the skin, thus reducing its rate of oxidation^{146,147}. This improves its transport and saturation into skin cells over alpha-tocopherol.

In order to understand tocotrienols' power against sun damage, it's important to understand that the sun emits radiation through the production of UV rays^{147,148}. When these rays come in contact with our skin, oxidative damage can occur, increasing signs of aging and risk for skin ailments. At high enough doses, it can cause significant tissue damage due to toxic levels of radiation. This can manifest into a plethora of diseases and has been shown to increase risk of diabetes, cancer, and hypertension¹⁴⁹. Normally, this radiation penetrates into the skin, effecting and destroying the cells. Tocotrienols can counter radiation damage and exhibit photoprotective attributes¹⁵⁰. In animal studies, supplementation of tocotrienols before exposure to radiation protected mice against injury by reducing inflammation and improving the skin's ability to regenerate¹⁵¹. Because of their high permeability, topical applications of tocotrienols can be quickly absorbed and act as potent antioxidants, reducing damage^{94,152,153}. Tocotrienols have also been shown to have a natural SPF rating of 5.5, further reducing penetration of the sun's UV rays¹⁵⁴. In general, vitamin E has been shown to protect from UV rays and reduce instances of skin cancer and prolong the healthy plasticity of the skin^{155 154}. Healthier skin cells also retain their ability to act as the first line of defense against injury or infection¹⁵⁶.

Burns, MRSA, and Other Skin Injuries

In times of injury, the body must undergo a complex orchestra of healing mechanisms to promote cell regrowth. This activity increases the metabolic needs for vitamins and nutrients as the body works to heal itself. Studies have shown how nutrient deficiencies can slow down this process. Conversely, improving certain vitamins' availability can promote a faster wound repair. Vitamin E, specifically tocotrienols, may improve wound healing rates due to their anti-inflammatory and antioxidant traits. In clinical trials, vitamin E has been shown to improve healing from burns through the use

of topical creams that penetrate easily and increase healing responses¹⁵⁷. Moreover, further research with tocotrienols has specifically shown them to improve defense mechanisms against bacterial infections at times of skin injury.

Methicillin-resistant *Staphylococcus aureus*, or MRSA, is an example of a resilient bacterium that thrives on the skin and is extremely difficult to eradicate. MRSA can lead to problematic infections and is commonly found in hospitals and public settings. The treatment of MRSA with antibiotics over time has only strengthened the resilience of these bacteria, making them (and many infections like it) difficult to successfully manage through these means. However, treatment of MRSA with annatto tocotrienol in addition to antibiotics was found to reduce bacteria numbers 10x more than the antibiotic alone in an innovative animal study¹⁵. This study reveals the innate ability for tocotrienols to improve immune system functioning against bacteria so tocotrienols may help overcome the growing evolution of bacteria resistant to antibiotics. Additionally, tocotrienols have dramatic wound-healing effects by greatly reducing inflammation levels and improving cell regeneration¹⁵⁸. This lessens the exposure time of injured skin to bacteria and greatly diminishes risk of infection. By focusing on improving skin health and the skin's ability to heal, a person can reduce their risk of more serious ailments simply by applying a natural preventative therapy.



Tocotrienol is 50x more potent than tocopherol as an antioxidant

Tocotrienols benefit the skin through:



Reducing inflammation



Improving cellular regeneration



Combating oxidative stress



Exhibiting photoprotective attributes

Other Emerging Benefits of Annatto Tocotrienols

Tocotrienols have been established as the most potent antioxidant member of the vitamin E family, showcasing their efficacy in comparison to their tocopherol counterparts. Already, numerous studies have yielded insight into the health benefits of tocotrienols for a wide range of ailments, including bone diseases, metabolic syndrome and skin disorders. However, new areas of research are exploring the outskirts of less traditional fields of study with tocotrienol therapy.

Radiation Protection

In the past decade, novel research from the Armed Forces Radiobiology Research Institute (AFRRI, Bethesda, MD) has produced extensive research on tocotrienols as a countermeasure against radiation¹⁵⁹. This research has determined that delta- and gamma-tocotrienols are incredibly effective at reducing radical oxygen species (ROS) and reactive nitrogen species (RNS), primary sources of radiation-induced damage^{151,160,161}. Tocotrienols exhibit profound antioxidant properties, supporting the hypothesis that “strong antioxidants make strong radioprotectors¹⁵¹.”

Despite their strength, tocotrienols are unable to completely eradicate the effects of radiation, such as the severe damage to blood cell-producing bone marrow. However, tocotrienols display unmistakable



stimulatory effects toward blood cell health and production, restoring fresh blood supply damaged by ionizing radiation. In radiation experiments with mice, delta- and gamma-tocotrienols successfully regenerated blood cells by supporting white blood cell count. Additionally, studies have shown delta-tocotrienols were able to regenerate lymphocytes. The ability for tocotrienols to restore bone marrow health has also been evident; in studies, treatment 24 hours prior to radiation exposure proved to be more effective than post-radiation treatment^{160,161}.

Radiation damage can also cause severe internal injury to the digestive system. Tocotrienols were found to reduce gastrointestinal damage and improve metabolic bioavailability of antioxidants during radiation treatment in non-human primates^{162,163}.

Eye Health

Vitamin E has been known as a beneficial nutrient for eye health since the first studies of age-related eye deterioration. Since this time, vitamin E has become a staple in eye-health supplement formulas, though few have included the use of tocotrienols. In fact, the majority of studies focused predominantly on the use of alpha-tocopherol alone. With the rising evidence of tocotrienol's efficacy, and the astounding interference of tocopherols, tocotrienol therapy deserves a closer look. Studies have determined the development of central vision loss and eye degeneration may have its roots in the growth and damage of blood vessels in the retina. Tocotrienols display potent anti-angiogenic properties, reducing the spread of vasculature through the eye and reducing the leaking of blood vessels^{164,165}.

In cases of glaucoma, a condition affecting 3 million Americans each year, increased ocular pressure within the eyes threatens many patients with the risk of blindness. When surgical procedures are considered, the potential of harmful scarring can reduce the effectiveness of the healing process. Recent studies have determined tocotrienols may reduce this scarring and even combat cataract development^{166,167}.

In a Malaysian study, annatto tocotrienol was able to delay the onset and progression of cataracts within rats by reducing oxidative stress¹⁶⁸. Additional studies investigating the development of cataracts in diabetic rats found that annatto tocotrienol halted the progression of cataracts, compared to control rats whose cataract development worsened to stage 3 and stage 4¹⁶⁹.



Other Budding Topics

A handful of studies are exploring new uses for tocotrienols. Tocotrienols are currently under investigation for treating trauma-induced stroke, reducing the side effects of diabetic neuropathy and autonomic nerve disorders, as well as counteracting gastric injury¹⁷⁰⁻¹⁷⁵.

Conclusion

The volume of research surrounding vitamin E has proven how valuable of a nutrient this antioxidant is. However, a new paradigm has challenged the perspective of alpha-tocopherol as the prime vitamin E antioxidant. With tocotrienols exhibiting greater radical scavenging and anti-inflammatory benefits, and given the vast diversity of clinical applications of tocotrienols, the decision for the daily use of annatto tocotrienol is more than a viable option, it is a compelling one. Only annatto tocotrienols have been efficiently and delicately extracted to be free of any potential tocopherol interactions. With over 170 scientific references in this review alone, this ingredient has shown incredible promise for a variety of chronic health conditions. The addition of this simple plant extract - safely used as a food colorant for hundreds of years - has only begun to showcase its many healing properties. Only the innovative use of annatto tocotrienol has the possibility to lead the forefront of tocotrienol supplementation, vitamin E research, and clinical efficacy.



References

1. Evans HM, Bishop KS. On the Existence of a Hitherto Unrecognized Dietary Factor Essential for Reproduction. *Science*. Dec 8 1922;56(1458):650-651.
2. Qureshi AA, Khan DA, Mahjabeen W, Qureshi N. Dose-dependent modulation of lipid parameters, cytokines, and RNA by delta-tocotrienol in hypercholesterolemic subjects restricted to AHA Step-1 diet. *Brit J of Med & Med Res*. 2015;6(4):351-366.
3. Qureshi AA, Khan DA, Mahjabeen W, Trias AM, Silswal N, Qureshi N. Impact of delta-tocotrienol on inflammatory biomarkers and oxidative stress in hypercholesterolemic subjects. *Clin. Exp. Cardiology*. 2015;6(4):1000367.
4. Pervez MA, Khan DA, Ijaz A, Khan S. Effects of Delta-tocotrienol Supplementation on Liver Enzymes, Inflammation, Oxidative stress and Hepatic Steatosis in Patients with Nonalcoholic Fatty Liver Disease. *The Turkish journal of gastroenterology : the official journal of Turkish Society of Gastroenterology*. Mar 2018;29(2):170-176.
5. Wong WY, Ward LC, Fong CW, Yap WN, Brown L. Anti-inflammatory gamma- and delta-tocotrienols improve cardiovascular, liver and metabolic function in diet-induced obese rats. *European journal of nutrition*. Feb 2017;56(1):133-150.
6. Baliarsingh S, Beg ZH, Ahmad J. The therapeutic impacts of tocotrienols in type 2 diabetic patients with hyperlipidemia. *Atherosclerosis*. Oct 2005;182(2):367-374.
7. Chin KY, Abdul-Majeed S, Fozi NF, Ima-Nirwana S. Annatto tocotrienol improves indices of bone static histomorphometry in osteoporosis due to testosterone deficiency in rats. *Nutrients*. Nov 10 2014;6(11):4974-4983.
8. Chin KY, Gengatharan D, Mohd Nasru FS, et al. The Effects of Annatto Tocotrienol on Bone Biomechanical Strength and Bone Calcium Content in an Animal Model of Osteoporosis Due to Testosterone Deficiency. *Nutrients*. Dec 14 2016;8(12).
9. Shen CL, Klein A, Chin KY, et al. Tocotrienols for bone health: a translational approach. *Annals of the New York Academy of Sciences*. Aug 2017;1401(1):150-165.
10. Shen CL, Yang S, Tomison MD, Romero AW, Felton CK, Mo H. Tocotrienol supplementation suppressed bone resorption and oxidative stress in postmenopausal osteopenic women: a 12-week randomized double-blinded placebo-controlled trial. *Osteoporos Int*. Jan 12 2018.
11. Springett GM, Husain K, Neuger A, et al. A Phase I Safety, Pharmacokinetic, and Pharmacodynamic Presurgical Trial of Vitamin E delta-tocotrienol in Patients with Pancreatic Ductal Neoplasia. *EBioMedicine*. Dec 2015;2(12):1987-1995.
12. Thomsen CB, Andersen RF, Steffensen KD, Adimi P, Jakobsen A. Delta tocotrienol in recurrent ovarian cancer. A phase II trial. *Pharmacological research*. Mar 2019;141:392-396.
13. Marzagalli M, Moretti RM, Messi E, et al. Targeting melanoma stem cells with the Vitamin E derivative delta-tocotrienol. *Scientific reports*. Jan 12 2018;8(1):587.
14. Montagnani Marelli M, Marzagalli M, Moretti RM, et al. Vitamin E delta-tocotrienol triggers endoplasmic reticulum stress-mediated apoptosis in human melanoma cells. *Scientific reports*. Jul 27 2016;6:30502.
15. Pierpaoli E, Orlando F, Cironi O, Simonetti O, Giacometti A, Provinciali M. Supplementation with tocotrienols from Bixa orellana improves the in vivo efficacy of daptomycin against methicillin-resistant *Staphylococcus aureus* in a mouse model of infected wound. *Phytomedicine : international journal of phytotherapy and phytopharmacology*. Dec 1 2017;36:50-53.
16. Pennock JF, Hemming FW, Kerr JD. A reassessment of tocopherol in chemistry. *Biochemical and biophysical research communications*. Nov 30 1964;17(5):542-548.
17. Olcott HS, Emerson OH. Antioxidants and the autoxidation of fats. IX. The antioxidant properties of the tocopherols. *J. Am. Chem. Soc.*. 1937;59(6):1008-1009.
18. Shahidi F, de Camargo AC. Tocopherols and Tocotrienols in Common and Emerging Dietary Sources: Occurrence, Applications, and Health Benefits. *International journal of molecular sciences*. Oct 20 2016;17(10).
19. Qureshi AA, Khan DA, Mahjabeen W, Qureshi N. Dose-dependent Modulation of Lipid Parameters, Cytokines and RNA by Ω -tocotrienol in Hypercholesterolemic Subjects Restricted to AHA Step-1 Diet. *British Journal of Medicine & Medical Research*. 2015;6(4):351-366.
20. Yap SP, Yuen KH, Wong JW. Pharmacokinetics and bioavailability of alpha-, gamma- and delta-tocotrienols under different food status. *The Journal of pharmacy and pharmacology*. Jan 2001;53(1):67-71.
21. Serbinova E, Kagan V, Han D, Packer L. Free radical recycling and intramembrane mobility in the antioxidant properties of alpha-tocopherol and alpha-tocotrienol. *Free radical biology & medicine*. 1991;10(5):263-275.
22. Zou L, Akoh CC. Antioxidant activities of annatto and palm tocotrienol-rich fractions in fish oil and structured lipid-based infant formula emulsion. *Food chemistry*. Feb 1 2015;168:504-511.
23. Palozza P, Verdecchia S, Avanzi L, et al. Comparative antioxidant activity of tocotrienols and the novel chromanyl-polyisoprenyl molecule FeAox-6 in isolated membranes and intact cells. *Molecular and cellular biochemistry*. Jul 2006;287(1-2):21-32.
24. Muller L, Theile K, Bohm V. In vitro antioxidant activity of tocopherols and tocotrienols and comparison of vitamin E concentration and lipophilic antioxidant capacity in human plasma. *Molecular nutrition & food research*. May 2010;54(5):731-742.
25. Qureshi AA, Mo H, Packer L, Peterson DM. Isolation and identification of novel tocotrienols from rice bran with hypocholesterolemic, antioxidant, and antitumor properties. *Journal of agricultural and food chemistry*. Aug 2000;48(8):3130-3140.
26. Winkler-Moser JK, Bakota EL, Hwang HS. Stability and Antioxidant Activity of Annatto (Bixa orellana L.) Tocotrienols During Frying and in Fried Tortilla Chips. *Journal of food science*. Feb 2018;83(2):266-274.

27. Mo H, Elson CE. Studies of the isoprenoid-mediated inhibition of mevalonate synthesis applied to cancer chemotherapy and chemoprevention. *Experimental biology and medicine*. Jul 2004;229(7):567-585.
28. Yu SG, Thomas AM, Gapor A, Tan B, Qureshi N, Qureshi AA. Dose-response impact of various tocotrienols on serum lipid parameters in 5-week-old female chickens. *Lipids*. May 2006;41(5):453-461.
29. Nobel Prize. http://nobelprize.org/nobel_prizes/medicine/laureates/1985/. 2008; Available from: http://nobelprize.org/nobel_prizes/medicine/laureates/1985/.
30. Pearce BC, Parker RA, Deason ME, Qureshi AA, Wright JJ. Hypcholesterolemic activity of synthetic and natural tocotrienols. *Journal of medicinal chemistry*. Oct 2 1992;35(20):3595-3606.
31. Song BL, DeBose-Boyd RA. Insig-dependent ubiquitination and degradation of 3-hydroxy-3-methylglutaryl coenzyme A reductase stimulated by delta- and gamma-tocotrienols. *The Journal of biological chemistry*. Sep 1 2006;281(35):25054-25061.
32. Qureshi AA, Pearce BC, Nor RM, Gapor A, Peterson DM, Elson CE. Dietary alpha-tocopherol attenuates the impact of gamma-tocotrienol on hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase activity in chickens. *The Journal of nutrition*. Feb 1996;126(2):389-394.
33. Kim HJ, Min DB. Effects, quenching mechanisms, and kinetics of alpha-, beta-, gamma-, and delta-tocotrienol on chlorophyll photosynthesized oxidation of lard IFT. 2007.
34. Khanna S, Patel V, Rink C, Roy S, Sen CK. Delivery of orally supplemented alpha-tocotrienol to vital organs of rats and tocopherol-transport protein deficient mice. *Free radical biology & medicine*. Nov 15 2005;39(10):1310-1319.
35. Pearson CK, Barnes MM. The absorption and distribution of the naturally occurring tocochromanols in the rat. *The British journal of nutrition*. Jun 1970;24(2):581-587.
36. Patel V, Rink C, Gordillo GM, et al. Oral tocotrienols are transported to human tissues and delay the progression of the model for end-stage liver disease score in patients. *The Journal of nutrition*. Mar 2012;142(3):513-519.
37. Anwar K, Iqbal J, Hussain MM. Mechanisms involved in vitamin E transport by primary enterocytes and in vivo absorption. *Journal of lipid research*. Sep 2007;48(9):2028-2038.
38. Fairus S, Nor RM, Cheng HM, Sundram K. Alpha-tocotrienol is the most abundant tocotrienol isomer circulated in plasma and lipoproteins after postprandial tocotrienol-rich vitamin E supplementation. *Nutrition journal*. Jan 17 2012;11:5.
39. Qureshi AA, Khan DA, Silswal N, Saleem S, Qureshi N. Evaluation of Pharmacokinetics, and Bioavailability of Higher Doses of Tocotrienols in Healthy Fed Humans. *Journal of clinical & experimental cardiology*. Apr 2016;7(4).
40. Qureshi AA, Khan DA, Saleem S, et al. Pharmacokinetics and bioavailability of annatto delta-tocotrienol in healthy fed subjects. *Journal of clinical & experimental cardiology*. 2015;6:411.
41. Qureshi AA, Sami SA, Salser WA, Khan FA. Synergistic effect of tocotrienol-rich fraction (TRF(25)) of rice bran and lovastatin on lipid parameters in hypercholesterolemic humans. *The Journal of nutritional biochemistry*. Jun 2001;12(6):318-329.
42. Qureshi AA, Sami SA, Salser WA, Khan FA. Dose-dependent suppression of serum cholesterol by tocotrienol-rich fraction (TRF25) of rice bran in hypercholesterolemic humans. *Atherosclerosis*. Mar 2002;161(1):199-207.
43. Trias AM, Tan B. *Alpha-Tocopherol: A Detriment to Tocotrienol Benefits, in Tocotrienols: Vitamin E Beyond Tocopherols*,. 2nd ed. Boca Raton: CRC Press; 2013.
44. Mensink RP, van Houwelingen AC, Kromhout D, Hornstra G. A vitamin E concentrate rich in tocotrienols had no effect on serum lipids, lipoproteins, or platelet function in men with mildly elevated serum lipid concentrations. *The American journal of clinical nutrition*. Feb 1999;69(2):213-219.
45. Heng KS, Hejar AR, Stanslas J, Ooi JF. Potential of mixed tocotrienol supplementation to reduce cholesterol and cytokines level in adults with metabolic syndrome. *Mal J Nutr*. 2015;22(2):231-243.
46. Mustad VA, Smith CA, Ruey PP, Edens NK, DeMichele SJ. Supplementation with 3 compositionally different tocotrienol supplements does not improve cardiovascular disease risk factors in men and women with hypercholesterolemia. *The American journal of clinical nutrition*. Dec 2002;76(6):1237-1243.
47. Ikeda S, Tohyama T, Yoshimura H, Hamamura K, Abe K, Yamashita K. Dietary alpha-tocopherol decreases alpha-tocotrienol but not gamma-tocotrienol concentration in rats. *The Journal of nutrition*. Feb 2003;133(2):428-434.
48. Uchida T, Nomura S, Ichikawa T, Abe C, Ikeda S. Tissue distribution of vitamin E metabolites in rats after oral administration of tocopherol or tocotrienol. *Journal of nutritional science and vitaminology*. 2011;57(5):326-332.
49. Shibata A, Nakagawa K, Tsuduki T, Miyazawa T. alpha-Tocopherol suppresses antiangiogenic effect of delta-tocotrienol in human umbilical vein endothelial cells. *The Journal of nutritional biochemistry*. Apr 2015;26(4):345-350.
50. Shibata A, Kawakami Y, Kimura T, Miyazawa T, Nakagawa K. alpha-Tocopherol Attenuates the Triglyceride- and Cholesterol-Lowering Effects of Rice Bran Tocotrienol in Rats Fed a Western Diet. *Journal of agricultural and food chemistry*. Jul 6 2016;64(26):5361-5366.
51. Khor HT, Ng TT. Effects of administration of alpha-tocopherol and tocotrienols on serum lipids and liver HMG CoA reductase activity. *International journal of food sciences and nutrition*. 2000;51 Suppl:S3-11.
52. Shibata A, Nakagawa K, Sookwong P, Tsuduki T, Asai A, Miyazawa T. alpha-Tocopherol attenuates the cytotoxic effect of delta-tocotrienol in human colorectal adenocarcinoma cells. *Biochemical and biophysical research communications*. Jun 25 2010;397(2):214-219.
53. Guthrie N, Gapor A, Chambers AF, Carroll KK. Inhibition of proliferation of estrogen receptor-negative MDA-MB-435 and -positive MCF-7 human breast cancer cells by palm oil tocotrienols and tamoxifen, alone and in combination. *The Journal of nutrition*. Mar 1997;127(3):544S-548S.
54. Sontag TJ, Parker RS. Influence of major structural features of tocopherols and tocotrienols on their omega-oxidation by tocopherol-omega-hydroxylase. *Journal of lipid research*. May 2007;48(5):1090-1098.
55. Uchihara Y, Kidokoro T, Tago K, Mashino T, Tamura H, Funakoshi-Tago M. A major component of vitamin E, alpha-tocopherol

- inhibits the anti-tumor activity of crizotinib against cells transformed by EML4-ALK. *European journal of pharmacology*. Apr 15 2018;825:1-9.
56. Khor HT, Chirng DY, Ong KK. Tocotrienols inhibit HMG-CoA reductase activity in the guinea pig *Nutr. Res.* 1995(15):537-544.
 57. Miyamoto K, Shiozaki M, Shibata M, Koike M, Uchiyama Y, Gotow T. Very-high-dose alpha-tocopherol supplementation increases blood pressure and causes possible adverse central nervous system effects in stroke-prone spontaneously hypertensive rats. *Journal of neuroscience research*. Feb 2009;87(2):556-566.
 58. Li Z, Evans C, Cade J. Dietary vitamin E intake and blood pressure in UK adolescents: a longitudinal study. Paper presented at: American Society for Nutrition Annual Meeting; Boston.
 59. Carr AC, Zhu BZ, Frei B. Potential antiatherogenic mechanisms of ascorbate (vitamin C) and alpha-tocopherol (vitamin E). *Circulation research*. Sep 1 2000;87(5):349-354.
 60. Khanna S, Heigel M, Weist J, et al. Excessive alpha-tocopherol exacerbates microglial activation and brain injury caused by acute ischemic stroke. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*. Mar 2015;29(3):828-836.
 61. Klein EA, Thompson IM, Jr., Tangen CM, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *Jama*. Oct 12 2011;306(14):1549-1556.
 62. Bjorkblom B, Wibom C, Jonsson P, et al. Metabolomic screening of pre-diagnostic serum samples identifies association between alpha- and gamma-tocopherols and glioblastoma risk. *Oncotarget*. Jun 14 2016;7(24):37043-37053.
 63. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation*. Mar 7 2017;135(10):e146-e603.
 64. Qureshi AA, Burger WC, Peterson DM, Elson CE. The structure of an inhibitor of cholesterol biosynthesis isolated from barley. *The Journal of biological chemistry*. Aug 15 1986;261(23):10544-10550.
 65. Qureshi AA, Reis JC, Papasian CJ, Morrison DC, Qureshi N. Tocotrienols inhibit lipopolysaccharide-induced pro-inflammatory cytokines in macrophages of female mice. *Lipids in health and disease*. Dec 16 2010;9:143.
 66. Qureshi AA, Tan X, Reis JC, et al. Suppression of nitric oxide induction and pro-inflammatory cytokines by novel proteasome inhibitors in various experimental models. *Lipids in health and disease*. Oct 12 2011;10:177.
 67. Yam ML, Abdul Hafid SR, Cheng HM, Nesaretnam K. Tocotrienols suppress proinflammatory markers and cyclooxygenase-2 expression in RAW264.7 macrophages. *Lipids*. Sep 2009;44(9):787-797.
 68. Qureshi AA, Khan DA, Mahjabeen W, Papasian CJ, Qureshi N. Nutritional Supplement-5 with a Combination of Proteasome Inhibitors (Resveratrol, Quercetin, delta-Tocotrienol) Modulate Age-Associated Biomarkers and Cardiovascular Lipid Parameters in Human Subjects. *Journal of clinical & experimental cardiology*. Mar 2 2013;4(3).
 69. Qureshi AA, Khan DA, Mahjabeen W, Trias AM. Impact of delta-tocotrienol on inflammatory biomarkers and oxidative stress in hypercholesterolemic subjects *Journal of clinical & experimental cardiology*. 2015;6(4):10000367.
 70. Qureshi AA, Khan DA, Mahjabeen W, Papasian CJ, Qureshi N. Suppression of Nitric Oxide Production and Cardiovascular Risk Factors in Healthy Seniors and Hypercholesterolemic Subjects by a Combination of Polyphenols and Vitamins. *Journal of clinical & experimental cardiology*. Jun 7 2012;55:8.
 71. Nwankwo T, Yoon SS, Burt V, Gu Q. Hypertension among adults in the United States: National Health and Nutrition Examination Survey, 2011-2012. *NCHS data brief*. Oct 2013(133):1-8.
 72. Newaz MA, Nawal NN. Effect of gamma-tocotrienol on blood pressure, lipid peroxidation and total antioxidant status in spontaneously hypertensive rats (SHR). *Clinical and experimental hypertension*. Nov 1999;21(8):1297-1313.
 73. Newaz MA, Yousefipour Z, Nawal N, Adeeb N. Nitric oxide synthase activity in blood vessels of spontaneously hypertensive rats: antioxidant protection by gamma-tocotrienol. *Journal of physiology and pharmacology : an official journal of the Polish Physiological Society*. Sep 2003;54(3):319-327.
 74. Rasool AH, Rahman AR, Yuen KH, Wong AR. Arterial compliance and vitamin E blood levels with a self emulsifying preparation of tocotrienol rich vitamin E. *Archives of pharmacol research*. Sep 2008;31(9):1212-1217.
 75. Rasool AH, Yuen KH, Yusoff K, Wong AR, Rahman AR. Dose dependent elevation of plasma tocotrienol levels and its effect on arterial compliance, plasma total antioxidant status, and lipid profile in healthy humans supplemented with tocotrienol rich vitamin E. *Journal of nutritional science and vitaminology*. Dec 2006;52(6):473-478.
 76. Kooyenga DKea. Antioxidants modulate the course of carotid atherosclerosis: A four year report In: Editors KNaLP, ed. *Micronutrients and Health* Illinois AOCS Press 2001:366-375.
 77. Strong JP, Malcom GT, McMahan CA, et al. Prevalence and extent of atherosclerosis in adolescents and young adults: implications for prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study. *Jama*. Feb 24 1999;281(8):727-735.
 78. Muid S, Froemming GR, Rahman T, Ali AM, Nawawi HM. Delta- and gamma-tocotrienol isomers are potent in inhibiting inflammation and endothelial activation in stimulated human endothelial cells. *Food & nutrition research*. 2016;60:31526.
 79. Rahman TA, Hassim NF, Zulkafli N, Muid S, Kornain NK, Nawawi H. Atheroprotective effects of pure tocotrienol supplementation in the treatment of rabbits with experimentally induced early and established atherosclerosis. *Food & nutrition research*. 2016;60:31525.
 80. Black TM, Wang P, Maeda N, Coleman RA. Palm tocotrienols protect ApoE +/- mice from diet-induced atheroma formation. *The Journal of nutrition*. Oct 2000;130(10):2420-2426.
 81. Qureshi AA, Salser WA, Parmar R, Emeson EE. Novel tocotrienols of rice bran inhibit atherosclerotic lesions in C57BL/6 ApoE-deficient mice. *The Journal of nutrition*. Oct 2001;131(10):2606-2618.
 82. Chao JT, Gapor A, Theriault A. Inhibitory effect of delta-tocotrienol, an HMG CoA reductase inhibitor, on monocyte-endothelial cell adhesion. *Journal of nutritional science and vitaminology*. Oct 2002;48(5):332-337.

83. Theriault A, Chao JT, Gapor A. Tocotrienol is the most effective vitamin E for reducing endothelial expression of adhesion molecules and adhesion to monocytes. *Atherosclerosis*. Jan 2002;160(1):21-30.
84. Naito Y, Shimozawa M, Kuroda M, et al. Tocotrienols reduce 25-hydroxycholesterol-induced monocyte-endothelial cell interaction by inhibiting the surface expression of adhesion molecules. *Atherosclerosis*. May 2005;180(1):19-25.
85. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in Obesity Among Adults in the United States, 2005 to 2014. *Jama*. Jun 7 2016;315(21):2284-2291.
86. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States. 2011.
87. Kim Y, Gromovsky AD, Brown JM, Chung S. Gamma-tocotrienol attenuates the aberrant lipid mediator production in NLRP3 inflammasome-stimulated macrophages. *The Journal of nutritional biochemistry*. Aug 2018;58:169-177.
88. Buckner T, Fan R, Kim Y, Kim J, Chung S. Annatto Tocotrienol Attenuates NLRP3 Inflammasome Activation in Macrophages. *Current developments in nutrition*. Jun 2017;1(6):e000760.
89. Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology*. Feb 2006;43(2 Suppl 1):S99-S112.
90. Allen L, Ramalingam L, Menikdiwela K, et al. Effects of delta-tocotrienol on obesity-related adipocyte hypertrophy, inflammation and hepatic steatosis in high-fat-fed mice. *The Journal of nutritional biochemistry*. Oct 2017;48:128-137.
91. Expert Panel on the Detection E, and Treatment of High Blood Cholesterol in Adults. *Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)*. JAMA2001.
92. WorldHealthOrganization. *Definition, diagnosis, and classification of diabetes mellitus and its complications: report of a WHO consultation*. Geneva1999.
93. Qureshi AA, Sami SA, Khan FA. Effects of stabilized rice bran, its soluble and fiber fractions on blood glucose levels and serum lipid parameters in humans with diabetes mellitus Types I and II. *The Journal of nutritional biochemistry*. Mar 2002;13(3):175-187.
94. Sen CK, Khanna S, Roy S. Tocotrienols: Vitamin E beyond tocopherols. *Life sciences*. Mar 27 2006;78(18):2088-2098.
95. Chin KY, Ima-Nirwana S. The effects of alpha-tocopherol on bone: a double-edged sword? *Nutrients*. Apr 10 2014;6(4):1424-1441.
96. Abdul-Majeed S, Mohamed N, Soelaiman IN. The use of delta-tocotrienol and lovastatin for anti-osteoporotic therapy. *Life sciences*. Mar 15 2015;125:42-48.
97. Chin KY, Abdul-Majeed S, Mohamed N, Ima-Nirwana S. The Effects of Tocotrienol and Lovastatin Co-Supplementation on Bone Dynamic Histomorphometry and Bone Morphogenetic Protein-2 Expression in Rats with Estrogen Deficiency. *Nutrients*. Feb 15 2017;9(2).
98. Ibrahim N, Khamis MF, Mod Yunoh MF, Abdullah S, Mohamed N, Shuid AN. Targeted delivery of lovastatin and tocotrienol to fracture site promotes fracture healing in osteoporosis model: micro-computed tomography and biomechanical evaluation. *PLoS one*. 2014;9(12):e115595.
99. Soelaiman IN, Ramli ESM, Suhaimi FH, Ahmad F. Potential benefits of annatto tocotrienol in glucocorticoid induced osteoporosis: an animal study *J Osteopor Phys*. 2017;5(2):1000203.
100. Abdul-Majeed S, Mohamed N, Soelaiman IN. Effects of tocotrienol and lovastatin combination on osteoblast and osteoclast activity in estrogen-deficient osteoporosis. *Evidence-based complementary and alternative medicine : eCAM*. 2012;2012:960742.
101. Wong SK, Chin KY, Suhaimi FH, Ahmad F, Ima-Nirwana S. Exploring the potential of tocotrienol from Bixa orellana as a single agent targeting metabolic syndrome and bone loss. *Bone*. Nov 2018;116:8-21.
102. Gambacciani M, Levancini M. Hormone replacement therapy and the prevention of postmenopausal osteoporosis. *Przegląd menopauzalny = Menopause review*. Sep 2014;13(4):213-220.
103. Nordin BE, Morris HA. The calcium deficiency model for osteoporosis. *Nutrition reviews*. Mar 1989;47(3):65-72.
104. Ima Nirwana S, Fakhurazi H. Palm vitamin e protects bone against dexamethasone-induced osteoporosis in male rats. *The Medical journal of Malaysia*. Jun 2002;57(2):136-144.
105. Shen CL, Yang S, Tomison MD, Romero AW, Felton CK, Mo H. Tocotrienol supplementation suppressed bone resorption and oxidative stress in postmenopausal osteopenic women: a 12-week randomized double-blinded placebo-controlled trial. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. Apr 2018;29(4):881-891.
106. Clarke BL, Khosla S. Androgens and bone. *Steroids*. Mar 2009;74(3):296-305.
107. Sunycz JA. The use of calcium and vitamin D in the management of osteoporosis. *Therapeutics and clinical risk management*. Aug 2008;4(4):827-836.
108. Nishida N, Yano H, Nishida T, Kamura T, Kojiro M. Angiogenesis in cancer. *Vascular health and risk management*. 2006;2(3):213-219.
109. Wada S, Satomi Y, Murakoshi M, Noguchi N, Yoshikawa T, Nishino H. Tumor suppressive effects of tocotrienol in vivo and in vitro. *Cancer letters*. Nov 18 2005;229(2):181-191.
110. Yano Y, Satoh H, Fukumoto K, et al. Induction of cytotoxicity in human lung adenocarcinoma cells by 6-O-carboxypropyl-alpha-tocotrienol, a redox-silent derivative of alpha-tocotrienol. *International journal of cancer*. Jul 10 2005;115(5):839-846.
111. Theriault A, Chao JT, Wang Q, Gapor A, Adeli K. Tocotrienol: a review of its therapeutic potential. *Clinical biochemistry*. Jul 1999;32(5):309-319.
112. Elson CE. Suppression of mevalonate pathway activities by dietary isoprenoids: protective roles in cancer and cardiovascular disease. *The Journal of nutrition*. Jun 1995;125(6 Suppl):1666S-1672S.
113. Miyazawa T, Shibata A, Nakagawa K, Tsuzuki T. Anti-angiogenic function of tocotrienol. *Asia Pacific journal of clinical nutrition*. 2008;17 Suppl 1:253-256.
114. Nakagawa K, Eitsuka T, Inokuchi H, Miyazawa T. DNA chip analysis of comprehensive food function: inhibition of angiogenesis and telomerase activity with unsaturated vitamin E, tocotrienol. *BioFactors*. 2004;21(1-4):5-10.

115. Nesaretnam K, Guthrie N, Chambers AF, Carroll KK. Effect of tocotrienols on the growth of a human breast cancer cell line in culture. *Lipids*. Dec 1995;30(12):1139-1143.
116. Nesaretnam K, Meganathan P. Tocotrienols: inflammation and cancer. *Annals of the New York Academy of Sciences*. Jul 2011;1229:18-22.
117. Shun MC, Yu W, Gapor A, et al. Pro-apoptotic mechanisms of action of a novel vitamin E analog (alpha-TEA) and a naturally occurring form of vitamin E (delta-tocotrienol) in MDA-MB-435 human breast cancer cells. *Nutrition and cancer*. 2004;48(1):95-105.
118. Sugahara R, Sato A, Uchida A, et al. Anatto Tocotrienol Induces a Cytotoxic Effect on Human Prostate Cancer PC3 Cells via the Simultaneous Inhibition of Src and Stat3. *Journal of nutritional science and vitaminology*. 2015;61(6):497-501.
119. Campbell SE, Rudder B, Phillips RB, et al. gamma-Tocotrienol induces growth arrest through a novel pathway with TGFbeta2 in prostate cancer. *Free radical biology & medicine*. May 15 2011;50(10):1344-1354.
120. Constantinou C, Hyatt JA, Vraha PS, et al. Induction of caspase-independent programmed cell death by vitamin E natural homologs and synthetic derivatives. *Nutrition and cancer*. 2009;61(6):864-874.
121. Kaneko S, Sato C, Shiozawa N, et al. Suppressive Effect of Delta-Tocotrienol on Hypoxia Adaptation of Prostate Cancer Stem-like Cells. *Anticancer research*. Mar 2018;38(3):1391-1399.
122. Wada S, Naito Y, Matsushita Y, et al. Delta-tocotrienol suppresses tumorigenesis by inducing apoptosis and blocking the COX-2/PGE2 pathway that stimulates tumor-stromal interactions in colon cancer. *J Funct Foods*. 2017;35:428-435.
123. Shibata A, Nakagawa K, Tsuduki T, Miyazawa T. delta-Tocotrienol treatment is more effective against hypoxic tumor cells than normoxic cells: potential implications for cancer therapy. *The Journal of nutritional biochemistry*. Aug 2015;26(8):832-840.
124. Gillen CD, Walmsley RS, Prior P, Andrews HA, Allan RN. Ulcerative colitis and Crohn's disease: a comparison of the colorectal cancer risk in extensive colitis. *Gut*. Nov 1994;35(11):1590-1592.
125. Luna J, Masamunt MC, Rickmann M, et al. Tocotrienols have potent antifibrogenic effects in human intestinal fibroblasts. *Inflammatory bowel diseases*. Mar 2011;17(3):732-741.
126. Ji X, Wang Z, Geamanu A, Goja A, Sarkar FH, Gupta SV. Delta-tocotrienol suppresses Notch-1 pathway by upregulating miR-34a in nonsmall cell lung cancer cells. *International journal of cancer*. Dec 1 2012;131(11):2668-2677.
127. Ji X, Wang Z, Geamanu A, Sarkar FH, Gupta SV. Inhibition of cell growth and induction of apoptosis in non-small cell lung cancer cells by delta-tocotrienol is associated with notch-1 down-regulation. *Journal of cellular biochemistry*. Oct 2011;112(10):2773-2783.
128. Ji X, Wang Z, Sarkar FH, Gupta SV. Delta-tocotrienol augments cisplatin-induced suppression of non-small cell lung cancer cells via inhibition of the Notch-1 pathway. *Anticancer research*. Jul 2012;32(7):2647-2655.
129. Malafa MP, Sebt S. *Delta-Tocotrienol Treatment and Prevention of Pancreatic Cancer*. Lee Moffitt Cancer Center & Research Institute, University of South Florida (Tampa): US2008/0004233. 2008.
130. Husain K, Centeno BA, Chen DT, Hingorani SR, Sebt SM, Malafa MP. Vitamin E delta-tocotrienol prolongs survival in the LSL-KrasG12D/+;LSL-Trp53R172H/+;Pdx-1-Cre (KPC) transgenic mouse model of pancreatic cancer. *Cancer prevention research*. Oct 2013;6(10):1074-1083.
131. Husain K, Centeno BA, Coppola D, Trevino J, Sebt SM, Malafa MP. delta-Tocotrienol, a natural form of vitamin E, inhibits pancreatic cancer stem-like cells and prevents pancreatic cancer metastasis. *Oncotarget*. May 9 2017;8(19):31554-31567.
132. Husain K, Francois RA, Hutchinson SZ, et al. Vitamin E delta-tocotrienol levels in tumor and pancreatic tissue of mice after oral administration. *Pharmacology*. 2009;83(3):157-163.
133. Husain K, Francois RA, Yamauchi T, Perez M, Sebt SM, Malafa MP. Vitamin E delta-tocotrienol augments the antitumor activity of gemcitabine and suppresses constitutive NF-kappaB activation in pancreatic cancer. *Molecular cancer therapeutics*. Dec 2011;10(12):2363-2372.
134. Springett GM, Husain K, Neuger AM, et al. A phase I dose-escalation study of the safety, PK, and PD of vitamin E delta-tocotrienol administered to subjects with resectable exocrine neoplasia. Paper presented at: 102nd Annual Meeting of the American Association for Cancer Research 2011; Orlando, FL.
135. Nasr M, Nafee N, Saad H, Kazem A. Improved antitumor activity and reduced cardiotoxicity of epirubicin using hepatocyte-targeted nanoparticles combined with tocotrienols against hepatocellular carcinoma in mice. *European journal of pharmaceuticals and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V*. Sep 2014;88(1):216-225.
136. He L, Mo H, Hadisusilo S, Qureshi AA, Elson CE. Isoprenoids suppress the growth of murine B16 melanomas in vitro and in vivo. *The Journal of nutrition*. May 1997;127(5):668-674.
137. Lapidot T, Sirard C, Vormoor J, et al. A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. *Nature*. Feb 17 1994;367(6464):645-648.
138. Visvader JE, Lindeman GJ. Cancer stem cells: current status and evolving complexities. *Cell stem cell*. Jun 14 2012;10(6):717-728.
139. Al-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ, Clarke MF. Prospective identification of tumorigenic breast cancer cells. *Proceedings of the National Academy of Sciences of the United States of America*. Apr 1 2003;100(7):3983-3988.
140. Collins AT, Berry PA, Hyde C, Stower MJ, Maitland NJ. Prospective identification of tumorigenic prostate cancer stem cells. *Cancer research*. Dec 1 2005;65(23):10946-10951.
141. Giordano A, Fucito A, Romano G, Marino IR. Carcinogenesis and environment: the cancer stem cell hypothesis and implications for the development of novel therapeutics and diagnostics. *Frontiers in bioscience : a journal and virtual library*. May 1 2007;12:3475-3482.
142. Singh SK, Clarke ID, Terasaki M, et al. Identification of a cancer stem cell in human brain tumors. *Cancer research*. Sep 15 2003;63(18):5821-5828.
143. Subramaniam D, Kaushik G, Dandawate P, Anant S. Targeting Cancer Stem Cells for Chemoprevention of Pancreatic Cancer.

- Current medicinal chemistry*. 2018;25(22):2585-2594.
144. Luk SU, Yap WN, Chiu YT, et al. Gamma-tocotrienol as an effective agent in targeting prostate cancer stem cell-like population. *International journal of cancer*. May 1 2011;128(9):2182-2191.
 145. Xiong A, Yu W, Tiwary R, Sanders BG, Kline K. Distinct roles of different forms of vitamin E in DHA-induced apoptosis in triple-negative breast cancer cells. *Molecular nutrition & food research*. Jun 2012;56(6):923-934.
 146. Traber MG, Podda M, Weber C, Thiele J, Rallis M, Packer L. Diet-derived and topically applied tocotrienols accumulate in skin and protect the tissue against ultraviolet light-induced oxidative stress. *Asia Pacific journal of clinical nutrition*. Mar 1997;6(1):63-67.
 147. Suzuki YJ, Tsuchiya M, Wassall SR, et al. Structural and dynamic membrane properties of alpha-tocopherol and alpha-tocotrienol: implication to the molecular mechanism of their antioxidant potency. *Biochemistry*. Oct 12 1993;32(40):10692-10699.
 148. Watson M, Holman DM, Maguire-Eisen M. Ultraviolet Radiation Exposure and Its Impact on Skin Cancer Risk. *Seminars in oncology nursing*. Aug 2016;32(3):241-254.
 149. Multhoff G, Radons J. Radiation, inflammation, and immune responses in cancer. *Frontiers in oncology*. 2012;2:58.
 150. Thiele JJ, Hsieh SN, Ekanayake-Mudiyanselage S. Vitamin E: critical review of its current use in cosmetic and clinical dermatology. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.]*. Jul 2005;31(7 Pt 2):805-813; discussion 813.
 151. Ghosh SP, Kulkarni S, Hieber K, et al. Gamma-tocotrienol, a tocol antioxidant as a potent radioprotector. *International journal of radiation biology*. Jul 2009;85(7):598-606.
 152. Weber C, Podda M, Rallis M, Thiele JJ, Traber MG, Packer L. Efficacy of topically applied tocopherols and tocotrienols in protection of murine skin from oxidative damage induced by UV-irradiation. *Free radical biology & medicine*. 1997;22(5):761-769.
 153. Traber MG, Rallis M, Podda M, Weber C, Maibach HI, Packer L. Penetration and distribution of alpha-tocopherol, alpha- or gamma-tocotrienols applied individually onto murine skin. *Lipids*. Jan 1998;33(1):87-91.
 154. Yap WNea. Gamma- and delta-tocotrienols inhibit cutaneous melanosis (hallmark of melanoma) by suppressing constitutive and UV-induced tyrosinase activation. Paper presented at: 102nd Annual Meeting of the American Association for Cancer Research 2011; Orlando, FL.
 155. Packer L, Weber SU, Rimbach G. Molecular aspects of alpha-tocotrienol antioxidant action and cell signalling. *The Journal of nutrition*. Feb 2001;131(2):369S-373S.
 156. Burclaff J, Mills JC. Plasticity of differentiated cells in wound repair and tumorigenesis, part II: skin and intestine. *Disease models & mechanisms*. Aug 31 2018;11(9).
 157. Pereira GG, Guterres SS, Balducci AG, Colombo P, Sonvico F. Polymeric films loaded with vitamin E and aloe vera for topical application in the treatment of burn wounds. *BioMed research international*. 2014;2014:641590.
 158. Xu C, Bentinger M, Savu O, et al. Mono-epoxy-tocotrienol-alpha enhances wound healing in diabetic mice and stimulates in vitro angiogenesis and cell migration. *Journal of diabetes and its complications*. Jan 2017;31(1):4-12.
 159. Institute AFRRC. 2011; <http://www.usuhs.mil/afrr/research/rcp.htm>.
 160. Kulkarni S, Ghosh SP, Satyamitra M, et al. Gamma-tocotrienol protects hematopoietic stem and progenitor cells in mice after total-body irradiation. *Radiation research*. Jun 2010;173(6):738-747.
 161. Li XH, Fu D, Latif NH, et al. Delta-tocotrienol protects mouse and human hematopoietic progenitors from gamma-irradiation through extracellular signal-regulated kinase/mammalian target of rapamycin signaling. *Haematologica*. Dec 2010;95(12):1996-2004.
 162. Li XH, Ghosh SP, Ha CT, et al. Delta-tocotrienol protects mice from radiation-induced gastrointestinal injury. *Radiation research*. Dec 2013;180(6):649-657.
 163. Pannkuk EL, Laiakis EC, Fornace AJ, Jr., Fatanmi OO, Singh VK. A Metabolomic Serum Signature from Nonhuman Primates Treated with a Radiation Countermeasure, Gamma-tocotrienol, and Exposed to Ionizing Radiation. *Health physics*. Jul 2018;115(1):3-11.
 164. Shibata A, Nakagawa K, Sookwong P, Tsuduki T, Oikawa S, Miyazawa T. delta-Tocotrienol suppresses VEGF induced angiogenesis whereas alpha-tocopherol does not. *Journal of agricultural and food chemistry*. Sep 23 2009;57(18):8696-8704.
 165. Miyazawa T, Shibata A, Sookwong P, et al. Antiangiogenic and anticancer potential of unsaturated vitamin E (tocotrienol). *The Journal of nutritional biochemistry*. Feb 2009;20(2):79-86.
 166. Tappeiner C, Meyenberg A, Goldblum D, et al. Antifibrotic effects of tocotrienols on human Tenon's fibroblasts. *Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie*. Jan 2010;248(1):65-71.
 167. Tanito M, Itoh N, Yoshida Y, Hayakawa M, Ohira A, Niki E. Distribution of tocopherols and tocotrienols to rat ocular tissues after topical ophthalmic administration. *Lipids*. May 2004;39(5):469-474.
 168. Abdul Nasir NA, Agarwal R, Vasudevan S, Tripathy M, Alyautdin R, Ismail NM. Effects of topically applied tocotrienol on cataractogenesis and lens redox status in galactosemic rats. *Molecular vision*. 2014;20:822-835.
 169. Abdul Nasir NA, Agarwal R, Sheikh Abdul Kadir SH, et al. Reduction of oxidative-nitrosative stress underlies anticataract effect of topically applied tocotrienol in streptozotocin-induced diabetic rats. *PLoS one*. 2017;12(3):e0174542.
 170. Rink C, Christoforidis G, Khanna S, et al. Tocotrienol vitamin E protects against preclinical canine ischemic stroke by inducing arteriogenesis. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. Nov 2011;31(11):2218-2230.
 171. Kuhad A, Chopra K. Attenuation of diabetic nephropathy by tocotrienol: involvement of NFkB signaling pathway. *Life sciences*. Feb 27 2009;84(9-10):296-301.
 172. Anderson SL, Qiu J, Rubin BY. Tocotrienols induce IKBKAP expression: a possible therapy for familial dysautonomia. *Biochemical and biophysical research communications*. Jun 20 2003;306(1):303-309.

173. Nur Azlina MF, Kamisah Y, Chua KH, Qodriyah HM. Tocotrienol Attenuates Stress-Induced Gastric Lesions via Activation of Prostaglandin and Upregulation of COX-1 mRNA. *Evidence-based complementary and alternative medicine : eCAM*. 2013;2013:804796.
174. Rodzian MN, Aziz Ibrahim IA, Nur Azlina MF, Nafeeza MI. Pure tocotrienol concentrate protected rat gastric mucosa from acute stress-induced injury by a non-antioxidant mechanism. *Polish journal of pathology : official journal of the Polish Society of Pathologists*. Apr 2013;64(1):52-58.
175. Anderson SL, Rubin BY. Tocotrienols reverse IKAP and monoamine oxidase deficiencies in familial dysautonomia. *Biochemical and biophysical research communications*. Oct 14 2005;336(1):150-156.



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