Please note this documentation is available for various countries all over the world and hence it may contain statements or product classification not applicable to your country. The claims made are in reference to ingredients only, hence they do not refer to finished products. Marketers of finished products containing the ingredient described herein are responsible for determining whether the claims made for such products are lawful and in compliance with the laws of the country in which they will market the products. Please note that the physiological activity of the ingredient described herein is based on scientific literature done on Tocotrienols not necessarily sponsored or done with Theraprime™ tocotrienols.
What are Tocotrienols?

Tocotrienols are a form of natural Vitamin E. Natural Vitamin E is composed of eight distinct molecules. Four of these molecules are known as “tocopherols” and the other four are the subject of this paper: “tocotrienols.” Both the tocopherol and tocotrienol families consist of members which are named alpha, beta, delta and gamma. Each of the tocotrienol molecules, alpha-tocotrienol, beta-tocotrienol, delta-tocotrienol and gamma-tocotrienol, have proven antioxidant and anti-inflammatory activity as well as potential health benefits which have been demonstrated in hundreds of published medical research studies.

What is the Difference between Tocotrienols and Tocopherols?

Chemical Difference: The main difference between tocopherols and tocotrienols chemically is that the side chains of the tocotrienol molecules are unsaturated. Tocopherols do not have any double bonds within the molecules and have a long appendage on the end of the molecule. Tocotrienols, on the other hand, have a short appendage on the end of the molecule and three double bonds on each molecule [Figure 1]. These structural variances manifest in tremendous differences functionally for these two distinct Vitamin E sub-families. For example, scientists theorize that tocopherols’ long appendage and lack of double bonds are responsible for their poor functional effects in the body. The functional distinction between tocopherols and tocotrienols is demonstrated in several different ways, one of which is tocotrienols’ far superior antioxidant activity.

Health Benefit Difference: From a health benefit standpoint, there has been some controversy over the primary form of Vitamin E that has been marketed for many years, d-alpha tocopherol (and particularly with its synthetically produced cousin, dl-alpha tocopherol). Fortunately, in the case of tocotrienols, there has been no such controversy, and the studies have been extremely positive. In fact, as you’ll see below, hundreds and hundreds of medical research studies have consistently shown remarkable potential for tocotrienols’ clinical use in humans.

![Figure 1. The chemical structures of Tocotrienols and Tocopherols](image-url)
WHERE ARE TOCOTRIENOLS FOUND IN NATURE?

Tocotrienol Sources: Tocotrienols occur naturally in various vegetable sources, particularly in certain grains and oils such as wheat germ, soybean oil, barley, oats and palm oil. In general, tocotrienols are found in much lower concentrations than tocopherols in most foods. However, higher concentrations are found in a few distinct places such as rice bran oil, palm oil and in the annatto bean.

Tocotrienols in the Diet. Unfortunately, since tocotrienols are found in very low concentrations in most food sources, practically no one obtains efficacious doses of tocotrienols from their diet [Figure 2]. Human clinical research has settled on doses in the range of 50mg to 100mg per day. But unless you eat mega portions of concentrated sources of tocotrienols such as rice bran or palm oil or annatto beans every day, you’ll have to take a tocotrienol supplement to enjoy their diverse health benefits. For example, even though it’s one of nature’s richest sources, palm oil sold commercially has less than 1/10 of 1% of tocotrienol content by weight! So to obtain a therapeutic dose from this rich source, you’d have to drink down about a 4 ounce cup of palm oil every day!

BGG—The Ultimate Source for Tocotrienols. BGG’s tocotrienol products come under our industry-leading family of Vitamin E products called TheraPrime®. We’re proud to point out that, unlike other tocotrienol suppliers, products derived from each of the three key sources of tocotrienols are available from BGG North America: BGG provides tocotrienols from palm oil, from rice bran oil, and also from annatto. While the different suppliers of tocotrienols fight amongst themselves saying “our tocotrienols from palm are the best” or “our tocotrienols from rice bran are the best,” BGG takes the high road and leaves this decision up to our customers. We are happy to recommend a specific tocotrienol for a specific application, or we can also provide all three sources for the “Ultimate Tocotrienol” product—a mixture of all the commercially produced sources. And it’s not just this comprehensive offering allowing our customers to choose their source that separates BGG’s tocotrienol offerings from other companies; we also are capable of providing industry-leading concentrations of tocotrienols. We offer tocotrienol oleoresin up to 90% pure while our competitors only provide their tocotrienols in the 50% - 70% pure range. Have space issues with your formulation? Want to limit the number of caps in your formula’s daily dose to one versus having to go to two or three caps per day? Want to provide your customers with the purest, most concentrated tocotrienol on the market? The solution to all these issues is the same: BGG’s Super Concentrated Tocotrienols!

BGG has some excellent technology which allows us to offer tocotrienols that have industry-leading concentrations.

Tocotrienols occur naturally in various vegetable sources, particularly in certain grains and oils such as wheat germ, soybean oil, barley, oats and palm oil.

WHAT ARE THE MAIN DIFFERENCES BETWEEN THE THREE MAJOR SOURCES OF TOCOTRIENOLS?

ANNATTO

- 99% tocotrienol
- 1% tocopherol
- 95% delta tocotrienol
- 5% gamma tocotrienol
- 5% alpha tocotrienol

PALM

- 75% tocotrienol
- 25% tocopherol
- 75% gamma, alpha, delta-tocotrienol
- 25% alpha tocotrienol

RICE

- 50% tocotrienol
- 50% tocopherol
- 50% alpha & gamma tocotrienol
- 50% alpha & gamma tocopherol

While some people think the lack of tocopherols is a benefit for annatto tocotrienols, we must point out that there is very limited research on the annatto variety. A review of all of the human clinical studies on tocotrienols did not find any study that specified that the tocotrienols were sourced from annatto. So we cannot say with certainty that the unique breakdown of primarily delta-tocotrienol from annatto will have excellent health benefits in humans.

The majority of the positive human research was done on palm oil tocotrienols, most likely because they have been available commercially the longest. There is also positive research in humans on rice bran tocotrienols, a great example of which is a very positive study on their cholesterol-lowering effects at a daily dose of 100mg. And while each product has great potential as a health-giving supplement, there are also some small issues with each as well:

- Manufacturers have reported that palm oil tocotrienols can be difficult to encapsulate without the addition of other oils to enhance fluidity.
- Rice bran tocotrienols are available in the lowest concentrations, which may lead to space issues in certain formulas.
- Annatto tocotrienols cannot be used in worldwide formulas since they are not accepted by regulators in Europe.

Even though we pointed out above that there are no published human clinical studies that specify annatto as the source, there is a positive study for neuroprotection that was done with delta-tocotrienols (which represent 90% of the contents of the annatto-sourced tocotrienols). However, in this study, the delta form was derived from palm. This example shows us that it’s very difficult to come to firm conclusions at this juncture in the history of tocotrienols regarding which source or form to use. One important point did become apparent when reviewing the human research—the vast majority of the positive human studies featured a mixture of the different forms (primarily alpha, delta and gamma) rather than a single form. BGG’s position is that all the different forms are very good products and should have benefits in human health. We offer each of these forms in our TheraPrime® family of Vitamin E products and allow our customers to decide which form they’d like to use for their particular application.
We want to once again point out that BGG has some excellent technology which allows us to offer tocotrienols that have industry-leading concentrations. Here are some key specifications from our four best-selling tocotrienol products:

### OILS

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<th>Minimum Total Tocopherols</th>
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### WATER DISPERSEABLE POWDERS

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Tocotrienols have been the subject of many human clinical trials demonstrating diverse potential in preventative as well as therapeutic applications. Based on all the human studies we reviewed, we feel that a basic dose of 100mg per day for general health is reasonable.

### WHAT DOSAGE IS RECOMMENDED?

The range of dosages in the published human clinical research is wide. A study published in the American Journal of Clinical Nutrition showed that at a low dosage of only 60mg per day, positive results in improving blood lipid levels were found. In only 30 days, the decrease in LDL cholesterol ranged from 3.3% and the decrease in total cholesterol ranged from 3.6% (Tan, et al, 1991). However, in one study on neuroprotection, the only dosage given was 17mg/kg of body weight each day. The results were very good, but heavier subjects were taking over 500mg of tocotrienols per day (Aruzu, et al, 2013). Unfortunately, there was no dose dependence element in this study, so we may have seen similar results at much lower dosages.

A very positive study on rice-bran tocotrienols’ effect on blood lipids did analyze dose dependence. They tested various dosages from 25mg up to 200mg per day. They found an excellent effect at 100mg per day; in fact, the effect was better at 100mg than at 200mg (Qureshi, et al, 2002).

Based on all the human studies we reviewed, we feel that a basic dose of 100mg per day for general health is reasonable. A logical range of dosages would start at 100mg per day leading up to 200mg per day. Broken down by condition, following are our recommendations:

- **Cardiovascular Health**: 60mg – 100mg per day
- **Neuroprotection**: 100mg – 200mg per day
- **Liver Protection**: 200mg per day
- **Kidney Protection**: 200mg per day
- **Diabetes**: 200mg per day
- **Systemic Inflammation**: 200mg per day
- **Immunity**: 200mg per day
- **Anti-Aging**: 100mg – 200mg per day
- **Hair Growth**: 100mg per day

### OVERVIEW OF EXISTING RESEARCH ON TOCOTRIENOLS

CLOSE TO 500 POSITIVE STUDIES!

There are close to 500 medical research studies showing a variety of potential health benefits for tocotrienols. This is such a phenomenal quantity of positive research that it’s hard to imagine that tocotrienols are not a household word and aren’t being sold at every major retailer and pharmacy chain. But this will undoubtedly change in the not-too-distant future: As the plethora of research becomes better known in the supplement industry and by consumers, we’re sure to see much wider distribution of these healthy superstars.

### HISTORY OF VITAMIN E RESEARCH

The early research on Vitamin E was mainly focused on tocopherols. Yet the research on tocotrienols shows a much more potent molecule with a more diverse and consistently positive body of medical research. In the last several years, tocotrienols have enjoyed much more focused investigation as evidenced by the volume of studies which has greatly escalated due to the extremely promising early results. In fact, in just the last five years since 2010, there have been about 250 positive studies published! It will be very interesting to see how much more is found out about tocotrienols’ health benefits in the future: with the current trajectory of research, we should be up over 1000 positive studies early in the next decade, and with a few new health benefits found. With this single fact alone—that scientists are vigorously mining the benefits of tocotrienols in their laboratories and clinics around the world—all serious supplement brands should take a hard look at adding a pure tocotrienol product to their portfolio as well as including tocotrienols in condition-specific formulas.

Several of the published studies were conducted as state-of-the-art, double-blind, placebo-controlled human clinical studies; meanwhile, in the case of certain areas of research such as cancer prevention, there have been scores of positive pre-clinical animal research trials as well as in-vitro experiments, but no human studies. Nevertheless, the human research has clinically validated a variety of health benefits that tocotrienols can imbue on consumers (all of which have been further corroborated by myriad pre-clinical experiments).

There are close to 500 medical research studies showing a variety of potential health benefits for tocotrienols.
ARIES OF HUMAN RESEARCH: THE CLINICALLY-VALIDATED BENEFITS

Tocotrienols have been the subject of many human clinical trials demonstrating diverse potential in preventative as well as therapeutic applications. In total, there have been more than ten distinct areas of human research. Following is a complete list of these different areas along with a brief synopsis of the existing human research in each area.

1. Cardiovascular Health: Extensive research has been completed showing tocotrienols’ positive effects on blood lipid profiles in various groups including hypercholesterolemic patients; people with type-2 diabetes; patients undergoing dialysis; as well as healthy, older adults with no health concerns.

2. Neuroprotection: In two excellent human clinical trials, tocotrienols protected brain white matter and showed potential to prevent a neurodegenerative disease. Additionally, cohort studies and case-control studies have further established the case for tocotrienols’ strong neuroprotective effects.

3. Kidney Protection: Protection against inflammation in the kidneys as well as nitrosative stress of the kidneys have been demonstrated in diabetic patients.

4. Liver Protection: Tocotrienols showed the potential to delay the progression of end-stage liver disease; they also were shown capable of protecting the liver of patients with high cholesterol.

5. Diabetes: Diabetic patients supplementing with tocotrienols had lower blood glucose levels. And two separate clinical trials showed that diabetics had improved blood lipid profiles after supplementing with tocotrienols.


7. Anti-Aging: Tocotrienols showed an extremely statistically significant reduction in DNA damage in healthy, older adults.

8. Hair Growth: Tocotrienols taken internally significantly increased hair growth versus placebo in a randomized human clinical trial.

9. Skin Health: Topically applied, tocotrienols prevented lipid peroxidation in humans. In a separate trial, tocotrienols combined with tocopherols and applied topically reduced photo-aging of human skin.

10. Antioxidant: Along with tocotrienols’ anti-inflammatory activity, their antioxidant action is at the heart of many of their condition-specific benefits. In a few human clinical trials, tocotrienols improved key antioxidant markers such as superoxide dismutase in the blood of human subjects; they have also been shown to circulate in lipoproteins where they are effective in neutralizing hydroxyl radicals.

11. Anti-Inflammatory: Tocotrienols prevented inflammation and reduced the key blood marker for inflammation, high sensitivity C-reactive protein, in diabetic patients.

PRE-CLINICAL RESEARCH: CANCER PREVENTION AND TUMOR REDUCTION

In addition to the clinically-validated health benefits listed above, there are several other potential health benefits that have been demonstrated in extensive pre-clinical animal trials and in-vitro experiments. In no other area has there been as much research as in the realm of cancer prevention and tumor reduction. In fact, there are close to 200 studies in this area alone showing preventive and also potential therapeutic benefits in the fight against breast cancer; leukemia; liver and pancreatic cancers; melanoma and other forms of skin cancer; gastric, bladder and colon cancers; mesothelioma; prostate cancer; lung cancer; lymphomas; oral cancer; brain cancer; and bone marrow cancer. In addition, tocotrienols have shown an ability to protect against the deleterious effects of radiation and radioactivity in various different models.

There is one published study in relation to cancer in humans. This was a very interesting case control study done on women with breast lumps. This study found that women with malignant breast lumps had much lower levels of tocotrienols than those with benign breast lumps. The researchers concluded: “The higher adipose tissue concentration of tocotrienols in benign patients provides support for the idea that tocotrienols may provide protection against breast cancer.” (Nesaretnam, et al, 2007).

OTHER PRE-CLINICAL RESEARCH

Along with tocotrienols’ anti-inflammatory activity, their antioxidant action is at the heart of many of their condition-specific benefits.

There has been roughly an equal number of emerging health benefits defined in pre-clinical research that have yet to be validated in human trials as benefits that have been clinically validated (which we outlined above). As we just pointed out, the research in the area of cancer has been massive. After cancer, the most substantial pre-clinical work has been done on tocotrienols’ ability to support bone health. In total, there have been 24 pre-clinical trials, most of which were done on rodents. Results vary from enhancing bone formation to maintaining bone strength to preventing bone loss and preventing osteoporosis in rat models of aging. Additionally, tocotrienols showed potential for preventing bone diseases, healing fractures and even for protecting cells responsible for bone formation against oxidative stress.

After bone health, the highest number of pre-clinical studies (eight) were done on digestive health. Results include preventing gastric lesions, protecting gastric mucosa as well as possible benefits for people suffering from Crohn’s disease.

Another focus of pre-clinical research has been in the fight against obesity where seven positive studies have been published. Potential benefits include combating metabolic disorder and suppressing adipogenesis.

The last area with multiple pre-clinical studies has been on tocotrienols’ potential against pancreatitis where four studies have been done.

In addition, there are several nascent areas of research where only one or two positive pre-clinical studies have been done. These include improving endurance, treating allergies, improving fertility and enhancing the health of embryos. There has also been a study showing that tocotrienols may have a hormone-like function.

And lastly, similar to such highly effective supplements as AstaZine® Natural Astaxanthin and ApplePhenol® polyphenols, tocotrienols have revealed in two different trials that they can extend the life of C. elegans worms, a model organism used in life extension research.

Health Benefits of Tocotrienols versus Tocopherols. It’s very interesting to note that in many of the studies we’ve introduced so far, comparisons were made between tocotrienols and tocopherols. On a comparative level, tocotrienols have consistently demonstrated far superior clinical potential than tocopherols.

Please Note: While this review is principally dedicated to an examination of tocotrienols’ potential health benefits that have been validated in human clinical research, we briefly mention these other potential benefits from pre-clinical research in order that the Reader may fully understand the wide range of possible applications. For a complete list of over 460 abstracts showing all of the research referenced throughout this review, please contact BGG at our North America headquarters by e-mail at support@ bggworld.com or by telephone at 949.748.7348.
INTERNAL ORGAN PROTECTION BY TOCOTRIENOLS

Introduction

We briefly referenced some of the research showing that tocotrienols may protect certain important internal organs above. Now we’ll examine tocotrienols’ protective properties in regards to various internal organs in more detail. It seems that whatever organ scientists zoom in on in their research on tocotrienols, evidence emerges that tocotrienols may have preventative properties and, in some cases, may even play a therapeutic role. Unfortunately, tocotrienols have not been studied yet in regards to all the different internal organs in the human body. But since the research on the organs studied to date has been so consistently positive, the probability is quite high that tocotrienols might effectively protect all our organs. Tocotrienols’ anti-inflammatory and antioxidant properties are well established; so provided that tocotrienols can reach each of the different organs in the body, they should logically afford protection to these organs by virtue of their ability to modulate inflammation and eliminate free radicals. As an example, tocotrienols protection of the brain is well established with several human clinical trials and dozens of supporting pre-clinical studies; however, examination of the existing literature reveals that no one thus far has tested tocotrienols’ ability to protect our eyes. But provided that tocotrienols can cross the blood retinal barrier and get into the retina and macula, they should be quite capable of protecting the eyes from inflammatory conditions and oxidation. Rather than speculate any further, let’s jump right in and begin our review of the literature on tocotrienols’ protection of internal organs. We’ll proceed by listing a particular organ and examining first the research in humans. Then, supporting pre-clinical research will be briefly summarized.

Since the research on the organs studied to date has been so consistently positive, the probability is quite high that tocotrienols might effectively protect all our organs.

Figure 4. The dose dependent decreases of TRF25 plus AHA Step-1 diet on the concentrations of serum total cholesterol and LDL-cholesterol as compared to their respective baseline values.

HEART

Scientists and doctors generally agree that one of the best ways to protect our heart is to maintain LDL cholesterol and other hazardous blood lipids at low levels and prevent oxidation of the cholesterol that is present in our bodies. By doing this, we can maintain our blood vessels clear of blockages and keep blood pumping to our hearts. Additionally, by maintaining silent (systemic) inflammation at low levels (as measured by C-reactive protein in our blood), we can further prevent cardiovascular diseases and protect our hearts.

Tocotrienols have revealed in several human clinical studies and over 50 pre-clinical trials that they are effective performers in both of these key cardiovascular protective measurements. Here, we summarize a few of the best studies:

Tocotrienols dose-dependently reduce LDL cholesterol, total cholesterol, triglycerides and apolipoprotein B in hypercholesterolemic human volunteers. This study was done on 90 volunteers with high cholesterol. The study tested subjects at different daily dosages of 25mg, 50mg, 100mg and 200mg. The best results were found at 100mg per day—at this dosage, total serum cholesterol was reduced by 20%, on average over a 35 day period. LDL was reduced by 25%, apolipoprotein B was reduced by 14%, and triglycerides were reduced by 12% (Figure 4) (Qureshi, et al, 2002).

Tocotrienols prevent inflammation and reduce CRP in patients with Type-2 diabetes. In a randomized double-blind, placebo-controlled study, 44 subjects with Type-2 diabetes were given either tocotrienol enriched canola oil or plain canola oil (placebo) for 8 weeks. High-sensitivity C-reactive protein (which is deemed by experts to be the key indicator of silent inflammation) decreased significantly as did urine microalbumin [Table 1] (Highlight, et al, 2014).

Tocotrienols reduce LDL, total cholesterol, ApoB as well as glucose levels in patients with high cholesterol. In this double-blind crossover study, patients were given either 200mg of tocotrienol-rich fraction or placebo for only four weeks. Improvements were seen at statistically significant levels in all the blood lipid parameters tested; tocotrienols reduced blood glucose levels by 12% as well. This is a very encouraging result in only four weeks of supplementation (Qureshi, et al, 1991a) [Table 2 & 3].

Tocotrienols improve blood lipid profiles in healthy older adults. This study was done on 62 volunteers who were healthy without elevated cholesterol levels or other chronic health conditions. The placebo-controlled study showed improvements in plasma cholesterol as well as in antioxidant vitamin levels. In addition, a reduction in protein damage was found (Chin, et al, 2011).

Total Cholesterol and LDL Cholesterol lowered by tocotrienol-rich fraction in healthy volunteers. In just thirty days, subjects without any health issues taking a tocotrienol rich supplement (with 42mg of tocotrienols and 18mg of tocopherols) had reductions in both total cholesterol and LDL. All subjects taking the tocotrienol supplement had reductions in both parameters tested with the total reduction reaching over 35% in some subjects (Tan, et al, 1991) [Table 4].

Type 2 diabetic patients with high cholesterol experience reduction in LDL and other cardiovascular risk markers. This study points out that 80% of diabetic patients will die from an atherosclerotic event. So the researchers did a randomized, double-blind, placebo-controlled study to test if tocotrienols could help these patients reduce their cholesterol levels. In a 60 day study, they found an average reduction of LDL of 42%. Total cholesterol also went down an average of 30% while total serum lipids decreased by 23% (Balasubrahmanya, et al, 2009b) [Table 5].

Pre-Clinical Heart Research:

1. Tocotrienols reversed cardiovascular, metabolic and liver changes in rats that were fed a high-carbohydrate, high-fat diet. The researchers concluded: “These results suggest that tocotrienols protect the heart and liver, and improve plasma glucose and lipid profiles with minimal changes in abdominal obesity in this model of human metabolic syndrome” (Wong, et al, 2012).
2. Tocotrienols protected against damage from arterial blockage in rabbits with high cholesterol (Das, et al, 2012).
5. Tocotrienols suppressed triglycerides, cholesterol and VLDL in-vitro and decreased cholesterol and triglyceride levels in mice (Zaiden, et al, 2010).
6. Tocotrienols prevented atherosclerosis in mice. (This study identified a mechanism of action for this effect) (Li, et al, 2013).
8. Tocotrienols inhibited atherosclerosis and decreased LDL, triglyceride and total cholesterol levels in mice (Qureshi, et al, 2001).
9. Tocotrienols are more effective than tocopherols in reducing cholesterol levels in cholesterol-fed rabbits. Additionally, they offer significant protection against degeneration of arterial walls caused by fatty deposits and scar tissue (Teoh, et al, 1994).
10. Tocotrienols reduced LDL cholesterol by a huge factor (average 60%) as well as other cardiovascular risk factors in pigs with inherited high cholesterol levels (Qureshi, et al, 1991).

As we mentioned above, there are many more pre-clinical trials; some are further back up to the studies cited above, and some explore new pathways for tocotrienols’ cardiovascular protective properties. For a complete list of over 450 abstracts showing all of the published research on tocotrienols, please contact BGG at our North American headquarters by e-mail at support@bggworld.com or by telephone at 949.748.7348. Also, for a comprehensive review of tocotrienols potential in positively affecting blood lipids, please contact BGG and ask for the white paper titled, “Cholesterol Lowering Effects of Tocotrienols.”

Table 1: The effect of Tocotrienols-enriched canola oil on serum glucose, inflammation and oxidative status.

Table 2: Effects of palm tocotrienols on serum lipid concentrations in hypercholesterolemic humans.

Tocotrienols have been clinically validated for their ability to protect our brains. In fact, there are a total of seven different published studies in humans of various types - placebo-controlled studies.

Table 3: Effects of palm tocotrienols on serum cholesterol, triglyceride, and LDL-C concentrations in hypercholesterolemic humans.

People in the highest tercile of total tocotrienols levels were over 90% less likely to have these cognitive issues than people in the lowest tercile.
Brain

Tocotrienols have been clinically validated for their ability to protect our brains. In fact, there are a total of seven different published studies in humans of various types—placebo-controlled studies, cohort studies, and case control studies—all pointing toward the same conclusion. If you want to protect your body’s most vital organ (the brain), you should strongly consider supplementing with tocotrienols every day. In addition to the human research, there have been more than 30 pre-clinical trials in this area providing additional indication of tocotrienols’ neuroprotective effects. We’ll go through each of the human studies and then briefly summarize some of the supporting pre-clinical research as well.

Potential in Treating Fatal Neurodegenerative Disease. Dysautonomia is a potentially fatal disease that can be passed down in families. Dysautonomia affects nerves that carry information from the brain to various organs including the heart and digestive system. This study examined the effect of medium length tocotrienol supplementation on patients with familial dysautonomia in regards to cardiovascular issues common in people suffering from this disease. The markers used were frequency of hypertensive crises and cardiac function. After three to four months, approximately 80% of patients supplementing with tocotrienol had experienced a significant decrease in the number of crises. The researchers concluded, “Based on these findings, we hypothesize that tocotrienol therapy will improve the long-term clinical outlook and survival of individuals with familial dysautonomia” (Rubin, et al, 2008).

Protection of Brain White Matter. This study took 121 volunteers with white matter lesions (confirmed by MRI) over 35 years of age and randomized them to receive either tocotrienols or placebo twice a day for two years. Results showed that the placebo group’s white matter lesions increased over the course of two years whereas the subjects supplementing with tocotrienols’ white matter lesions remained essentially unchanged. The difference in volume of lesions between the placebo and treatment groups was extremely statistically significant after two years (Gopalan, et al, 2014).

High Levels of Tocotrienols and Tocopherols Correlate to Reduced Risk of Cognitive Impairment in Older Adults. A group of researchers from Finland and Sweden led by Professor Francesca Mangialasche has been very active over the last few years in studying the relationship between levels of Vitamin E compounds and age-related cognitive impairment. Professor Mangialasche is a medical doctor as well as a PhD who specializes in Geriatrics. She led a cohort study in 2013 in Finland which followed 140 older subjects with no sign of cognitive impairment for eight years. At the end of eight years, analyses showed that subjects with higher serum levels of beta-tocotrienols, total tocotrienols and gamma tocopherols had a significantly lower incidence of cognitive impairment (Mangialasche, et al, 2013a).

Low Levels of Tocotrienols and Tocopherols Found in Alzheimer’s Patients and People with Mild Cognitive Impairment. Researchers led by Dr. Mangialasche did a different type of study called a “case control study” in which they took 166 people with Alzheimer’s disease, 96 people with mild cognitive impairment, and finally 187 cognitively normal people and measured levels of Vitamin E compounds in their plasma. They found that people with Alzheimer’s and mild cognitive impairment had lower levels of Vitamin E. The greatest statistical significance was found when measuring tocotrienol levels—in fact, people in the highest tercile of total tocotrienols levels were over 90% less likely to have these cognitive issues than people in the lowest tercile (Mangialasche, et al, 2012).

Additional Case Control Study and Cohort Study Validate Same Results. Two studies similar to those discussed above were completed by Dr. Mangialasche’s group as well. The case control study had an even higher correlation between Alzheimer’s and mild cognitive impairment incidence when measuring Vitamin E levels of tocotrienols and tocopherols. In this case the correlation was 98% (Mangialasche, et al, 2013b). The cohort study in this series led by Dr. Mangialasche again found that low levels of plasma Vitamin E correlated directly to higher levels of Alzheimer’s disease when analyzing a group of 232 subjects over 80 years of age during a six year period (Mangialasche, et al, 2010).

Another Human Study. Lastly, one additional human clinical trial showed potential for tocotrienols as a neuroprotectant. In this study, patients suffering from Friedreich’s ataxia (an inherited disease that causes damage to the central nervous system) showed possible benefits from tocotrienol supplementation (Abruzzo, et al, 2013).

Pre-Clinical Brain Health Research. While we will not reference all of the pre-clinical research as there are many of them, we will briefly look at a few highlights in this area.

3. Tocotrienols improved cognitive function in rats and exhibited a positive influence on memory and spatial learning (Tanid, et al, 2011).
4. Tocotrienols provide neuroprotection against glutamate injury (Selvaraju, et al, 2014).
6. Tocotrienols may protect against neural degeneration through their neuroprotective function (Fuku, et al, 2011).
9. Tocotrienols were multi-fold more potent than tocopherol in protecting against mercury toxicity (Shichiri, et al, 2007).
10. Alpha-tocotrienol provides the most potent neuroprotection among Vitamin E analogs in rat striatal cultures (Otsakada, et al, 2004).
12. Tocotrienols protect rat brains from oxidative damage and its ensuing adverse alterations (Karnat and Devasagayam, 1995).

There are many more pre-clinical trials. For a complete list of over 450 abstracts showing all of the published research on tocotrienols, please contact BGG at our North American headquarters by e-mail at support@bggworld.com or by telephone at 949.748.7348. Also, for a more comprehensive review of tocotrienols’ potential in positively affecting brain health, please contact BGG and ask for the white paper titled, “Brain Health in a Capsule.”

Liver

The liver is another critical organ that tocotrienols seem to protect. While the research on tocotrienols’ benefits for the liver and the other organs we’ll examine below isn’t as deep as it is for the heart and brain, the liver research is still very solid evidence that tocotrienols have a beneficial effect. There are two excellent human clinical trials showing different ways in which tocotrienols can protect the liver. Plus, there are eight extremely promising animal trials showing a wide range of benefits for the liver. So while we wait for additional research on tocotrienols’ ability to support our livers and the other organs that we’ll review below, it seems that it would be wise for people wishing to protect their livers strongly consider supplementing with tocotrienols. Fortunately, from what has been happening recently, we probably won’t have to wait much longer, of the ten studies we will review in this section, seven of them (including both human clinical trials) have been done in the last three years (since 2012).

Tocotrienols protect the livers of adults with high blood lipids. High cholesterol levels can damage your liver. So the researchers who did this study wanted to see if tocotrienols could help protect the livers of people with Non-Alcoholic Fatty Liver Disease (NAFLD) and high cholesterol levels. Although most people don’t know much about this disease (and frighteningly, most people who have it don’t know they do), it is extremely common in the USA and around the world. A study published in 2013 claims that 19% of Americans have NAFLD (Lazo, et al, 2013). The Cleveland Clinic reports that the true figure may be as high as 1/3 of the US general population. This disease can progress to far more serious liver conditions that can be debilitating or even fatal.

This study was a randomized human clinical trial on 87 volunteers with NAFLD and high blood lipid levels. The treatment group received 200mg of tocotrienols per day for one year. At the end of the study, results were compared with the placebo group. Of the subjects taking tocotrienols, none saw their NAFLD condition worsen, while some of the placebo group did. The group taking tocotrienols showed a significant rate of remission, and normalized the hepatic-echogenic response was significantly higher for them as well. The study concluded “This is the first clinical trial that showed the hepatoprotective effects of mixed palm tocotrienols in hypercholesterolemic adults with NAFLD” (Magosso, et al, 2013) [Table 6].

Tocotrienols delay the progression of end-stage liver disease model in human clinical trial. In the study above, we saw that tocotrienols are effective in treating the widespread early-stage disease of the liver, Non-Alcoholic Fatty Liver Disease. In this trial, we see that they may also be effective for helping people with the most serious liver condition that often results in death, End Stage Liver Disease. This study first tested bioavailability and went on to compare the effects of tocotrienols with tocopherol.
Table 6. Subjects parameters changes after 1-year treatment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tocotrienols (n = 30)</th>
<th>Placebo (n = 34)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>-0.6</td>
<td>-0.3</td>
<td>0.527</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>-0.3</td>
<td>-0.2</td>
<td>0.055</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>-0.01</td>
<td>0.02</td>
<td>0.778</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>-0.2</td>
<td>-0.1</td>
<td>0.652</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>-0.2</td>
<td>-0.2</td>
<td>0.814</td>
</tr>
<tr>
<td>ALP (IU/L)</td>
<td>7.0</td>
<td>1.4</td>
<td>0.471</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>-4.8</td>
<td>-3.4</td>
<td>0.207</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>-5.9</td>
<td>-0.6</td>
<td>0.118</td>
</tr>
<tr>
<td>GGT (IU/L)</td>
<td>-1.4</td>
<td>-4.2</td>
<td>0.364</td>
</tr>
<tr>
<td>C-tp (mg/L)</td>
<td>-0.2</td>
<td>-0.2</td>
<td>0.835</td>
</tr>
<tr>
<td>Apo B (g/L)</td>
<td>-0.01</td>
<td>-0.03</td>
<td>0.046</td>
</tr>
<tr>
<td>Lp(A) (mg/dL)</td>
<td>2.3</td>
<td>0.4</td>
<td>0.524</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>-5.1</td>
<td>-1.9</td>
<td>0.524</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>0.5</td>
<td>0.5</td>
<td>0.490</td>
</tr>
<tr>
<td>Systolic (mmHg)</td>
<td>0.1</td>
<td>0.6</td>
<td>0.660</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>-0.3</td>
<td>-2.4</td>
<td>0.607</td>
</tr>
</tbody>
</table>

Tocotrienols delay the progression of end-stage liver disease model in human clinical trial.

They gave 80 people tocotrienol supplements for 20 weeks and found that the levels increased over time in the liver, cardiac muscle, brain, skin, blood, and adipose tissue. "In prospective liver transplantation patients, oral tocotrienols lowered the model for End Stage Liver Disease score in 50% of patients supplemented, whereas only 20% of the tocopherol-supplemented patients demonstrated a reduction in the score. This work provides, to our knowledge, the first evidence demonstrating that orally supplemented tocotrienols are transported to vital organs of adult humans. The findings of this study, in the context of the current literature, lay the foundation for Phase II clinical trials [Phase II trials are a step in pharmaceutical drug development] testing the efficacy of tocotrienols against stroke and End Stage Liver Disease in humans" (Pate et al., 2012). This outstanding study is clearly proclaiming that the results of this clinical trial are so strong that it merits a high level (and expensive) Phase III clinical trial for drug development.

Pre-Clinical Liver Protection Trials
1. Tocotrienols reversed liver, cardiovascular and metabolic changes in rats fed a high-carb/high-fat diet (Wong et al., 2012).
2. Alpha-tocotrienol proved to be more effective than alpha tocopherol in two different liver injury models (Tan et al., 2015).
3. Tocotrienols may prevent hepatic steatosis and ameliorate stress and subsequent inflammation in the liver (Muto et al., 2013).
4. Tocotrienols protected against biochemical and ultrastructural changes in rats (Jayusman et al., 2014).
5. Tocotrienols reduced the severity of hepatocarcinogenesis in rats (Nesaretnam et al., 1993).
6. Tocotrienols significantly reduced the peroxidation potential in rat livers (Nesaretnam et al., 1993).
7. Tocotrienols provided liver protective properties in adult rats (Kamisah et al., 2014).
8. Tocotrienols induced low levels of hepatocellular adenomas in rats (Tasaki et al., 2009).

Fig. 5. Mean changes in plasma TAG normalized to baseline. Values are presented as mean ± standard error of the mean. TAG data were normalized using baseline values. "Significant difference (P<0.05) compared with placebo at each time point based on independent t-test. At week 16, there was a marginal difference between TRF and placebo groups (P=0.05). Abbreviations: TAG, triacylglycerols; TRF, tocotrienol-rich fraction.

KIDNEYS
Similar to the research on tocotrienols' ability to protect the liver, there is precisely the same number of positive studies with regards to the kidneys. A total of 10 studies—2 human clinical trials and 8 supporting animal trials. And also similar to the research on tocotrienols' benefits for liver health, the research on kidney health is very new. In fact, all the kidney research has been done over the last six years. Tocotrienols show multiple protective effects for the kidneys in double-blind, placebo-controlled study on diabetic patients. This study covered a lot of ground. A group of 50 patients with Type-2 diabetes took part in this double-blind, placebo-controlled, randomized study. They were given either 200mg of canola oil with tocotrienols or pure canola oil (as a placebo) for eight weeks. At the end of the study, people who had taken tocotrienols had significant improvements in a few different measurements:
- A decrease in microalbumin (this is an early sign of diabetic kidney disease).
- A decrease in high sensitivity C-reactive protein (this is a key marker of silent inflammation in the body).
- A slight increase in nitric oxide level (another marker of silent inflammation).

The researchers concluded that tocotrienols can protect the kidneys against inflammation and nitrosative stress. They are more potent in these two functions than is alpha tocopherol (Nowak et al., 2012).

Pre-Clinical Kidney Protection Trials
1. Tocotrienols prevented kidney damage and reduced oxidative stress in rats (Buxin et al., 2013).
2. Both rice bran oil tocotrienols and palm oil tocotrienols improved kidney function and also glycemic status in diabetic rats (Siddiqui et al., 2010).
3. Tocotrienols protect against acute kidney injury in rats (Khan et al., 2010).
4. Gamma-tocotrienol protected against kidney cell death and kidney injury associated with oxidative stress. They are more potent in these two functions than is alpha tocopherol (Nowak et al., 2012).
5. Tocotrienols protect against kidney dysfunction in rats (Rashid Khan et al., 2015).
6. Tocotrienols protected diabetic rats against nephropathy (Siddiqui et al., 2013).
7. Tocotrienols protect the kidneys of rats against iron-induced dysfunction and oxidative stress (Gupta and Chopra, 2009).
8. Tocotrienols exerted a marked protective effect of the kidneys of diabetic rats (Kuhad and Chopra, 2009).
Patients receiving the tocotrienol-rich fraction had significantly improved blood lipid profiles as compared to the placebo group.

**DIGESTIVE AND ELIMINATORY ORGANS**

While there has not been any human study to date in this area, there have been seven very promising pre-clinical trials:

1. Tocotrienols protected rats against stress-induced gastric lesions by reducing gastric acidity and activating Prostaglandin E-2 and by increasing the COX-1 enzyme (these are two causes of inflammation) (Nur Azlina, et al, 2013).
2. Tocotrienols have potent anti-fibrogenic effects in human cells and "could be useful to treat or prevent bowel fibrosis in Crohn's Disease patients" (Luna, et al, 2011a).
3. Tocotrienols protected the gastrointestinal tract in rats and blocked stress-induced changes in gastric acidity and gastrin levels (as compared to tocopherols which did not have this positive effect) (Azlina, et al, 2005).
4. Tocotrienols are effective in preventing aspirin-induced gastric lesions in rats (Nafeeza, et al, 2002).
5. Tocotrienols inhibited transforming growth factor in cells extracted from Crohn's Disease patients (Luna, et al, 2011b).

**REPRODUCTIVE ORGANS**

There is a single pre-clinical animal trial showing potential protective benefits of tocotrienols in the female and also one in the male reproductive organs. The female study was related to chemotherapy (which leads to ovarian failure and infertility). When administered a chemotherapy drug, female rats had many changes including reduced ovulation rate, inflammatory cell infiltration, and abnormal ovaries. However, when tocotrienols were administered concurrently with the chemotherapy drug, the negative changes were completely reversed. Tocotrienols “confer protection of ovarian morphology and function in vivo” (Saleh, et al, 2015).

The male study examined the effects that a tocotrienol-rich fraction has in preventing damage caused by insecticides to the sperm of rats. Sperm is produced in the testes; these organs can be adversely affected by exposure to pesticides, rendering the male incapable of impregnating a female. The researchers in this study subjected male rats to a common pesticide that is known to adversely affect sperm characteristics. Tocotrienols had a profound effect:

- Sperm counts increased
- Motility of sperm improved
- Viability of the sperm also improved
- Abnormal sperm morphology decreased
- SOD (antioxidant) activity increased
- Glutathione levels increased
- DNA damage in the sperm also decreased

The study concluded that tocotrienols show the potential to reduce the negative effects of insecticides on sperm and male fertility (Taib, et al 2014) 

**PANCREAS**

Similar to our review of digestive and eliminatory health above, there are no human trials showing that tocotrienols have health benefits for the pancreas. But there are four solid pre-clinical trials we will summarize here:

1. Tocotrienols showed a range of activity in a model of chronic pancreatitis. The researchers concluded: “Tocotrienols improve quantitative measures of chronic pancreatic damage. They may be of benefit in human chronic pancreatitis” (Gonzalez, et al, 2011).
2. Tocotrienols were more potent than tocopherols in controlling inflammation and oxidation in a rat model of pancreatitis (Liang, et al, 2019).
We wish that more research had been done on all the different organs in the body to see if tocotrienols can protect every organ. While this is simply hypothesizing, based on everything in the published literature, we believe that tocotrienols can protect every organ that they can reach. We hope to see more research on organs such as the eyes since there has been none to date; and we also hope to see more human trials to validate some of the areas where research in mammals has shown outstanding potential. Notwithstanding all of the above, with close to 500 positive medical research studies, it is clearly evident that tocotrienols are an extraordinary supplement that may have benefits across most of our internal organs. They have been documented to reach most of our organs in bioavailability research, and once they get into various organs, their anti-inflammatory and antioxidant activity seem to kick in to provide protection. It’s also important to point out that numerous studies we cited in this review show potential therapeutic benefits for tocotrienols to treat many diverse maladies. And it’s also important that our readers understand that various other mechanisms besides anti-inflammation and scavenging of free radicals have been identified in the literature showing how tocotrienols are combatting various mistakes. Tocotrienols are a very special nutraceutical indeed!

**Fig. 7.** Effects of TRF on (a) SOD activity and (b) GSH content in epididymal sperm of FNT-treated rats. The values are expressed as means ± SEM, and P<0.05 was the level of significance. Significant difference as compared with the control group at P<0.01. bSignificant difference as compared with the TRF group at P<0.01. cSignificant difference as compared with the FNT group at P<0.05.

**Fig. 8.** Effects of TRF on DNA damage, (a) tail DNA, (b) tail moment, (c) olive tail moment, and (d) tail length, in epididymal sperm of FNT-treated rats. The values are expressed as means ± SEM, and P<0.05 was the level of significance. Significant difference as compared with the control group at P<0.01. bSignificant difference as compared with the TRF group at P<0.01. cSignificant difference as compared with the FNT group at P<0.05.

While we didn’t dwell on this research, we’d like to point out that there have been almost 200 different studies published showing that tocotrienols can protect a variety of organs from developing cancer. And many of these studies show that tocotrienols can also shrink tumors. The list of organs is long—breasts, lungs, liver, kidneys, pancreas, stomach, intestines, bladder, colon, skin, prostate, mouth, and brain—and the types of cancer are also diverse. The reason we didn’t dwell on this research is because it has all been done in animals, and there are no human studies to validate the pre-clinical studies. But the sheer volume of studies is another indicator that tocotrienols may be effective in humans as well in protecting internal organs against the ravaging effects of cancer. Again, we hope to see human research in this area in the future.

BGG highly recommends that supplement brands market a stand-alone tocotrienols SKU based on the positive human clinical research that has been published. And we also strongly recommend that supplement brands include tocotrienols in formula for heart health, brain health, liver & kidney protection and of course, in anti-inflammatory and antioxidant products. For more information, please contact BGG at our North American headquarters by e-mail at support@bggworld.com or by telephone at 949.748.7348.
THE ANTI-AGING EFFECT OF TOCOTRIENOLS

Introduction

As the world’s population gets older and older, more efforts are being made by astute people to live longer and to improve the quality of life as we age. Great efforts are made by many individuals including eating healthier foods, exercising regularly, using well-researched supplements—which are all actions that can help protect vital organs that can fail in old age such as our hearts and brains. Which makes sense, since heart disease is the #1 killer in the developed world, while neurodegenerative diseases are the fastest increasing maladies over the last decade. And of course, trying to stave off cancer, the #2 killer, is also on top of most middle-aged people’s minds as well.

It’s interesting to note that tocotrienols have shown potential protective effects in all three of these critical areas—cardiovascular health, brain health, and loads of pre-clinical research has shown great potential for tocotrienols in the fight against cancer. In addition, tocotrienols have shown a propensity to protect other internal organs. And they’ve also been documenting in the literature as having anti-inflammatory and antioxidant activity, both of which are known causes of many life-threatening diseases.

While we won’t go into all of the research demonstrating these potential benefits, we encourage interested parties to contact BGG and ask for the respective white papers which cover these areas of research in more detail.

Tocotrienols have shown a propensity to protect other internal organs.

In two separate studies, tocotrienols have also shown that they can also make the worm live longer.

Life Extension

We briefly mentioned that tocotrienols have been the subject of two positive animal trials showing that they have life extending properties in our overview of research above. When discussing “anti-aging,” perhaps the best place to start is discussing the potential to extend life. There is a very simple animal that is commonly used in life extension research because in some ways, it mimics human lifespan. This animal is a worm called Caenorhabditis elegans (or C. elegans for short). Some very good antioxidants and/or anti-inflammatory agents such as Asta®® Natural Astaxanthin and ApplePhenon® Polyphenols have been documented to prolong the life of this organism. In two separate studies, tocotrienols have also shown that they can also make this worm live longer.

In the most recent study, hydrogen peroxide was used to create oxidative stress in the worms, which significantly shortened their lifespan. However, when the worms were fed a tocotrienol-rich fraction before the oxidative stress, their lifespan returned to normal (Aan, et al, 2013). In today’s modern world, human beings are subject to unprecedented levels of oxidative stress that previous generations never experienced. Things like pollution, chemicals and preservatives in the food we eat and cosmetics we use, increased stress of a modern lifestyle, and even increased UV exposure due to depletion of the ozone layer all increase oxidation in our bodies. Should the research in C. elegans translate to humans, tocotrienols would be an excellent supplement to help our bodies fight this increased oxidation and preserve a long lifespan.

The second test was similar, but it used ultraviolet B irradiation to shorten the lifespan of the worms. These scientists measured something called “protein carbonyl” in the worms because it’s a good indicator of oxidative damage during aging. The worms fed tocotrienols had less accumulation of protein carbonyl than the control group. And, as expected, they lived longer when fed tocotrienols before being subjected to UV irradiation. This study also tested alpha-tocopherol in the same manner, but found that this common form of Vitamin E, unlike tocotrienols, had absolutely no effect. The researchers tried something else—in one group of worms, they exposed them to UV irradiation first and then afterward, they fed them the tocotrienols. Interestingly, post-treatment with tocotrienols also increased their lifespan back to normal. They concluded: "The administration of tocotrienols to animals results in a reduction of oxidative stress risks. These data indicate that tocotrienols merit further investigation as possible agents for anti-aging and oxidative stress prevention. In addition, they suggest that C. elegans will continue to provide provocative clues into the mechanism of ageing" (Adachi and Ishii, 2000).

HUMAN STUDY: TOCOTRIENOLS REDUCE DNA DAMAGE

We’ve seen that tocotrienols can extend the lifespan of a model animal used in life extension research, but what can it do for humans? An excellent human clinical study shows that tocotrienols can reduce DNA damage in healthy, older people. DNA damage over time is a key contributing factor to the aging process. In fact, as far back as 1981 in a paper published in the Quarterly Review of Biology by the University of Chicago, Drs. Gensler and Bernstein declared DNA damage to be the primary cause of aging (Gensler and Bernstein, 1981). It is also widely believed that DNA damage is a leading cause of various forms of cancer. So, we can see how relevant it would be to our discussion if tocotrienols can reduce DNA damage.

The human clinical study showing this effect was a true state-of-the-art study: Randomized, double-blind and placebo-controlled. This study used a group of 64 volunteers who were generally healthy. The age range was from middle age to elderly (37 – 78 years old). Subjects in the treatment group took 160mg daily of tocotrienols for 6 months. The results were extremely statistically significant: People taking tocotrienols had less DNA damage after 3 months and damage remained low at the end of the study after 6 months. Other markers also showed improvements from tocotrienol supplementation, and the researchers noted that one of the key markers known as “sister chromatid exchange” showed even better results in the older subset of the tocotrienol group (Chin, et al, 2008).

This study is particularly noteworthy in discussing the anti-aging effects of tocotrienols. It’s a very well-designed study done under top conditions and treats what very well may be the key marker for aging, DNA damage.

Figure 9 Survival curves and mean lifespan of C. elegans treated with TRF. TRF+H2O2+TRF and TRF+H2O2 restored the mean lifespan of the H2O2-treated worms to that of the control group. The results are expressed as the means ± S.D. with n = 150. P<0.05 was the level of significance.
SUPPORTING PRE-ClinICAL TRIALS

In addition to this landmark clinical trial, there are several supporting preclinical trials which lend further weight to tocotrienols as an excellent anti-aging supplement. These studies look at anti-aging from different angles, with the common denominator that they all show promising results. We’ll briefly explore some of the more interesting studies:

1. A recent in-vitro study showed that a tocotrienol-rich fraction was effective in modulating cellular aging (Khee, et al, 2014).
2. Sarcopenia is a common affliction of old age as defined by a loss of muscle tissue. Tocotrienols may reverse the aging of cells due to sarcopenia by replenishing the regenerative capacity of the cells (Lim, et al, 2013).
3. A well-published researcher named Dr. Makpol has done a series of fascinating studies on tocotrienols’ capacity in anti-aging. In his most recent study, Dr. Makpol found that tocotrienols exhibited strong antioxidant activity in human diploid cells, leading the researchers to conclude that they have potential as an anti-aging entity (Makpol, et al, 2013).
4. Similar to DNA damage as a main cause of aging and cancer formation, some scientists now believe that telomere length is also a key factor in both aging and carcinogenesis. Fortunately, tocotrienols have been shown to be capable of restoring telomere length in human diploid cells (Makpol, et al, 2011a).
5. A group led by Dr. Makpol also found gamma-tocotrienol effective in preventing telomere shortening due to induced oxidative stress (Makpol, et al, 2010).
6. A metabolite of alpha-tocotrienol was reported to be a potent cell protector against oxidative stress and aging (Shrader, et al, 2011).
8. Leading us into the next section of this review on skin health, Dr. Makpol once again came up with a novel look at tocotrienols’ potential as an anti-aging supplement. He took human skin cells and subjected them to stress. Then he introduced gamma-tocotrienol and ran the test again. He found that gamma-tocotrienol was effective at preventing cell death and delaying aging in these skin cells (Makpol, 2012b).

PREVENTION OF SKIN AGING BY TOCOTRIENOLS

While many people would say that outward appearance is less significant than inward health when discussing aging, there certainly is a huge market for products that may help improve skin health and appearance. Cosmetics are a multi-billion dollar industry, and over the last several years products that can help with skin quality and health from the inside out have become much more popular. Research has shown that tocotrienols may work in both capacities: Topically, two human clinical trials show that tocotrienols may benefit the skin. Internally, several pre-clinical trials show that tocotrienols may also protect and heal the skin. To wrap up our review of tocotrienols’ anti-aging potential, we’ll look at how they may help maintain the body’s largest organ, the skin, in a more youthful state.

Lester Packer, PhD, is one of the most famous names in the study of antioxidant science. He’s been author or co-author of over 800 scientific papers. Dr. Packer was one of the authors of a human clinical trial showing the benefit of alpha-tocotrienol applied topically to the skin. This study featured a topical solution containing 5% alpha-tocotrienol. The subjects applied this solution to their skin for one week, and then benzoyl peroxide, a drug commonly prescribed for skin conditions such as acne, was applied during the second week, during which time the alpha-tocotrienol application continued. The problem with this drug is that, like most drugs, it has unwanted side effects. In this case, the side effects can actually be harmful to the skin. Fortunately, the alpha-tocotrienol application counteracted the lipid peroxidation of the skin caused by the drug (Weber, et al, 2003).

The most deleterious onslaught that human skin suffers over the course of a lifetime in most people is simply Sun exposure. The sun’s UV rays that feel so nice at the beach is slowly damaging our skin; in fact, it can potentially cause skin cancer over time. The technical term for UV damage to the skin is “photo-aging.” In a paper published in the respected scientific journal, “Journal of the European Academy of Dermatology and Venereology,” a human clinical trial examined the protective effects of a combination of tocotrienols and tocopherols on photo-aging. This study begins by pointing out that “recent finding suggest that tocotrienols have superior activity than tocopherols.” The researchers recruited 30 volunteers with skin photosenstivity for this study, and had them apply the tocotrienol/ tocopherol solution to a small area of skin. For comparative purposes, they had them apply retinol (a form of Vitamin A commonly used in topical products for photo-aging) to a similar sized area of skin. Then, they subjected the volunteers’ skin to UVB light and tested the tocotrienol/tocopherol section and the retinoid section versus a control section that had a topical product with no active ingredient applied. The conclusion: “The pre-treatment with the Vitamin E formulation highly protects against photodamage, and all reactions to irradiation were significantly lower in the areas treated with the topical Vitamin E formulation compared to those treated with the simple vehicle [control area with no active ingredient] or Vitamin A. The use of a new topical formulation containing significant concentrations of tocotrienols and tocopherols represents a promising strategy to reduce photo-induced skin damage” (Pedrelli, et al, 2012).

In addition to these human clinical studies, there are several pre-clinical studies lending excellent support to tocotrienols’ anti-aging potential in skin, both when applied topically and when taken internally:

• Similar to the human study described above wherein topical application of a tocotrienol/tocopherol solution protected against photo-aging, in the animal model for photo-aging in humans, tocotrienols fed internally to mice reduced photo-aging. This study compared tocotrienols effect to tocopherols on the skin of hairless mice that were subjected to UVB-induced skin damage. They found that dietary tocotrienols protect the skin better than alpha-tocopherol against damage induced by UVB (Yamada, et al, 2008).
• Dr. Makpol did a study purely on tocotrienols’ effect on skin pigmentation. He and his colleagues found that tocotrienols may be useful in improving skin pigmentation caused by UVA exposure (Makpol, et al, 2014). This result has potential significance for preventing age spots and other unsightly skin blemishes.
• In a different angle on tocotrienols’ skin benefits, alpha-, delta-, and gamma- tocotrienol all showed potential as anti-scarring agents (Tappener, et al, 2013).
• Tocotrienols protect human skin cells against hydrogen peroxide induced stress and increase collagen synthesis (Makpol, et al, 2012c).
• Gamma-tocotrienol delayed cell aging in human skin cells subjected to stress (Makpol, et al, 2012c).
• Finally, let’s look at a study done way back in 1997 by Dr. Lester Packer and others. This study found that both tocotrienols taken internally as well as tocotrienols applied topically protect tissue against UV light-induced oxidative stress (Traber, et al, 1997).

Conclusion

There are very few nutraceutical ingredients that have the power of tocotrienols in regards to anti-aging. Human clinical research, pre-clinical animal trials, as well as in-vitro studies in test tubes have shown a variety of potential benefits against aging from tocotrienol use. Among the most significant findings:

• Tocotrienols reduced DNA damage in a landmark human clinical trial.
• Tocotrienols prolonged the lifespan of an animal commonly used in life extension research.
• Tocotrienols showed the capacity to modulate cellular aging.
• Tocotrienols positively affect telomere length.
• Tocotrienols applied topically counteracted lipid peroxidation of the skin in a human clinical trial.
• Tocotrienols in combination with tocopherols greatly reduced photo-aging of human skin in another human clinical trial.
• And let’s not forget, hundreds of studies have been done showing potential for tocotrienols against the two leading causes of death, cardiovascular disease and cancer, as well as other life-threatening conditions.

The combination of positive effects witnessed in many research studies lead us to the conclusion that tocotrienols, along with natural astaxanthin, are the leading nutraceuticals in the fight against aging. As we mentioned above, there are many more published studies on tocotrienols’ numerous benefits. For a complete list of over...
Tocotrienols reduce LDL, total cholesterol, ApoB as well as glucose levels in patients with high cholesterol.

Research on tocotrienols positive effects on diabetes and on cholesterol levels, all lead to the conclusion that they may be an effective agent against development of metabolic syndrome.

**DIABETES RESEARCH**

People suffering from Type-2 diabetes are extremely prone to atherosclerosis. In fact, 80% of these patients will die from an atherosclerotic event (Baliarsingh, et al, 2005). Fortunately, in a human clinical trial, tocotrienols have shown great promise in improving blood lipid levels of diabetics; this, in turn, should lower the risk of atherosclerosis and premature death in these diabetic patients. And they have also shown this cholesterol-lowering effect in several other human clinical trials involving different groups of non-diabetic subjects. (For more information on this research, please contact BGG North America and ask for our White Paper titled “Cholesterol Lowering Effects of Tocotrienols.”)

Tocotrienols reduce LDL, total cholesterol, ApoB as well as glucose levels in patients with high cholesterol. In this double-blind crossover study, patients were given either 200mg of tocotrienol-rich fraction or placebo. After only four weeks, improvements were seen at statistically significant levels in all the blood lipid parameters tested. And very interestingly, in this short time frame, tocotrienols also reduced blood glucose levels by 12% as well. This is a very encouraging result in only four weeks of supplementation and shows great promise from two angles for diabetic patients—both in controlling blood lipid levels as well as reducing blood glucose levels (Duresi, et al, 1999).

Type 2 diabetic patients with high cholesterol experience reduction in LDL and other cardiovascular risk markers. This study points out that 80% of diabetic patients will die from an atherosclerotic event. So the researchers did a randomized double-blind, placebo-controlled study to test if tocotrienols could help these patients reduce their cholesterol levels. In a 60 day study, they found an average reduction of LDL of 42%. Total cholesterol also went down an average of 30%, while total serum lipids decreased by 23% (Baliarsingh, et al, 2005). This reduction in blood lipid levels could potentially reduce the incidence of the overwhelming cause of death in Type 2 diabetics by decreasing the chance of atherosclerosis.

Animal Research Related to Diabetes. A great deal of research has been done in animal models showing that tocotrienols may be of benefit to people with diabetes:

1. Tocotrienols showed fantastic potential in diabetic rats. Over a period of eight weeks, rats supplemented with tocotrienols showed improvements in a variety of positive ways:
   a. Blood glucose levels decreased
   b. Total cholesterol decreased
   c. LDL (bad) cholesterol decreased
   d. Triglycerides were also reduced
   e. HDL (good) cholesterol increased
   f. Superoxide dismutase (SOD—an excellent antioxidant) levels increased
   g. Vitamin C levels also increased
   h. Glycated hemoglobin concentrations decreased.

2. Finally, tocotrienol-rich fraction supplementation resulted in a protective effect on the vessel wall. The researchers concluded that “tocotrienol-rich fraction lowers the blood glucose level and improves dyslipidemia. Levels of oxidative stress markers were also reduced by administration of tocotrienol-rich fraction. Vessel wall integrity was maintained due to the positive effects mediated by tocotrienol-rich fraction” (Budi, et al, 2009).


5. Tocotrienols modulated the release of profibrotic cytokines, oxidative stress, ongoing chronic inflammation and apoptosis and protected the kidneys in diabetic rats (Kuhad and Chopra, 2009a).

6. In a very interesting study, tocotrienols showed a potential to prevent cognitive deficits associated with diabetes in diabetic rats (Kuhad, et al, 2009).


8. Tocotrienols reduced blood glucose and glibenclamide levels in diabetic rats. It also prevented an increase in advanced glycation end products in normal rats (Wan Nazaimoon and Khalid, 2002).

9. Finally, the last animal study on diabetic rats also showed promise for anti-obesity. This study concluded: "This study suggests that tocotrienol suppresses insulin-induced differentiation and Akt phosphorylation in 3T3-L1 preadipocytes. Furthermore, tocotrienol could act as an antidiopgenic vitamin in the nutrient-mediated regulation of body fat through its effects on differentiation" (U-Ondio, et al, 2009). To put this more simply, tocotrienols showed a potential to regulate insulin in cells that may become fat cells, so they may be effective for preventing the increase of body fat.

While we cannot infer any clear benefits in humans from animal research, the variety and depth of these animal trials are indicative of great potential for tocotrienols in treating diabetic humans.

**METABOLIC SYNDROME AND OBESITY RESEARCH**

As we mentioned earlier, there has not been any human research to date on tocotrienols’ effects on obesity; all the studies to date have been pre-clinical research done on animals or in test tubes. However, this pre-clinical research, when put in context of the human and animal research on tocotrienols positive effects on diabetes and on cholesterol levels, all lead to the conclusion that they may be an effective agent against development of metabolic syndrome.

- The first study of significance with regards to obesity is directly above (the last citation in the section on Diabetes) wherein tocotrienols showed a propensity of preventing the increase of body weight.
- 2. Tocotrienol-rich fraction supplementation resulted in a protective effect on the vessel wall.
- 5. Tocotrienols modulated the release of profibrotic cytokines, oxidative stress, ongoing chronic inflammation and apoptosis and protected the kidneys in diabetic rats (Kuhad and Chopra, 2009a).
- 6. In a very interesting study, tocotrienols showed a potential to prevent cognitive deficits associated with diabetes in diabetic rats (Kuhad, et al, 2009).
- 8. Tocotrienols reduced blood glucose and glibenclamide levels in diabetic rats. It also prevented an increase in advanced glycation end products in normal rats (Wan Nazaimoon and Khalid, 2002).
- 9. Finally, the last animal study on diabetic rats also showed promise for anti-obesity. This study concluded: "This study suggests that tocotrienol suppresses insulin-induced differentiation and Akt phosphorylation in 3T3-L1 preadipocytes. Furthermore, tocotrienol could act as an antidiopgenic vitamin in the nutrient-mediated regulation of body fat through its effects on differentiation" (U-Ondio, et al, 2009). To put this more simply, tocotrienols showed a potential to regulate insulin in cells that may become fat cells, so they may be effective for preventing the increase of body fat.
Tocotrienols (particularly delta-tocotrienol and gamma-tocotrienol) prevented accumulation of triglyceride and lipid droplets in mouse adipose cells. The researchers concluded that tocotrienols may be useful as an anti-metabolic disorder agent (Burdeos, et al, 2014). Gamma-tocotrienol suppresses the creation of new fat cells in human adipose derived stem cells. The authors concluded “Gamma-tocotrienol may constitute a new dietary avenue to attenuate hypertrophic obesity in humans” (Zhao, et al, 2014). Put simply, gamma-tocotrienol may be effective in reducing childhood obesity according to this study.

In more exciting research just this year led by the same lead researcher as above, mice were fed a high fat diet to test the effects of gamma-tocotrienol on several different parameters. Several good results were found after four weeks in the group of mice supplemented with gamma-tocotrienol:

- Weight gain was reduced
- Glucose levels decreased
- Insulin levels also decreased
- Pro-inflammatory cytokines were reduced
- Glucose tolerance improved
- Insulin signaling in adipose tissue was enhanced

They also tested gamma-tocotrienol on human adipose tissue and found positive results as well (Zhao, et al, 2015).


In a different type of study, it was found that tocotrienols may be utilized as a preventative agent in obesity and also in osteoporosis caused by steroid use (Ima-Nirwana and Suhaniza, 2004).

In summary, we refer to a review paper published in the journal Current Pharmaceutical Design in 2011. This review examined all the research up to that point (and we must point out that a great deal of positive research has been done in this area since that review was published to further display tocotrienols’ potential in this area). “This review evaluates the effects of tocotrienols on the risk factors of metabolic syndrome using data from human, animal and in vitro studies. Tocotrienols improved lipid profiles and reduced atherosclerotic lesions, decreased blood glucose and glycated hemoglobin concentrations, normalized blood pressure, and inhibited adipogenesis” (Weng-Yew and Brown, 2011).

**Conclusion**

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**HUMAN CLINICAL RESEARCH**

The ability of tocotrienols to positively affect the immune system has been demonstrated in a human clinical trial as well as in supporting animal trials. The human trial employed an interesting system to test tocotrienols’ ability to modulate immunity: The body’s reaction to vaccination allows scientists to closely examine the body’s immune response. After an immunization is given, several different immune markers in the blood can be positively affected by subsequent administration of an immune modulating substance. This study used the tetanus toxoid immunization and tested to see what happened if they gave healthy subjects a tocotrienol-rich fraction versus placebo after receiving this vaccine. Tetanus is a deadly disease; the vaccine given is made up of deactivated tetanus toxins.

This was a true state-of-the-art study. Besides being placebo-controlled it was also randomized and double-blind. The study was conducted over the period of eight weeks on healthy females. The treatment group took 400mg of tocotrienol-rich fraction daily and the others took a placebo. Blood samples were taken on the first day of the study. Then half-way through the study (after four weeks), all of the volunteers were vaccinated with the tetanus toxoid vaccine and their blood was again sampled. At the end of the study (after eight weeks), blood was sampled for the last time.

Results for the tocotrienol group were excellent. Statistically significant improvements were found in several different immune markers:

- Production of interferon gamma increased
- Interleukin-4 production was enhanced
- Anti-tetanus IgG production was augmented
- Interleukin-6 was decreased

The researchers were very pleased with these results. They concluded that tocotrienol-rich fraction has immune-stimulatory effects. They also said that tocotrienols have potential clinical benefits to enhance immune response to vaccines [Figure 10 & 11], Mahalagam, et al (2011).

**PRE-ClinICAL RESEARCH**

There have been solid supporting studies to corroborate the findings in the extremely promising human trial outlined above. The first study we’ll review was done separately on both young mice (four months old) and old mice (23 months old). The rate of tocotrienol feeding was 0.1% of total feed consumption in both groups, and the tocotrienol groups were both tested against a placebo (control) diet. This trial lasted six weeks. Lymphocyte production was lower on average in the older mice as expected, however, the older mice in the tocotrienol group had significantly higher lymphocyte production. This study went on to test the effects of the different tocotrienols in mouse cells in vitro. All of the tocotrienols stimulated lymphocyte proliferation in old mice, with alpha-tocotrienol performing the best. Gamma-tocotrienol was second best, while delta-tocotrienol still increased lymphocyte proliferation, but at a lower rate than the other two tocotrienols tested. The conclusion drawn was that tocotrienols have a positive effect on age-related decline in T cell function (Ren, et al, 2010). This is particularly important if the same benefit translates to humans, as immune system performance is known to deteriorate with age.

In a rodent study that directly supports the human clinical trial described above, mice were given different forms of Vitamin E and then tested after being immunized with the tetanus toxoid vaccine. The Vitamin E forms tested were a tocotrienol-rich fraction (the same form that showed excellent results in the human study), delta-tocotrienol, and also alpha-tocopherol. The common Vitamin E form alpha-tocopherol did not perform well, while both the tocotrienol-rich fraction and the delta-tocotrienol performed very well. The conclusion: “Supplementation with delta-tocotrienol or tocotrienol-rich fraction can enhance immune response to tetanus toxoid immunization and production of cytokines that promote cell-mediated (Th1) immune response” (Radhakrishnan, et al, 2013).

While delta-tocotrienols tested positively in the study above, gamma-tocotrienols showed great promise for immune-stimulatory effects in the last study we’ll review. This trial was also done in mice, but this time gamma-tocotrienols were tested against another tocotrienol, Alpha. Both showed a positive effect, but gamma-tocotrienol far outperformed alpha-tocotrienol this time. Gamma-tocotrienols were more effective in suppressing T cell proliferation and cytokine production. Among other markers showing improvement, gamma-tocotrienols were also effective in modulating glutathione in lymphocytes (Winker, et al, 2011).

**Conclusion**

While we hope to see more research to demonstrate tocotrienols’ potential in modulating the immune system, particularly double-blind, placebo-controlled human clinical trials, the existing literature in this area is very promising. Since tocotrienols are not readily available in significant quantities in the human diet, people wishing to enhance their immunity may find good results from daily supplementation with nutrients such as tocotrienols and astaxanthin.

As we mentioned above, there are many more published studies on tocotrienols’ many benefits. For a complete list of over 450 abstracts showing all of the published research on tocotrienols, please contact BGG at our North American headquarters by e-mail at support@bggnorthamerica.com or by telephone at 949.748.1348.

**HAIR LOSS**

Currently, you may find that your hair is growing in bald spots. At least, that’s what a placebo-controlled clinical study on volunteers suffering from hair loss showed. This study took 38 volunteers and gave them either 100mg per day of tocotrienols or a placebo for eight months. They were monitored for number of hairs in a pre-determined scalp area as well as the weight of 20 strands of hair clippings that were each measured out to be 1 cm in length. These measurements were taken before the trial started, after 4 months, and then again at the end of the study after 8 months.

After 8 months of tocotrienol supplementation, there was no change in hair volume (as measured by the weight of 20 strands). But remarkably, the number of hairs increased by a whopping 34.5% in the tocotrienol group (Table 8, Becoy, et al, 2010). This is a phenomenal result in only 8 months, and we hope to see more research in this area in the future to further validate this finding.

**Conclusion**

Put simply, there are very few nutritional supplements that can match tocotrienols’ health-giving properties. The one that comes to mind (which is also distributed by BGG North America) is AstaZine™ Natural Astaxanthin. Other than astaxanthin, we can’t think of any other supplement with so many diverse benefits and so much research backing up these benefits. We sincerely hope to see more human clinical trials in the near future, as unfortunately, in some very promising areas, the only existing research is in animal models to date. But with over 450 positive studies, we’re sure to see more human trials in the near future.

In the meantime, supplement brands wishing to add a superstar supplement to their lineups should definitely go with tocotrienols. And we’re proud to say that BGG provides different tocotrienol products from each of the three major sources—palm oil, rice bran oil and annatto.

<table>
<thead>
<tr>
<th>Supplementation</th>
<th>Baseline</th>
<th>4 months</th>
<th>8 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocotrienol supplementation</td>
<td>268.4 ± 111.3</td>
<td>320.8 ± 121.1</td>
<td>363.1 ± 120.9 (34.5%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>269.0 ± 98.3</td>
<td>269.2 ± 92.4</td>
<td>298.7 ± 88.9 (−0.1%)</td>
</tr>
</tbody>
</table>

Table 8: Mean numbers of hairs at baseline and after 4 and 8 months of tocotrienol and placebo supplementation (mean ± SD, percentage change from baseline).


