White Papers:

Tocotrienol vs Tocopherol
Vitamin E Isoforms Compared for
Therapy Beyond Cell Damage

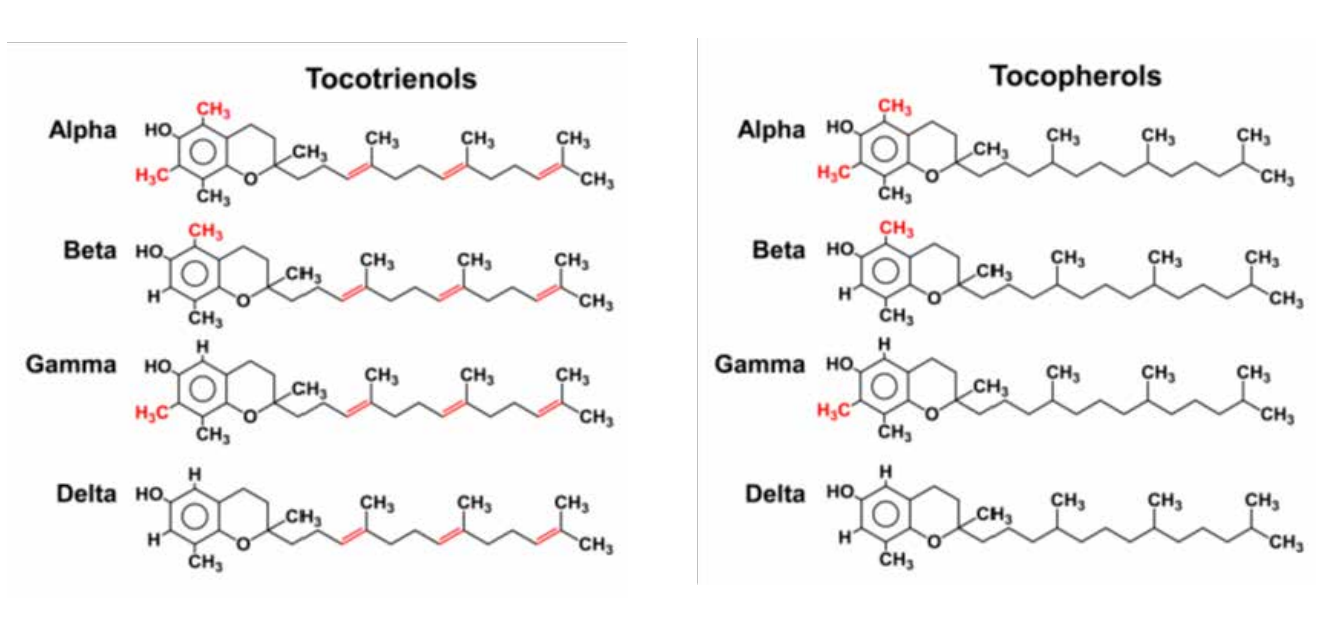

Table of Contents

Contents

1. Executive Summary

Known for its antioxidant properties, Vitamin E protects the human body from harmful compounds called free radicals.

Discovered almost a century ago, Vitamin E is said to have therapeutic benefits for several diseases beyond cancer. These benefits are provisioned through the two isoforms of Vitamin E: tocopherol and tocotrienol.

These isoforms of Vitamin E can be further categorized into alpha (α-), beta (β-), gamma (γ-), and delta (δ-) tocopherols and tocotrienols. Of these, the most active Vitamin E in humans is Alpha (α-) Tocopherol.

Unfortunately, this has resulted in the oversight of tocotrienols, with only 3% of publications related to Vitamin E performing research on them. The little research that has been done on tocotrienols has found them to have anti-inflammatory and antioxidant properties that are superior to the same in α-tocopherol.

In this whitepaper, we discuss the biochemical and physical makeup of the two Vitamin E isoforms and compare them for therapeutic benefits beyond cancer.

2. Introduction

In 1922, a research physician Dr. Herbert M. Evans, and his assistant Katherine S. Bishop discovered Vitamin E (α-tocopherol) at the University of California in Berkeley. The discovery was made to prevent fetal resorption in pregnant, vitamin E-deficient rats fed lard-containing diets that were easily oxidizable.

Known for its antioxidant properties, Vitamin E protects the human body from harmful compounds called free radicals. These radicals are typically formed when our body converts food into energy. However, they can also come from air pollution, cigarette smoke, and UV light.

Today, there are two naturally occurring isoforms of Vitamin E: tocopherol and tocotrienol. Both these isoforms of Vitamin E can be further categorized into four forms: alpha (α-), beta (β-), gamma (γ-), and delta (δ-). Of these, the most active Vitamin E in humans is Alpha (α-) Tocopherol.

Unfortunately, this has resulted in the oversight of tocotrienols, with only 3% of publications related to Vitamin E performing research on them. The little research that has been done on tocotrienols has found them to have anti-inflammatory and antioxidant properties that are superior to the same in α-tocopherol.

Discovered much later than α-tocopherol in the mid-1960s , tocotrienols are said to lower lipids and reduce cardiovascular diseases and inhibition of cancers.

Some of the properties unique to tocotrienols that are not found in tocopherols include potent radio protectant against radiation damage and depleting inflammation through downregulation of transcription factor NF-κB activation.

Other than cancer , vitamin E has shown to have therapeutic benefits for eye, bone, neurological, nephrological, and cardiovascular diseases. However, to get a better understanding of Vitamin E's therapeutic potentials as well as its modes of action and protective effects beyond cancer, we need to perform a comparison of its two isoforms: tocopherols against tocotrienols. This whitepaper does exactly that.

In this whitepaper, we will discuss the biochemical and physical makeup of the two Vitamin E isoforms, including the source of tocotrienol and bioavailability and pharmacokinetics of Vitamin E before comparing tocopherols against tocotrienols for therapeutic benefits beyond cancer.

Niki E, Traber M, G: A History of Vitamin E. Ann Nutr Metab 2012;61:207-212
Pennock JF et al., "Reassessment of tocopherol in chemistry," Biochemical and Biophysical Research Communications, vol. 17, no. 5 (November 30, 1964): 542-548

Whittle KJ et al., "The isolation and properties of delta-tocotrienol from Hevea latex," The Biochemical Journal, vol. 100, no. 1 (July 1966): 138-145

Sylvester P et al., "Role of tocotrienols in the prevention of cardiovascular disease and breast cancer," Current Topics in Nutraceutical Research, vol. 1, no. 2 (May 2003): 121-136

Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med. 1994;330:1029-35

3. Biochemical and Physical Properties of Vitamin E Isoforms

As stated in the introduction, Vitamin E has two naturally occurring isoforms: tocopherol and tocotrienol that can be further categorized into four forms: alpha (α-), beta (β-), gamma (γ-), and delta (δ-).

In its original form, Vitamin E is a yellow colored adhesive liquid or oil that immediately oxidizes when exposed to oxygen, transition metal ions, and light. Vitamin E isoforms are not water-soluble. Instead, they are dissolved in alcohol, organic solvents, and vegetable oils.

In addition to the above, the two Vitamin E isoforms possess the same basic chemical structure. This means that a C16 isoprenoid side chain is attached at the C-2 of a chromane ring in both isoforms of Vitamin E. However, unlike tocopherols that have a saturated phytyl isoprenoid side chain at these locations, tocotrienols have an unsaturated farnesyl isoprenoid side chain at C-3 , C-7 and C-11 .

The collective term used for the Vitamin E isoformstocopherol and tocotrienol is tocochromanols. Amphipathic molecules essential in the human diet, tocochromanols have a lipophilic isoprenoid side chain and a polar chromanol ring. The penetration of tocotrienol into fatty tissues, such as the brain and liver, is potentially enhanced by its unsaturated isoprenoid side chain. This also enables better distribution on the cell membranes.

In nature, Vitamin E includes dextrorotatory enantiomers comprising of only one stereoisomer. While tocopherols contain three chiral stereocenters at C-2, C- 4 and C-8 , tocotrienols have only one chiral stereocenter at C-2; this is because the C_C unsaturation in the isoprenoid tail does not allow the other two chiral stereocenters.

Bramley, P., Elmadfa, I., Kafatos, A., Kelly, F., Manios, Y., Roxborough, H., et al. (2000). Vitamin E. J Sci Food Agric 80, 913–938.

Falk, Jon & Munné-Bosch, Sergi. (2010). Tocochromanol functions in plants: Antioxidation and beyond. Journal of experimental botany. 61. 1549-66

Suzuki, Y. J., Tsuchiya, M., Wassall, S. R., Choo, Y. M., Govil, G., Kagan, V. E., et al. (1993). Structural and dynamic membrane properties of alpha-tocopherol and alphatocotrienol: implication to the molecular mechanism of their antioxidant potency. Biochemistry 32, 10692–10699

Colombo,M. L. (2010). An update on vitamin E, tocopherol and tocotrienol—perspectives. Molecules 15, 2103–2113

3.1 Source of Tocotrienol

Unlike palm oil and rice bran, annatto seeds contain only one type of Vitamin E isoform, which is tocotrienol . Annatto is said to have many benefits; these include antimicrobial properties , healthy digestion , strengthening bones , prevention of birth defects, eye care , skin care , wound healing , relief from stomach issues, expectorant properties , diuretic properties, hepatoprotective properties, gonorrhea treatment, diabetes control , and anticancer potential.

On extracting annatto seeds' lipid fraction with a Soxhlet apparatus, Frega et.al. (1998) found that the antioxidant fraction contained only tocotrienols but no tocopherols. In fact, the seeds comprised mainly of δ-tocotrienol. Gas chromatography-mass spectrometry confirmed tocotrienols' presence. Along with high-performance liquid chromatography, the gas chromatography also established the δ-tocotrienol quantities; these were 140–147 mg/100 g dry seeds and 5.2–5.5% wt./ of lipid extract. At present, there are no species of vegetables with comparable δ-tocotrienol concentrations.

3.2 Bioavailability and Pharmacokinetics of Vitamin E

Alpha-tocopherol transfer protein (αTTP) regulates the body-wide distribution of Vitamin E isoforms tocopherol and tocotrienol. However, a study has found that αTTP has a lower affinity to bind to α-tocotrienol than α-tocopherol.

Frega, N., Mozzon, M., & Bocci, F. (1998). Identification and estimation of tocotrienols in the annatto lipid fraction by gas chromatography–mass spectrometry. J Am Oil Chem Soc 75, 1723–1727

Galindo Cuspinera, Veronica & Westhoff, Dennis & Rankin, Scott. (2003). Antimicrobial Properties of Commercial Annatto Extracts against Selected Pathogenic, Lactic Acid, and Spoilage Microorganisms. Journal of food protection. 66. 1074-8

Cozma-Petruţ, A., Loghin, F., Miere, D., & Dumitraşcu, D. L. (2017). Diet in irritable bowel syndrome: What to recommend, not what to forbid to patients!. World journal of gastroenterology, 23(21), 3771–3783.

Analysis of the seed Bixa orellana, L. (annatto) and the waste generated in the extraction of its pigments
Wurts, M.L.; Torreblanca, R.A. Archivos Latinoamericanos de Nutricion 33(3): 606-619 1983

Mercadante, A.Z.; Steck, A.; Pfander, H Isolation and structure elucidation of minor carotenoids from annatto (Bixa orellana L.) seeds. Phytochemistry 46(8): 1379-1383 1997

Kiokias, S., & Gordon, M. H. (2003). Antioxidant properties of annatto carotenoids. Food chemistry, 83, 523-529. doi: 10.1016/S0308-8146(03)00148-1

O N Irobi, M Moo-Young, and W A Anderson, Antimicrobial activity of annatto (bixa orellana) extract, International Journal of Pharmacognosy 34 (1996), no. 2, 87–90

shaik sha valli khan, Patan & Ekambaranellore, Prakash & Rao, K.. (2002). Callus induction and plantlet regeneration in Bixa orellana L., an Annatto-yielding tree. In Vitro Cellular & Developmental Biology - Plant. 38. 186-190

Teles, Flávio & Anjos, Felipe & Machado, Tarcilo & Lima, Roberta. (2014). Bixa orellana (annatto) exerts a sustained hypoglycemic effect in experimental diabetes mellitus in rats. Medical Express

Júnior, Antonio & Asad, Lídia & Oliveira, Eduardo & Kovary, Karla & Asad, Nazia & Felzenszwalb, Israel. (2005). Antigenotoxic and antimutagenic potential of an annatto pigment (norbixin) against oxidative stress. Genetics and molecular research : GMR. 4. 94-9

Morley, S., Cecchini, M., Zhang, W., Virgulti, A., Noy, N., Atkinson, J., & Manor, D. (2008). Mechanisms of ligand transfer by the hepatic tocopherol transfer protein. The Journal of biological chemistry, 283(26), 17797–17804

Hosomi, A., Arita, M., Sato, Y., Kiyose, C., Ueda, T., Igarashi, O., et al. (1997). Affinity for α-tocopherol transfer protein as a determinant of the biological activities of vitamin E analogs. FEBS Lett 409, 105–108

Unbounded isoforms of Vitamin E to an αTTP in the liver are prone to catabolization via cytochrome P450 (CYP4F2)-initiated ω-hydroxylation and oxidation by ω-hydroxylase.

As a result of these two neutralizing interactions, α-tocopherol is said to be the predominant isoform to be accumulated in tissues where other vitamin E isoforms are metabolized to carboxychromanols, hydroxycarboxychromanol, and carboxyethylhydroxychroman derivatives.

This led to a decade-long debate around the ability of orally-administered tocotrienols to reach vital organs in the body; this affected the research on tocotrienols in the 1990s. Although αTTP has a lower affinity towards tocotrienols, we cannot say for sure, if and how much, the transport of orally administered tocotrienols to vital organs depends on αTTP.

In one study, female mice were rendered infertile when αTTP is knockout, where they suffered from α-tocopherol deficiency in spite of dietary α- tocopherol supplementation. Interestingly, oral supplementation of α-tocotrienol to female mice restored fertility in these αTTP knockout mice under α-tocopherol deficiency. This suggests other transport machinery or mechanisms for the absorption and transport of tocotrienols beyond the αTTP.

In a 2003 study, the pharmacokinetics of α-, γ-, and δ-tocotrienol via intramuscular, intraperitoneal, intravenous, and oral routes in rats were determined. It was found that the absorption of tocotrienols administered via intramuscular and intraperitoneal routes was negligible and should be avoided.

The study also found that tocotrienols have incomplete absorption and limited bioavailability in rats, where the bioavailability of α-tocotrienol was approximately 28%, and 9% for both γ- and δ-tocotrienols. It was observed that that time need to reach peak plasma concentration for α-, γ-, and δ-tocotrienol was 3.3, 3.0 and 2.8 h respectively, while the half-life was approximately 3 h for α-tocotrienol and 2 h for γ- and δ-tocotrienols in rats.

Jiang, Q. (2014). Natural forms of vitamin E: metabolism, antioxidant, and anti-inflammatory activities and their role in disease prevention and therapy. Free Radic Biol Med 72, 76–90

Birringer, M., Pfluger, P., Kluth, D., Landes, N., & Brigelius-Flohé, R. (2002). Identities and differences in the metabolism of tocotrienols and tocopherols in HepG2 cells. J Nutr 132, 3113–3118

Jishage, K. -i., Arita, M., Igarashi, K., Iwata, T., Watanabe, M., Ogawa, M., et al. (2001). α-Tocopherol transfer protein is important for the normal development of placental labyrinthine trophoblasts in mice. J Biol Chem 276, 1669–1672

Khanna, S., Patel, V., Rink, C., Roy, S., & Sen, C. K. (2005a). Delivery of orally supplemented α-tocotrienol to vital organs of rats and tocopherol-transport protein deficient mice. Free Radic Biol Med 39, 1310–1319

Yap, S. P., Yuen, K. H., & Lim, A. B. (2003). Influence of route of administration on the absorption and disposition of α,- γ- and δ-tocotrienols in rats. J Pharm Pharmacol 55, 53–58

A separate study found that the half-life of α-, γ-, and δ-tocotrienol in plasma in humans was estimated to be 2.3, 4.4, and 4.3 h, respectively. Furthermore, another study found that the half-life of α-tocopherol and γ-tocopherol in humans was 57 and 13 h, respectively.

4. Vitamin E as An Antioxidant

Considered to be one of the most effective antioxidants available today, Vitamin E gets its antioxidant property from the hydroxyl group, more specifically from the aromatic ring of tocochromanols.

This ring of tocochromanols provisions hydrogen to neutralize free radicals or reactive oxygen species (ROS). The sheer number of ethyl groups on the chromanol ring determines, to a large extent, the reaction rates between Vitamin E isoforms.
Generally, both tocopherol and tocotrienol, which includes their α-, β- and γ-isoforms, are said to have similar antioxidant activity. However, some studies show the superiority of α-tocotrienol over α- tocopherol in neutralizing the peroxyl radicals and lipid peroxidation in rat liver and liposomal membranes.

For instance, palm tocotrienol rich fraction (TRF) was found to be more than α-tocopherol in attenuating thiobarbituric reactive substances in human umbilical vein endothelial cell (HUVEC) cells [29]. Additionally, γ-tocotrienol elicited a stronger, protective effect against oxidative damage in rat brain mitochondria . Moreover, another study found that the administration of tocotrienols abated protein carbonylation and extended mean life span, where α-tocopherol supplementation had no effect.

Yap, S. P., Yuen, K. H., & Wong, J.W. (2001). Pharmacokinetics and bioavailability of α-, γ- and δ-tocotrienols under different food status. J Pharm Pharmacol 53, 67–71

Leonard, S. W., Paterson, E., Atkinson, J. K., Ramakrishnan, R., Cross, C. E., & Traber, M. G. (2005). Studies in humans using deuterium-labeled α- and γ-tocopherols demonstrate faster plasma γ-tocopherol disappearance and greater γ-metabolite production. Free Radic Biol Med 38, 857–866

Ghafoorunissa, Hemalatha, S., & Rao, M. V. (2004). Sesame lignans enhance antioxidant activity of vitamin E in lipid peroxidation systems.Mol Cell Biochem262, 195–202

Serbinova, E., Kagan, V., Han, D., & Packer, L. (1991). Free radical recycling and intramembrane mobility in the antioxidant properties of alpha-tocopherol and alpha-tocotrienol. Free Radic Biol Med 10, 263–275

Suzuki, Y. J., Tsuchiya, M., Wassall, S. R., Choo, Y. M., Govil, G., Kagan, V. E., et al. (1993). Structural and dynamic membrane properties of alpha-tocopherol and alphatocotrienol: implication to the molecular mechanism of their antioxidant potency. Biochemistry 32, 10692–10699

labyrinthine trophoblasts in mice. J Biol Chem 276, 1669–1672.
Kamat, J. P., & Devasagayam, T. P. A. (1995). Tocotrienols from palm oil as potent inhibitors of lipid peroxidation and protein oxidation in rat brain mitochondria. Neurosci Lett 195, 179–182

Adachi, H., & Ishii, N. (2000). Effects of tocotrienols on life span and protein carbonylation in Caenorhabditis elegans. J Gerontol Ser A Biol Med Sci 55, B280–B285

5. Tocopherol and Tocotrienol Compared for Vitamin E Therapy Beyond Cancer

5.1 Bone Diseases Osteoporosis

A metabolic bone disease, osteoporosis is the degeneration of microarchitecture and bone density, which can lead to a fragile done and even fracture.

In the pathogenesis of osteoporosis, we find the involvement of both oxidative stress and inflammation. One study finds that the effects of vitamin E isoforms have been widely explored in many experimental osteoporosis models since they are known to be anti-inflammatory and anti-oxidative agents. The study also finds tocopherol supplementation's effects on bone to be inconsistent and somewhat contradictory.

Some studies show high α-tocopherol to affect bone in relaxed animals negatively but provide protection in stressed animals. , , Additionally, a recent study found an increase in bone resorption and a decrease in bone mass in mice fed with high-dose α-tocopherol. The reason cited for this was an increase in osteoclast fusion and differentiation.
There were some studies that displayed the beneficial effects ofα-tocopherol on bone loss while other studies did show this effect but instead exhibited improved bone quality due to α-tocopherol. ,

Chin, K. Y., & Ima-Nirwana, S. (2014a). The effects of alpha-tocopherol on bone: a doubleedged sword? Nutrients 6, 1424–1441

Arjmandi, B., Juma, S., Beharka, A., Bapna, M., Akhter, M., & Meydani, S. (2002). Vitamin E improves bone quality in the aged but not in young adult male mice. J Nutr Biochem 13, 543

Hampson, G., Edwards, S., Sankaralingam, A., Harrington, D. J., Voong, K., Fogelman, I., et al. (2015). Circulating concentrations of vitamin E isomers: association with bone turnover and arterial stiffness in post-menopausal women. Bone 81, 407–412

Smith, B. J., Lucas, E. A., Turner, R. T., Evans, G. L., Lerner, M. R., Brackett, D. J., et al. (2005). Vitamin E provides protection for bone in mature hindlimb unloaded male rats. Calcif Tissue Int 76, 272–279

Fujita, K., Iwasaki, M., Ochi, H., Fukuda, T., Ma, C., Miyamoto, T., et al. (2012). Vitamin E decreases bone mass by stimulating osteoclast fusion. Nat Med 18, 589–594

Chai, S. C.,Wei, C. I., Brummel-Smith, K., & Arjmandi, B. H. (2008). The role of vitamin E in reversing bone loss. Aging Clin Exp Res 20, 521–527

Feresin, R. G., Johnson, S. A., Elam, M. L., Kim, J. S., Khalil, D. A., Lucas, E. A., et al. (2013). Effects of vitamin e on bone biomechanical and histomorphometric parameters in ovariectomized rats. J Osteoporos 2013, 825985

Research that compared the effect of tocotrienols versus tocopherols on osteoporosis found that when compared with tocotrienols, tocopherols were either comparable or less effective in protecting bone in animals.

Another study found tocotrienols supplement to reduce oxidative stress product malondialdehyde (MDA) as well as preserving and increasing antioxidant enzyme activities in vivo. Additionally, it was shown in an in vitro study that γ-tocotrienol homolog decreased oxidative damage on primary osteoblast culture.

In another research, it was found that tocotrienols exerted its biological actions not only by antioxidant property but by suppressing the mevalonate pathway. This pathway is said to promote bone loss by regulating osteoblastogenesis and osteoclastogenesis through activation of GTPase.

Finally, it was found by a recent study that supplementing mice with emulsified γ-tocotrienol via subcutaneous injection significantly protected them from ovariectomy-induced bone loss.

5.2 Cardiovascular Diseases

According to research, Vitamin E isoforms have therapeutic benefits for cardiovascular diseases as well. A chronic inflammatory disorder, a cardiovascular disease occurs due to the infiltration of lymphocyte into the arterial wall, smooth muscle cell proliferation, and damage in the arterial wall caused by the accumulation of extracellular matrix.

A study investigated the effects tocotrienol rich fraction (TRF) on the microscopic development of atherosclerosis and lipid peroxidation in the aorta of rabbits. It was found that, after 10 weeks of treatment with TRF, cholesterol-fed rabbits had lower aortic contents of MDA, less intimal thickening, and greater preservation of the internal elastic lamina, consistent with reduced lipid peroxidation as compared to the rabbits fed with a normal diet.

Hermizi, H., Faizah, O., Ima-Nirwana, S., Ahmad Nazrun, S., & Norazlina, M. (2009). Beneficial effects of tocotrienol and tocopherol on bone histomorphometric parameters in Sprague–Dawley male rats after nicotine cessation. Calcif Tissue Int 84, 65–74

Maniam, S., Mohamed, N., Shuid, A. N., & Soelaiman, I. N. (2008). Palm tocotrienol exerted better antioxidant activities in bone than alpha-tocopherol. Basic Clin Pharmacol Toxicol 103, 55–60

Muhammad, N., Luke, D. A., Shuid, A. N., Mohamed, N., & Soelaiman, I. N. (2012). Two different isomers of vitamin e prevent bone loss in postmenopausal osteoporosis rat model. Evid Based Complement Alternat Med 2012, 161527

Abd Manan, N., Mohamed, N., & Shuid, A. N. (2012). Effects of low-dose versus high-dose gamma-tocotrienol on the bone cells exposed to the hydrogen peroxide-induced oxidative stress and apoptosis. Evid Based Complement Alternat Med 2012, 680834

Nizar, A. M., Nazrun, A. S., Norazlina, M., Norliza, M., & Ima Nirwana, S. (2011). Low dose of tocotrienols protects osteoblasts against oxidative stress. Clin Ter 162, 533–538

Mo, H., Yeganehjoo, H., Shah, A., Mo, W. K., Soelaiman, I. N., & Shen, C. L. (2012)

Deng, L., Ding, Y., Peng, Y.,Wu, Y., Fan, J., Li,W., et al. (2014). Gamma-tocotrienol protects against ovariectomy-induced bone loss via mevalonate pathway as HMG-CoA reductase inhibitor. Bone 67, 200–207

Nafeeza, M. I., Norzana, A. G., Jalaluddin, H. L., & Gapor, M. T. (2001). The effects of a tocotrienol-rich fraction on experimentally induced atherosclerosis in the aorta of

The prevention of atherosclerosis through the modulation of activities of peroxisome proliferator-activated receptors (PPAR) by tocotrienol-enriched palm oil was also shown by a separate study.

A recent study that was conducted to compare TRF in patients undergoing chronic hemodialysis showed that TRF supplementation showed improvement in lipid profiles in terms of plasma total cholesterol, triglycerides, and high-density lipoprotein (HDL) when compared with placebo.

The above-mentioned studies suggest that TRF supplementation can improve lipid profiles to prevent atherosclerosis. On the other hand, and too much surprise, dietary supplementation with α-tocopherol (400 IU/d) oxidized HDL-2 and HDL-3, showing a proatherogenic effect.

Another study described the superior effect of another tocopherol isoform γ-tocopherol over α-tocopherol in terms of preventing oxidative stress, where γ-tocopherol but not α-tocopherol supplementation reduced biomarkers of oxidative stress in patients with metabolic syndrome.

In a clinical study conducted in healthy men, the supplementation of a γ-tocopherol-rich mixture of tocopherols attenuated postprandial hyperglycemia-induced MDA level, oxidative stress, and vascular endothelial dysfunction, independent of inflammation.

In a separate study, the effects of α-tocopherol, α-tocotrienol, or TRF on in vivo platelet thrombosis and ex vivo platelet aggregation were compared. After intravenous injection in anesthetized dogs, tocotrienols were significantly better than tocopherols in inhibiting cyclic flow reductions.

rabbits. Malays J Pathol 23, 17–25

Li, F., Tan,W., Kang, Z., & Wong, C.W. (2010). Tocotrienol enriched palm oil prevents atherosclerosis through modulating the activities of peroxisome proliferators-activated receptors. Atherosclerosis 211, 278–282

Daud, Z. A., Tubie, B., Sheyman, M., Osia, R., Adams, J., Tubie, S., et al. (2013). Vitamin E tocotrienol supplementation improves lipid profiles in chronic hemodialysis patients. Vasc Health Risk Manag 9, 747–761

Wade, L., Nadeem, N., Young, I. S., Woodside, J. V., McGinty, A., McMaster, C., et al. (2013). Alpha-tocopherol induces proatherogenic changes to HDL2 & HDL3: an in vitro and ex vivo investigation. Atherosclerosis 226, 392–397

Devaraj, S., Leonard, S., Traber, M. G., & Jialal, I. (2008). Gamma-tocopherol supplementation alone and in combination with alpha-tocopherol alters biomarkers of oxidative stress and inflammation in subjects with metabolic syndrome. Free Radic Biol Med 44, 1203–1208

Mah, E., Noh, S. K., Ballard, K. D., Park, H. J., Volek, J. S., & Bruno, R. S. (2013). Supplementation of a gamma-tocopherol-rich mixture of tocopherols in healthy men protects against vascular endothelial dysfunction induced by postprandial hyperglycemia. J Nutr Biochem 24, 196–203

Qureshi, A. A., Karpen, C. W., Qureshi, N., Papasian, C. J., Morrison, D. C., & Folts, J. D. (2011). Tocotrienols-induced inhibition of platelet thrombus formation and platelet aggregation in stenosed canine coronary arteries. Lipids Health Dis 10, 58

The research above suggests that tocotrienols provide a better therapeutic benefit for cardiovascular diseases than tocopherols.

5.3 Diabetes

A 2004 prospective study found that the intake of vitamin E reduced the risk of the onset of type 2 diabetes after a 23-year follow-up. Another study found that TRF reduced total cholesterol, low-density lipoprotein (LDL), and total lipid in diabetic patients.

In a separate study, patients were given tocotrienol-enriched canola oil (200 mg/day tocotrienols). The results showed a significant reduction in serum C-reactive protein (CRP) and urine microalbumin.

Another study found that that α-, γ-, and δ-tocotrienols but not α-tocopherol, could bind PPARα and increase its interaction with LXXLL motif of PGC-1α peptide. A separate study found α-tocopherol to accelerate wound healing, in addition to reducing plasma MDA level and increasing glutathione peroxidase activities in diabetic rats.

Finally, TRF was shown to have a protective effect on blood vessel walls, lowering levels of MDA and 4-hydroxynonenal.

5.4 Eye Disorders

A form of eye disorder, Cataractogenesis, or simply cataract is characterized by the progression of lenticular opacities; nitrosative and oxidative stress in the lenticular cells are said to be the drivers of this eye disorder.

In one study, it was observed that topical tocotrienol in the range of 0.01–0.05% reduced nitrosative and oxidative stress, delaying the onset and progression of cataract. However, the

Montonen, J., Knekt, P., Järvinen, R., & Reunanen, A. (2004). Dietary antioxidant intake and risk of type 2 diabetes. Diabetes Care 27, 362–366

Baliarsingh, S., Beg, Z. H., & Ahmad, J. (2005). The therapeutic impacts of tocotrienols in type 2 diabetic patients with hyperlipidemia. Atherosclerosis 182, 367–374

Haghighat, N., Vafa, M., Eghtesadi, S., Heidari, I., Hosseini, A., & Rostami, A. (2014). The effects of tocotrienols added to canola oil on microalbuminuria, inflammation, and nitrosative stress in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. Int J Prev Med 5, 617–623

Fang, F., Kang, Z., & Wong, C. (2010). Vitamin E tocotrienols improve insulin sensitivity through activating peroxisome proliferator-activated receptors. Mol Nutr Food Res 54, 345–352

Musalmah, M., Fairuz, A. H., Gapor,M. T., & Ngah,W. Z. (2002). Effect of vitamin E on plasma malondialdehyde, antioxidant enzyme levels and the rates of wound closures during wound healing in normal and diabetic rats. Asia Pac J Clin Nutr 11(Suppl. 7), S448–S451

Budin, S. B., Othman, F., Louis, S. R., Bakar, M. A., Das, S., & Mohamed, J. (2009). The effects of palm oil tocotrienol-rich fraction supplementation on biochemical parameters, oxidative stress and the vascular wall of streptozotocin-induced diabetic rats. Clinics (Sao Paulo) 64, 235–244

same study also found that 0.2% or higher concentration of topical tocotrienol led to increased lens oxidative stress and aggravated cataractogenesis.

Another study found that the level of α-tocotrienol was significantly higher than α-tocopherol in administered tissues, but there was not much difference in the intraocular penetration of γ-tocotrienol and γ-tocopherol.

However, it was shown by a separate study that only α-tocotrienol significantly inhibited the growth of fibroblasts but no other isoforms of vitamin E such as α-tocopherol.

5.5 Inflammatory Diseases

According to a study, vitamin E isoforms could attenuate PGD2 and PGE2, respectively, with varying potencies, in lipopolysaccharide-induced RAW264.7 macrophage and IL-1β- induced lung epithelial cell models.

The study found that the production of LTB4 and LTC4 in HL-60 cells and human neutrophils, when stimulated with ionophore (A23187), was abrogated by γ-, δ-tocopherol, and γ-tocotrienol. α-Tocopherol was much less potent in reducing leukotrienes as compared to γ-tocotrienol.

Another study found that that γ-tocotrienol was more potent than all tocopherol isoforms in ameliorating lipopolysaccharide-induced RAW246.7 macrophage production of IL-6 and G-CSF, probably via the downregulation of NF-κB activation and suppression of CCAAT-enhancer binding protein (C/EBP).

Finally, the screening of different vitamin E isoforms in a house dust mite-induced asthma mouse model identified γ-tocotrienol as the promising candidate in treating asthma.

5.6 Lipid Disorder

A group of conditions, lipid disorders involve high levels of fatty molecules, such as cholesterol and triglycerides in the blood. In the 1980s, the cholesterol-lowering properties of tocotrienols

Montonen, J., Knekt, P., Järvinen, R., & Reunanen, A. (2004). Dietary antioxidant intake and risk of type 2 diabetes. Diabetes Care 27, 362–366

Baliarsingh, S., Beg, Z. H., & Ahmad, J. (2005). The therapeutic impacts of tocotrienols in type 2 diabetic patients with hyperlipidemia. Atherosclerosis 182, 367–374

Haghighat, N., Vafa, M., Eghtesadi, S., Heidari, I., Hosseini, A., & Rostami, A. (2014). The effects of tocotrienols added to canola oil on microalbuminuria, inflammation, and nitrosative stress in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. Int J Prev Med 5, 617–623

Fang, F., Kang, Z., & Wong, C. (2010). Vitamin E tocotrienols improve insulin sensitivity through activating peroxisome proliferator-activated receptors. Mol Nutr Food Res 54, 345–352

Musalmah, M., Fairuz, A. H., Gapor,M. T., & Ngah,W. Z. (2002). Effect of vitamin E on plasma malondialdehyde, antioxidant enzyme levels and the rates of wound closures during wound healing in normal and diabetic rats. Asia Pac J Clin Nutr 11(Suppl. 7), S448–S451

Budin, S. B., Othman, F., Louis, S. R., Bakar, M. A., Das, S., & Mohamed, J. (2009). The effects of palm oil tocotrienol-rich fraction supplementation on biochemical parameters, oxidative stress and the vascular wall of streptozotocin-induced diabetic rats. Clinics (Sao Paulo) 64, 235–244

started to gain traction, and they were found to inhibit HMG-CoA reductase, a mechanism, which is not prevalent in tocopherols.

In a separate study, tocotrienols were observed to inhibit HMG-CoA reductase by post-transcriptional suppression of the enzyme itself. Additionally, one study found that γ- tocotrienol has a 30-fold increase over α-tocotrienol in inhibiting HMG-CoA reductase.

The same study also used a hypercholesterolemia and atheroma model of rabbits on an atherogenic diet and found that treatment with 50 mg/day TRF led to a larger reduction in serum total cholesterol, lipid peroxide, and LDL as compared to treatment with 50 mg/day α-tocopherol. However, their effects were similar for serum triglyceride and HDL.

5.7 Nephropathy

This condition occurs due to damage or disease to the kidney. Often dialysis is required as a treatment if a transplant is not possible.

Recently, a vitamin E-coated membrane has been developed, which serves to reduce circulating lipid peroxidation during dialysis.

Additionally, one study found that membrane-bounded α-tocopherol could effectively reduce 8-hydroxy-2-deoxyguanosine (8-OHdG) level in the leukocyte DNA of chronic hemodialysis patients.

Other studies have demonstrated that membrane coated with α-tocopherol could increase red blood cell survivability and decrease serum-free 4-hydroxynonenal during dialysis. , Finally, a study found that when combined with insulin, tocotrienol drastically suppressed TNF-α-induced NF-κB and caspase 3 activation.

Pearce, B. C., Parker, R. A., Deason, M. E., Qureshi, A. A., & Wright, J. J. K. (1992). Hypocholesterolemic activity of synthetic and natural tocotrienols. J Med Chem 35, 3595–3606

Parker, R. A., Pearce, B. C., Clark, R. W., Gordon, D. A., & Wright, J. J. (1993). Tocotrienols regulate cholesterol production in mammalian cells by post-transcriptional suppression of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. J Biol Chem 268, 11230–11238

Teoh, M. K., Chong, J. M., Mohamed, J., & Phang, K. S. (1994). Protection by tocotrienols against hypercholesterolaemia and atheroma. Med J Malaysia 49, 255–262

Cruz, D. N., de Cal, M., & Ronco, C. (2008). Oxidative stress and anemia in chronic hemodialysis: the promise of bioreactive membranes. Contrib Nephrol 161, 89–98

Tarng, D. -C., Huang, T. -P., Liu, T. -Y., Chen, H. -W., Sung, Y. -J., & Wei, Y. -H. (2000). Effect of vitamin E-bonded membrane on the 8-hydroxy 2[prime]-deoxyguanosine level in leukocyte DNA of hemodialysis patients. Kidney Int 58, 790–799

Odetti, P., Traverso, N., Monacelli, F.,Menini, S., Vazzana, J., Tasso, B., et al. (2006). Vitamin E-coated filter decreases levels of free 4-hydroxyl-2-nonenal during haemodialysis sessions. Free Radic Res 40, 207–212

Usberti,M., Gerardi, G., Bufano, G., Tira, P., Micheli, A., Albertini, A., et al. (2002). Effects of erythropoietin and vitamin E-modified membrane on plasma oxidative stress markers and anemia of hemodialyzed patients. Am J Kidney Dis 40, 590–599

Kuhad, A., & Chopra, K. (2009a). Attenuation of diabetic nephropathy by tocotrienol: involvement of NFkB signaling pathway. Life Sci 84, 296–301

5.8 Neurological Diseases

The main mediator of excitatory signals in the mammalian central nervous system is glutamate. When glutamate in the extracellular spaces reaches extreme amounts, it can lead to several neurodegenerative diseases.
Several studies have identified that nanomolar α-tocotrienols were more effective than α-tocopherol in preventing glutamate-induced injury and death.

However, some studies found that vitamin E isoforms, both TRF and α-tocopherol could protect glutamate-injured neuronal cells and astrocytes through their anti-oxidative properties.

Another study demonstrated that that γ-/δ-tocotrienol exhibited not only antioxidant effects but also a receptor signal-mediated neuroprotective action.

Finally, clinical studies were conducted to evaluate the neuroprotective effects of vitamin E supplementation in patients treated with cisplatin chemotherapy. Oral α-tocopherol (400 mg/day) or placebo started before chemotherapy and continued for 3 months after cisplatin treatment in a total of 108 patients. The results showed that both the incidence and the severity of neurotoxicity were significantly lower in the α-tocopherol supplemented group as compared to the placebo.

5.9 Radiation Damages

Exposure to radiation damage can be lethal. At a low dose of radiation, it can cause hematopoietic syndrome, a condition in which blood cells, platelets, and bone marrow are damaged. At high doses beyond 10.0 Gy, radiation damage can reach the central nervous system and cause cognitive dysfunction, cerebrovascular collapse, shock, and pneumonitis, where death is certain within two weeks.

Khanna, S., Roy, S., Slivka, A., Craft, T. K., Chaki, S., Rink, C., et al. (2005b). Neuroprotective properties of the natural vitamin E alpha-tocotrienol. Stroke 36, 2258–2264

Khanna, S., Parinandi, N. L., Kotha, S. R., Roy, S., Rink, C., Bibus, D., et al. (2010). Nanomolar vitamin E alpha-tocotrienol inhibits glutamate-induced activation of phospholipase A2 and causes neuroprotection. J Neurochem 112, 1249–1260

Khanna, S., Roy, S., Ryu, H., Bahadduri, P., Swaan, P. W., Ratan, R. R., et al. (2003). Molecular basis of vitamin E action: tocotrienolmodulates 12-lipoxygenase, a keymediator of glutamate-induced neurodegeneration. J Biol Chem278, 43508–43515

Sen, C. K., Khanna, S., Roy, S., & Packer, L. (2000). Molecular basis of vitamin E action. Tocotrienol potently inhibits glutamate-induced pp 60(c-Src) kinase activation and death of HT4 neuronal cells. J Biol Chem275, 13049–13055

Rati Selvaraju, T., Khaza'ai, H., Vidyadaran, S., Sokhini Abd Mutalib, M., Ramachandran, V., & Hamdan, Y. (2014). Cytoprotective effect of tocotrienol-rich fraction and alphatocopherol vitamin E isoforms against glutamate-induced cell death in neuronal cells. Int J Vitam Nutr Res 84, 140–151

Nakaso, K., Tajima, N., Horikoshi, Y., Nakasone, M., Hanaki, T., Kamizaki, K., et al. (2014). The estrogen receptor beta-PI3K/Akt pathway mediates the cytoprotective effects of tocotrienol in a cellular Parkinson's disease model. Biochim Biophys Acta 1842, 1303–1312

Pace, A., Giannarelli, D., Galie, E., Savarese, A., Carpano, S., Della Giulia, M., et al. (2010). Vitamin E neuroprotection for cisplatin neuropathy: a randomized, placebocontrolled trial. Neurology 74, 762–766

Waselenko, J. K.,MacVittie, T. J., Blakely,W. F., Pesik, N.,Wiley, A. L., Dickerson,W. E., et al.

The use of α-tocopherol as a radioprotector has been found partially effective in mouse models since 1986. More recent research shows γ-tocotrienol to be a better radioprotectant than α-tocopherol.

However, it is now widely accepted that both γ- and δ-tocotrienols are effective radioprotectants demonstrated in many pre-clinical studies.

Finally, a study suggests that γ-Tocotrienol is considered to be more efficacious than tocopherols against radiation damage due to its superior potency in inducing gene expression when tested in human endothelial cells. The inability of tocopherols to inhibit HMG-CoA reductase may explain why tocotrienols are better radioprotectants.

(2004). Medical management of the acute radiation syndrome: recommendations of the strategic national stockpile radiation working group. Ann Intern Med 140, 1037–1051

Bichay, T. J., & Roy, R. M. (1986). Modification of survival and hematopoiesis in mice by tocopherol injection following irradiation. Strahlenther Onkol 162, 391–399

Ghosh, S. P., Kulkarni, S., Hieber, K., Toles, R., Romanyukha, L., Kao, T. -C., et al. (2009). Gamma-tocotrienol, a tocol antioxidant as a potent radioprotector. Int J Radiat Biol 85, 598–606

Kulkarni, S., Ghosh, S. P., Satyamitra, M., Mog, S., Hieber, K., Romanyukha, L., et al. (2010). Gamma-tocotrienol protects hematopoietic stem and progenitor cells in mice after total-body irradiation. Radiat Res 173, 738–747

Berbée, M., Fu, Q., Boerma, M., Sree Kumar, K., Loose, D., & Hauer-Jensen, M. (2012). Mechanisms underlying the radioprotective properties of γ-tocotrienol: comparative gene expression profiling in tocol-treated endothelial cells. Genes Nutr 7, 75–81

Qureshi, A. A., Pearce, B. C., Nor, R. M., Gapor, A., Peterson, D. M., & Elson, C. E. (1996). Dietary α-tocopherol attenuates the impact of γ-tocotrienol on hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase activity in chickens. J Nutr 126, 389–394

6. Benefits of Annatto Tocotrienol

As mentioned in an earlier section, tocotrienol is the only vitamin E isoform present in annatto seeds that are said to contain a high amount of tocotrienol.

As revealed earlier, annatto is said to have many benefits including antimicrobial properties, healthy digestion, strengthening bones, prevention of birth defects, eye care, skincare, wound healing, relief from stomach issues, expectorant properties, diuretic properties, hepatoprotective properties, gonorrhea treatment, diabetes control, and anticancer potential.

In addition to the above, several benefits have been linked to the use of annatto tocotrienols. In fact, one study considers them to be more potent antioxidants than fish oil. 88 Moreover, data published in scientific journals suggest that the consumption of annatto tocotrienols may lead to the following health benefits:

- Slowing down of the denigrative process associated with aging 89
- Improved arterial health 90
- Prevention and control of prostate, skin, pancreatic, and breast cancer 91
- Lowered LDL and total cholesterol 92
- Control of diabetes 93
- Nervous system protection to prevent injuries related to a stroke

The use of α-tocopherol as a radioprotector has been found partially effective in mouse models since 1986. More recent research shows γ-tocotrienol to be a better radioprotectant than α-tocopherol.

However, it is now widely accepted that both γ- and δ-tocotrienols are effective radioprotectants demonstrated in many pre-clinical studies.

Finally, a study suggests that γ-Tocotrienol is considered to be more efficacious than tocopherols against radiation damage due to its superior potency in inducing gene expression when tested in human endothelial cells. The inability of tocopherols to inhibit HMG-CoA reductase may explain why tocotrienols are better radioprotectants.

7. Conclusion

Known for its antioxidant properties, Vitamin E protects the human body from harmful compounds called free radicals.
Discovered almost a century ago, Vitamin E is said to have therapeutic benefits for several diseases beyond cancer. These benefits are provisioned through the two isoforms of Vitamin E: tocopherol and tocotrienol.

These isoforms of Vitamin E can be further categorized into alpha (α-), beta (β-), gamma (γ-), and delta (δ-) tocopherols and tocotrienols. Of these, the most active Vitamin E in humans is alpha (α-) Tocopherol.

Unfortunately, this has resulted in the oversight of tocotrienols, with only 3% of publications related to Vitamin E performing research on them. The little research that has been done on tocotrienols has found them to have anti-inflammatory and antioxidant properties that are superior to the same in α-tocopherol.

In this whitepaper, we have discussed the biochemical and physical makeup of the two Vitamin E isoforms and compared them for therapeutic benefits beyond cancer. The findings of the whitepaper tend to agree with the research on tocotrienols that finds the anti-inflammatory and antioxidant properties in them to be superior to the same in α-tocopherol.

This results in therapeutic benefits for diseases beyond cancer such as osteoporosis, cardiovascular diseases, diabetes, eye disorders, inflammatory diseases, lipid disorder, nephropathy, neurological diseases, and radiation damages.