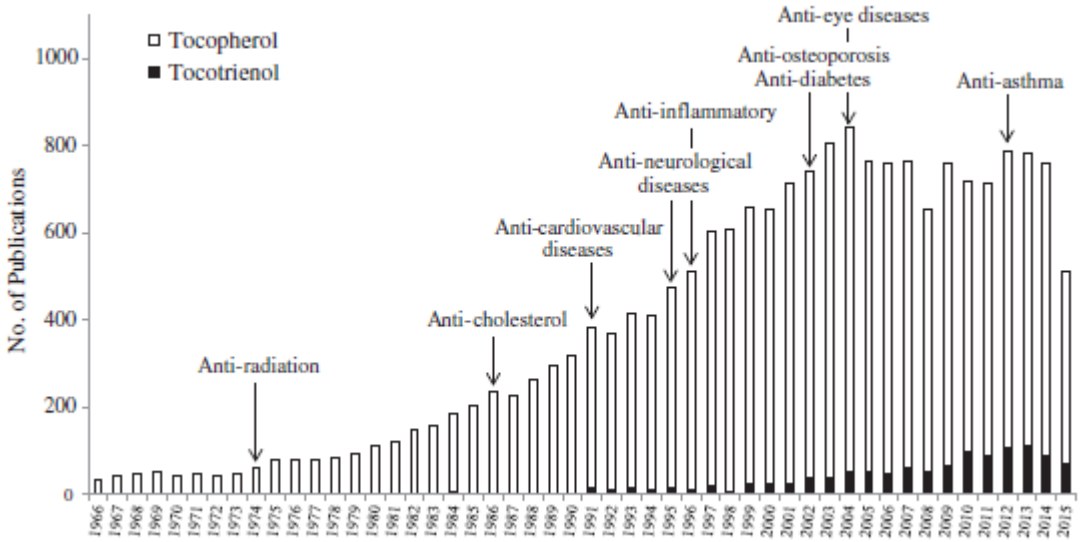
Vitamin E therapy beyond cancer: Tocopherol versus tocotrienol (Hong Yong Peh et al, Pharmacology & Therapeutics 162 (2016) 152–169)

David Terrero, Phd
Scientific Advisor
Bixahuman Lab

The discovery of vitamin E (α-tocopherol) began in 1922 as a vital component required in reproduction. Today, there are eight naturally occurring vitamin E isoforms, namely α-, β-, γ- and δ-tocopherol and α-, β-, γ- and δ- tocotrienol. Vitamin E is potent antioxidants, capable of neutralizing free radicals directly by donating hydrogen from its chromanol ring. α-Tocopherol is regarded the dominant form in vitamin E as the α-tocopherol transfer protein in the liver binds mainlyα-tocopherol, thus preventing its degradation. That contributed to the oversight of tocotrienols and resulted in less than 3% of all vitamin E publications studying tocotrienols. Nevertheless, tocotrienols have been shown to possess superior antioxidant and anti-inflammatory properties over α-tocopherol. In particular, inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase to lower cholesterol, attenuating inflammation via downregulation of transcription factor NF-κB activation, and potent radio protectant against radiation damage are some properties unique to tocotrienols, not tocopherols. Aside from cancer, vitamin E has also been shown protective in bone, cardiovascular, eye, nephrological and neurological diseases. In light of the different pharmacological properties of tocopherols and tocotrienols, it becomes critical to specify which vitamin E isoform(s) are being studied in any future vitamin E publications. This review provides an update on vitamin E therapeutic potentials, protective effects and modes of action beyond cancer, with comparison of tocopherols against tocotrienols. With the concerted efforts in synthesizing novel vitamin E analogs
and clinical pharmacology of vitamin E, it is likely that certain vitamin E isoform(s) will be therapeutic agents against human diseases besides cancer.

Vitamin E is one of the most widely consumed vitamins known for its antioxidant capacity and multiple health benefits. In 1912, Casimir Funk coined the term“vitamine” (obtained from vital and amine, meaning amine of life) as it was hypothesized that vitamine was chemical amines present in micronutrient food factors which prevented beriberi and other dietary-deficiency diseases (Funk, 1912). It was validated
subsequently that not all vitamine, such as vitamin C and vitamin E, contained amine group, thus it was shortened to “vitamin” in English. The discovery of vitamin E began in 1922 by Herbert Evans and
Katherine Bishop when they isolated an uncharacterized fat-soluble compound from green leafy vegetables which is required for reproduction (Evans & Bishop, 1922). Upon identifying the compound in 1924, it was termed as tocopherol (obtained from Greek words tokos and phero, meaning to bear children), also known as α-tocopherol presently. The search beyond α-tocopherol isoform started in 1947 by Stern et al., and it was in 1964 when tocotrienols were first discovered (Sen, Khanna, Rink, & Roy, 2007). Despite its discovery in 1964, it was only until 1980s where tocotrienol research took off in various diseases, which triggered the debate of supremacy between tocopherols and tocotrienols. α-Tocopherol was the main focus of vitamin E research and regarded as the major isoform with themost potent antioxidant and biological activity. However, recent studies have shown otherwise, where tocotrienols may triumph with its superior anticholesterolemic (unique to tocotrienols only), antioxidant, anticancer,
anti-inflammatory, cardioprotective and neuroprotective properties. Despite the steady growth in publications of tocotrienols since 1966, it comprises merely 3% of all vitamin E research papers
listed in PubMed (Fig. 1). Currently, there are eight naturally occurring isoforms in the vitamin E family.



Increasing trend of tocotrienol publications, although it comprises approximately 3% of vitamin E research only. Number of tocopherols (white bars) and tocotrienols (black bars) publications per year since 1966 identified in PubMed were tabulated. The respective arrows indicate the year where novel therapies beyond cancer by tocotrienols are discovered. Information was accessed on 24th September 2015.

1.2. Biochemical and physical properties of vitamin E isoforms

Vitamin E can be classified into tocopherols and tocotrienols, resulting in a total of eight isoforms: namelyα-, β-, γ-, and δ-tocopherol, andα-, β-, γ-, and δ-tocotrienol (Fig. 2). Vitamin E in its pure formis a yellow viscous oil/liquid that oxidizes readily when exposed to light, oxygen and transition metal ions. They are not water-soluble but dissolved in alcohol, organic solvents and vegetable oils (Bramley et al., 2000). They have the

same basic chemical structure where a C16 isoprenoid side chain is attached at the C-2 of a chromane ring. Tocotrienols differ from tocopherols with an unsaturated farnesyl isoprenoid side chain at C-3′, C-7′
and C-11′ over a saturated phytyl isoprenoid side chain (Fig. 2). The Greek letter prefixes of both tocopherols and tocotrienols depend on the number and position of methyl groups on the chromanol ring,
whereby α-isoform is 2,5,7,8-tetramethyl; β-isoformis 2,5,8-trimethyl; γ-isoform is 2,7,8-trimethyl; and δ-isoform is 2,8-dimethyl. Therefore, using the α-isoform, the structural terminology for α-tocopherol is
2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-6-chromanol while α-tocotrienol is 2,5,7,8-tetramethyl-2-(4,8,12-trimethyldeca-3,7,11-trienyl)-6-chromanol. Tocochromanols are amphipathic molecules
with a polar chromanol ring and lipophilic isoprenoid side chain. The unsaturated isoprenoid side chain of tocotrienols potentially enhances its penetration into fatty tissues, such as the brain and liver, and better
distribution on the cell membranes (Suzuki et al., 1993). Vitamin E in nature consists of the dextrorotatory enantiomers only with a single stereoisomer. Tocopherols contain three chiral stereocenters at C-2, C- 4′ and C-8′ (e.g.,: d-RRR-α-tocopherol), while tocotrienols contain only one chiral stereocenter at C-2 as the other two chiral stereocenters are not possiblewith C_C unsaturation in the isoprenoid tail (Colombo, 2010).

Source of Tocotrienol

Annatto seeds are unique as unlike rice bran and palm oil, it contain only tocotrienol (mostly δ-tocotrienol), but no tocopherols (Frega, Mozzon, & Bocci, 1998). The lipid fraction of annatto (*Bixa orellana* L.) seeds was extracted with a Soxhlet apparatus with *n*-hexane and isolated by thin-layer chromatography. The fatty-soluble antioxidant fraction contained only tocotrienols, mainly δ-tocotrienol, but no tocopherols. The presence of tocotrienols was confirmed by gas chromatography-mass spectrometry. The quantities of δ-tocotrienol were 140–147 mg/100 g dry seeds and 5.2–5.5% wt/wt of lipid extract, determined by gas chromatography and high-performance liquid chromatography, respectively. Currently no vegetable species seems to contain comparable concentrations of δ-tocotrienol.

Identification and estimation of tocotrienols in the annatto lipid fraction by gas chromatography-mass spectrometry(N. Frega M. Mozzon F. Bocci) JAOCS, 1998

Natural sources of tocopherols and tocotrienols.

Plants and fruits											
Species	Common name	Tissue	Tocopherol (TP, μg/g tissue)				Tocotrienol (T3, μg/g tissue)				% of T3
			α	β	γ	δ	α	β	γ	δ	
Bixa orellana L.[a]	Lipstick tree	Seed	1758	528.1	606.5	174.7	18.7	1.84	534.7	977.9	53.9
Hevea brasiliensis Müll.Arg.[a]	Rubber tree	Latex	5.0	1.10	241.6	506.3	522.4	-	196.7	1870	77.6
Delphinium ajacis L.[b]	Larkspur	Seed	120	78	83	-	566	153	-	-	71.9
Rosmarinus officinalis L.[a]	Rosemary	Seed	2883	435.2	30.8	-	560.5	300.3	109.4	-	22.5

Reference: aHorvath et al. (2006), bMatthaus, Vosmann, Pham, and Aitzetmüller (2003), chttp://tocotrienol.org/, dPanfili, Fratianni, and Irano (2003), eChoi, Jeong, and Lee (2007), fZielinski, Ciska, and Kozlowska (2001).

Specie	Common name	Tissue	Tocopherol (TP μg/g tissue)				Tocotrienol (T3 μg/g tissue)				%T3
			α	β	γ	δ	α	β	γ	δ	
Bixa Orellana	Lipstick tree	Seed	1758	528.1	606.5	174.7	18.7	1.84	534.7	977.9	53.9

A study has also shown that αTTP has 8.5 fold lower affinity to bind to α-tocotrienol than α-tocopherol (Hosomi et al., 1997). In the liver, unbounded isoforms of vitamin E to αTTP will be susceptible to catabolization via cytochrome P450 (CYP4F2)-initiated ω-hydroxylation and oxidation by ω-hydroxylase (Jiang, 2014). Due to these two antagonizing interactions, α-tocopherol is regarded as the predominant isoform to be accumulated in tissues where other vitamin E isoforms are metabolized to carboxychromanols, hydroxycarboxychromanol and carboxyethylhydroxychroman derivatives (for tocotrienols) (Birringer, Pfluger, Kluth, Landes, & Brigelius-Flohé, 2002; Lodge, Ridlington, Leonard, Vaule, & Traber, 2001). With that in mind, it led to a huge debate for a decade if orally administered tocotrienols can reach vital organs in the body, which dampened the research on tocotrienols in the 1990s.

Despite the fact that αTTP has a lower affinity towards tocotrienols, it is not clear, or to what extent, 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 (Jishage et al., 2001). Interestingly, oral supplementation of α-tocotrienol to female mice restored fertility in these αTTP knockout mice under α-tocopherol deficiency (Khanna, Patel, Rink, Roy, & Sen, 2005a). This suggests other transportmachinery or mechanisms for the absorption and transport of tocotrienols beyond the αTTP.

Following up on the debate of tocotrienol viability, pharmacokinetics studies on tocotrienolswere performed. A study in 2003 determined the pharmacokinetics of α-, γ-, and δ-tocotrienol via intramuscular, intraperitoneal, intravenous and oral routes in rats (Yap, Yuen, & Lim, 2003). The absorption of tocotrienols administered via intramuscular and intraperitoneal routes was negligible and should be avoided. 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 (Yap et al., 2003). The time required 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 (Yap et al., 2003). In humans, the half-life of α-, γ-, and δ-tocotrienol in plasmawas estimated to be 2.3, 4.4 and 4.3 h, respectively (Yap, Yuen, & Wong, 2001), while the half-life of α-tocopherol and γ-tocopherol was 57 and 13 h, respectively (Leonard et al., 2005). In a separate double-blind placebo-controlled study, human subjects took tocotrienol supplements at a dose of 250 mg/day for 8 weeks, where the mean plasma levels of α-, γ-, and δ-tocotrienol were 0.8 μM, 0.54 μMand 0.09 μM, respectively (O'Byrne et al., 2000). As tocotrienols are oil-based compounds, it faces limited bioavailability. As emulsions are known to increase absorption of fat-soluble compounds, based on self-emulsifying drug delivery systems technology (Gao & Morozowich, 2005), self-emulsifying formulations of tocotrienols were produced, such as Tocovid™ SupraBio™ and Naturale3. The supplementation of Tocovid SupraBio™ elevated peak plasma concentration of α- tocotrienol in humans to approximately 3 μM, a threefold increase as compared to 0.8 μM in previous study without self-emulsification (Khosla et al., 2006). Although tocotrienols are notwell-absorbed in the liver, they appear to be similarly absorbed as tocopherolswith dietary fat and are secreted

3. Vitamin E as an antioxidant

Vitamin E is widely accepted as one of the most potent antioxidant. The antioxidant property is attributed to the hydroxyl group from the aromatic ring of tocochromanols,which donates hydrogen to neutralize free radicals or reactive oxygen species (ROS). In homogenous solutions and in vitro assays, the reaction rates between the vitamin E isoforms largely depends on the number of methyl groups on the chromanol

ring. The antioxidant activity of α-, β- and γ-isoforms of both tocopherol and tocotrienol is similar, except the δ-isoform whichhas weaker activity, when tested in pyrogallolsulfonphthalein and 2,7-dichlorodihydrofluorescein diacetate assays (Peh et al., 2015; Yoshida, Saito, Jones, & Shigeri, 2007).

However, the distinction of antioxidant activities in biological systems

between tocopherols and tocotrienols is clear. Free radicals attack on cell membrane results in peroxyl radicals and lipid peroxidation which is responsible for hypercholesterolemia and cardiovascular diseases.

Studies have displayed the superiority of α-tocotrienol over α- tocopherol in neutralizing the peroxyl radicals and lipid peroxidation in rat liver and liposomal membranes (Ghafoorunissa, Hemalatha,

& Rao, 2004; Serbinova, Kagan, Han, & Packer, 1991; Suzuki et al., 1993). In HUVEC (human umbilical vein endothelial cell) cells, palm tocotrienol rich fraction (TRF) was more efficient than α-tocopherol in

attenuating thiobarbituric reactive substances (TBARS) (Ghafoorunissa et al., 2004). In rat brain mitochondria, γ-tocotrienol elicited stronger protective effect against oxidative damage (Kamat & Devasagayam, 1995). Interestingly in Caenorhabditis elegans, administration of tocotrienols abated protein carbonylation and extended mean life span, where α-tocopherol supplementation had no effect (Adachi & Ishii, 2000). This could be explained with a few possible mechanisms. Firstly, tocotrienols are more uniformly distributed in the cell membrane bilayer (Palozza et al., 2006). Secondly, tocotrienols have a stronger disordering effect on phospholipids due to its unsaturated isoprenoid side chain which results in its “arc” conformation over the chromanol ring, thus rendering a more effective interaction to lipid radicals (Serbinova et al., 1991; Simone, Palozza, Watson, & Preedy, 2008). Lastly, tocotrienols have a higher recycling efficiency from its chromanoxyl radicals over tocopherols (Packer, Weber, &

Rimbach, 2001; Theriault et al., 1999). The antioxidant efficacy of vitamin E on reactive nitrogen species

(RNS) is gaining more attention recently. RNS includes nitric oxide (NO), nitrogen dioxide (NO2) andperoxynitrite (ONOO\\). The reaction of α-tocopherol with NO2 yields a nitrosating agent,while γ-tocopherol reduces NO2 to NO without generating nitrosating species (Cooney et al., 1995). It was hypothesized that possessing an unsubstituted 5- position on the chromanol ring, γ- and δ-isoforms, but not α- and β-isoforms of vitamin E, renders the ability to neutralize RNS (Christen et al., 1997). The scavenging of NO2 and ONOO\\by γ-tocopherol is superior to that of α-tocopherol, which resulted in the formation of 5-nitro-γ-tocopherol. Thiswas proven in a study where 5-nitro-γ-tocopherol was detected in the plasma of zymosan-induced peritonitis in rats (Christen, Jiang, Shigenaga, & Ames, 2002). Similarly in radiological threat, nitric oxide synthase (NOS) is stimulated and produced RNS, where only prophylactic administration of γ-tocotrienol among the vitamin E isoforms protected mice from radiation damage (Berbée et al., 2009; Ghosh et al., 2009).

4. Vitamin E therapy beyond cancer

4.1. Bone diseases

Osteoporosis is a metabolic bone disease, which is manifested with the degeneration of bone density and microarchitecture, leading to bone fragility and fracture. The causes of osteoporosis include estrogen deficiency due to menopause in women, testosterone deficiency in men, prolonged use of glucocorticoid, chronic smoking, alcohol abuse, inflammatory bowel syndrome, and so on (Iniguez-Ariza & Clarke, 2015). Both oxidative stress and inflammation are implicated in the pathogenesis of osteoporosis. As anti-oxidative and anti-inflammatory agents, the effects of vitamin E isoforms have been widely explored in a variety of experimental osteoporosis models. The effects of tocopherol supplementation on bone are inconsistent and somehow contradictory (Chin & Ima-Nirwana, 2014a). High-dose α-tocopherol was shown to exert negative effect on bone in normal animals but was protective in stressed animals (Arjmandi et al., 2002; Hampson et al., 2015; Smith et al., 2005). A recent study showed that there was increased bone resorption and decreased bone mass in mice fed with high-dose α-tocopherol, probably due to increased osteoclast fusion and differentiation (Fujita et al., 2012), which was however, not supported by another report (Iwaniec et al., 2013). Some studies exhibited beneficial effects ofα-tocopherol on

bone losswhile others did not but instead showing improved bone quality (Chai, Wei, Brummel-Smith, & Arjmandi, 2008; Feresin et al., 2013).When compared with tocotrienols, tocopherols revealed either comparable or less effective in protecting bone in animals (Hermizi, Faizah, Ima-Nirwana, Ahmad Nazrun, & Norazlina, 2009; Maniam, Mohamed, Shuid, & Soelaiman, 2008; Mehat, Shuid, Mohamed, Muhammad, & Soelaiman, 2010; Muhammad, Luke, Shuid, Mohamed, & Soelaiman, 2012).

The bone-protective effects of tocotrienols have been demonstrated in various animal models which were subjected to estrogen deficiency, testosterone deficiency, glucocorticoid, nicotine and oxidizing reagents.

In general, the studies have shown that tocotrienols increased osteoblast number, mineral deposition, and bone formation activity and decreased osteoclast number, erosion on bone, and bone resorption activity, thus preventing the degeneration of bone mineral density and bone microarchitecture in osteopenic animals. These effects could be attributed to various activities exerted by tocotrienols. It is well-established that oxidative stress is implicated in the development of osteoporosis (Ibanez et al., 2014). Supplementation of tocotrienols reduced oxidative stress product malondialdehyde (MDA), preserved and increased antioxidant enzyme activities in vivo (Abd Manan, Mohamed, & Shuid, 2012; Maniam et al.,

2008). In an in vitro study, it was shown that γ-tocotrienol homologue decreased oxidative damage on primary osteoblast culture (Nizar, Nazrun, Norazlina, Norliza, & Ima Nirwana, 2011). Tocotrienols exerted its biological actions not only by anti-oxidant property, but by suppressing mevalonate pathway which promotes bone loss by regulating osteoblastogenesis and osteoclastogenesis through activation of GTPase (Mo et al., 2012). A recent study found that mice supplemented with emulsified γ-tocotrienol via subcutaneous injection were significantly protected from ovariectomy-induced bone loss as evaluated by various bone structural parameters, bonemetabolic gene expression levels and serum levels of biochemical markers for bone resorption and bone formation (Deng et al., 2014). The effect of tocotrienol was achieved by downregulating the activity of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. Other mechanisms by which tocotrienol executes its boneprotective activity include preventing proinflammatory cytokines such as IL-1, IL-6 and TNF-α, and enhancing genes related to bone formation

and osteoblast activity as such alkaline phosphatase, beta-catenin, collagen type I α 1, and osteopontin (Chin & Ima-Nirwana, 2014b; Norazlina, Lee, Lukman, Nazrun, & Ima-Nirwana, 2007; Norazlina et al., 2010).

4.2. Cardiovascular diseases

Atherosclerosis is a chronic inflammatory disorder that occurs as a result of lymphocyte infiltration to the arterial wall, smooth muscle cell proliferation and damage in the arterialwall caused by extracellular

matrix accumulation. The effects of tocotrienol rich fraction (TRF) on the microscopic development of atherosclerosis and lipid peroxidation in the aorta of rabbits have been investigated (Nafeeza, Norzana, Jalaluddin, & Gapor, 2001). 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 normal diet. Another study showed that tocotrienol-enriched palm oil prevented atherosclerosis through modulating the activities of peroxisome proliferator-activated receptors (PPAR) (Li, Tan, Kang, & Wong, 2010). Recently, a clinical trial was conducted to compare TRF (180 mg tocotrienols, 40 mg tocopherols) with placebo (0.48 mg tocotrienols, 0.88 mg tocopherols) in patients undergoing chronic hemodialysis, in which accelerated atherosclerosis might be contributed by dyslipidemia, inflammation and an impaired antioxidant system (Daud et al., 2013). TRF supplementation showed improvement in lipid profiles in terms of plasma total cholesterol, triglycerides, and high-density lipoprotein (HDL), when compared with placebo. The changes in the TRF group were associated with higher plasma apolipoprotein A1 level and lower cholesteryl-ester transfer protein activity. These studies suggest TRF supplementation improved lipid profiles to prevent atherosclerosis. It is rather controversial for the effects of tocopherol isoforms in atherosclerosis models. In a study of chronic ethanol consumption induced atherosclerosis in animals, elevation of inflammatory cells,

disorganization of endothelium and increase in pro-inflammatory mediators were observed in the ethanol group. Significant amelioration of endothelial wall changes, along with the restoration of elevated mediators was found in α-tocopherol-treated animals (Shirpoor, Norouzi, Khadem Ansari, Ilkhanizadeh, & Gharaaghaji, 2013). However, quite on the contrary, dietary supplementation with α-tocopherol (400 IU/d) oxidized HDL-2 and HDL-3, surprisingly showing a proatherogenic effect (Wade et al., 2013). Data on the superior effect of another tocopherol isoform γ-tocopherol over α-tocopherol were described in terms of preventing oxidative stress, where γ-tocopherol but not α-tocopherol supplementation reduced biomarkers of oxidative stress in patients with metabolic syndrome (Devaraj, Leonard, Traber, & Jialal, 2008). In a clinical study conducted in healthy men, the supplementation of γ-tocopherol-rich mixture of tocopherols attenuated postprandial hyperglycemia-induced MDA level, oxidative stress and vascular endothelial dysfunction, independent of inflammation (Mah et al., 2013). Myocardial ischemia reperfusion injury resulted fromsevere impairment of coronary blood supply produces a spectrum of clinical syndromes. Although all of the tocotrienol isoforms have shown some degree of cardioprotection, γ-tocotrienol was found to be the most potent in boosting pro-survival genes in myocardial ischemic injurymodel (Das, Das, Wang, Powell, & Das, 2008). The differential interaction of mitogen-activated protein kinase (MAPK)with caveolin 1/3 in conjunction with proteasome stabilization was proposed to play a unique role in tocotrienols-mediated cardioprotection. Another study investigated the cardioprotective property of γ-tocotrienol and/or resveratrol. Both agents showed the protection alone, and furthermore acted synergistically, providing a greater degree of cardioprotection than either alone,

Thromboembolic events are the likely cause of various clinical pathologies including renal and splenic microinfarctions, stroke and heart failure. The effects of α-tocopherol, α-tocotrienol, or TRF on in vivo platelet thrombosis and ex vivo platelet aggregation were compared (Qureshi et al., 2011). After intravenous injection in anesthetized dogs, tocotrienols were significantly better than tocopherols
in inhibiting cyclic flow reductions, a measure of the acute platelet-mediated thrombus formation, and collagen-induced platelet aggregation. These data suggest that tocotrienols provide a better therapeutic benefit in conditions like platelet thrombosis, stroke and myocardial infarction, as compared to tocopherols.

4.3. Diabetes

Diabetes mellitus often results in various complications due to nitrosative and oxidative stress induced by high levels of glucose in the blood. A 2004 prospective cohort study demonstrated that the
intake of vitamin E reduce the risk of onset of type 2 diabetes after a 23-year follow-up (Montonen, Knekt, Järvinen, & Reunanen, 2004). TRF reduces total cholesterol, low-density lipoprotein (LDL) and total lipid in diabetic patients (Baliarsingh, Beg, & Ahmad, 2005). Patients given tocotrienol-enriched canola oil (200 mg/day tocotrienols) also showed significant reduction in serum C-reactive protein (CRP) and urine microalbumin (Haghighat et al., 2014). This could be due to the increase in PPAR target gene expression when Db/Db mice were fed with TRF, increasing insulin sensitivity (Fang, Kang, & Wong, 2010). It was further shown in vitro that α-, γ-, and δ-tocotrienols but not α-tocopherol, could bind PPARα and increase its interaction with LXXLL motif of PGC-1α peptide (Fang et al., 2010). Using Wistar rats placed on a diet high in fructose, it was demonstrated that combination treatment with α-lipoic acid and either α-tocopherol alone or TRF can both prevent and reversed metabolic and cardiovascular changes in fructose-fed rats (Patel, Matnor, Iyer, & Brown, 2011). Wound healing was accelerated by α-tocopherol, together with reduced plasma MDA level and increased glutathione peroxidase activities in diabetic rats (Musalmah, Fairuz, Gapor, & Ngah, 2002). Impaired endothelial function in streptozotocin-induced diabetic rats was improved with both TRF and α-tocopherol that were isolated from palm oil (Muharis, Top, Murugan, & Mustafa, 2010). Another study also demonstrated that TRF can reduce erythrocyte membrane MDA levels and leukocyte DNA damage together with increased SOD and glutathione (GSH) in erythrocytes (Matough et al., 2014). However, TRF was unable to reduced serum advanced glycation end products in diabetic rats, only lowering blood glucose and glycated hemoglobin

levels (Wan Nazaimoon & Khalid, 2002). TRF also resulted in reduced serum glucose, glycated hemoglobin concentrations, low-density lipoprotein cholesterol, plasma total cholesterol and triglyceride levels while having higher SOD activity (Budin et al., 2009). TRF was also shown to have a protective effect on blood vessel walls, lowering levels of MDA and 4-hydroxynonenal (Budin et al., 2009).

4.4. Eye disorders

Cataractogenesis, a form of eye disorder characterized by the progression of lenticular opacities, has been shown to be driven by nitrosative and oxidative stress in the lenticular cells. Using a galactose-induced experimental cataracts in rats, 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 (Abdul Nasir et al., 2014). However, 0.2% or higher concentration of topical tocotrienol led to increased lens oxidative stress and aggravates cataractogenesis (Abdul Nasir et al., 2014). In studying the distribution of vitamin E in ocular tissue from topical administration, the level of α-tocotrienol was significantly higher than α-tocopherol in administered tissues (Tanito et al., 2004). However, the intraocular penetration of γ-tocotrienol and γ-
tocopherol did not differ significantly (Tanito et al., 2004). Using Tenon's capsule fibroblast cultures, indicative of fibrosis from post-glaucoma filtration surgery with excessive fibroblast proliferation
and extracellular matrix production, it was shown that only α-tocotrienol significantly inhibited growth of fibroblasts, but not other isoforms of vitamin E such as α-tocopherol (Meyenberg et al., 2005). On the other hand, α-tocopherol was also shown to protect rat lens against ultraviolet-B photo damage (Reddy, Nayak, Reddy, & Bhat, 2001).

4.5. Inflammatory diseases

In lipopolysaccharide-induced RAW264.7 macrophage and IL-1β- induced lung epithelial cell models, vitamin E isoforms could attenuate PGD2 and PGE2, respectively,with varying potencies: γ-tocotrienol≈δ- tocopherol N γ-tocopherol ≫ α-/β-tocopherol (Jiang et al., 2008). Likewise, 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 with IC50 of 40–60 μM as compared to γ-tocotrienol with IC50 of approximately 5 μM (Jiang et al., 2008). It has been shown that γ-tocotrienolwas 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) (Wang & Jiang, 2013). In asthma, it was observed that patients had lower levels of antioxidants in the lungs,which sparks off the usage ofα-tocopherol (regarded as the main vitamin E isoform back in 1990s) for asthma (Kelly, Mudway, Blomberg, Frew, & Sandström, 1999). A study showed that oral γ-tocopherol in ovalbumin-induced allergic asthma and rhinitis in rats decreased eosinophilia in the lung, nose and sinus duct (Wagner et al., 2008). It also abrogated inflammatory cytokines (IL-4, IL-5 and IL-13) in the bronchoalveolar lavage fluid and mucus production in the airways. However, tocopherols in asthma yielded inconclusive outcomes in subsequent studies (Cook-Mills, Abdala-Valencia, & Hartert, 2013; McCary, Abdala-Valencia, Berdnikovs, & Cook-Mills, 2011), thus
the investigation was shifted towards using tocotrienols for asthma. The screening of different vitamin E isoforms in a house dust miteinduced asthma mouse model has identified γ-tocotrienol as the promising candidate in treating asthma (Peh et al., 2015). In that study, 30–250 mg/kg oral γ-tocotrienol attenuated inflammatory leukocytes infiltration into the airways, mucus hypersecretion in the bronchial epithelium, inflammatory cytokines in bronchoalveolar lavage fluid and house dustmite-specific IgE in the serum; and restored antioxidants capacity in the lungs. Thesewere mediated by inhibition of NF-kB nuclear translocation and promoting nuclear Nrf2 level, whereby α-

tocopherol failed to modulate NF-κB and Nrf-2 activation. The protective effects of γ-tocotrienol were comparable to those of prednisolone.
Notably, γ-tocotrienol was able to decrease neutrophil infiltration into the airways and neutrophils-related cytokines (e.g.,: G-CSF), which is not achievable by corticosteroids (Ito et al., 2008). In another study, γ-
tocotrienol was also shown to be superior among vitamin E isoforms in suppressing IL-13-induced production of eotaxin-3 by inhibiting STAT6 in human lung epithelial A549 cells (Wang et al., 2012). Taken together, γ-tocotrienol may have therapeutic potential in treating asthma, and it may be considered as an add-on therapy to corticosteroid for optimal asthma control. As for allergic dermatitis, in a randomized, double-blind, placebo controlled trial, patients were fed 400 mg/day α-tocopherol for 60 days, and beneficial effects were observed (Javanbakht et al., 2010; Kosari, Alikhan, Sockolov, & Feldman, 2010). In a murine picryl chloride-induced dermatitis model, mice developed scratching behavior, dermal thickening, mast cell degranulation and heightened histamine levels in serum (Tsuduki, Kuriyama, Nakagawa, & Miyazawa, 2013). Oral 1 mg/day of rice bran tocotrienol (97.5% of tocotrienol—3.5%

4.6. Lipid disorder

Lipid disorders are a group of conditions that involve high levels of fatty molecules, such as cholesterol and triglycerides in the blood. Tocotrienols research gained traction with the discovery of its cholesterol-lowering properties in the 1980s (Qureshi, Burger, Peterson, & Elson, 1986), via the inhibition of HMG-CoA reductase, a mechanism which is not prevalent in tocopherols (Pearce, Parker, Deason, Qureshi, & Wright, 1992; Qureshi, Sami, Salser, & Khan, 2002). Tocotrienols were observed to inhibit HMG-CoA reductase by post-transcriptional suppression of the enzyme itself (Parker, Pearce, Clark, Gordon, & Wright, 1993). Interestingly, γ- tocotrienol has a 30-fold increase over α-tocotrienol in inhibiting HMG-CoA reductase (Teoh, Chong, Mohamed, & Phang, 1994). A double-blind 8 weeks pilot study in hypercholesterolemic human subjects revealed that γ-tocotrienol may be the most potent cholesterol
inhibitor among the vitamin E isoforms, where it reduced serum levels of total cholesterol, LDL, apolipoprotein B, thromboxane, platelet factor 4 and glucose (Qureshi et al., 1991). In a 2002 study, it was shown that the American Heart Association's Step-1 diet and TRF25 (25–200 mg/day) from rice bran reduced serum total cholesterol, LDL, triglycerides and apolipoprotein B in hypercholesterolemic patients (Qureshi et al., 2002). The combination of 270 mg citrus flavonoids and 30 mg tocotrienols in hypercholesterolemic patients also reduced serum total cholesterol, LDL, triglycerides and apolipoprotein B (Roza, Xian-Liu, & Guthrie, 2007). Mixed tocotrienols treatment on hypercholesterolemic patients with nonalcoholic fatty liver disease resulted in a higher percentage having normal hepatic echogenic response (Magosso et al., 2013). TRF (180 mg tocotrienols and 40 mg tocopherols) also found beneficial to patients undergoing chronic hemodialysis, decreasing serum total cholesterol, triglycerides, LDL and cholesteryl-ester transfer protein activity, while increasing serum HDL and apolipoprotein A1 (Daud et al., 2013). However, a 1997 study using palm TRF (40 mg γ- and α-tocotrienols and 16 mg α-tocopherol) only reduced serum TBARS, but serum total cholesterol, LDL-cholesterol and triglyceride levels remained unaffected (Kooyenga et al., 1997). Another similar study in 1999 revealed that oral palm TRF
(35 mg tocotrienols and 20 mg α-tocopherol) had no effect on serum lipid level, lipoprotein level or platelet function (Mensink, van Houwelingen, Kromhout, & Hornstra, 1999). Both of these earlier
studies using TRF preparations with relatively higher proportion of α-tocopherol demonstrated no effects on hypercholesterolemia, which might be due to the opposing action by tocopherols on HMGCoA reductase, as it has been shown that α-tocopherol increased HMG-CoA reductase activity in avian (Qureshi et al., 2002). Using a hypercholesterolemia and atheroma model of rabbits on atherogenic diet, treatment with 50 mg/day TRF (72% γ-tocotrienol, 18% α-, β-tocotrienols, and 10% α-tocopherol) led to
a larger reduction in serum total cholesterol, lipid peroxide and LDL as compared to treatment with 50 mg/day α-tocopherol, but their effects were similar for serum triglyceride and HDL (Teoh et al., 1994). Another study also demonstrated that TRF reduced aortic content of MDA and degree of

intimal thickening in treated cholesterol-fed rabbit model of atherosclerosis, preserving the continuity of the internal elastic lamina (Nafeeza et al., 2001). Hyperlipidemia induced chronic renal dysfunction was also studied in rats on an atherogenic diet, where TRF (100 mg/kg) reduced dyslipidemia and development of chronic renal dysfunction (Rashid Khan, Ahsan, Siddiqui, & Siddiqui, 2015). Using human monocytederived macrophages to study atherogenesis, α-tocotrienol or FeAOX-6 (a novel compound that combines antioxidant structural features of both tocopherols and carotenoids) was shown to reduce cholesterol accumulation in the cells, with α-tocotrienol reducing to a larger extent (Napolitano, Avanzi, Manfredini, &Bravo, 2007).

4.7. Nephropathy

Nephropathy occurs as a result of damage or disease to the kidney and often requires dialysis as a treatment if a transplant is not possible.There has been development of a vitamin E-coated membrane which serves to reduce circulating lipid peroxidation during dialysis (Cruz, de Cal, & Ronco, 2008). Membrane-bounded α-tocopherol could effectively reduce 8-hydroxy-2-deoxyguanosine (8-OHdG) level in leukocyte DNA of chronic hemodialysis patients (Tarng et al., 2000). It has been demonstrated that membrane coated with α-tocopherol was able to increase red blood cell survivability and decrease serum free 4-hydroxynonenal during dialysis (Odetti et al., 2006;Usberti et al., 2002). In a model of diabetic nephropathy using streptozotocin-induced diabetic rats, tocotrienol was found to be more effective than α-
tocopherol in restoring renal function. When combined with insulin, tocotrienol drastically suppressed TNF-α-induced NF-κB and caspase 3 activation (Kuhad & Chopra, 2009a). Another study comparing the
effects of palm oil-TRF (PO-TRF) and rice bran oil-TRF (RBO-TRF), revealed that PO-TRF was a more effective nephroprotective and hypoglycemic preparation for diabetic nephropathy (Siddiqui, Rashid
Khan, & Siddiqui, 2010). This difference could be due to the relatively higher concentration of tocotrienol in PO-TRF as compared to RBO-TRF (Siddiqui et al., 2010). Using a model of lipid-induced diabetic nephropathy in rats, both PO-TRF and RBO-TRF were shown to improve renal function, serum lipid profile and glycemic status (Siddiqui, Ahsan, Khan, & Siddiqui, 2013). Exposure to high levels of chromium compounds or high intake of monosodium glutamate can lead to nephrotoxicity. In a potassium
dichromate ($K_2Cr_2O_7$)-induced acute renal injury rat model, TRF (200 mg/kg) treatment preserved kidney proximal reabsorptive function, glomerular function and redox status (Khan et al., 2010). In a monosodium glutamate-induced nephrotoxicity model, α-tocopherol (100 and 200 mg) reduced oxidative stress and restored renal function in rats (Paul, Abhilash, Varghese, Alex, & Harikumaran Nair, 2012).

4.8. Neurological diseases

Glutamate is the major mediator of excitatory signals in the mammalian central nervous system. Extreme amounts of glutamate in the extracellular spaces can lead to numerous neurodegenerative diseases. The prevention of glutamate-induced neural cytotoxicity and neurodegeneration by vitamin E have been extensively investigated (Khanna et al., 2003; Khanna et al., 2005b; Khanna et al., 2010; Rati Selvaraju
et al., 2014; Selvaraju et al., 2014; Sen, Khanna, Roy, & Packer, 2000). Sen and co-workers identified that nanomolar α-tocotrienols were more effective than α-tocopherol in preventing glutamate-induced injury and death by suppressing c-Src/ERK, 12-lipoxygenase phosphorylation and cytosolic phospholipase A2 (Khanna, Roy, et al., 2005b; Khanna et al., 2003; Khanna et al., 2010; Sen et al., 2000). In contrast, other laboratories found that vitamin E isoforms, both TRF and α-tocopherol could protect glutamate-injured neuronal cells and astrocytes through their anti-oxidative properties (Rati

Selvaraju et al., 2014; Selvaraju et al., 2014). External oxidative and neurotoxic agents such as Fe2+ ions, 1- methyl-4-phenylpyridiniumion (MPP+) and high-fat diet induced substantial neural cytotoxicity and cause neurological disorders in animal models (Crouzin et al., 2010; Gutierres et al., 2012; Nakaso et al., 2014). It was identified that transient receptor potential cation channel V1 was involved in the Fe2+-induced neuronal death and a negative modulation of this channel activity by α-tocopherol might account, at
least in part, for the long-lasting neuroprotection against oxidative stress (Crouzin et al., 2010). High-fat diets have an important role in neurodegenerative diseases and neurological disturbances. The effects
of high-fat diets on ectonucleotidase activities in synaptosomes of cerebral cortex, hippocampus and striatumof ratswere examined,where α-tocopherol was capable of modulating the adenine nucleotide hydrolysis in that experimental model (Gutierres et al., 2012). It was demonstrated that γ-/δ-tocotrienol exhibited not only antioxidant effects but also a receptor signal-mediated neuroprotective action (Nakaso et al., 2014). In a cellular Parkinson's disease model induced by MPP+,

Clinical studies were conducted to evaluate the neuroprotective effects of vitamin E supplementation in patients treated with cisplatin chemotherapywhich is associatedwith severe peripheral neurotoxicity in up to 90% of patients (Pace et al., 2010). 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.Both the incidence and the severity of neurotoxicity were significantly lower in α-tocopherol supplemented group as compared to the placebo. In a small cohort of multiple sclerosis patients, nine subjects treated for 30 months with γ-tocopherol failed to decrease disease annual relapse rate (Pantzaris, Loukaides, Ntzani, &
Patrikios, 2013). Another clinical study aimed to evaluate the protective activity of mixed tocotrienols in humans with white matter lesions (WMLs), which are regarded as manifestations of cerebral small vessel
disease, reflecting varying degrees of neurodegeneration and tissue damage (Gopalan et al., 2014). A total of 121 volunteers aged ≥35 years with cardiovascular risk factors and magnetic resonance imaging-confirmed WMLs were randomized to receive 200 mg mixed tocotrienols or placebo twice a day for 2 years. Mixed tocotrienols were found to attenuate the progression of WMLs.

4.9. Radiation damages

Radiation damage can be lethal at moderate to high doses. Despite its rare occurrence, there is an unmet medical need for humans exposed to radiation leakage. At lower dose of radiation, from 0.5–5.5 Gy, it results in hematopoietic syndrome, where blood cells, platelets and bone marrow are damaged, making victims prone to secondary infections and hemorrhage. Patients would survive at the lower range, but
death prevails within six weeks for 50% of victims beyond 3.5 Gy dose. Moderate doses of radiation, from5.5–10.0 Gy, affects the hematopoietic cells and gastrointestinal tract, where victims may develop sepsis, as bacteria can translocate through the defective intestinal mucosa barrier into the bloodstream. Death is probable within three weeks of radiation exposure. At high doses beyond 10.0 Gy, radiation damage reaches the central nervous systemand causes cognitive dysfunction, cerebrovascular
collapse, shock and pneumonitis, where death is certain within two weeks (Waselenko et al., 2004). Current radioprotector includes amifostinewhich has significant side effects and a limitedwindowof efficacy (Brizel et al., 2000; Rades et al., 2004). The transfer of energy from radiation to biomolecules has two actions: direct action — ionization of biomolecules fromradiation, and indirect action—radiolysis of water to produce hydroxyl radicals to attack biomolecules (Michaels & Hunt, 1978). Thus, radiation also induces oxidative damage via the production of reactive oxygen/nitrogen species by activating xanthine oxidase and nitric oxide synthase enzymes (Deliconstantinos, Villiotou, & Stavrides, 1996; Leach, Van Tuyle, Lin, Schmidt-Ullrich, &Mikkelsen, 2001). As radiation damage at high doses is irreversible, the research focus shifted towards radiation countermeasure, to

prophylactically prevent radiation damage to staff prone to radiation exposure. The radioprotector must have minimal/negligible side effects with antioxidant potential and can be consumed at a national level in the emergency like nuclear plant explosion or leakage. The use of α-tocopherol as a radioprotector has been found partially effective in mousemodels since 1986 (Bichay & Roy, 1986). More recently, γ-tocotrienol was shown to be a better
radioprotectant than α-tocopherol (Ghosh et al., 2009). It is now widely accepted that both γ- and δ-tocotrienols are effective radioprotectants demonstrated in many pre-clinical studies (Kulkarni et al., 2010). γ-Tocotrienol is considered to bemore efficacious than tocopherols against radiation damage due to its superior potency in inducing gene expression when tested in human endothelial cells (Berbée et al., 2012). The synergistic radioprotection of γ-tocotrienol (administered subcutaneously at 200 mg/kg dose)
and pentoxifylline in mice exposed to 11.5 Gy total body irradiation, was shown to be due to phosphodiesterase inhibition (Kulkarni et al., 2013a). Radioprotectant γ-tocotrienol was also shown to upregulate expression of G-CSF to promote the proliferation and survival of white blood cells such as neutrophils, thus reducing hematopoietic syndrome (Kulkarni, Singh, Ghosh, Posarac, & Singh, 2013b). This finding was further elaborated when G-CSF antibody co-administered with subcutaneous 200 mg/kg γ-tocotrienol prior to irradiation dampened the anticipated radioprotective effects in mice (Singh et al., 2014a). Gastrointestinal syndrome developed post-irradiation in mouse jejunum was also ameliorated when treated with 200 mg/kg of γ-tocotrienol subcutaneously, via the elevation of anti-apoptotic and down-regulation of pro-apoptotic factors (Suman et al., 2013). HMG-CoA reductase inhibition was also implicated as a key mechanism of γ-tocotrienol radioprophylactic properties as co-administration of mevalonate together with γ-tocotrienol conferred no radioprotection to irradiated mice (Berbée et al., 2009). Inability of tocopherols to inhibit HMG-CoA reductase may explain why tocotrienols are better radioprotectants (Pearce et al., 1992; Qureshi et al., 1996). δ-Tocotrienol (subcutaneous 150–300 mg/kg)
was also effective as a radioprotectant and acted through G-CSF as well (Satyamitra et al., 2011; Singh et al., 2014b). It attenuated gastrointestinal syndrome post-irradiation by decreasing IL-1β, IL-6 and protein kinase 6 (a stress-induced kinase which enhances apoptosis) in mouse intestines (Li et al., 2013).

6. Summary and future outlook

Vitamin E research is nearly a century long in a couple of years time. The masses knowvitamin E (α-tocopherol) as a fertility factor and a key component in cosmetic products. However, the public is unaware that there are a total of 8 naturally occurring forms within the vitamin E family, and an additional seven relatively physiologically inactive forms created in synthetic dl-rac-α-tocopherol (Burton et al., 1998; Traber & Arai, 1999). Tocotrienols, consisting of one half of vitamin E family, has been the subject of approximately 3% of the studies published when obtained from PubMed. The scientific community recognizes that vitamin E is one of the most potent antioxidants in protecting biological
systems from oxidative/nitrosative damage (Cooney et al., 1995; van Acker, Koymans, & Bast, 1993). The presented biological activities of vitamin E beyond include cancer in bone, cardiovascular, eye, inflammatory, allergic and neurological diseases, as well as diabetes, lipid disorder and potentially a radioprotectant against radiation damage (Fig. 4). In addition to vitamin E ability to neutralize free radicals as an antioxidant, it has also been shown to modulate signaling pathways including PPAR, C/EBP, STAT6, NF-κB and Nrf2, as well as signaling/ inflammatory molecules such as apoptotic regulators (Bcl-2 and caspase-3), cytokines (IL-1β, IL-4, IL-5, IL-6, IL-13, TNF-α, TGF-β and GCSF),
kinases (c-Src, ERK, MAPK, PI3K, PK6 and PKC) and enzymes (AP, Cat, GPx, SOD, eNOS, GTPase, HMG-CoA reductase, HO-1, COX-2, 5- LOX, 12-LOX and PLA2) (Table 2). α-Tocopherol had been regarded as the main isoform of vitamin E after the discovery of αTTP in the liver which selectively binds to α- tocopherol to prevent its degradation (Min, Kovall, & Hendrickson, 2003), thus explaining its much longer half-life in the plasma over the other seven isoforms (Leonard et al., 2005). Despite that, γ-tocotrienol was observed to be absorbed significantly faster than α-tocopherol in the intestines (Tsuzuki et al., 2007). Aside from bioavailability issue, tocotrienols were shown to have

comparable or superior efficacies in various diseases covered in this review (refer to Table 3 for tocopherol versus tocotrienol comparison in various diseases). In particular, tocopherols do not have cholesterol-lowering properties via the inhibition of HMG-CoA reductase as observed by tocotrienols (Qureshi et al., 2002). Supplementation of tocotrienols has potential to prevent atherosclerosis (Daud et al., 2013), and tocotrienolswere shown to have better therapeutic benefits over tocopherols in platelet thrombosis (Qureshi et al., 2011). Tocotrienols anti-inflammatory actions are superior to α-tocopherol, possibly due to the ability to inhibit activation of STAT6 and NF-κB (Peh et al., 2015;Wang et al., 2012). Both γ-tocopherol and γ-tocotrienol, but not α-tocopherol, abrogate COX and 5-LOX-mediated eicosanoids in biological system to reduce inflammation (Jiang, 2014). The use of α-/γ-tocotrienol in neurological diseases was found to have
better protective effects than tocopherols in pre-clinical models of glutamate-induced injury and Parkinson's disease (Khanna et al., 2010; Nakaso et al., 2014). The use of vitamin E as radioprotectant against radiation damage has elucidated γ-tocotrienol as a better candidate over α-tocopherol when micewere exposed towhole body irradiation (Ghosh et al., 2009; Kulkarni et al., 2010). Nonetheless, despite vitamin E (tocopherols) has an established safety record, it is necessary to ascertain the safety of tocotrienols in chronic studies and determine themaximumtolerated dose since tocotrienols differ quite substantially from tocopherols. In the clinical trial registry portal byNational Institute of Health, there are only 25 clinical trials on tocotrienols out of 927 trials on vitamin E (Table 4). In light of this, it is highly recommended that future research claims on vitamin E to specify the specific form employed to prevent any confusion.
For instance, vitamin E was reported to perform below expectations in clinical trial in preventing cardiovascular diseases, and actually increase all-cause of mortality in test subjects (Miller et al., 2005). It is scientifically inaccurate to discount vitamin E on the whole when the study only adopted the use of α-tocopherol. In recent decade, vitamin E took quite a hitwhen clinical trials yielded disappointing or conflicting results (Cook-Mills et al., 2013; Greenberg, 2005; Lee, Cook, Gaziano, et al., 2005; Lonn et al., 2005; Riccioni et al., 2006). The isoform of vitamin E applied inmost clinical trials thenwas α-tocopherol. As shown in clinical trials registered and papers published, tocotrienols holds barely 3% foot hold in the entire vitamin E collection. With tocotrienols success

References

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.

Abdul Nasir, N. A., Agarwal, R., Vasudevan, S., Tripathy, M., Alyautdin, R., & Ismail, N. M. (2014). Effects of topically applied tocotrienol on cataractogenesis and lens redox status in galactosemic rats. Mol Vis 20, 822–835.

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.

Aghdassi, E., Wendland, B. E., Steinhart, A. H., Wolman, S. L., Jeejeebhoy, K., & Allard, J. P. (2003). Antioxidant vitamin supplementation in Crohn's disease decreases oxidative stress: a randomized controlled trial. Am J Gastroenterol 98, 348–353.

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.

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

Bandt, M. D., Grossin, M., Driss, F., Pincemail, J., Babin-Chevaye, C., & Pasquier, C. (2002). Vitamin E uncouples joint destruction and clinical inflammation in a transgenic mouse model of rheumatoid arthritis. Arthritis Rheum 46, 522–532.

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.

Berbée, M., Fu, Q., Boerma, M., Wang, J., Kumar, K. S., & Hauer-Jensen, M. (2009). γ-Tocotrienol ameliorates intestinal radiation injury and reduces vascular oxidative stress after total-body irradiation by an HMG-CoA reductase-dependent mechanism. Radiat Res 171, 596–605.

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

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.
Bitiren, M., Karakilcik, A., Zerin, M., Ozardalı, I., Selek, S., Nazlıgül, Y., et al. (2010). Protective effects of selenium and vitamin E combination on experimental colitis in blood plasma and colon of rats. Biol Trace Elem Res 136, 87–95.
Blanchard, B., Heurtaux, T., Garcia, C., Moll, N. M., Caillava, C., Grandbarbe, L., et al. (2013). Tocopherol derivative TFA-12 promotes myelin repair in experimental models of multiple sclerosis. J Neurosci 33, 11633–11642.
Bousvaros, A., Zurakowski, D., Duggan, C., Law, T., Rifai, N., Goldberg, N. E., et al. (1998). Vitamins A and E serum levels in children and young adults with inflammatory bowel disease: effect of disease activity. J Pediatr Gastroenterol Nutr 26, 129–135.
Bramley, P., Elmadfa, I., Kafatos, A., Kelly, F., Manios, Y., Roxborough, H., et al. (2000). Vitamin E. J Sci Food Agric 80, 913–938.
Brigelius-Flohe, R., & Traber, M. G. (1999). Vitamin E: function and metabolism. FASEB J 13, 1145–1155.
Brizel, D. M.,Wasserman, T. H., Henke, M., Strnad, V., Rudat, V., Monnier, A., et al. (2000). Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. J Clin Oncol 18, 3339–3345.
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.
Burton, G. W., Traber,M. G., Acuff, R. V., Walters, D. N., Kayden, H., Hughes, L., et al. (1998). Human plasma and tissue alpha-tocopherol concentrations in response to supplementation with deuterated natural and synthetic vitamin E. Am J Clin Nutr 67, 669–684.
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.
Cheng, G., Zielonka, J., McAllister, D., Mackinnon, A., Joseph, J., Dwinell, M., et al. (2013). Mitochondria-targeted vitamin E analogs inhibit breast cancer cell energy metabolism and promote cell death. BMC Cancer 13, 285.
Chin, K. Y., & Ima-Nirwana, S. (2014a). The effects of alpha-tocopherol on bone: a doubleedged sword? Nutrients 6, 1424–1441.
Chin, K. Y., & Ima-Nirwana, S. (2014b). Effects of annatto-derived tocotrienol supplementation on osteoporosis induced by testosterone deficiency in rats. Clin Interv Aging 9, 1247–1259.
Choi, Y., Jeong, H. -S., & Lee, J. (2007). Antioxidant activity of methanolic extracts from some grains consumed in Korea. Food Chem 103, 130–138.
Chojkier, M., Houglum, K., Lee, K. S., & Buck, M. (1998). Long- and short-termed-α-tocopherol supplementation inhibits liver collagen α1(I) gene expression. Am J Physiol Gastrointest Liver Physiol 275, G1480–G1485.
Christen, S., Jiang, Q., Shigenaga, M. K., & Ames, B. N. (2002). Analysis of plasma tocopherols α, γ, and 5-nitro-γ in rats with inflammation by HPLC coulometric detection. J Lipid Res 43, 1978–1985.
Christen, S., Woodall, A. A., Shigenaga, M. K., Southwell-Keely, P. T., Duncan, M. W., & Ames, B. N. (1997). γ-Tocopherol trapsmutagenic electrophiles such as NOx and complements α-tocopherol: physiological implications. Proc Natl Acad Sci 94, 3217–3222.
Cloarec, M. J., Perdriset, G. M., Lamberdiere, F. A., Colas-Belcour, J. F., Sauzieres, J. P., Neufeld, H. N., et al. (1987). Alpha-tocopherol: effect on plasma lipoproteins in hypercholesterolemic patients. Isr J Med Sci 23, 869–872.
Colombo,M. L. (2010). An update on vitamin E, tocopherol and tocotrienol—perspectives. Molecules 15, 2103–2113.
Compadre, C. M., Singh, A., Thakkar, S., Zheng, G., Breen, P. J., Ghosh, S., et al. (2014). Molecular dynamics guided design of tocoflexol: a new radioprotectant tocotrienol with enhanced bioavailability. Drug Dev Res 75, 10–22.
Cook-Mills, J. M., Abdala-Valencia, H., & Hartert, T. (2013). Two faces of vitamin E in the lung. Am J Respir Crit Care Med 188, 279–284.
Cooney, R. V., Harwood, P. J., Franke, A. A., Narala, K., Sundström, A. -K., Berggren, P. -O., et al. (1995). Products of γ-tocopherol reaction with NO2 and their formation in rat insulinoma (RINm5F) cells. Free Radic Biol Med 19, 259–269.
Crouzin, N., Ferreira, M. C., Cohen-Solal, C., Barbanel, G., Guiramand, J., & Vignes, M. (2010). Neuroprotection induced by vitamin E against oxidative stress in hippocampal neurons: involvement of TRPV1 channels. Mol Nutr Food Res 54, 496–505.
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.
Das, M., Das, S., Wang, P., Powell, S. R., & Das, D. K. (2008). Caveolin and proteasome in tocotrienol mediated myocardial protection. Cell Physiol Biochem 22, 287–294.

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.
de Diego-Otero, Y., Romero-Zerbo, Y., Bekay, R. e., Decara, J., Sanchez, L., Fonseca, F. R. -d., et al. (2008). α-Tocopherol protects against oxidative stress in the fragile X knockout mouse: an experimental therapeutic approach for the Fmr1 deficiency. Neuropsychopharmacology 34, 1011–1026.
Deliconstantinos, G., Villiotou, V., & Stavrides, J. C. (1996). Alterations of nitric oxide synthase and xanthine oxidase activities of human keratinocytes by ultraviolet B radiation: potential role for peroxynitrite in skin inflammation. Biochem Pharmacol 51, 1727–1738.
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.
Devaraj, S., & Jialal, I. (2000). Alpha tocopherol supplementation decreases serum Creactive protein and monocyte interleukin-6 levels in normal volunteers and type 2 diabetic patients. Free Radic Biol Med 29, 790–792.
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.
Evans, H. M., & Bishop, K. S. (1922). On the existence of a hitherto unrecognized dietary factor essential for reproduction. Science, 650–651.
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.
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.
Freedman, J. E., Li, L., Sauter, R., & Keaney, J. F. (2000). α-Tocopherol and protein kinase C inhibition enhance platelet-derived nitric oxide release. FASEB J 14, 2377–2379.
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.
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.
Funk, C. (1912). The etiology of the deficiency diseases. J State Med 20, 341–368.
Gao, P., & Morozowich, W. (2005). Development of supersaturatable self-emulsifying drug delivery system formulations for improving the oral absorption of poorly soluble drugs. Expert Opin Drug Deliv 3, 97–110.
Ghafoorunissa, Hemalatha, S., & Rao, M. V. (2004). Sesame lignans enhance antioxidant activity of vitamin E in lipid peroxidation systems.Mol Cell Biochem262, 195–202.
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.
Gopalan, Y., Shuaib, I. L., Magosso, E., Ansari, M. A., Abu Bakar, M. R., Wong, J. W., et al. (2014). Clinical investigation of the protective effects of palm vitamin E tocotrienols on brain white matter. Stroke 45, 1422–1428

Goudarzvand, M., Javan,M., Mirnajafi-Zadeh, J., Mozafari, S., & Tiraihi, T. (2010). Vitamins E and D3 attenuate demyelination and potentiate remyelination processes of hippocampal formation of rats following local injection of ethidium bromide. Cell Mol Neurobiol 30, 289–299.
Greenberg, E. R. (2005). Vitamin E supplements: good in theory, but is the theory good? Ann Intern Med 142, 75–76.
Gueck, T., Aschenbach, J. R., & Fuhrmann, H. (2002). Influence of vitamin E on mast cell mediator release. Vet Dermatol 13, 301–305.
Gutierres, J. M., Kaizer, R. R., Schmatz, R., Mazzanti, C. M., Vieira, J. M., Rodrigues, M. V., et al. (2012). Alpha-tocopherol regulates ectonucleotidase activities in synaptosomes from rats fed a high-fat diet. Cell Biochem Funct 30, 286–292.
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.
Haleagrahara, N., Swaminathan, M., Chakravarthi, S., & Radhakrishnan, A. (2014). Therapeutic efficacy of vitamin E δ-tocotrienol in collagen-induced rat model of arthritis. Biomed Res Int 2014, 1–8.
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.
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.
Horvath, G., Wessjohann, L., Bigirimana, J., Jansen, M., Guisez, Y., Caubergs, R., et al. (2006). Differential distribution of tocopherols and tocotrienols in photosynthetic and non-photosynthetic tissues. Phytochemistry 67, 1185–1195.
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.
Ibanez, L., Ferrandiz, M. L., Brines, R., Guede, D., Cuadrado, A., & Alcaraz, M. J. (2014). Effects of Nrf2 deficiency on bone microarchitecture in an experimental model of osteoporosis. Oxidative Med Cell Longev 2014, 726590.
Ikeda, S., Toyoshima, K., & Yamashita, K. (2001). Dietary sesame seeds elevate α- and γ-tocotrienol concentrations in skin and adipose tissue of rats fed the tocotrienol-rich fraction extracted from palm oil. J Nutr 131, 2892–2897.
Iniguez-Ariza, N. M., & Clarke, B. L. (2015). Bone biology, signaling pathways, and therapeutic targets for osteoporosis. Maturitas 82, 245–255.
Ito, K., Herbert, C., Siegle, J. S., Vuppusetty, C., Hansbro, N., Thomas, P. S., et al. (2008). Steroid-resistant neutrophilic inflammation in a mouse model of an acute exacerbation of asthma. Am J Respir Cell Mol Biol 39, 543–550.
Iwaniec, U. T., Turner, R. T., Smith, B. J., Stoecker, B. J., Rust, A., Zhang, B., et al. (2013). Evaluation of long-term vitamin E insufficiency or excess on bone mass, density, and microarchitecture in rodents. Free Radic Biol Med 65, 1209–1214.
Javanbakht, M. H., Keshavarz, S. A., Djalali, M., Siassi, F., Eshraghian, M. R., Firooz, A., et al. (2010). Randomized controlled trial using vitamins E and D supplementation in atopic dermatitis. J Dermatol Treat 22, 144–150.
Jenkins, J. K., Huang, H., Ndebele, K., & Salahudeen, A. K. (2001). Vitamin E inhibits renal mRNA expression of COX II, HO I, TGFβ, and osteopontin in the rat model of cyclosporine nephrotoxicity. Transplantation 71, 331–334.
Jiang, Q. (2014). Natural forms of vitamin E: metabolism, antioxidant, and antiinflammatory activities and their role in disease prevention and therapy. Free Radic Biol Med 72, 76–90.
Jiang, F., Liao, Z., Hu, L. -H., Du, Y. -Q., Man, X. -H., Gu, J. -J., et al. (2011). Comparison of antioxidative and antifibrotic effects of α-tocopherol with those of tocotrienol-rich fraction in a rat model of chronic pancreatitis. Pancreas 40, 1091–1096.
Jiang, Q., Moreland, M., Ames, B. N., & Yin, X. (2009). A combination of aspirin and γ-tocopherol is superior to that of aspirin and α-tocopherol in anti-inflammatory action and attenuation of aspirin-induced adverse effects. J Nutr Biochem 20, 894–900.
Jiang, Q., Yin, X., Lill, M. A., Danielson, M. L., Freiser, H., & Huang, J. (2008). Long-chain carboxychromanols, metabolites of vitamin E, are potent inhibitors of cyclooxygenases. Proc Natl Acad Sci 105, 20464–20469.
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.
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.
Karrer, P., Fritzsche, H., Ringier, B., & Salomon, H. (1938). Synthesis of alpha-tocopherol (vitamin E). Nature 141, 1057.
Kelly, F. J., Mudway, I., Blomberg, A., Frew, A., & Sandström, T. (1999). Altered lung antioxidant status in patients with mild asthma. Lancet 354, 482–483.
Khan, M. R., Siddiqui, S., Parveen, K., Javed, S., Diwakar, S., & Siddiqui, W. A. (2010). Nephroprotective action of tocotrienol-rich fraction (TRF) from palm oil against potassium dichromate (K2Cr2O7)-induced acute renal injury in rats. Chem Biol Interact 186, 228–238.
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., 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.
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.

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.
Khosla, P., Patel, V., Whinter, J. M., Khanna, S., Rakhkovskaya, M., Roy, S., et al. (2006). Postprandial levels of the natural vitamin E tocotrienol in human circulation. Antioxid Redox Signal 8, 1059–1068.
Kiyose, C., Muramatsu, R., Kameyama, Y., Ueda, T., & Igarashi, O. (1997). Biodiscrimination of alpha-tocopherol stereoisomers in humans after oral administration. Am J Clin Nutr 65, 785–789.
Kooyenga, D. K., Geller, M.,Watkins, T. R., Gapor, A., Diakoumakis, E., & Bierenbaum, M. L. (1997). Palm oil antioxidant effects in patients with hyperlipidaemia and carotid stenosis-2 year experience. Asia Pac J Clin Nutr 6, 72–75.
Kosari, P., Alikhan, A., Sockolov,M., & Feldman, S. R. (2010). Vitamin E and allergic contact dermatitis. Dermatitis 21, 148–153.
Kosowski, A., & Clouatre, D. L. (2008). Vitamin E: natural vs. synthetic. Tocotrienols: vitamin E beyond tocopherolsVol. 1. (pp. 61–75). Boca Raton: CRC Press, 61–75.
Kuemmerle, N. B., Brandt, R. B., Chan,W., Krieg, R. J., Jr., & Chan, J. C. M. (1997). Inhibition of transforming growth factor β1 induction by dietary vitamin E in unilateral ureteral obstruction in rats. Biochem Mol Med 61, 82–86.
Kuhad, A., Bishnoi, M., Tiwari, V., & Chopra, K. (2009). Suppression of NF-κβ signaling pathway by tocotrienol can prevent diabetes associated cognitive deficits. Pharmacol Biochem Behav 92, 251–259.
Kuhad, A., & Chopra, K. (2009a). Attenuation of diabetic nephropathy by tocotrienol: involvement of NFkB signaling pathway. Life Sci 84, 296–301.
Kuhad, A., & Chopra, K. (2009b). Tocotrienol attenuates oxidative–nitrosative stress and inflammatory cascade in experimental model of diabetic neuropathy. Neuropharmacology 57, 456–462.
Kulkarni, S., Chakraborty, K., Kumar, K. S., Kao, T. -C., Hauer-Jensen, M., & Ghosh, S. P. (2013a). Synergistic radioprotection by gamma-tocotrienol and pentoxifylline: role of cAMP signaling. ISRN Radiol 2013, 390379.
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.
Kulkarni, S., Singh, P. K., Ghosh, S. P., Posarac, A., & Singh, V. K. (2013b). Granulocyte colony-stimulating factor antibody abrogates radioprotective efficacy of gammatocotrienol, a promising radiation countermeasure. Cytokine 62, 278–285.
Leach, J. K., Van Tuyle, G., Lin, P. S., Schmidt-Ullrich, R., & Mikkelsen, R. B. (2001). Ionizing radiation-induced, mitochondria-dependent generation of reactive oxygen/nitrogen. Cancer Res 61, 3894–3901.
Lee, I., Cook, N. R., Gaziano, J., et al. (2005). Vitamin e in the primary prevention of cardiovascular disease and cancer: The women's health study: a randomized controlled trial. JAMA 294, 56–65.
Lekli, I., Ray, D., Mukherjee, S., Gurusamy, N., Ahsan, M. K., Juhasz, B., et al. (2010). Coordinated autophagy with resveratrol and gamma-tocotrienol confers synergetic cardioprotection. J Cell Mol Med 14, 2506–2518.
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.
Li, X. H., Ghosh, S. P., Ha, C. T., Fu, D., Elliott, T. B., Bolduc, D. L., et al. (2013). Deltatocotrienol protects mice from radiation-induced gastrointestinal injury. Radiat Res 180, 649–657.
Li, G., Lee, M. -J., Liu, A. B., Yang, Z., Lin, Y., Shih, W. J., et al. (2012). The antioxidant and anti-inflammatory activities of tocopherols are independent of Nrf2 in mice. Free Radic Biol Med 52, 1151–1158.
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.
Lodge, J., Ridlington, J., Leonard, S., Vaule, H., & Traber, M. (2001). α- and γ-tocotrienols are metabolized to carboxyethyl-hydroxychroman derivatives and excreted in human urine. Lipids 36, 43–48.
Lonn, E., Bosch, J., Yusuf, S., Sheridan, P., Pogue, J., Arnold, J. M. O., et al. (2005). Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. JAMA 293, 1338–1347.
Luna, J., Masamunt,M. C., Llach, J., Delgado, S., & Sans, M. (2011a). Palmoil tocotrienol rich fraction reduces extracellular matrix production by inhibiting transforming growth factor-β1 in human intestinal fibroblasts. Clin Nutr 30, 858–864.
Luna, J., Masamunt, M. C., Rickmann, M., Mora, R., España, C., Delgado, S., et al. (2011b).

Tocotrienols have potent antifibrogenic effects in human intestinal fibroblasts.
Inflamm Bowel Dis 17, 732–741.
Magosso, E., Ansari, M. A., Gopalan, Y., Shuaib, I. L.,Wong, J.W., Khan, N. A., et al. (2013).
Tocotrienols for normalisation of hepatic echogenic response in nonalcoholic fatty
liver: a randomised placebo-controlled clinical trial. Nutr J 12, 166.
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.
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.
Marin, T., Contreras, P., Castro, J. F., Chamorro, D., Balboa, E., Bosch-Morato, M., et al.
(2014). Vitamin E dietary supplementation improves neurological symptoms
and decreases c-Abl/p73 activation in Niemann–Pick C mice. Nutrients 6,
3000–3017.
Martinelli, D., Catteruccia, M., Piemonte, F., Pastore, A., Tozzi, G., Dionisi-Vici, C., et al.
(2012). EPI-743 reverses the progression of the pediatric mitochondrial
disease—genetically defined Leigh Syndrome. Mol Genet Metab 107, 383–388.
Matough, F. A., Budin, S. B., Hamid, Z. A., Abdul-Rahman, M., Al-Wahaibi, N., &
Mohammed, J. (2014). Tocotrienol-rich fraction from palm oil prevents oxidative
damage in diabetic rats. Sultan Qaboos Univ Med J 14, e95–e103.
Matthaus, B., Vosmann, K., Pham, L. Q., & Aitzetmüller, K. (2003). FA and tocopherol composition
of vietnamese oilseeds. J Am Oil Chem Soc 80, 1013–1020.
McCary, C. A., Abdala-Valencia, H., Berdnikovs, S., & Cook-Mills, J. M. (2011). Supplemental
and highly elevated tocopherol doses differentially regulate allergic inflammation:
reversibility of α-tocopherol and γ-tocopherol's effects. J Immunol 186, 3674–3685.
Mehat, M. Z., Shuid, A. N., Mohamed, N., Muhammad, N., & Soelaiman, I. N. (2010). Beneficial
effects of vitamin E isomer supplementation on static and dynamic bone
histomorphometry parameters in normal male rats. J Bone Miner Metab 28, 503–509.
Mensink, R. P., van Houwelingen, A. C., Kromhout, D., & Hornstra, G. (1999).AvitaminE concentrate
rich in tocotrienols had no effect on serum lipids, lipoproteins, or platelet function
inmenwithmildly elevated serumlipid concentrations. Am J Clin Nutr 69, 213–219.
Meyenberg, A., Goldblum, D., Zingg, J. -M., Azzi, A., Nesaretnam, K., Kilchenmann, M., et al.
(2005). Tocotrienol inhibits proliferation of human Tenon's fibroblasts in vitro: a
comparative study with vitamin E forms and mitomycin C. Ger J Ophthalmol 243,
1263–1271.
Michaels, H. B., & Hunt, J.W. (1978). Amodel for radiation damage in cells by direct effect
and by indirect effect: a radiation chemistry approach. Radiat Res 74, 23–34.
Miller, I. I. I. E. R., Pastor-Barriuso, R., Dalal, D., Riemersma, R. A., Appel, L. J., & Guallar, E.
(2005). Meta-analysis: high-dosage vitamin E supplementation may increase allcause
mortality. Ann Intern Med 142, 37–46.
Min, K. C., Kovall, R. A., & Hendrickson, W. A. (2003). Crystal structure of human α-
tocopherol transfer protein bound to its ligand: implications for ataxia with vitamin
E deficiency. Proc Natl Acad Sci 100, 14713–14718.
Mishima, K., Tanaka, T., Pu, F., Egashira, N., Iwasaki, K., Hidaka, R., et al. (2003). Vitamin E
isoforms alpha-tocotrienol and gamma-tocopherol prevent cerebral infarction in
mice. Neurosci Lett 337, 56–60.
Miyoshi, N., Naniwa, K., Kumagai, T., Uchida, K., Osawa, T., & Nakamura, Y. (2005). α-Tocopherol-
mediated caspase-3 up-regulation enhances susceptibility to apoptotic
stimuli. Biochem Biophys Res Commun 334, 466–473.
Mo, H., Yeganehjoo, H., Shah, A., Mo, W. K., Soelaiman, I. N., & Shen, C. L. (2012).
Mevalonate-suppressive dietary isoprenoids for bone health. J Nutr Biochem 23,
1543–1551.
Montonen, J., Knekt, P., Järvinen, R., & Reunanen, A. (2004). Dietary antioxidant intake and
risk of type 2 diabetes. Diabetes Care 27, 362–366.
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.
Muharis, S. P., Top, A. G. M., Murugan, D., & Mustafa, M. R. (2010). Palm oil tocotrienol
fractions restore endothelium dependent relaxation in aortic rings of
streptozotocin-induced diabetic and spontaneously hypertensive rats. Nutr Res 30,
209–216.
Mukherjee, S., Lekli, I., Das, M., Azzi, A., & Das, D. K. (2008). Cardioprotection with alphatocopheryl
phosphate: amelioration of myocardial ischemia reperfusion injury is
linked with its ability to generate a survival signal through Akt activation. Biochim
Biophys Acta 1782, 498–503.

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.
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 rabbits. Malays J Pathol 23, 17–25.
Nakamura, H., Furukawa, F., Nishikawa, A., Miyauchi, M., Son, H. Y., Imazawa, T., et al. (2001). Oral toxicity of a tocotrienol preparation in rats. Food Chem Toxicol 39, 799–805.
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.
Napolitano, M., Avanzi, L., Manfredini, S., & Bravo, E. (2007). Effects of new combinative antioxidant FeAOX-6 and α-tocotrienol on macrophage atherogenesis-related functions. Vasc Pharmacol 46, 394–405.
Netscher, T. (2007). Synthesis of vitamin E. Vitam Horm 76, 155–202.
Nicod, N., & Parker, R. S. (2013). Vitamin E secretion by Caco-2monolayers to APOA1, but not to HDL, is vitamer selective. J Nutr 143, 1565–1572.
Niess, A. M., Sommer, M., Schneider, M., Angres, C., Tschositsch, K., Golly, I. C., et al. (2000). Physical exercise-induced expression of inducible nitric oxide synthase and heme oxygenase-1 in human leukocytes: effects of rrr-α-tocopherol supplementation. Antioxid Redox Signal 2, 113–126.
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.
Norazlina, M., Hermizi, H., Faizah, O., Nazrun, A. S., Norliza, M., & Ima-Nirwana, S. (2010). Vitamin E reversed nicotine-induced toxic effects on bone biochemical markers in male rats. Arch Med Sci 6, 505–512.
Norazlina,M., Ima-Nirwana, S., Gapor, M. T., & Khalid, B. A. (2000). Palm vitamin E is comparable to alpha-tocopherol in maintaining bone mineral density in ovariectomised female rats. Exp Clin Endocrinol Diabetes 108, 305–310.
Norazlina, M., Lee, P. L., Lukman, H. I., Nazrun, A. S., & Ima-Nirwana, S. (2007). Effects of vitamin E supplementation on bone metabolism in nicotine-treated rats. Singap Med J 48, 195–199.
O'Byrne, D., Grundy, S., Packer, L., Devaraj, S., Baldenius, K., Hoppe, P. P., et al. (2000). Studies of LDL oxidation following α-, γ-, or δ-tocotrienyl acetate supplementation of hypercholesterolemic humans. Free Radic Biol Med 29, 834–845.
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.
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.
Packer, L.,Weber, S. U., & Rimbach, G. (2001). Molecular aspects of α-tocotrienol antioxidant action and cell signalling. J Nutr 131, 369S–373S.
Palozza, P., Verdecchia, S., Avanzi, L., Vertuani, S., Serini, S., Iannone, A., et al. (2006). Comparative antioxidant activity of tocotrienols and the novel chromanyl-polyisoprenyl molecule FeAox-6 in isolated membranes and intact cells.Mol Cell Biochem287, 21–32.
Panfili, G., Fratianni, A., & Irano, M. (2003). Normal phase high-performance liquid chromatography method for the determination of tocopherols and tocotrienols in cereals. J Agric Food Chem 51, 3940–3944.
Pantzaris, M. C., Loukaides, G. N., Ntzani, E. E., & Patrikios, I. S. (2013). A novel oral nutraceutical formula of omega-3 and omega-6 fatty acids with vitamins (PLP10) in relapsing remitting multiple sclerosis: a randomised, double-blind, placebo-controlled proof-of-concept clinical trial. BMJ Open 3, e002170.
Park, H. A., Kubicki, N., Gnyawali, S., Chan, Y. C., Roy, S., Khanna, S., et al. (2011). Natural vitamin E alpha-tocotrienol protects against ischemic stroke by induction of multidrug resistance-associated protein 1. Stroke 42, 2308–2314.
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.
Patel, J., Matnor, N. A., Iyer, A., & Brown, L. (2011). A regenerative antioxidant protocol of vitamin E and alpha-lipoic acid ameliorates cardiovascular and metabolic changes in fructose-fed rats. Evid Based Complement Alternat Med 2011, 120801.
Paul, M. V. S., Abhilash, M., Varghese, M. V., Alex, M., & Harikumaran Nair, R. (2012). Protective

effects of α-tocopherol against oxidative stress related to nephrotoxicity by monosodium glutamate in rats. Toxicol Mech Methods 22, 625–630.
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.
Peh, H. Y., Ho, W. E., Cheng, C., Chan, T. K., Seow, A. C. G., Lim, A. Y., et al. (2015). Vitamin E isoform γ-tocotrienol downregulates house dust mite–induced asthma. J Immunol 195, 437–444.
Pennock, J. (1983). The biosynthesis of chloroplastidic terpenoid quinones and chromanols. Biochem Soc Trans 11, 504–510.
Qureshi, A. A., Burger, W. C., Peterson, D. M., & Elson, C. E. (1986). The structure of an inhibitor of cholesterol biosynthesis isolated from barley. J Biol Chem 261, 10544–10550.
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.
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.
Qureshi, A. A., Qureshi, N., Wright, J. J., Shen, Z., Kramer, G., Gapor, A., et al. (1991). Lowering of serum cholesterol in hypercholesterolemic humans by tocotrienols (palmvitee). Am J Clin Nutr 53, 1021S–1026S.
Qureshi, A., Reis, J., Papasian, C., Morrison, D., & Qureshi, N. (2010). Tocotrienols inhibit lipopolysaccharide-induced pro-inflammatory cytokines in macrophages of female mice. Lipids Health Dis 9, 1–15.
Qureshi, A. A., Sami, S. A., Salser,W. A., & Khan, F. A. (2002). Dose-dependent suppression of serum cholesterol by tocotrienol-rich fraction (TRF25) of rice bran in hypercholesterolemic humans. Atherosclerosis 161, 199–207.
Rades, D., Fehlauer, F., Bajrovic, A., Mahlmann, B., Richter, E., & Alberti,W. (2004). Serious adverse effects of amifostine during radiotherapy in head and neck cancer patients. Radiother Oncol 70, 261–264.
Radhakrishnan, Tudawe, Chakravarthi, Chiew, & Haleagrahara (2014). Effect of γ-tocotrienol in counteracting oxidative stress and joint damage in collageninduced arthritis in rats. Exp Theor Med 7, 1408–1414.
Rahman, S., Blok, R. B., Dahl, H. H.M., Danks, D.M., Kirby, D.M., Chow, C. W., et al. (1996). Leigh syndrome: clinical features and biochemical and DNA abnormalities. Ann Neurol 39, 343–351.
Rashid Khan, M., Ahsan, H., Siddiqui, S., & Siddiqui, W. A. (2015). Tocotrienols have a nephroprotective action against lipid-induced chronic renal dysfunction in rats. Ren Fail 37, 136–143.
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.
Reddy, G. B., Nayak, S., Reddy, P. Y., & Bhat, K. S. (2001). Reduced levels of rat lens antioxidant vitamins upon in vitro UVB irradiation. J Nutr Biochem 12, 121–124.
Riccioni, G., Bucciarelli, T., Mancini, B., Di Ilio, C., Capra, V., & D'Orazio, N. (2006). The role of the antioxidant vitamin supplementation in the prevention of cardiovascular diseases. Expert Opin Investig Drugs 16, 25–32.
Roza, J. M., Xian-Liu, Z., & Guthrie, N. (2007). Effect of citrus flavonoids and tocotrienols on serum cholesterol levels in hypercholesterolemic subjects. Altern Ther Health Med 13, 44–48.
Sadun, A. A., Chicani, C., Ross-Cisneros, F. N., et al. (2012). EFfect of epi-743 on the clinical course of the mitochondrial disease leber hereditary optic neuropathy. Arch Neurol 69, 331–338.
Sadun, A., Morgia, C., & Carelli, V. (2011). Leber's hereditary optic neuropathy. Curr Treat Options Neurol 13, 109–117.
Satyamitra, M. M., Kulkarni, S., Ghosh, S. P., Mullaney, C. P., Condliffe, D., & Srinivasan, V. (2011). Hematopoietic recovery and amelioration of radiation-induced lethality by the vitamin E isoform δ-tocotrienol. Radiat Res 175, 736–745.
Selvaraju, T. R., Khaza'ai, H., Vidyadaran, S., Abd Mutalib, M. S., & Vasudevan, R. (2014). The neuroprotective effects of tocotrienol rich fraction and alpha tocopherol against glutamate injury in astrocytes. Bosn J Basic Med Sci 14, 195–204.
Sen, C. K., Khanna, S., Rink, C., & Roy, S. (2007). Tocotrienols: the emerging face of natural vitamin E. Vitam Horm 76, 203–261.
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.
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.
Shirpoor, A., Norouzi, L., Khadem Ansari, M. H., Ilkhanizadeh, B., & Gharaaghaji, R. (2013). Vasoprotective effect of vitamin E: rescue of ethanol-induced atherosclerosis and inflammatory stress in rat vascular wall. Int Immunopharmacol 16, 498–504.
Siddiqui, S., Ahsan, H., Khan, M. R., & Siddiqui, W. A. (2013). Protective effects of tocotrienols against lipid-induced nephropathy in experimental type-2 diabetic rats by modulation in TGF-β expression. Toxicol Appl Pharmacol 273, 314–324.
Siddiqui, S., Rashid Khan, M., & Siddiqui, W. A. (2010). Comparative hypoglycemic and nephroprotective effects of tocotrienol rich fraction (TRF) from palm oil and rice bran oil against hyperglycemia induced nephropathy in type 1 diabetic rats. Chem Biol Interact 188, 651–658.
Simone, R., Palozza, P., Watson, R., & Preedy, V. (2008). Antioxidant activity of tocotrienols in cells and serum. Tocotrienols: vitamin E beyond tocopherolsVol. 1. (pp. 99–108). CrC Press, 99–108.
Singh, V. K., Singh, P. K., Wise, S. Y., Posarac, A., & Fatanmi, O. O. (2013). Radioprotective properties of tocopherol succinate against ionizing radiation in mice. J Radiat Res 54, 210–220.
Singh, P. K., Wise, S. Y., Ducey, E. J., Brown, D. S., & Singh, V. K. (2011). Radioprotective efficacy of tocopherol succinate is mediated through granulocyte-colony stimulating factor. Cytokine 56, 411–421.
Singh, V. K., Wise, S. Y., Fatanmi, O. O., Scott, J., Romaine, P. L. P., Newman, V. L., et al. (2014a). Progenitors mobilized by gamma-tocotrienol as an effective radiation countermeasure. PLoS One 9, e114078.
Singh, V. K., Wise, S. Y., Scott, J. R., Romaine, P. L. P., Newman, V. L., & Fatanmi, O. O. (2014b). Radioprotective efficacy of delta-tocotrienol, a vitamin E isoform, ismediated through granulocyte colony-stimulating factor. Life Sci 98, 113–122.
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.
Sontag, T. J., & Parker, R. S. (2002). Cytochrome P450 ω-hydroxylase pathway of tocopherol catabolism: novel mechanism of regulation of vitamin E status. J Biol Chem 277, 25290–25296.
Suman, S., Datta, K., Chakraborty, K., Kulkarni, S. S., Doiron, K., Fornace, A. J., Jr., et al. (2013). Gamma tocotrienol, a potent radioprotector, preferentially upregulates expression of anti-apoptotic genes to promote intestinal cell survival. Food Chem Toxicol 60, 488–496.
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.
Tanito, M., Itoh, N., Yoshida, Y., Hayakawa, M., Ohira, A., & Niki, E. (2004). Distribution of tocopherols and tocotrienols to rat ocular tissues after topical ophthalmic administration. Lipids 39, 469–474.
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.
Tasaki, M., Umemura, T., Inoue, T., Okamura, T., Kuroiwa, Y., Ishii, Y., et al. (2008). Induction of characteristic hepatocyte proliferative lesion with dietary exposure of Wistar Hannover rats to tocotrienol for 1 year. Toxicology 250, 143–150.
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.
Theriault, A., Chao, J. -T.,Wang, Q., Gapor, A., & Adeli, K. (1999). Tocotrienol: a review of its therapeutic potential. Clin Biochem 32, 309–319.
Traber, M. G. (2007). Vitamin E regulatory mechanisms. Annu Rev Nutr 27, 347–362.
Traber, M. G., & Arai, H. (1999). Molecular mechanisms of vitamin E transport. Annu Rev Nutr 19, 343–355.
Tsuduki, T., Kuriyama, K., Nakagawa, K., & Miyazawa, T. (2013). Tocotrienol (unsaturated vitamin E) suppresses degranulation of mast cells and reduces allergic dermatitis in mice. J Oleo Sci 62, 825–834.
Tsuzuki, W., Yunoki, R., & Yoshimura, H. (2007). Intestinal epithelial cells absorb γ-tocotrienol faster than α-tocopherol. Lipids 42, 163–170.
Uchida, T., Abe, C., Nomura, S., Ichikawa, T., & Ikeda, S. (2012). Tissue distribution of α- and γ-tocotrienol and γ-tocopherol in rats and interference with their accumulation by α-tocopherol. Lipids 47, 129–139.

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.
van Acker, S. A. B. E., Koymans, L. M. H., & Bast, A. (1993). Molecular pharmacology of vitamin E: structural aspects of antioxidant activity. Free Radic Biol Med 15, 311–328.
Venditti, P., Napolitano, G., Di Stefano, L., Agnisola, C., & Di Meo, S. (2011). Effect of vitamin E administration on response to ischaemia–reperfusion of hearts from coldexposed rats. Exp Physiol 96, 635–646.
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.
Wagner, J. G., Jiang, Q., Harkema, J. R., Ames, B. N., Illek, B., Roubey, R. A., et al. (2008). γ-Tocopherol prevents airway eosinophilia and mucous cell hyperplasia in experimentally induced allergic rhinitis and asthma. Clin Exp Allergy 38, 501–511.
Wan Nazaimoon,W. M., & Khalid, B. A. (2002). Tocotrienols-rich diet decreases advanced glycosylation end-products in non-diabetic rats and improves glycemic control in streptozotocin-induced diabetic rats. Malays J Pathol 24, 77–82.
Wang, Y., & Jiang, Q. (2013). γ-Tocotrienol inhibits lipopolysaccharide-induced interlukin-6 and granulocyte colony-stimulating factor by suppressing C/EBPβ and NF-κB in macrophages. J Nutr Biochem 24, 1146–1152.
Wang, Y., Moreland, M., Wagner, J. G., Ames, B. N., Illek, B., Peden, D. B., et al. (2012). Vitamin E forms inhibit IL-13/STAT6-induced eotaxin-3 secretion by up-regulation of PAR4, an endogenous inhibitor of atypical PKC in human lung epithelial cells. J Nutr Biochem 23, 602–608.
Waselenko, J. K.,MacVittie, T. J., Blakely,W. F., Pesik, N.,Wiley, A. L., Dickerson,W. E., et al. (2004). Medical management of the acute radiation syndrome: recommendations of the strategic national stockpile radiation working group. Ann Intern Med 140, 1037–1051.
Yanamala, N., Kapralov, A. A., Djukic, M., Peterson, J., Mao, G., Klein-Seetharaman, J., et al. (2014). Structural re-arrangement and peroxidase activation of cytochrome c by anionic analogues of vitamin E, tocopherol succinate and tocopherol phosphate. J Biol Chem 289, 32488–32498.
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.
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.
Yoshida, Y., Saito, Y., Jones, L. S., & Shigeri, Y. (2007). Chemical reactivities and physical effects in comparison between tocopherols and tocotrienols: physiological significance and prospects as antioxidants. J Biosci Bioeng 104, 439–445.
Zielinski, H. (2008). Tocotrienols: distribution and sources cereals — role in human health. Tocotrienols: vitamin E beyond tocopherolsVol. 1. (pp. 23–42). Boca Raton: CRC Press, 23–42.
Zielinski, H., Ciska, E., & Kozlowska, H. (2001). The cereal grains: focus on vitamin E. Czech J Food Sci 19, 182–188.