Published in final edited form as:

Biomed Pharmacother. 2005 August ; 59(7): 380–387. doi:10.1016/j.biopha.2005.06.005.

Alpha-tocopherol: roles in prevention and therapy of human disease

J.M. Tucker^a and D.M. Townsend^{b,*}

^aDepartment of Cell and Molecular Pharmacology, College of Pharmacy, Medical University of South Carolina, Charleston, SC, USA

^bDepartment of Pharmaceutical Sciences, College of Pharmacy, Medical University of South Carolina, 173 Ashley Avenue, BSB 305B, Charleston, SC 29425, USA

Abstract

Alpha-tocopherol, one of the eight isoforms of vitamin E, is the most potent fat-soluble antioxidant known in nature. For years, it was thought that α -tocopherol only functioned as a scavenger of lipid peroxyl radicals, specifically, oxidized low-density lipoprotein (oxLDL), thereby serving as a chief antioxidant for the prevention of atherosclerosis. In recent years, the many roles of α -tocopherol have been uncovered, and include not only antioxidant functions, but also pro-oxidant, cell signaling and gene regulatory functions. Decades of clinical and preclinical studies have broadened our understanding of the antioxidant vitamin E and its utility in a number of chronic, oxidative stress-induced pathologies. The results of these studies have shown promising, albeit mixed reviews on the efficacy of α -tocopherol in the prevention and treatment of heart disease, cancer and Alzheimer's disease. Future studies to uncover cellular and systemic mechanisms may help guide appropriate clinical treatment strategies using vitamin E across a diverse population of aging individuals.

Keywords

Cardiovascular disease; Alzheimer's disease; Cancer; Oxidative stress

1. Introduction

Vitamin E is the name given to a family of eight molecules, each consisting of a chromanol ring with an aliphatic side chain. They consist of two groups, tocopherols and tocotrienols, based on the side chain being saturated or unsaturated, respectively. Within each group, there are four isoforms, α , β , γ , and δ named for specific methyl group substitutions at positions 5, 7 and 8 of the chromanol ring [1]. Tocopherols have three chiral centers, and the α -isoform is most commonly found in the 2*R*,4'*R*,8'*R* configuration. Although the β -, γ -, δ - are absorbed by humans through the intestine, they are not recognized by the liver protein, α -tocopherol transfer protein (α -TTP) and replenished in circulation like the α -isoform [2]. Also, α -tocopherol functions as the most potent naturally occurring scavenger

*Corresponding author., townsed@musc.edu (J.M. Tucker).

of reactive oxygen and reactive nitrogen species (ROS and RNS), surpassed only by recently developed synthetic compounds [3].

Dietary vitamin E is obtained mainly from plant sources including sunflower seeds, olive oil and almonds, which contain high amounts of α -tocopherol, while most other oils and seed oils are rich in γ -tocopherol. Although the majority of western dietary vitamin E consists of γ -tocopherol, the α -isoform is predominant in vitamin E supplements [4] in the form of RRR- α -tocopherol or molar equivalent tocopherol esters. RRR- α -tocopherol supplementation is considered safe below the tolerable upper intake level of 1000 mg daily for adults, as established by the Institute of Medicine. However, some studies have shown that vitamin E supplementation is safe in clinical trials in amounts up to 1073 mg (1600 International Units (IU) [5]. These levels are far above the recommended vitamin E intake of 400 IU/day. Absorption of this vitamin occurs in the small intestine along with other fat-soluble nutrients. Pancreatic lipases and bile salts aid in the formation of micelles. The bioavailability of vitamin E is impacted by the levels of dietary fats as well as plant sterols that share similar digestion and absorption pathways [6,7].

The α -tocopherol isoform of vitamin E inhibits the radical chain propagation within lipid domains by its own conversion into an oxidized product, α -tocopheroxyl free radical [8,9] (Fig. 1). Alpha-tocopherol reacts with lipid peroxyl radicals at a rate several orders of magnitude faster than the peroxyl radical propagation reaction [4]. The original form can be regenerated by reduction by ascorbate (vitamin C) or ubiquinol-10 [1]. This regeneration enhances the antioxidant capacity of vitamin E and has led to the clinical investigation of vitamin C use in concert with vitamin E supplementation [4].

2. Vitamin E uptake and transport

Vitamin E and other fat-soluble nutrients are emulsified by bile salts and pancreatic enzymes into micelle particles in the small intestine. All vitamin E isoforms are transported purportedly in a similar fashion as dietary cholesterol, via the selective cholesterol uptake activity of the Niemann Pick C1-like protein localized in the brush border membrane [10]. Once inside the enterocyte, cholesterol trafficking is controlled by the activity of ATP-binding cassette (ABC) transporters, a pathway potentially shared by vitamin E and its derivatives [11]. These transporters are controlled at the transcriptional level by liver X receptors, nuclear factors whose agonists include oxidized cholesterol and plant sterols [12]. Supporting the hypothesis that vitamin E is transported in a similar fashion as cholesterol is the observation that ABCA1 plays a role in the efflux of α -tocopherol in cultured macrophages and fibroblasts [13]. The transporters ABCA1 and ABCG1 enable cholesterol uptake into the lymphatic system [14,15] while ABCG5 and ABCG8 control the efflux of cholesterol into the intestinal lumen. The transcriptional activation of ABCG5 and ABCG8 by sterol-induced liver X receptors reduces the overall intestinal absorption of cholesterol [16]. Chylomicrons, containing all eight equally represented isoforms of vitamin E among other lipid soluble nutrients, are secreted from enterocytes into the lymph and are released into the circulation via the thoracic duct. Lipoprotein lipases, bound to the endothelium, hydrolyze triacylglycerols from the surface of the chylomicron particle, and subsequently, free fatty acids and monoacylglycerols are released as the particle becomes smaller from the

loss of surface molecules [2]. During this process, some vitamin E is transferred to high-density lipoproteins (HDL) and the rest remain in the chylomicron until the particle is taken into hepatocytes via LDL receptor and LDL receptor-related protein-mediated endocytosis [17]. Several other factors may be involved in the uptake of vitamin E in HDL and particle remnants in the liver, including the scavenger receptor B type I (SR-BI) [18]. In hepatocytes, RRR α -tocopherol is selectively bound to the α -tocopherol transfer protein (α -TTP), a Sec14 protein family member expressed in the liver, brain and placenta [19,20], while other isoforms of vitamin E are excreted in the bile. Individuals that lack a functional α -TTP suffer from a neuro-degenerative disease called ataxia with vitamin E deficiency [21], suggesting a role for this protein in the retention and subsequent plasma dispersal of α -tocopherol. After binding to α -TTP, α -tocopherol is trafficked into late endosomes/lysosomes and then into very low-density lipoprotein (VLDL) particles at the plasma membrane; a process that is proposed to involve the Golgi apparatus and/or the ABCA1 transporter [13,22,23]. Excess α -tocopherol is secreted from the liver in the form of VLDL particles, which are broken down by lipoprotein lipases of peripheral cell endothelium and transferred into lipoprotein particles (HDL, LDL, VLDL remnants) and either taken up by the liver or delivered to cells via receptor-mediated and non-receptor mediated pathways [2].

3. Oxidative stress and human disease

Oxidative stress is a necessary phenomenon in growth, development and differentiation. Such processes as proliferation, wounding and aging incite the generation of lipid hydroperoxides from cell membrane phospholipids. These reactive lipids can function as signaling molecules and can induce apoptosis. The specific levels of ROS and RNS, respectively, within a cell can determine a number of processes including the activity of specific enzymes and proteases, changes in ion levels (such as Ca^{2+}), the expression of genes and whether a cell lives (mitosis) or dies (apoptosis or necrosis) [24]. Several naturally occurring free radical scavengers, including beta-carotene, ascorbate and vitamin E, help maintain homeostatic levels of these reactive species by terminating a chain reaction of oxidizing events [1]. Survival enzymes such as glutathione peroxidase (GPx) and superoxide dismutase (SOD) are also responsible for the maintenance of oxidative homeostasis.

In situations of elevated oxidative stress, $\text{O}_2^{\bullet}$ can react with nitric oxide (NO) and produce peroxynitrite (ONOO^-), a potent oxidant of proteins, lipids and DNA [25]. Chronic, unbridled oxidative damage has been implicated as the culprit behind many chronic diseases, including cancer, atherosclerosis, diabetes, Alzheimer's [26–28] and other neurodegenerative diseases [26,29,30]. ROS, superoxide and hydrogen peroxide [31] play a key role as signaling molecules in the angiotensin II (AngII) system, a major signaling pathway for cardiovascular homeostasis. Alterations in AngII-mediated redox signaling have been observed in hypertension and atherosclerosis [32].

Modulation of enzyme transcription and/or activity by vitamin E has been shown in genes involved in oxidative stress, proliferation, inflammation and apoptosis. Such genes include, but are not limited to, SOD, NO synthase, cyclooxygenase-2, NADPH oxidase, nuclear factor kappa B, phospholipase A2, protein phosphatase 2A, 5-lipoxygenase, activator protein-1, pregnane X receptor, and protein kinase C [4,33]. Data extracted from cellular and

animal models have consistently shown that the gene regulatory effects of vitamin E reduce the levels of O₂ and lipid peroxides, and diminish the number and severity of atherogenic events [33].

Excess levels of vitamin E present in the liver activate the pregnane X receptor, a transcription factor that may lead to the expression of drug resistance genes including cytochrome P450, glutathione S-transferase A2, multidrug resistance-associated protein 2 (ABCC2), and hydroxysteroid sulfotransferase (SULT2–40/41) [34–37]. During transport via plasma lipoproteins, vitamin E protects the carrier particle from free radical peroxidative damage. This is one of the major and well-characterized modes of α -tocopherol antioxidant functions. However, cellular and preclinical animal models have demonstrated the existence of several “nonantioxidant” functions of vitamin E.

The downstream effects of oxidative damage are associated with several human pathologies including atherosclerosis [peroxidation of lipids (oxLDL) in fatty streak formation in the sub-endothelial space of blood vessels], cancer (oxidative damage to DNA and mutagenesis, resistance to free radical-inducing chemotherapy or radiation), and Alzheimer’s disease (oxidative damage-induced neuronal apoptosis, β -amyloid expression-secretion plaque formation).

4. Atherosclerosis

Reactive species in the vasculature are generated predominantly by the activity of NAD(P)H oxidase [38], xanthine oxidase, endothelial NO synthase (eNOS) and the mitochondrial respiratory chain [39,40]. One of the first events in atherogenesis is the oxidative modification of LDL induced by ROS and/or RNS. Oxidized LDL (oxLDL) stimulates CD36 and scavenger receptor-A (SR-A) expression in monocytes, macrophages and smooth muscle cells. This induces foam cell formation in macrophages as oxLDL uptake and retention are enhanced by the activity of these receptors. Further, oxLDL induces hypertrophy and hyperplasia of smooth muscle cells, which, in turn, narrow the vascular lumen. OxLDL also stimulates a pro-inflammatory state, inducing the expression of endothelial adhesion molecules, chemotaxis of leukocytes and inhibiting the migration of macrophages outside the sub-endothelial space. Taken together, oxLDL enhances many factors that contribute to the formation of an atherosclerotic lesion [25]. In addition, there are growing lines of evidence for candidate oxidative stress pathway genes that may predispose the vasculature of individuals to a pro-inflammatory/atherogenic condition. These include genes encoding p22^{phox} (an NAD(P)H oxidase), mitochondrial SOD, manganese SOD and NO synthase 3 [41–43]. Other polymorphisms associated with cardiovascular disease have previously been reviewed at length [44]. Alpha-tocopherol hampers the pro-atherogenic effects of oxidative stress not only by acting as a potent free radical scavenger, but also as a regulator of gene expression. The SR-A and CD36 scavenger receptors, mentioned above, are down-regulated in the presence of α -tocopherol [45–47]. Thus, gene regulation may be an important component of anti-atherogenic effects of vitamin E.

5. Clinical utility of alpha-tocopherol for cardiovascular disease

Although there is mounting evidence for the efficacy of α -tocopherol and other antioxidants such as vitamin C in the treatment and/or prevention of cardiovascular disease, there are conflicting reports on the use of vitamin E in clinical studies. Of five primary prevention studies, four showed no positive effect of vitamin E in the incidence of cardiovascular disease events (α -Tocopherol Beta-Carotene Cancer Prevention Study (ATBC) [48], Primary Prevention Project (PPP) [49], Vitamin E Atherosclerosis Prevention Study (VEAPS) [50], Age-Related Eye Disease Study (AREDS) [51], one showing a benefit of vitamin E (Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) Study [52]). Of the secondary intervention trials for vitamin E, that is, in testing the occurrence of endpoints of cardiovascular disease in subjects who have already undergone a disease event. Of seven clinical studies, four show no concise beneficial effect (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infartomiocardico (GISSI) [53], The Heart Outcomes Prevention Evaluation (HOPE) [54], Heart Protection Study (HPS), Womens' Angiographic Vitamin and Estrogen Trial (WAVE) [55], HDL-Atherosclerosis Treatment Study (HATS) [56] while the other three demonstrated a positive outcome for individuals with higher vitamin E intake [Cambridge Heart Antioxidant Study (CHAOS) [57], Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE) [58], and the Transplant-associated Arteriosclerosis study [59].] The authors of a meta-analysis of seven randomized trials [60] concluded that there were no significant differences in individuals given vitamin E, alone or in combination with beta-carotene, on mortality or incidence of stroke. Taken together, there is no concrete evidence of vitamin E as an intervening agent to reduce the mortality caused by cardiovascular disease, particularly in high-risk individuals [60].

A number of explanations have been proposed for the lack of consistency in the results of randomized trials. Certain factors in the trial subjects were not taken into consideration namely, general lifestyle, diet and fitness (all factors that are difficult to accurately assess) that may play a role in cardio-vascular disease risk. Also, the trials vary from the use of vitamin supplements to the survey of antioxidant rich food intake. The use of the latter is more complex due to the additional nutrients such as flavonoids, lycopenes, polyphenols that are present in antioxidant rich foods. It is widely accepted in the medical community that a 'healthy diet' is essential in the prevention of cardiovascular disease and some dietary intervention studies have shown a benefit of antioxidant rich foods such as fruits and vegetables or a 'Mediterranean' diet [61,62]. This may suggest that antioxidants like vitamin E may act synergistically with other naturally occurring compounds to maintain a healthy cardiovascular system. In addition to its antioxidant function, α -tocopherol has been shown to have other effects on cellular processes, namely on the immune system, proliferation and apoptosis, which makes it an interesting candidate for the study of its anti-cancer properties.

6. Cancer

The capacity of vitamin E, particularly α -tocopherol, to quench free radical damage, induce apoptosis and impact expression of oncogenes makes it a strong candidate for chemotherapeutic strategies. Earlier studies showed that vitamin E inhibited carcinogenesis

and UV-induced DNA damage in animal models [63–66]. These preclinical data also revealed that this micronutrient might stimulate an anti-tumor immune response by inducing chemotaxis of macrophages and lymphocytes to the tumor site [67]. Tumor responses seen following vitamin E treatment may also be due to activation of anti-tumor factors, including tumor necrosis factors (TNF- α and TNF- β) and wild-type p53 [68]. Furthermore, vitamin E and its derivatives have shown potent apoptotic effects in several human cancer cell lines [69,70] and also enhance the efficacy of chemotherapeutic agents in animal models [71]. In addition to its enhancement of apoptotic pathways, vitamin E can also inhibit tumor survival factors such as protein kinase C (PKC) [65]. PKC is a well-established anti-apoptotic factor expressed in several tumor types. Amazingly, vitamin E, specifically α -tocopherol succinate (α -TS), has a tumor-specific impact in prostate and breast tissue, as treatment did not cause apoptosis in normal epithelial cells [72]. Through its proven efficacy in several cancer cell studies and promising results from preliminary clinical trials, α -TS has been dubbed the most effective form of vitamin E in the adjuvant treatment of cancer [73] when used in combination with other micronutrients (such as vitamin C, retinoic acid and carotenoids) during chemotherapy or radiation [74]. However, other clinical trials have given mixed reviews on the use of vitamin E during chemotherapy. Bairati et al. [75], conducted a multi-center, randomized, double-blind placebo controlled trial of 540 patients with stage I or II head and neck cancer, being concurrently treated with radiation therapy. Patients were treated daily with 400IU α -tocopherol and or placebo during radiation and continued 3 years beyond. Unexpectedly, patients supplemented with α -tocopherol had a higher incidence of second primary cancers and a lower degree of cancer-free survival [76]. One study showed that α -tocopherol helped to prevent in the prevention of oral squamous cell carcinomas even though three prospective randomized trials using vitamin E as a chemopreventive agent failed to show positive effects (CARET, ATBC and PHS) [77]. A few studies showed that α -tocopherol was of little to no benefit in preventing lung cancer [78].

The uptake and absorption of vitamin E, being similar to dietary cholesterol, is an interesting parallel, since it may, in some cases, counteract the uptake and delivery of excess cholesterol to tissues [79]. Abnormal LDL cholesterol metabolism has shown an association with many forms of cancer including prostate, breast, pancreatic, squamous cell and small cell lung cancer [80–83]. LDL is the primary carrier of essential polyunsaturated fatty acids, such as linoleic acid and arachidonic acid (AA) [84]. The carriage of excess AA into cells may enhance proliferation through its conversion to prostaglandin E2 (by cyclooxygenase-2) and downstream regulation of immediate early genes (such as *c-fos*) [85,86]. Hence, the effects of vitamin E derivatives on cancer cells in vivo may begin with its effects on LDL uptake.

As mentioned in the previous section, several reasons may exist for varied clinical reports on the effects of a dietary supplement. These could include variability in the forms of vitamin E used (α -tocopherol, α -TS), type of cancer, stage of disease and method of treatment [74,75]. Studies demonstrating the anti-cancer actions of vitamin E, particularly α -TS, in human cancer cells cannot be disregarded and warrant further examination.

7. Alzheimer's disease

Aside from heart disease and cancer, free radical damage is also involved in the etiology of several neurodegenerative diseases such as Alzheimer's. AD is the most common neurodegenerative disease, affecting nearly 15 million people worldwide [87] and present in almost half of individuals over the age of 85 [88]. Post-mortem AD brain biopsies show an accumulation of extracellular senile plaques in neurofibrillary tangles and cerebral blood vessels. The plaques themselves are comprised of fibrillar and non-fibrillar β -amyloid (AB) peptide and the resultant loss of neuronal function in the limbic and association cortices causes the major symptom of AD, dementia [89]. At the cellular level, AB renders oxidative damage to proteins and lipids, propagates ROS formation, stimulates NOS activity and oxidizes glutamine synthetase (a key enzyme an excitatory neurotransmission pathway). Potentiation of ROS generation by oxidized proteins eventually results in neuronal death. Therefore, the antioxidant function of α -tocopherol (in supplements) and dietary tocopherol as a therapeutic strategy for Alzheimer's disease has been studied in both the preclinical and clinical setting.

In several animal studies of oxidant-induced brain injury animal models, the use of α -tocopherol/tocopherol succinate, alone or in combination with other antioxidative nutrients (proanthocyanidin, ascorbic acid, beta-carotene), helps to reduce the levels of brain damaging ROS and/or oxidative products [90,91]. Epidemiological studies and clinical trials, similar to vitamin E supplementation and heart disease, show mixed results of modest benefit to no effect of this antioxidant in efforts to prevent AD and/or dementia. Response relies on many factors including the form of vitamin E administered (in supplemental form or from food sources), with a mixture of various tocopherols showing improved ability to protect against AD compared to α -tocopherol alone [92,93]. A separate clinical study showed that α -tocopherol supplementation did, in fact, delay or prevent the AD diagnosis of elderly individuals with signs of mild cognitive impairment [94]. The use of ascorbic acid in concert with vitamin E, as in many heart disease prevention trials, also may improve the effects of this micronutrient in patients with AD [95]. However, some clinical studies show no evidence for the utility of vitamin E in individuals affected by AD [96–98].

Cognitive benefit of vitamin E supplementation may often rely on genetic factors [92]. For example, individuals that carry an allele of the $\epsilon 4$ isoform of APOE were shown to benefit more from vitamin E compared to non- $\epsilon 4$ carrying subjects [89]. Several genes have shown association with AD predisposition, APOE $\epsilon 4$ being the most common [89,99]. APOE-associated VLDL particles are most abundant in brain tissue, which is consistent with mounting evidence that AD pathology is associated with cholesterol metabolism [87,100]. Individuals with high cholesterol were shown to be at an increased risk of developing AD [101]. To this end, patients administered cholesterol-lowering therapy (statins), demonstrated a decreased incidence of AD and lowered A β levels [102–105]. Several genetic factors may exist that could modulate the efficacy of vitamin E in AD. ABCA1 is a key transporter in the cellular efflux of HDL and influences the age of AD onset and cholesterol levels within cerebrospinal fluid [106]. Tangier disease patients, harboring mutations in ABCA1, are typically shown to have reduced plasma HDL levels and a concomitant increase in the risk for AD development [106,107]. Polymorphism in

CYP46A1, a central cholesterol catabolic enzyme in the brain, is also associated with this disease [108]. In addition, the ABC transporter-2 gene (ABCA2), which, like its close relative ABCA1 with high expression in the brain, is genetically linked to AD, involved in cholesterol trafficking and may have an additional role in resistance to oxidative stress [109,110].

Several lines of preclinical and clinical evidence indicate a preventive and therapeutic role for vitamin E in AD. In addition to an antioxidant function, the aforementioned nonantioxidant properties of α -tocopherol in modulating gene expression may also play a role in cell signaling pathways. Most data at the present time support its antioxidant role in the brain, although the precise mechanism for the protective effects of this nutrient against oxidative damage caused and perpetuated by AD remains elusive [94].

8. Conclusions

Inconsistencies in the results of vitamin E treatment in clinical trials may be due to the variety of doses used and forms of the supplied micronutrient (natural versus synthetic, and/or mixtures of the tocopherol isoforms). Bioavailability may also vary among individuals based on a number of genetic and environmental factors. In addition, males and females may have more differences since vitamin E is carried in different lipoproteins (LDL for males and HDL for females) [111]. Inter-individual variability also plays a factor in terms of risk. For example, individuals with chronic liver disease (cholestasis) and cystic fibrosis (reduced pancreatic enzyme secretion) have a hampered intestinal absorption of lipid soluble nutrients [112]. Hormone replacement therapy clinical trials also face similar inconsistencies when risk factors are attempted to be assessed for cardiovascular disease, Alzheimer's disease and breast cancer development [4]. Conflicting reports for the clinical efficacy of lipid soluble vitamins (E, C, beta-carotene, etc.) and exogenous hormones may be due to such variation in uptake and local concentrations for effected systems/tissues, not to mention the battery of genetic, environmental, and behavioral differences between individuals. Vitamin E, cholesterol, and other lipid soluble and sterol related compounds, may share common pathways of uptake and systemic/intracellular distribution. Each has been shown, in preclinical studies, to be effectors of gene expression and impact the local oxidative environment. Technological advances in biomedical science are moving toward the elucidation of each of these pathways in preclinical and clinical studies. As the understanding of these complex and often intersecting pathways is ever-increasing, future treatments will undoubtedly become more customized for individuals affected by cancer, heart disease and dementia, diseases that plague a majority of aging individuals.

References

- [1]. Schneider C. Chemistry and biology of vitamin E. *Mol Nutr Food Res* 2005;49:7–30. [PubMed: 15580660]
- [2]. Hacquebard M, Carpentier YA. Vitamin E: absorption, plasma transport and cell uptake. *Curr Opin Clin Nutr Metab Care* 2005;8:133–8. [PubMed: 15716790]
- [3]. Wijtmans M, Pratt DA, Valgimigli L, DiLabio GA, Pedulli GF, Porter NA. 6-Amino-3-pyridinols: towards diffusion-controlled chain-breaking antioxidants. *Angew Chem Int Ed Engl* 2003;42:4370–3. [PubMed: 14502714]

- [4]. Dutta A, Dutta SK. Vitamin E and its role in the prevention of atherosclerosis and carcinogenesis: a review. *J Am Coll Nutr* 2003;22: 258–68. [PubMed: 12897039]
- [5]. Hathcock JN, Azzi A, Blumberg J, Bray T, Dickinson A, Frei B, et al. Vitamins E and C are safe across a broad range of intakes. *Am J Clin Nutr* 2005;81:736–45. [PubMed: 15817846]
- [6]. Leonard SW, Good CK, Gugger ET, Traber MG. Vitamin E bioavailability from fortified breakfast cereal is greater than that from encapsulated supplements. *Am J Clin Nutr* 2004;79:86–92. [PubMed: 14684402]
- [7]. Richelle M, Enslin M, Hager C, Groux M, Tavazzi I, Godin JP, et al. Both free and esterified plant sterols reduce cholesterol absorption and the bioavailability of beta-carotene and alpha-tocopherol in normocholesterolemic humans. *Am J Clin Nutr* 2004;80:171–7. [PubMed: 15213045]
- [8]. Ingold KU, Webb AC, Witter D, Burton GW, Metcalfe TA, Muller DP. Vitamin E remains the major lipid-soluble, chain-breaking antioxidant in human plasma even in individuals suffering severe vitamin E deficiency. *Arch Biochem Biophys* 1987;259:224–5. [PubMed: 3688884]
- [9]. Burton GIK. Vitamin E: application of the principles of physical organic chemistry to the exploration of its structure and function. *Acc Chem Res* 1996;19:194–201.
- [10]. Altmann SW, Davis HR, Jr., Zhu LJ, Yao X, Hoos LM, Tetzloff G, et al. Niemann-Pick C1 like 1 protein is critical for intestinal cholesterol absorption. *Science* 2004;303:1201–4. [PubMed: 14976318]
- [11]. Traber MG. The ABCs of vitamin E and beta-carotene absorption. *Am J Clin Nutr* 2004;80:3–4. [PubMed: 15213020]
- [12]. Tang CK, Yi GH, Yang JH, Liu LS, Wang Z, Ruan CG, et al. Oxidized LDL upregulated ATP binding cassette transporter-1 in THP-1 macrophages. *Acta Pharmacol Sin* 2004;25:581–6. [PubMed: 15132822]
- [13]. Oram JF, Vaughan AM, Stocker R. ATP-binding cassette transporter A1 mediates cellular secretion of alpha-tocopherol. *J Biol Chem* 2001;276:39898–902. [PubMed: 11546785]
- [14]. Berge KE, Tian H, Graf GA, Yu L, Grishin NV, Schultz J, et al. Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters. *Science* 2000;290:1771–5. [PubMed: 11099417]
- [15]. Stefkova J, Poledne R, Hubacek JA. ATP-binding cassette (ABC) transporters in human metabolism and diseases. *Physiol Res* 2004;53: 235–43. [PubMed: 15209530]
- [16]. Repa JJ, Berge KE, Pomajzl C, Richardson JA, Hobbs H, Mangelsdorf DJ. Regulation of ATP-binding cassette sterol transporters ABCG5 and ABCG8 by the liver X receptors alpha and beta. *J Biol Chem* 2002;277:18793–800. [PubMed: 11901146]
- [17]. Cooper AD. Hepatic uptake of chylomicron remnants. *J Lipid Res* 1997;38:2173–92. [PubMed: 9392416]
- [18]. Out R, Kruijt JK, Rensen PC, Hildebrand RB, De Vos P, Van Eck M, et al. Scavenger receptor BI plays a role in facilitating chylomicron metabolism. *J Biol Chem* 2004;279:18401–6. [PubMed: 14970197]
- [19]. Copp RP, Wisniewski T, Hentati F, Larnaout A, Ben Hamida M, Kayden HJ. Localization of alpha-tocopherol transfer protein in the brains of patients with ataxia with vitamin E deficiency and other oxidative stress related neurodegenerative disorders. *Brain Res* 1999; 822:80–7. [PubMed: 10082886]
- [20]. Muller-Schmehl K, Beninde J, Finckh B, Florian S, Dudenhausen JW, Brigelius-Flohe R, et al. Localization of alpha-tocopherol transfer protein in trophoblast, fetal capillaries' endothelium and amnion epithelium of human term placenta. *Free Radic Res* 2004;38:413–20. [PubMed: 15190938]
- [21]. Morley S, Panagabko C, Shineman D, Mani B, Stocker A, Atkinson J, et al. Molecular determinants of heritable vitamin E deficiency. *Biochemistry* 2004;43:4143–9. [PubMed: 15065857]
- [22]. Arita M, Nomura K, Arai H, Inoue K. alpha-tocopherol transfer protein stimulates the secretion of alpha-tocopherol from a cultured liver cell line through a brefeldin A-insensitive pathway. *Proc Natl Acad Sci USA* 1997;94:12437–41. [PubMed: 9356467]

- [23]. Horiguchi M, Arita M, Kaempf-Rotzoll DE, Tsujimoto M, Inoue K, Arai H. pH-dependent translocation of alpha-tocopherol transfer protein (alpha-TTP) between hepatic cytosol and late endosomes. *Genes Cells* 2003;8:789–800. [PubMed: 14531858]
- [24]. Brune B The intimate relation between nitric oxide and superoxide in apoptosis and cell survival. *Antioxid Redox Signal* 2005;7:497–507. [PubMed: 15706097]
- [25]. Hamilton CA, Miller WH, Al-Benna S, Brosnan MJ, Drummond RD, McBride MW, et al. Strategies to reduce oxidative stress in cardiovascular disease. *Clin Sci (Lond)* 2004;106:219–34. [PubMed: 14733610]
- [26]. Halliwell B Role of free radicals in the neurodegenerative diseases: therapeutic implications for antioxidant treatment. *Drugs Aging* 2001; 18:685–716. [PubMed: 11599635]
- [27]. Butterfield DA. Amyloid beta-peptide (1–42)-induced oxidative stress and neurotoxicity: implications for neurodegeneration in Alzheimer's disease brain. A review. *Free Radic Res* 2002;36:1307–13. [PubMed: 12607822]
- [28]. Ogita H, Liao J. Endothelial function and oxidative stress. *Endothelium* 2004;11:123–32. [PubMed: 15370071]
- [29]. Hagen TM, Huang S, Curnutte J, Fowler P, Martinez V, Wehr CM, et al. Extensive oxidative DNA damage in hepatocytes of transgenic mice with chronic active hepatitis destined to develop hepatocellular carcinoma. *Proc Natl Acad Sci USA* 1994;91:12808–12. [PubMed: 7809125]
- [30]. Parthasarathy S, Santanam N, Ramachandran S, Meilhac O. Potential role of oxidized lipids and lipoproteins in antioxidant defense. *Free Radic Res* 2000;33:197–215. [PubMed: 10993475]
- [31]. Wilcox CS. Reactive oxygen species: roles in blood pressure and kidney function. *Curr Hypertens Rep* 2002;4:160–6. [PubMed: 11884272]
- [32]. Harrison DG, Cai H, Landmesser U, Griendling KK. Interactions of angiotensin II with NAD(P)H oxidase, oxidant stress and cardiovascular disease. *J Renin Angiotensin Aldosterone Syst* 2003;4:51–61. [PubMed: 12806586]
- [33]. Munteanu A, Zingg JM, Azzi A. Anti-atherosclerotic effects of vitamin E—myth or reality? *J Cell Mol Med* 2004;8:59–76. [PubMed: 15090261]
- [34]. Waxman DJ. P450 gene induction by structurally diverse xenochemicals: central role of nuclear receptors CAR, PXR, and PPAR. *Arch Biochem Biophys* 1999;369:11–23. [PubMed: 10462436]
- [35]. Falkner KC, Pinaire JA, Xiao GH, Geoghegan TE, Prough RA. Regulation of the rat glutathione S-transferase A2 gene by glucocorticoids: involvement of both the glucocorticoid and pregnane X receptors. *Mol Pharmacol* 2001;60:611–9. [PubMed: 11502894]
- [36]. Kast HR, Goodwin B, Tarr PT, Jones SA, Anisfeld AM, Stoltz CM, et al. Regulation of multidrug resistance-associated protein 2 (ABCC2) by the nuclear receptors pregnane X receptor, farnesoid X-activated receptor, and constitutive androstane receptor. *J Biol Chem* 2002;277:2908–15. [PubMed: 11706036]
- [37]. Runge-Morris M, Wu W, Kocarek TA. Regulation of rat hepatic hydroxysteroid sulfotransferase (SULT2–40/41) gene expression by glucocorticoids: evidence for a dual mechanism of transcriptional control. *Mol Pharmacol* 1999;56:1198–206. [PubMed: 10570047]
- [38]. Sorescu D, Szocs K, Griendling KK. NAD(P)H oxidases and their relevance to atherosclerosis. *Trends Cardiovasc Med* 2001;11:124–31. [PubMed: 11686001]
- [39]. Landmesser U, Harrison DG. Oxidative stress and vascular damage in hypertension. *Coron Artery Dis* 2001;12:455–61. [PubMed: 11696684]
- [40]. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. *Circ Res* 2000;87:840–4. [PubMed: 11073878]
- [41]. McBride MW, Carr FJ, Graham D, Anderson NH, Clark JS, Lee WK, et al. Microarray analysis of rat chromosome 2 congenic strains. *Hypertension* 2003;41:847–53. [PubMed: 12624007]
- [42]. Guzik TJ, West NE, Black E, McDonald D, Ratnatunga C, Pillai R, et al. Functional effect of the C242T polymorphism in the NAD(P)H oxidase p22phox gene on vascular superoxide production in atherosclerosis. *Circulation* 2000;102:1744–7. [PubMed: 11023926]
- [43]. Valenti L, Conte D, Piperno A, Dongiovanni P, Fracanzani AL, Fraquelli M, et al. The mitochondrial superoxide dismutase A16V polymorphism in the cardiomyopathy associated with hereditary haemochromatosis. *J Med Genet* 2004;41:946–50. [PubMed: 15591282]

- [44]. Gibbons GH, Liew CC, Goodarzi MO, Rotter JI, Hsueh WA, Siragy HM, et al. Genetic markers: progress and potential for cardiovascular disease. *Circulation* 2004;109:IV47–IV58. [PubMed: 15226250]
- [45]. Teupser D, Thiery J, Seidel D. Alpha-tocopherol down-regulates scavenger receptor activity in macrophages. *Atherosclerosis* 1999;144: 109–15. [PubMed: 10381284]
- [46]. Ricciarelli R, Zingg JM, Azzi A. Vitamin E reduces the uptake of oxidized LDL by inhibiting CD36 scavenger receptor expression in cultured aortic smooth muscle cells. *Circulation* 2000;102:82–7. [PubMed: 10880419]
- [47]. Devaraj S, Hugou I, Jialal I. Alpha-tocopherol decreases CD36 expression in human monocyte-derived macrophages. *J Lipid Res* 2001;42:521–7. [PubMed: 11290823]
- [48]. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta-carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* 1994; 330:1029–35. [PubMed: 8127329]
- [49]. de Gaetano G Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative group of the primary prevention project. *Lancet* 2001;357:89–95. [PubMed: 11197445]
- [50]. Hodis HN, Mack WJ, LaBree L, Mahrer PR, Sevanian A, Liu CR, et al. Alpha-tocopherol supplementation in healthy individuals reduces low-density lipoprotein oxidation but not atherosclerosis: the vitamin E atherosclerosis prevention study (VEAPS). *Circulation* 2002;106:1453–9. [PubMed: 12234947]
- [51]. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. *Arch Ophthalmol* 2001;119:1439–52. [PubMed: 11594943]
- [52]. Salonen RM, Nyyssönen K, Kaikkonen J, Porkkala-Sarataho E, Voutilainen S, Rissanen TH, et al. Six-year effect of combined vitamin C and E supplementation on atherosclerotic progression: the antioxidant supplementation in atherosclerosis prevention (ASAP) study. *Circulation* 2003;107:947–53. [PubMed: 12600905]
- [53]. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 1999;354:447–55. [PubMed: 10465168]
- [54]. Yusuf S, Dagenais G, Pogue J, Bosch J, Sleight P. Vitamin E supplementation and cardiovascular events in high-risk patients. The heart outcomes prevention evaluation study investigators. *N Engl J Med* 2000;342:154–60. [PubMed: 10639540]
- [55]. Waters DD, Alderman EL, Hsia J, Howard BV, Cobb FR, Rogers WJ, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. *J Am Med Assoc* 2002;288:2432–40.
- [56]. Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001;345:1583–92. [PubMed: 11757504]
- [57]. Stephens NG, Parsons A, Schofield PM, Kelly F, Cheeseman K, Mitchinson MJ. Randomised controlled trial of vitamin E in patients with coronary disease: cambridge heart antioxidant study (CHAOS). *Lancet* 1996;347:781–6. [PubMed: 8622332]
- [58]. Boaz M, Smetana S, Weinstein T, Matas Z, Gaftor U, Iaina A, et al. Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): randomised placebo-controlled trial. *Lancet* 2000;356:1213–8. [PubMed: 11072938]
- [59]. Fang JC, Kinlay S, Beltrame J, Hikiti H, Wainstein M, Behrendt D, et al. Effect of vitamins C and E on progression of transplant-associated arteriosclerosis: a randomised trial. *Lancet* 2002;359:1108–13. [PubMed: 11943259]
- [60]. Vivekananthan DP, Penn MS, Sapp SK, Hsu A, Topol EJ. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. *Lancet* 2003;361:2017–23. [PubMed: 12814711]
- [61]. John JH, Ziebland S, Yudkin P, Roe LS, Neil HA. Effects of fruit and vegetable consumption on plasma antioxidant concentrations and blood pressure: a randomised controlled trial. *Lancet* 2002;359:1969–74. [PubMed: 12076551]

- [62]. Singh N, Graves J, Taylor PD, MacAllister RJ, Singer DR. Effects of a 'healthy' diet and of acute and long-term vitamin C on vascular function in healthy older subjects. *Cardiovasc Res* 2002;56:118–25. [PubMed: 12237172]
- [63]. Shklar G, Schwartz J, Trickler DP, Niukian K. Regression by vitamin E of experimental oral cancer. *J Natl Cancer Inst* 1987;78:987–92. [PubMed: 3472005]
- [64]. Krol ES, Kramer-Stickland KA, Liebler DC. Photoprotective actions of topically applied vitamin E. *Drug Metab Rev* 2000;32:413–20. [PubMed: 11139138]
- [65]. Neuzil J, Weber T, Schroder A, Lu M, Ostermann G, Gellert N, et al. Induction of cancer cell apoptosis by alpha-tocopheryl succinate: molecular pathways and structural requirements. *FASEB J* 2001;15: 403–15. [PubMed: 11156956]
- [66]. Woutersen RA, Appel MJ, Van Garderen-Hoetmer A. Modulation of pancreatic carcinogenesis by antioxidants. *Food Chem Toxicol* 1999; 37:981–4. [PubMed: 10541454]
- [67]. Shklar G, Schwartz J. Tumor necrosis factor in experimental cancer regression with alphatocopherol, beta-carotene, canthaxanthin and algae extract. *Eur J Cancer Clin Oncol* 1988;24:839–50. [PubMed: 3139418]
- [68]. Schwartz JL, Antoniadis DZ, Zhao S. Molecular and biochemical reprogramming of oncogenesis through the activity of prooxidants and antioxidants. *Ann NY Acad Sci* 1993;686:262–78 (discussion 278–9). [PubMed: 8512252]
- [69]. Turley JM, Funakoshi S, Ruscetti FW, Kasper J, Murphy WJ, Longo DL, et al. Growth inhibition and apoptosis of RL human B lymphoma cells by vitamin E succinate and retinoic acid: role for transforming growth factor beta. *Cell Growth Differ* 1995;6:655–63. [PubMed: 7669719]
- [70]. J, SGaS Effects of vitamin E on oral carcinogenesis and oral cancer. In: Book New York: Marcel Dekker; 1993 p. 411–97 (PLaF J, Ed.).
- [71]. Kline K, Yu W, Sanders BG. Vitamin E and breast cancer. *J Nutr* 2004;134:3458S–3462S. [PubMed: 15570054]
- [72]. Israel K, Yu W, Sanders BG, Kline K. Vitamin E succinate induces apoptosis in human prostate cancer cells: role for Fas in vitamin E succinate-triggered apoptosis. *Nutr Cancer* 2000;36:90–100. [PubMed: 10798221]
- [73]. Prasad KN, Kumar B, Yan XD, Hanson AJ, Cole WC. Alphatocopheryl succinate, the most effective form of vitamin E for adjuvant cancer treatment: a review. *J Am Coll Nutr* 2003;22:108–17. [PubMed: 12672706]
- [74]. Prasad KN. Rationale for using high-dose multiple dietary antioxidants as an adjunct to radiation therapy and chemotherapy. *J Nutr* 2004;134:3182S–3183S. [PubMed: 15514298]
- [75]. Bairati I, Meyer F, Gelinas M, Fortin A, Nabid A, Brochet F, et al. A randomized trial of antioxidant vitamins to prevent second primary cancers in head and neck cancer patients. *J Natl Cancer Inst* 2005;97: 481–8. [PubMed: 15812073]
- [76]. Taylor PR, Greenwald P. Nutritional interventions in cancer prevention. *J Clin Oncol* 2005;23:333–45. [PubMed: 15637396]
- [77]. Scheer M, Kuebler AC, Zoller JE. Chemoprevention of oral squamous cell carcinomas. *Onkologie* 2004;27:187–93. [PubMed: 15138354]
- [78]. Caraballoso M, Sacristan M, Serra C, Bonfill X. Drugs for preventing lung cancer in healthy people. *Cochrane Database Syst Rev* 2003; (CD002141).
- [79]. RE Ostlund, Jr.. Phytosterols in human nutrition. *Annu Rev Nutr* 2002;22:533–49. [PubMed: 12055357]
- [80]. Freeman MR, Solomon KR. Cholesterol and prostate cancer. *J Cell Biochem* 2004;91:54–69. [PubMed: 14689582]
- [81]. Molony T Use of cholesterol drugs may decrease breast cancer risk. *J Dent Hyg* 2003;77:214.
- [82]. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Dietary meat, dairy products, fat, and cholesterol and pancreatic cancer risk in a prospective study. *Am J Epidemiol* 2003;157:1115–25. [PubMed: 12796048]
- [83]. Siemianowicz K, Gminski J, Stajszczyk M, Wojakowski W, Goss M, Machalski M, et al. Serum HDL cholesterol concentration in patients with squamous cell and small cell lung cancer. *Int J Mol Med* 2000; 6:307–11. [PubMed: 10934294]

- [84]. Habenicht AJ, Salbach P, Janssen-Timmen U. LDL receptor-dependent polyunsaturated fatty acid transport and metabolism. *Eicosanoids* 1992;5(Suppl.):S29–31. [PubMed: 1449825]
- [85]. Needleman P, Turk J, Jakschik BA, Morrison AR, Lefkowitz JB. Arachidonic acid metabolism. *Annu Rev Biochem* 1986;55:69–102. [PubMed: 3017195]
- [86]. Chen Y, Hughes-Fulford M. Prostaglandin E2 and the protein kinase A pathway mediate arachidonic acid induction of c-fos in human prostate cancer cells. *Br J Cancer* 2000;82:2000–6. [PubMed: 10864209]
- [87]. Puglielli L, Tanzi RE, Kovacs DM. Alzheimer's disease: the cholesterol connection. *Nat Neurosci* 2003;6:345–51. [PubMed: 12658281]
- [88]. Butterfield DA, Pocernich CB. The glutamatergic system and Alzheimer's disease: therapeutic implications. *CNS Drugs* 2003;17:641–52. [PubMed: 12828500]
- [89]. Tanzi RE, Bertram L. New frontiers in Alzheimer's disease genetics. *Neuron* 2001;32:181–4. [PubMed: 11683989]
- [90]. Berman K, Brodaty H. Tocopherol (vitamin E) in Alzheimer's disease and other neurodegenerative disorders. *CNS Drugs* 2004;18:807–25. [PubMed: 15377170]
- [91]. Goodman Y, Mattson MP. Secreted forms of beta-amyloid precursor protein protect hippocampal neurons against amyloid beta-peptide-induced oxidative injury. *Exp Neurol* 1994;128:1–12. [PubMed: 8070512]
- [92]. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Aggarwal N, et al. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. *J Am Med Assoc* 2002;287:3230–7.
- [93]. Morris MC, Evans DA, Tangney CC, Bienias JL, Wilson RS, Aggarwal NT, et al. Relation of the tocopherol forms to incident Alzheimer disease and to cognitive change. *Am J Clin Nutr* 2005;81:508–14. [PubMed: 15699242]
- [94]. Grundman M Vitamin E and Alzheimer disease: the basis for additional clinical trials. *Am J Clin Nutr* 2000;71:630S–636S. [PubMed: 10681271]
- [95]. Kontush A, Mann U, Arlt S, Ujeiy A, Luhrs C, Muller-Thomsen T, et al. Influence of vitamin E and C supplementation on lipoprotein oxidation in patients with Alzheimer's disease. *Free Radic Biol Med* 2001;31:345–54. [PubMed: 11461772]
- [96]. Tabet N, Birks J, Grimley Evans J. Vitamin E for Alzheimer's disease. *Cochrane Database Syst Rev* 2000; (CD002854).
- [97]. Luchsinger JA, Tang MX, Shea S, Mayeux R. Antioxidant vitamin intake and risk of Alzheimer disease. *Arch Neurol* 2003;60:203–8. [PubMed: 12580704]
- [98]. Kalmijn S, Feskens EJ, Launer LJ, Kromhout D. Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. *Am J Epidemiol* 1997;145:33–41. [PubMed: 8982020]
- [99]. Roses AD, Saunders AM. APOE is a major susceptibility gene for Alzheimer's disease. *Curr Opin Biotechnol* 1994;5:663–7. [PubMed: 7765750]
- [100]. Casserly I, Topol E. Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. *Lancet* 2004;363:1139–46. [PubMed: 15064035]
- [101]. Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ* 2001; 322:1447–51. [PubMed: 11408299]
- [102]. Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA. Statins and the risk of dementia. *Lancet* 2000;356:1627–31. [PubMed: 11089820]
- [103]. Cholesterol Wolozin B., statins and dementia. *Curr Opin Lipidol* 2004;15:667–72. [PubMed: 15529026]
- [104]. Simons M, Keller P, Dichgans J, Schulz JB. Cholesterol and Alzheimer's disease: is there a link? *Neurology* 2001;57:1089–93. [PubMed: 11571339]
- [105]. Refolo LM, Pappolla MA, LaFrancois J, Malester B, Schmidt SD, Thomas-Bryant T, et al. A cholesterol-lowering drug reduces beta-amyloid pathology in a transgenic mouse model of Alzheimer's disease. *Neurobiol Dis* 2001;8:890–9. [PubMed: 11592856]

- [106]. Wollmer MA, Streffer JR, Lutjohann D, Tsolaki M, Iakovidou V, Hegi T, et al. ABCA1 modulates CSF cholesterol levels and influences the age at onset of Alzheimer's disease. *Neurobiol Aging* 2003;24: 421–6. [PubMed: 12600718]
- [107]. Katzov H, Chalmers K, Palmgren J, Andreasen N, Johansson B, Cairns NJ, et al. Genetic variants of ABCA1 modify Alzheimer disease risk and quantitative traits related to beta-amyloid metabolism. *Hum Mutat* 2004;23:358–67. [PubMed: 15024730]
- [108]. Papassotiropoulos A, Streffer JR, Tsolaki M, Schmid S, Thal D, Nicosia F, et al. Increased brain beta-amyloid load, phosphorylated tau, and risk of Alzheimer disease associated with an intronic CYP46 polymorphism. *Arch Neurol* 2003;60:29–35. [PubMed: 12533085]
- [109]. Chen ZJ, Vulevic B, Ile KE, Soulika A, Davis W, Jr., Reiner PB, et al. Association of ABCA2 expression with determinants of Alzheimer's disease. *FASEB J* 2004;18:1129–31. [PubMed: 15155565]
- [110]. Mace S, Cousin E, Ricard S, Genin E, Spanakis E, Lafargue-Soubigou C, et al. ABCA2 is a strong genetic risk factor for early-onset Alzheimer's disease. *Neurobiol Dis* 2005;18:119–25. [PubMed: 15649702]
- [111]. Behrens WA, Thompson JN, Madere R. Distribution of alphetocopherol in human plasma lipoproteins. *Am J Clin Nutr* 1982;35: 691–6. [PubMed: 7072621]
- [112]. Jeffrey GP, Muller DP, Burroughs AK, Matthews S, Kemp C, Epstein O, et al. Vitamin E deficiency and its clinical significance in adults with primary biliary cirrhosis and other forms of chronic liver disease. *J Hepatol* 1987;4:307–17. [PubMed: 3036938]

Fig. 1.

Structure of α -tocopherol form of vitamin E (top) before the 6-OH group hydrogen is donated to a lipid radical. This reaction forms a stable lipid hydroperoxide and a tocopheroxyl radical (bottom). The original state of α -tocopherol can be regenerated by a reduction reaction with hydroxyl groups from other antioxidants such as vitamin C (ascorbate) or ubiquinol.