International Journal of Pharmacy and Biological Sciences-IJPBS™ (2019) 9 (3): 1008-1013
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Review Article | Pharmaceutical Sciences | Open Access | MCI Approved
UGC Approved Journal

Vitamin E Hydroquinone is an Endogenous Regulator of Ferroptosis Via Redox Control of 15-Lipoxygenase

Nagarathna PKM[1], Babiker Bashir[1], Godfrey[2], Harsha Vardhini N[2] and K. Ramesh[3]
Department of Pharmacology, Karnataka College of Pharmacy, Thirumenahalli, Bangaluru - 560064.

Received: 12 Mar 2019 / Accepted: 14 Apr 2019 / Published online: 1 Jul 2019
***Corresponding Author Email:** babiker141@gmail.com

Abstract

Ferro ptosis is a form of programmed cell death associated with inflammation, neuron degeneration and ischemia. Vitamin E (alpha-Tocopherol) has been reported to prevent Ferro ptosis but the mechanism by which this occurs is controversial and inhibits 15-lipoxygenase via reduction of the enzyme's non-heme iron from its active Fe3+ state to an inactive Fe2+ state1.Composed of vitamin E, four Tocopherols and four tocotrienols, works as anti-oxidant fat to break fat chain that prevent oxidation of fat .The liver is the focal point of regulating the absorption of lipoprotein lipase synthesis by reverse, which is the site of detoxification Alexei by cytochrome p450 enzymes systems in the oxidation (Phase 1), proposal (phase 2), and transporters (Phase 3)).The impact of a-Tocopherol in the prevention of chronic diseases believed to be associated with oxidative stress has often been studied, and beneficial effects have been demonstrated Due to the potent antioxidant properties of Tocopherols.

Keywords
Tocopherol, tocotrienol, metabolism, sulfation, Vitamin E metabolism; Long-chain metabolites of vitamin E; Vitamin E bioavailability; Vitamin E transport.

*****

INTRODUCTION:

Ferroptosis is a form of iron depend on the lipid oxidation mediated programmed cell death involved in a wide range of diseases of ailments including inflammation or ischemia-reperfusion injury, and neurodegeneration [1-5]. Vitamin E regulates the ferroptosis through the organization oxidoreductase enzyme 15-lipoxygenase (15-lo) through an unknown mechanism [6-8]. Include clinical benefits attributed to vitamin e cleaning oxidant stress, inflammation, and death of cells, each of which is caused by disease ferroptosis [1]. We suggest that the effect of vitamin "E" Anti-first results from the four-step mechanism biochemical: Aqueous oxidizing analysis of Quinon alpha tocoferol to alpha-tocoferol, inhibition of 15-lo through reduction of its non-heme fe3+ center to the inactive fe^{2+} state by Alpha-Tocopherol hydroquinone, reduction of quinone alpha-tocoferol to hydroquinone alpha-tocoferol, inhibition of the ferroptosis cascade by blocking formation of liped peroxidation products. Its findings formed the basis of the fat hypothesis linking plasma cholesterol levels to the evolution of the disease. Vitamin E is recognized as essential to human health.

methods of vitamin E:

1.General method for the chemical conversion of a vitamin E quinine to a vitamin E hydroquinone

The solution of quinine vitamin E (1 eq, approximately 0.5 g) in Tetrahydrofuran (15 ml). Then the vessel was purged with h2. lindlar catalyst (for the a-, gamma - and ácotrienol quinone). The resulting suspension at room temperature was moved overnight under atmosphere H2. When the reaction is finished, the baskets have been added. The resulting mud has been purified through fried repression. Filter cake washed in sequence with thf. The filter had obtained a pure product.

2.General method for the chemical conversion of a vitamin E chroman to a vitamin E quinine.

In the bottle round, the solution to the Chromium (one example, about 0.5 grams) in 2:1 acetonitrile: water mix (15 ml). This solution has been cooled to 0c. Ammonium nitrate Ceric solution (2.1 E) in water (5 ml) has been added with a drop point. The interaction mixture was moved at 0c for 2hore. When the interaction is complete, the mixture with the sat has been neutralized. aq. NaHCO3 and extract 3x with ethyl acetate. Organic phase dried up Na2So4 and concentrated in vacuo. the residue was purchased by silica gel chromatography to obtain pure product.

3.Cells and cell culture

Mouse striatal Q7 cells (STHdhQ7/Q7They were immortalized by large antigen-sv generators from coriel. Cells cultured in high glucose (25 mm) DMEM (Gibco) medium supplemented with fetal bovine serum (10% v/v; Sigma), penicillin (100 U/mL. Gibco), streptomycin (100sg / ML. Gibco. For routine maintenance, the cultural medium q7 also contained geneticin advances (g418; santa cruz biotechnology). Cells were routinely passed every 3-4 days, and cell density was maintained without wealth.

4.Cellular survival assay.

The death of the viral cell in the q7 cells was stimulated using RSL3, a previously described GPX4 suppressant. All four space isomers of RSL3 have been installed and purified using published methods. All subsequent cell treatment experiments used the single vacuum isomer (1s,3r)-RSL3, which was the most effective (ic50-200 nm) to prevent the validity of the q7 cell. To assess a complex rescue activity and a force from the death of viral cells.

5.Cellular lipid oxidation assay

Ferroptosis was induced by RSL3 (2µM final concentration) in Q7 cells as described above. The protective activity of co-treated compounds was assessed also as described above. The rate of cellular lipid oxidation after GPX4 inhibition was assessed by monitoring the time-dependent changes in green fluorescence of cells pre-labeled with BODIPY™ 581/591 C11 dye (5µM, 30minute labeling period; Thermo Fisher/Invitrogen) using the IncuCyte S3 live-cell imaging apparatus (Sartorius) using a 10x objective. Cells (three images per field; at least three replicate wells per condition) were imaged once hourly for up to 18 hours after compound and RSL3 addition. Quantification of cell images was performed using the IncuCyte Zoom software using the Basic Analyzer tool which utilized an algorithm that calculated the total green-positive area per well where "green-positive" was defined as 1.45 times the local background-subtracted fluorescent signal. After a 2-3-hour lag period post-RSL3 treatment, the cellular green fluorescence signal began increasing. The rate of change in total green-positive area per well from 3–9 hours post-compound treatment was calculated, then expressed relative to that observed in the RSL3-only control treatment group, which was defined as 100%.

6.Lipoxygenase enzyme inhibition assay

Enzyme assays (100µL final volume) were conducted in Corning 96 half-well black, flat bottom assay plates and contained final concentrations of 50µM arachidonic acid as a substrate, 1:10 (v:v) cholate mix (2% (w:v) sodium cholate and 2% (v:v) DMSO), 40µM dihydrorhodamine 123 and 3 U/mL rLOX15 in buffer A (100 mM Tris-HCl, pH 7.5). Stock solutions of test compounds were prepared in DMSO and then diluted to final assay concentrations in cholate mix such that final cholate and DMSO concentrations were maintained at 0.2%. Reactions were initiated by addition of 50µL of enzyme mix (80µM dihydrorhodamine 123 and 6 U/mL rLOX15 in buffer A) to wells containing 50µL substrate and cholate mix in Buffer A and linear rates were assessed via fluorescence, using excitation/emission of 500/536 nm, on a Molecular Devices Spectramax M2 every 10 seconds for 5 minutes at room temperature.

METABOLISM OF VITAMIN E

The metabolism of vitamin E in relation to absorption, transport, storage and excretion has been summarized in a number of publications (Machlin, 1984; McDowell, 1989). Information on the absorption and excretion of Tocopherols by farm animals is extremely sparse.

Absorption and transport:

Mechanism of absorption of vitamin E is similar to that of other fat-soluble vitamins (Weber, 1983). Its absorption is closely associated with that of fat, and is accelerated by the presence of bile. It is clear that species differ in their ability to absorb Tocopherols, especially since great variation has been reported for

a single species. Also, with labile substances like the Tocopherols a simple estimation of absorption based upon amounts present in the food and feces may be inaccurate.

Storage:

Vitamin E is stored throughout all body tissues with adipose tissue, liver and muscle representing the major storage deposits. Rates of depletion of a-Tocopherol from tissue of animals given vitamin E deficient diets vary considerably from tissue to tissue within a particular species (Diplock, 1985). Studies on the depletion of a Tocopherol in tissues of rats varied considerably, with the fastest loss occurring in the plasma, liver and heart muscle, intermediate for testes and heart muscle, while the slowest loss was found in the adipose tissue over a 6-wk depletion period (Bieri, 1972). There appears to be 2 different pools of vitamin E in the body, a labile pool and a fixed pool which is retained for long periods of time.

Excretion:

The major route of excretion of vitamin E is fecal elimination. Usually less than 1% of orally ingested vitamin E is excreted in the urine (Machlin, 1984). Excess Tocopherol is eliminated in the feces a-Tocopherol succinate eliminated 65% of the dose via the feces in 3 days and 80% in 6 days; 90% of the radioactivity was identified as free a-Tocopherol by isotope dilution.

WHY IS α -TOCOPHEROL A VITAMIN?

Although there are many antioxidants in the diet, Tocopherol is vitamin. -The role of (Tocopherol) is the role of anti-oxidation of the melted fat which prevents the spread of oxidation of fat is likely to be there lipids specific, probably derived from pufas (e.g., docosahexaenoic acid) which are essential for life and that vitamin E protects (10). I-tocoferol is the most efficient and safe vitamin E. A-tocopheroxyl radical is relatively long-term (178) and can be reduced to Alpha-Tocopherol by water soluble antioxidants such as ascorbic acid (179). Other forms of vitamin E, when they become extreme, be more interactive and can be easily formed connectors that are likely to be toxic and cytotoxic (80 1).

The integrity of Alpha-coferol can also be inferred from the relative lack of specific mechanisms for its metabolism. ref (6).

Vitamin E deficiency, antioxidant function, neurological disorder:

In humans, deficiency of vitamin E acute to abnormalities in nerve cells muscle that feature cancer acai spinocerebellar (of 8, 41-44) and muscle (9, 45). Peripheral neuropathy is most likely caused by the free radicalization of nerves and a dying back of sensory neurons. Similarly, vitamin E anemia a significant deficiency in premature infants, as a result of free radical damage (47). Reduced red blood cells age (48 and 49) increased exposure to peroxide-induced hemolysis is clear not only in severe deficiency, but also in the marginal vitamin E in the hypercholesterolemic subjects (50). Public vitamin E deficiency occurs only rarely in humans and is almost never caused by undernutrition. Vitamin E does not occur as a result of a genetic defect in the Tocopherol transferprotein (TTP) as a result of various fat malabsorption syndromes, as reviewed in reference 51. The frequency of human vitamin E deficiency is not known as a-ttp defects. Patients with familial isolated vitamin E, inherent genetic defect in the Genes-Tocopherol transfer protein (52, 53), have significantly reduced plasma levels of vitamin E and neurological disorders characteristic of vitamin E such as cerebellar ataxia, dysarthria, absent tendon reflexes, deep, vibratory and proprioceptive sensory loss positive Babinski sign (52). Can relieve symptoms of cash associated with this syndrome when given to those patients doses of vitamin E up to 2,000 mg per day (8-10). Also, symptoms of vitamin E deficiency resulting from chronic liver disease, fat malabsorption or abetalipoproteinemia are thanks to the high doses of vitamin E (7, 54). No therapeutic dose can be achieved through an optimal diet; patients must consume vitamin E supplements.

NONANTIOXIDANT FUNCTIONS?

Cellular signaling

The group examined intensively the role of vitamin e in cellular signaling, especially in relation to protein kinase c. Tocopherol prevents the proliferation of smooth muscle cells), decreases protein kinase C activity, and increases phosphoprotein phosphatase 2A activity, controls the expression of the tropomyosin genes). Not related to this job action anti-oxidation in vitamin E because b-Tocopherol, which is not similar activity antioxidant, do not perform any of these actions. Jobs; it actually cancels the effect of a-Tocopherol. Tocopherol effects on protein kinase C inhibition was also reported in human platelets, diabetic rat kidney human monocytes. Can be attributed to the mechanism of blocking protein kinase c by a-Tocopherol in part to the ease of generating diacylglycerol-derived membrane, which is fat activates the transfer of protein kinase c activity has also been suggested that the inhibition of protein kinase C activity is not due directly to the antioxidant capacity of Tocopherol , but requires the integration of Tocopherol in the membrane structure is most likely due to the direct interaction between-Tocopherol and protein kinase C in the cell membrane. a-Tocopherol modules the in

vitro expression of some significant proteins / enzymes in various cell types involved in atherogenesis). Enrichment of vitamin E to endothelial cells-regulates the expression of a protein cell adhesion vascular molecule cell adhesion, vascular-1, which reduces the adhesion of white cells oxidized ldl to the endothelium. Modern developments in the field of arachidonic acid cascade also showed that Alpha-Tocopherol can regulate these pathways, its effect is not always shared by other forms of vitamin E, see Review. Vitamin regulates the activities of phospholipase cytosolic a2 and cyclooxygenase. Enhance the activity of these two rate-limiting enzymes in the arachidonic acid cascade provides a mechanism of control that the vitamin E dose recognition promotes the release of prostacyclin, a powerful vasodilator and inhibitor of platelet aggregation.

Clinical significance:

alpha-Tocopherol is transported in plasma lipoproteins and delivered to tissues by all available mechanisms. This redundancy in alph-Tocopherol transport systems obviates the need for any specific plasma alpha –Tocopherol transport proteins. The only transport protein for alpha -Tocopherol is the hepatic alpha -TTP.

CONCLUSION:

To test the hypothesis that the Quinone or hydroquinone metabolites of Alpha-Tocopherol (αT) are responsible for its previously reported anti-ferroptotic activity, we evaluated the activity of Alpha-Tocopherol Quinone (αTQ) and hydroquinone (αTHQ) in a ferroptotic cell death assay using immortalized mouse striatal cells The sorting process is highly specific and does not tolerate the alteration in stereochemistry at C2. This preference. prevents a-Tocopherol from rapid v-oxidation-decv and thus keeps the excretion of the a-CEHC degradation product low.

ACKNOWLEGDEMENT:

Authors are very much thankful to Dr. Nagarathna PKM and Dr. K. Ramesh. Karnataka College of Pharmacy. Bengaluru, karnataka, for their constant help and support.

REFERENCE:

1. *Stockwell BR, Friedmann Angeli JP, Bayir H, Bush AI, Conrad M, Dixon SJ, et al. Ferroptosis: A Regulated Cell Death Nexus Linking Metabolism, Redox Biology and Disease. Cell. 2017; 171: 273–285. https://doi.org/10.1016/j.cell.2017.09.021 PMID: 28985560*
2. *Wenzel SE, Tyurina YY, Zhao J, St Croix CM, Dar HH, Mao G, et al. PEBP1 Wardens Ferroptosis by Enabling Lipoxygenase Generation of Lipid Death Signals. Cell. 2017; 171: 628–641.e26. https://doi. org/10.1016 /j. cell.2017.09.044 PMID: 29053969 3.*
3. *Drefs M, Thomas MN, Guba M, Angele MK, Werner J, Conrad M, et al. Modulation of Glutathione Hemostasis by Inhibition of 12/15-Lipoxygenase Prevents ROS-Mediated Cell Death after Hepatic Ischemia and Reperfusion. Oxid Med Cell Longev. 2017; 2017: 8325754. https://doi.org/10.1155/2017/8325754 PMID: 28811867 4.*
4. *Do Van B, Gouel F, Jonneaux A, Timmerman K, Gele ´ P, Pe ´trault M, et al. Ferroptosis, a newly characterized form of cell death in Parkinson's disease that is regulated by PKC. Neurobiol Dis. Elsevier Inc.; 2016; 94: 169–178. https://doi.org/10.1016/j.nbd.2016.05.011 PMID: 27189756 5.*
5. *Do Van B, Gouel F, Jonneaux A, Timmerman K, Gele ´ P, Pe ´trault M, et al. Ferroptosis, a newly characterized form of cell death in Parkinson's disease that is regulated by PKC. Neurobiol Dis. Elsevier B.V.; 2016; 94: 169–78. https://doi.org/10.1016/j.nbd.2016.05.011 PMID: 27189756.*
6. *Abawi FG, Sullivan TW, Scheidler SE (1985) Interaction of dietary fat with levels of vitamins A and E in broiler chicks. Poult Sci 64, 11921198.*
7. *Adams CR (1982) Feedlot cattle need supplemental vitamin E. Feedstuffs 54 (18), 2425.*
8. *Atwal AS, Hidiroglou M, Kramer JKG, Binns RM (1990) Effects of feeding a-Tocopherol and calcium salts of fatty acids on vitamin E content and fatty acid composition of cow's milk. J Dairy Sci 73, 2832-2841.*
9. *Jiang, Q. 2014. Natural forms of vitamin E: metabolism, antioxidant, and anti-inflammatory activities and their role in disease prevention and therapy. Free Radic. Biol. Med. 72: 76 – 90.*
10. *Birringer, M., P. Pfluger, D. Kluth, N. Landes, and R. Brigelius Flohe. 2002. Identities and differences in the metabolism of tocotrienols and Tocopherols in HepG2 cells. J. Nutr.m132: 3113 – 3118.*
11. *Sontag, T. J., and R. S. Parker. 2002. Cytochrome P450 omega hydroxylase pathway of Tocopherol Catabolism Novel mechanism of regulation of vitamin E status. J. Biol. Chem. 277, 25290 – 25296.*
12. *Jiang, Q., H. Frasier K. V. Wood, and X. Yin. 2007 Identification and quantitation of novel vitamin E metabolites, sulfated long anySokol, R. J., Guggenheim, M., Iannaccone, S. T., Barkhaus.*
13. *P.E., Miller, C., Silverman, A., Balistreri, W.F., and Heubi, J.E. (1985) Improved neurologic function after long-term correction of vitamin E deficiency in children with chronic cholestasis. N. Engl. J. Med. 313, 1580–1586*
14. *Sokol, R. J., Kayden, H. J., Bettis, D. B., Traber, M. G., Neville, H., Ringel, S., Wilson, W. B., and Stumpf, D. A. (1988) Isolated vitamin E deficiency in the absence of fat malabsorption— familial and sporadic cases: Characterization and investigation of causes J. Lab. Clin. Med. 111, 548–559*
15. *Kohlschu¨tter, A., Hubner, C., Jansen, W., and Lindner, S. G. (1988) A treatable familial neuromyopathy with*

vitamin E deficiency, normal absorption, and evidence of increased consumption of vitamin E. J. Inher. Metab. Dis. 11, 149–152

16. *Schuelke, M., Mayatepek, E., Inter, M., Becker, M., Pfeiffer, E., Speer, A., Hu¨bner, C., and Finckh, B. (1999) Treatment of ataxia in isolated vitamin E deficiency caused by α-Tocopherol transfer protein deficiency. J. Pediatr. 134, 240–244*
17. *Evans, H. M., and Bishop, K. S. (1922) On the existence of a hitherto unrecognized dietary factor essential for reproduction. Science 56, 650–651*
18. *Tappel, A. L. (1962) Vitamin E as the biological lipid antioxidant. Vitam. Horm. 20, 493–510*
19. *Esterbauer, H., Dieber-Rotheneder, M., Striegl, G., and Waeg, G. (1991) Role of vitamin E in preventing the oxidation of low density lipoprotein. Am. J. Clin. Nutr. 53, 314S–321S*
20. *Institute of Medicine. 2000. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. National Academy Press, Washington, DC.*
21. *Vivekananthan, D. P., M, S. Penn, S. K. Sapp and E. J. Topol. 2003. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. Lancet. 361: 2017 – 2023.*
22. *Bjelakovic, G, D. Nikolova, L. L. Gluud, R. G. Simonetti and C. Gluud.2007. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. JAMA.*
23. *Berry, D., J. K. Wathen, and M. Newell. 2009. B ayesian model averaging in meta-analysis: vitamin E supplementation and mortality. Clin. Trials. 6: 28 –4 1.*
24. *Cheung, M. C., X. Q. Zhao, A. Chait, J. J. Albers and B. G. Brown. 2001. Antioxidant supplements block the response of HDL to simvastatin-niacin therapy in patients with coronary artery disease and low HDL. Arterioscler. Thromb. Vasc. Biol. 21 :1320– 1326.*
25. *Brown, B. G., X. Q. Zhao, A. Chait, L. D. Fisher, M. C. Cheung, J. S. Morse, A. A. Dowdy, E. K. Marino, E. L. Bolson, P.Alaupovic, et al.2001 . Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N. Engl. J.Med.345 :1583 – 1592.*
26. *Lonn, E., J. Bosch, S. Yusuf, P. Sheridan, J. Pogue, J. M. Arnold, C. Ross, A. Arnold, P. Sleight, J. Probstfi eld, et al. 2005. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. Plack PA, Bieri JG. Metabolic products of α-Tocopherol in the livers of rats given intraperitoneal injectionsm of [14C]-α-Tocopherol. Biochim Biophys ActaÐSpec Sect Lipids Relat Subj. 1964; 84: 729±738.https://doi.org /10.1016/0926-6542(64)90031-9*
27. *Jain SK, Levine SN. Elevated lipid peroxidation and vitamin e-quinone levels in heart ventricles of streptozotocin-treated diabetic rats. Free Radic Biol Med. 1995; 18: 337±341. https://doi.org/10.1016/08 91-5849(94)00114-Y PMID: 7744318*
28. *Kiyose C, Kaneko K, Muramatsu R, Ueda T, Igarashi O. Simultaneous determination of RRR- and SRR-Alpha-Tocopherols and their quinones in rat plasma and tissues by using chiral high-performance liquid chromatography. Lipids. 1999; 34: 415±22. Available: http://www.ncbi.nlm.nih.gov/pubmed/10443975 PMID: 10443975*
29. *Upston JM, Witting PK, Brown AJ, Stocker R, Keaney JF. Effect of vitamin E on aortic lipid oxidation and intimal proliferation after arterial injury in cholesterol-fed rabbits. Free Radic Biol Med. 2001; 31:1245±53. https://doi.org/10.1016/S0891-5849(01)00721-3 PMID: 11705703*
30. *Terentis AC, Thomas SR, Burr JA, Liebler DC, Stocker R. Vitamin E oxidation in human atherosclerotic lesions. Circ Res. 2002; 90: 333±9. https://doi.org/10.1161 /hh0302.104454 PMID: 11861423*
31. *Mottier P, Gremaud E, Guy P a, Turesky RJ. Comparison of gas chromatography-mass spectrometry and liquid chromatography-tandem mass spectrometry methods to quantify Alpha-Tocopherol and alpha-Tocopherolquinone levels in human plasma. Anal Biochem. 2002; 301: 128±35. https://doi.org/10.1006/abio.2001.5486 PMID: 11811977*
32. *Shichiri M, Yoshida Y, Ishida N, Hagihara Y, Iwahashi H, Tamai H, et al. α-Tocopherol suppresses lipid peroxidation and behavioral and cognitive impairments in the Ts65Dn mouse model of Down syndrome. Free Radic Biol Med. Elsevier Inc.; 2011; 50: 1801±11. https://doi.org/10.1016/j.freeradbiomed.2011. 03.023 PMID: 21447382*
33. *Hinman AW. Methods of analyzing p-hydroquinone levels and ratios. WIPOÐWorld Intellectual Property Organization; WO2018/081644 A1, 2018. p. 90.*
34. *Siegel D, Bolton EM, Burr JA, Liebler DC, Ross D. The reduction of alpha-Tocopherolquinone by human NAD(P)H: quinone oxidoreductase: the role of alpha-Tocopherolhydroquinone as a cellular antioxidant. Mol Pharmacol. 1997; 52: 300±5. Available: http://www.ncbi.nlm.nih.gov/pubmed/9271353 PMID:9271353*
35. *Hayashi T, Kanetoshi A, Nakamura M, Tamura M, Shirahama H. Reduction of alpha-Tocopherolquinone to alpha-Tocopherolhydroquinone in rat hepatocytes. Biochem Pharmacol. 1992; 44: 489±93. Available: http://www.ncbi.nlm.nih.gov/pubmed/1510699 PMID: 1510699*
36. *Traber MG, Atkinson J. Vitamin E, antioxidant and nothing more. Free Radic Biol Med. 2007; 43: 4±15.https://doi.org/10.1016/j.freeradbiomed.2007. 03.024 PMID: 17561088*
37. *Zhao, Y., M. J. Lee, C. Cheung, J. H. Ju, Y. K. Chen, B. Liu, L. Q. Hu, and C. S. Yang. 2010. Analysis of multiple metabolites of Tocopherols andtocotrienols in mice and humans. J. Agric. Food Chem. 58 :4844 – 4852.*
38. *Maloney, D. J., and S. M. Hecht. 2005. A stereo controlled synthesis of delta-trans-tocotrienoloic acid. Org. Lett. 7: 4297 – 4300.*
39. *Freiser, H., and Q. Jiang. 2009. Optimization of the enzymatic hydrolysis and analysis of plasma*

conjugated gamma-CEHC and sulfated long chain carboxychromanols, metabolites of vitamin E. Anal. Biochem. 388: 260 – 265.

40. *Yang, K., and X. Han. 2011. Accurate quantification of lipid species by electrospray ionization mass spectrometry - Meet a key challenge in lipidomics. Metabolites. 1: 21 – 40.*
41. *Saito, H., C. Kiyose, H. Yoshimura, T. Ueda, K. Kondo, and O. Igarashi. 2003. Gamma-tocotrienol, a vitamin E homolog, is a natriuretic hormone precursor. J. Lipid Res. 44: 1530 – 1535.*
42. *Wallert, M., L. Schmolz, A. Koeberle, V. Krauth, M. Glei, F. Galli, O. Werz, M. Birringer, and S. Lorkowski. 2015. Alpha-Tocopherol long-chain metabolite alpha-13 ' -COOH affects the inflammatory response of lipopolysaccharide-activated murine RAW264.7 macrophages. Mol. Nutr. Food Res. 59: 1524 – 1534.*
43. *IUPAC-IUB Joint Commission on Biochemical Nomenclature (1982) Nomenclature of Tocopherols and related compounds. Recomendations 1981. Eur. J. Biochem. 123, 473–475*
44. *Sheppard, A. J., Pennington, J. A. T., and Weihrauch, J. L. (1993) Analysis and distribution of vitamin E in vegetable oils and foods. In Vitamin E in Health and Disease (Packer, L., and Fuchs, J., eds) pp. 9–31, Marcel Dekker, Inc., New York*
45. *Bunyan, J., McHale, D., Green, J., and Marcinkiewicz, S. (1961) Biological potencies of e- and z1-Tocopherol and 5-methyltocol Br. J. Nutr. 15, 253–257*
46. *Weiser, H., Vecchi, M., and Schlachter, M. (1986) Stereoisomers of a-tocopheryl acetate. IV. USP units and a-Tocopherol equivalents of all-rac-, 2-ambo- and RRR-a-Tocopherol evaluated by simultaneous determination of resorption-gestation, myopathy and liver storage capacity in rats. Int. J. Vit. Nutr. Res. 56, 45–56*
47. *Weiser, H., Riss, G., and Kormann, A. W. (1996) Biodiscrimination of the eight Alpha-Tocopherol stereoisomers results in preferential accumulation of the four 2R forms in tissues and plasma of rats. J. Nutr. 126, 2539–2549*
48. *Brin, M. F., Pedley, T. A., Emerson, R. G., Lovelace, R. E., Gouras, P., MacKay, C., Kayden, H. J., Levy, J., and Baker, H. (1986) Electrophysiological features of abetalipoproteinemia: functional consequences of vitamin E deficiency. Neurology 36, 669–673*
49. *Sokol, R. J., Guggenheim, M., Iannaccone, S. T., Barkhaus, P. E., Miller, C., Silverman, A., Balistreri, W. F., and Heubi, J. E. (1985) Improved neurologic function after long-term correction of vitamin E deficiency in children with chronic cholestasis. N. Engl. J. Med. 313, 1580–1586*
50. *Sokol, R. J., Kayden, H. J., Bettis, D. B., Traber, M. G., Neville, H., Ringel, S., Wilson, W. B., and Stumpf, D. A. (1988) Isolated vitamin E deficiency in the absence of fat malabsorption— familial and sporadic cases: Characterization and investigation of causes J. Lab. Clin. Med. 111, 548–559*
51. *Kohlschu¨tter, A., Hubner, C., Jansen, W., and Lindner, S. G. (1988) A treatable familial neuromyopathy with vitamin E deficiency, normal absorption, and evidence of increased consumption of vitamin E. J. Inher. Metab. Dis. 11, 149–152*
52. *Schuelke, M., Mayatepek, E., Inter, M., Becker, M., Pfeiffer, E., Speer, A., Hu¨bner, C., and Finckh, B. (1999) Treatment of ataxia in isolated vitamin E deficiency caused by a-Tocopherol transfer protein deficiency. J. Pediatr. 134, 240–244*
53. *Evans, H. M., and Bishop, K. S. (1922) On the existence of a hitherto unrecognized dietary factor essential for reproduction. Science 56, 650–651*
54. *Schwarz, K. (1965) Role of vitamin E, selenium, and related factors in experimental nutritional liver disease. Federation Proc. 24, 58–67*
55. *Tappel, A. L. (1962) Vitamin E as the biological lipid antioxidant. Vitam. Horm. 20, 493–510*
56. *Burton, G. W., and Ingold, K. U. (1986) Vitamin E: application of the principles of physical organic chemistry to the exploration of its structure and function. Acc. Chem. Res. 19, 194–201*
57. *Esterbauer, H., Dieber-Rotheneder, M., Striegl, G., and Waeg, G. (1991) Role of vitamin E in preventing the oxidation of low density lipoprotein. Am. J. Clin. Nutr. 53, 314S–321S*
58. *Stampfer, M., Hennekens, C., Manson, J., Colditz, G., Rosner, B., and Willett, W. (1993) Vitamin E consumption and the risk of coronary disease in women. N. Engl. J. Med. 328, 1444–1449*
59. *Rimm, E. R., Stampfer, M. J., Ascherio, A., Giovannucci, E., Colditz, G. A., and Willett, W. C. (1993) Vitamin E consumption and the risk of coronary heart disease in men. N. Engl. J. Med. 328, 1450–1456*
60. *Burton, G. W., Joyce, A., and Ingold, K. U. (1983) Is vitamin E the only lipid-soluble, chain-breaking antioxidant in human blood plasma and erythrocyte membranes? Arch. Biochem. Biophys. 221, 281–290*
61. *Ingold, K. U., Webb, A. C., Witter, D., Burton, G. W., Metcalfe, T. A., and Muller, D. P. R. (1987) Vitamin E remains the major lipid-soluble, chain breaking antioxidant in human plasma even in individuals suffering severe vitamin E deficiency Arch. Biochem. Biophys. 259, 224–225.*