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In vitro and *In vivo* Oxidation and Cleavage Products of Tocols : from chemical tuners to "*VitaminEome*" therapeutics. A Narrative Review

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Abbreviations :

AAPH: 2,2'-azobis[2-amidinopropane]hydrochloride

AMVN: 2,2'-azobis[2,4-dimethylvaleronitrile]

 α -T: α -Tocopherol

 $\alpha\text{-}TO\text{:} \alpha\text{-}tocopheroxyl radical}$

ATF4: Activating transcription factor 4

C/EBP β : CCAAT-enhancer binding protein β

CEHC: δ -carboxyethylhydroxychromanol

COX-1/-2: cyclooxygenase-1/-2

DLPC: dilinoleoyl phosphatidylcholine

DCM: Dichloromethane

HAT: Hydrogen Atom Transfer

HMG-CoA Red: Hydroxymethylglutaryl-Coenzyme A reductase

HO: hydroxyl radical

IL-8: interleukin 8

KLK2: Kallikrein Related Peptidase 2

L': lipid radical

LCMs: Long chain metabolites

LCMS: Liquid Chromatography, Mass Spectrometry

LO[:] alkoxy radical

LOO: alkylperoxy

5-LOX: 5-lipoxygenase

LTB4: leukotriene B4

MRP-associated proteins : Multidrug resistance-associated proteins

NF-κB: nuclear factor-kappa B

oQM: tocopheryl ortho quinone methide

PARP-1: poly(ADP-ribose) polymerase 1

Pgp: P-glycoprotein

PKC: Protein kinase C

PSA: Prostate Specific Antigen

PXR: pregnane X receptor

QTOF: Quadrupole time of flight

SCMs: Short chain metabolites

SET: Single Electron Transfer

SPLET: Sequential Proton Loss and Electron Transfer

TM4SF1: Transmembrane 4 L Six Family Member 1

Tocols: tocopherols and tocotrienols

TQ: tocopherylquinone

VCAM: Vascular cell adhesion protein

VEOP: vitamin E oxidation products

Abstract

Vitamin E components and vitamin E oxidation products (VEOP) define the "vitaminEome". VEOP are produced through biological and chemical processes. They are found at low concentrations *in vivo* and may play particular biological functions linked with chemoprevention and inflammatory processes. Much data have been reported leading to more insight into VEOP. VEOP are generated through peroxy-radical generating systems and via reactive oxygen and nitrogen species as well as enzymatically by a variety of enzymes. *In vivo*, VEOP and their catabolites may reach the blood circulation and display physiological properties. This narrative review expands upon parent vitamin E chemistry as well as VEOP chemical concepts. The *in vitro* and *in vivo* routes by which they can be generated are exhaustively approached. Finally, we will discuss therapeutic and chemopreventive opportunities that VEOP offer with a special focus on their cytotoxic and anti-inflammatory functions.

Keywords : vitamin E, vitamin E oxidation products, chemistry, tocopherylquinones, 5-nitro- γ - tocopherol, vitamin E long chain Metabolites, cytotoxicity, anti-inflammatory activities.

Highlights

- Vitamin E compounds act as antioxidants in different systems through different mechanisms
- Vitamin E oxidation product (VEOP) formation is affected by several intrinsic and extrinsic factors
- VEOP could be used as markers for several debilitating diseases
- VEOP are associated with potent anti-inflammatory and cytotoxic activities

Graphical Abstract



Introduction

Vitamin E is a nutrient that is considered to be a functional food. It is the most important fat-soluble antioxidant that protects biomembranes and low density lipoproteins from oxidation. In the past decades, the chemistry of vitamin E oxidation with peroxyl radical generating systems has been systematically studied. As a result, vitamin E oxidation products (VEOP) have generated biomarkers, which may help to understand the vitamin E redox cycle and turnover. In addition, VEOP may act as physiological and/or pharmacological tuners of vitamin E in a biological environment (Matsuo et al., 1989; Yamauchi et al., 1997, 2019; Rosenau et al. 2007a, 2009; Niki, 2007, 2014 and 2019).

By preserving living organisms against oxidation processes, Vitamin E (tocols) prevents the activation and the diffusion of free radicals formed during the lipoperoxidation process. In experimental models, free radicals are produced through physical methods such as thermolysis, photolysis, radiolysis as well as sonolysis along with chemical and electrochemical methods, which are performed by electron redox transfers. Free radicals are also generated in living systems, they comprise reactive oxygen and nitrogen species. The assessment of the anti-radical capacities of tocols requires a broad range of experimental models, starting from simple tests without other lipid co-substrates, testing in biological media, in preclinical trials and finally in clinical trials. When exerting their antioxidative actions, tocols are extensively oxidized and generate VEOP. This supports further investigations as to the isolation, purification, structural identification and definition of the biological properties of these VEOP. One of the main properties of Vitamin E is to block lipid peroxidation in a lipid bulk phase, by blocking radical chain reactions. Thus, vitamin E may react with alkoxy (LO[']), alkylperoxy (LOO[']) or hydroxyl (HO[']) radicals through mechanisms that will be developed in this review to give tocopherone derivatives and other recurrent stable which end products amongst tocopherylquinone (TQ), tocored, 5methyltocolderivatives, dimers and trimers and many others (see vide infra). Therefore, vitamin E introduces a lag phase during which lipoperoxidation slows down until reaching vitamin E depletion when the rate of peroxidation increases again.

The activity of α -Tocopherol (α -T) against lipoperoxidation has gained in interest, due to the impressive development of physical chemistry approaches. The chemical mechanism is

slow enough to allow a detailed characterization of the radical tocopheroxy. These studies were commonly performed by Electron Spin Resonance and Laser Flash analysis techniques (Kohl et al. 1969; Boguth and Niemann, 1971; Svanholm et al., 1974; Ozawa et al., 1978; Mukai et al, 1982; Doba et al., 1983; Matsuo and Matsumoto, 1983; Tsuchija et al., 1983). Electrochemical models showed that vitamin E analogs are low redox-potential molecules, that reduce free radicals with a higher redox potential (Svanholm et al., 1974; Burton and Ingold, 1986; Webster, 1999; William and Webster, 2004; Lee et al., 2005).

Nevertheless, current concepts of the antioxidant effects of α -T encompass some discrepancies (Cillard et al., 1980; Terao & Matsushita, 1986; Bowry & Stocker, 1993; Mukai et al, 1993). Indeed, although α-T is a well-known antioxidant agent and the main antioxidant carried by plasma lipoproteins (Herrera & Barbas, 2001), it is a pro-oxidant in vitro in strong oxidizing conditions such as high oxygen tension, in the presence of free metal ions, or at high concentrations (Cillard et al., 1980; Inglod, 1993; Bowry and Stocker, 1993; Mukai et al, 1993; Yoshida et al., 1994; Witting et al., 1995; Bowry et al., 1995; Kontush et al. 1996; Upston et al., 1999, 2002; Bernard et al., 2001; Zai-Qun, 2010). Beside its anti-oxidative potential, Boscoboinik et al. (1991) published the first report giving evidence that α-T regulated cell signaling and gene transcription. Therefore, they showed that α-T displayed bio-potencies. However, the key functions of vitamin E, other than being a non-antioxidant, are still under debate. Vitamin E and its oxidation products have been reported to display a wide range of biochemical and pharmacological potencies. To date, many VEOP have been characterized but little is known as to their bioavailability and their exact roles in the bioactivity of α -T. The aim of this review is firstly to expose the complex chemistry of vitamin E oxidation depending on the biological model. We will next report significant in vitro and in vivo biological properties of VEOP. This review is the first comprehensive report that combines both chemical and biological aspects.

A brief survey of Vitamin E chemistry

Tocols (Vitamin E) are amphipathic and lipophilic antioxidants that are biosynthesized mostly by plants and cyanobacteria (DellaPenna and Pogson, 2006; Khallouki et al. 2020). Tocols are very soluble in apolar solvents and slightly soluble in alcohols. Tocols are very sensitive to light in the presence of air or other oxidants. Their phenolic group can be esterified with various acids. The resulting products can retain some of their biological activities but not their antioxidant potential. Tocols differ in the number and position of methyl groups present on the chromanol ring. Their chemical structures consist of two fused rings (6-hydroxychroman) and a long hydrocarbon side chain attached at the 2-position of the chroman ring. In Tocopherols, the side chain is saturated while in tocotrienol this side chain is a farnesyl chain with three double bonds at positions 3', 7' and 11' (see figure 1).

 α -T is the most biologically active form amongst tocol congeners (Pennock et al., 1964). The human body preferentially retains α -T rather than any other vitamin E analog. In 1982, the Commission on Biochemical Nomenclature (International Union of Pure and Applied Chemistry and International Union of Biochemistry and Molecular Biology Joint Commission on Biochemical Nomenclature), encompassed tocotrienols into vitamin E components. Moreover, the modern concept of "vitamin E" includes a larger group of natural as well as synthetic vitamin E derived products. The different isoforms with their exact nomenclature are shown in figure 1 and table 1 (IUPAC-IUB, 1966, 1974, 1981).

 α -T dietary supplements are often in esterified forms obtained by esterification of the hydroxyl group at the C6-position of the chromanol ring with an acetate, linoleate, succinate, nicotinate or phosphate group. These esterified forms are more stable and more resistant to oxidation than their parent forms but are no more antioxidant due to the blocade of the phenolic group (Ruperez et al., 2001). On the other hand, tocotrienols have only one chiral center. However the configurations of the two first existing double bonds at the position 3' and 7', allow for 4 cis/trans geometric isomers. The only natural isomer of tocotrienol that exists is the 2R, 3', trans 7' trans also known as the (2*R*,3'*E*,7'*E*) configuration (Pennock et al., 1964 ; Drotleff et al. 2001).

Other important trivial denominations of commercial and therapeutic importance are described below:

- 2-epi-α-tocopherol is known as L-α-tocopherol (2S, 4'R, 8'R-α-tocopherol)
- 2-ambotocopherol corresponds to a mixture of D-α- and L- α-tocopherol which is obtained using synthesis with phytyl and achiral hydroquinone, this is also know as dlalpha-tocopherol
- The reduction of 5,7,8-tocotrienol in which the unsaturated 3', 7' and 11' are hydrogenated and two asymmetrical centers are created at C4' and C8' is a mixture of

2R, 4'R, 8'R; 2R, 4'R, 8'S; 2R, 4'S, 8'R and 2R, 4'S, 8'S, this mixture is known as 4'-ambo, 8'-ambo- α -tocopherol.

The fate of vitamin E with in vitro peroxy radical generating systems

Some known substrates of lipid peroxidation include constituents of cell membranes and plasma lipoproteins such as polyunsaturated fatty acids, cholesterol, phospholipids and lipoproteins. Lipoperoxidation occurs via reactions that by-pass the spin barrier between these lipids (the ground state is of singlet multiplicity) and oxygen (a biradical of triplet multiplicity in its fundamental state). There is consequently a need for a catalysis that will overcome this dissociation energy which will have an impact on allylic or bis allylic labile lipid protons. This leads to the formation of unstable hydroperoxides, which will break-down into toxic volatile secondary compounds (aldehydes, alcohols, ketones, epoxides). Such compounds are responsible for the oxidative deterioration of tissues. In food, the sustained oxidative damage of lipids is responsible for their changes in molecular structure and molar mass. This is associated with variations in the physical properties of lipids and a degradation in the quality of food. This causes organoleptic changes and loss of microbiological and nutritional properties. In vivo, if defensive systems are overwhelmed, these compounds could contribute to the development of certain cancers, neurodegenerative diseases and atherosclerosis. Several reviews have been published on this topic but much more mechanistic insight is required to improve our knowledge and our understanding of these processes (Frankel, 1980, 1998, 2005; Poisson & Narce, 2003; Niki, 2009; Bochkov et al. 2010; Yin et al., 2011; Niki, 2021). Lipoperoxidation proceeds in three steps: the initiation step, the propagation step and the termination step. The alkyl radical generated from an unsaturated lipid after hydrogen radical abstraction (carbon-centered radicals, L') is named the initiation step. There are many factors that influence the reaction at this stage. These include on the one hand, intrinsic factors such as the physical state of the system, the presence or not of pro-oxidants such as transition metal ions, the presence of biological heme or non-heme irons as well as initiating agents amongst many others. On the other hand, extrinsic factors include temperature, light, pH, oxygen partial pressure, and the presence of water (Hsieh & Kinsella, 1989). Lipid peroxidation can be triggered by photosentitizers such as pigments. This involves the formation of an excited singlet state of oxygen as observed with hydrophobic porphyrin derivatives (Jeong, 2016).

While the antioxidant power of vitamin E family members are well studied in vitro in various solvents and lipid suspensions, in vivo, lipid oxidation can occur through enzymatic reactions performed by oxidoreductases, lipooxygenases and cyclooxygenases (Yin et al., 2011; Hajeyah et al., 2020). Auto-oxidation of lipids may also take place in the presence of free radicals that may already be present in the medium. As illustrated for linoleate (figure 2), a vulnerable bis allylic carbon atom forms a radical with a low rate constant reaction between two cis double bonds of the fatty acid) (-CH=CH-CH₂-CH=CH-). The radical formed at C-11 (highlighted in bold), is delocalized over the five carbons from C-9 to C-13 (Porter et al., 1980, 1981, 1984, 1986, 1996; Davis, et al., 2006; Xu et al., 2009). The radical formed is then stabilized by intramolecular rearrangements leading to a conjugated diene, which can subsequently react with dioxygen to form a lipid peroxyl radical (LOO'). Because of its constant high rate, the lipid peroxy-radical will attack another polyunsaturated lipid molecule in a continuous process, causing the formation of a new lipid radical (L⁻). This is associated with the formation of an unstable primary lipid hydroperoxide (LOOH), and this is termed the propagation step. In the termination step, lipoperoxidation occurs when radicals combine and stop the propagation step. In vivo, lipid hydroperoxides can either be metabolized through a selenoperoxidase-mediated two electron reduction to give rise to the corresponding less toxic alcohols, or may entail a one electron reduction to generate a free radical-mediated chain peroxidation, hence decomposing into low reactive peroxyl radicals (LOO[•]) as afore mentioned. However, depending on whether they react with specific transition metals, redox cycles with Iron and Copper being the most reactive, these hydroperoxides may then produce extremely reactive alkoxyl radicals (LO[•]) (Halliwell and Gatteridje, 1984; Sevanian & Hochstein, 1985). The decomposition of hydroperoxides may also generate hydroxyl radicals (HO') via the well-known reactions of "Fenton and Haber Weiss", through the "Beckman-Radi-Freeman pathway" or the "Cadenas-Poderoso shunt" during a nitrative stress (reviewed in Boveris et al., 2008).

Antioxidants may stop lipid peroxidation through different mechanisms. They can directly interrupt the propagation of the radical chain reaction, they can act as metal chelators, inhibiting the catalysis of the production of free radicals, or they can act as quenchers in the case of photo-oxidation by active singlet-oxygen. They may also act as "synergists": molecules that help to increase the antioxidant activity such as phospholipids (Frankel, 1998; Bandarra et al., 1999). As shown by α -T in various *in vivo or in vitro* systems, the energy of

dissociation of its phenolic moiety is weak and therefore facilitates the radical reactions via a dehydrogenating oxidation. Moreover, with any other co-substrate lipid (unsaturated fatty acid, phospholipid, or cholesterol) in homogeneous solutions, in aqueous dispersions such as micelles or liposomes (used as a model to mimic the *in vivo* lipid oxidations), and in biological fluids such as plasma, vitamin E reacts with peroxy radicals to form different oxidation products (VEOP). The antioxidant activity of vitamin E is deep-rooted by its chemical structure, and is also adapted to its level, its mobility, and its solubility either in a dispersed system or in a homogeneous phase. Its antioxidant potential will also depend on the physical state of a given microenvironment of the system (Huang et al., 1996). Vitamin E is more powerful as an antioxidant in polar emulsified media such as oil-water emulsions, plasma membrane and phospholipids with a high surface/volume (HSV) ratio, than in a continuous lipid phase such as oils due to its hydrophobic nature (Frankel et al., 1994). This behavior is known as Porter's polar paradox (Porter, 1993) which unfortunately disregards the influence of many other factors.

In homogeneous solutions as well as in heterogeneous lipid bilayers, α -T inhibits lipid peroxidation either by trapping the chain-carrying LOO' or by scavenging the initiator (the initial oxidant ROO'). α-T acts as a radical proton donor to a peroxyl radical, and transforms itself into a tocopheroxy radical of weak reactivity. This reaction is fast and is even faster than the reaction of lipids with other lipid peroxy radicals (Niki et al., 1984). In vitro, kinetic studies indicated that the rate constant for α -T + ROO' $\rightarrow \alpha$ -TO' + ROOH is greater than 10⁶ M⁻¹s⁻¹(Winterle et al., 1984; Min and Boff 2002; Naumov and Vasil'ev 2003; Choe and Min 2006). The speed with which tocols react with a peroxy radical reflects their direct respective antioxidant properties (Burton and Inglod, Kamal-eldin & Appelqvist, 1996). One molecule of α -T can scavenge two molecules of radicals such as LOO. The mechanisms involved in this effect take place in a stepwise fashion. 1) α -T deactivates free radicals through a Hydrogen Atom Transfer (HAT), which acts via a homolytic breaking of the O-H bond of the chromanol backbone, giving rise to a more stable α -tocopheroxyl radical (α -TO[·]), also called the α -tocopheryl-semiquinone radical. 2) α -TO[•] may also be formed via a Single Electron Transfer (SET) in which an electron is first transferred from α -T to the radical, and the tocophenoxy radical cation is then deprotonated. 3) Another proposed mechanism relies on a Sequential Proton Loss and Electron Transfer (SPLET). SPLET proceeds first by a deprotonation of α -T's phenolic group, forming a α -tocopheroxy anion, which in turn transfers an electron to the radical, giving rise to the α -tocopheroxy radical. In addition, tocols may also undergo another SPLET to form a relatively less reactive chromanoxylium cation, which is stable for a few hours in dry lipophilic solvents at low temperatures (Wilson et al., 2006). Subsequent electron and proton transfers may lead to the formation of tocopherylquinone methide (oQM) from either the tocopheroxy radical or the tocopheroxy cation. Moreover, experimental systems often lead to an unusual reactivity of the 5a-methyl group of α -T in both apolar and polar media (Goodhue and Risley, 1964; Skinner and Parkhurst, 1971; Suarna and Southwell, 1989). The 5a-methyl group of the chromanol backbone (see structure figure 1 above) is also critically involved in the formation of oQM. This is not observed with other tocol congeners, which are partially methylated, such as γ - and δ -T. These tocols show other oxidation behaviors (see vide infra). The HAT mechanism predominates in apolar solvents, SET and SPLET are more prevalent in polar solvents, whereas all three mechanisms may coexist in micellar or heterogeneous systems (Najafi et al., 2011; Wang et al., 2019). Figure 3 depicts the three main possible intermediates obtained that will lead to α -T oxidation products.

Generation of oQM is governed by the type of oxidant used, solvent polarity and its hydration state (Rosenau et al., 2007a). oQM contains an α , β -ethylenic ketone which may be converted via a 1,4-addition with nucleophiles, into covalent quinone-Nucleophile residues. In addition, hetero-Diels-Alder reactions may also occur and usually give rise to α -T dimers and trimers (Nilsson et al., 1968a,b; Schröder and Netscher, 2001; Rosenau et al., 2002).

 α -TO' forms resonance-stabilized tocopherol radicals, and amongst these forms the position 8 is predominant (this is depicted in the figure 4). α -TO are stable enough to inhibit the formation of another radical and to stop the propagation of a chain reaction. α -TO may give rise to different metabolites. The major metabolites are 8a-lipiddioxy-α-tocopherone (I), 8a-alkoxy-α-tocopherone (II), their hydrolysis products 8a-hydroxy-α-tocopherone (III) and 8a-hydroxyperoxy- α -tocopherone (IV), and the end product α -tocopherylquinone (α -TQ, V). When the amount of dioxygen (O_2) is limiting, α -T can react directly with the alkyl radicals in position C-6 instead of position C-8a to give 6-O- α -tocopheryl ethers (VI) in appreciable amounts. Another group of α -TO metabolites are C-4a/C-5-epoxy-8a-hydroperoxy- α tocopherone (VII), C7/C8-epoxy-8a-hydroperoxy-α-tocopherones (VIII) and their respective hydrolyzable products α -tocopherolquinone-2,3-oxide (α-TOE1, IX) and α tocopherolquinone-5,6-oxide (α-TQE2, X). Furthermore, α-T may also undergo a selfcoupling reaction to form α -tocopheryl spiro-dimers (XI), α -tocopheryl ethano-dimers (XII) and α -tocopheryl spiro-trimers (XIII) (Kamal-Eldin & Appelqvist, 1996; Liebler et al., 1996; Rosenau et al., 2002, 2005, 2007a,b, 2009; Kamal-Eldin et al., 2008). Compounds X-XII display antioxidant activities (Csallany, 1970; Yamauchi et al., 1988). The formation of 5-alkyloxy-7,8-dimethyltocol (XIV) is also observed. The manifold of vitamin E oxidation products described in this review is depicted in Figure 5.

From a mechanistic point of view, some interesting features can be reported: Two α -TO's may combine either to form a non-radical product (recombination) or may also lead through a disproportionation reaction to the parent α -T and oQM. α -T can give hydroxy- and peroxyketal tocopherones (Winterle et al., 1984; Rosenau et al., 2007b), spiro-dimers (XI) and spiro-trimers (XIII) with good yields via o-QM and the respective Diels Alder reaction, mainly in inert and aprotic solvents (Suarna et al., 1988; Krol et al., 2001; Schröder and Netscher, 2001; Rosenau et al., 2007a,b). A revisited mechanism involved in the formation of these dimers and trimers as well as in the formation of the 5-alkyloxy-dimethyltocol has been solved by Rosenau et al. 2007b. This reaction proceeded via a heterolytic reaction with oQM as an intermediate, ruling out the occurrence of 5a-C-centered radical intermediates as earlier proposed (Goodhue and Risley, 1964; Nilsson et al., 1968a; Suarna et al., 1988).

Furthermore, several other reactions may also be in competition hence limiting the antioxidant capacities of tocols. Solvolysis is a crucial contributor in tocol oxidation processes. Indeed, protic solvents may interact with phenols, hence preventing the interaction of phenolic OH with radicals (Iwatsuki et al., 1994). As an example, with ethanol as a solvent, α -T gives rise to 8a-ethoxy-tocopherone (XV) (Svanholm et al., 1974; Jore and Ferradini, 1985; Sumarno et al., 1987; Suarna and Southwell-Keely, 1989; Litwinienko and Ingold, 2007; Reichardt and Welton, 2011; Losada-Barreiro et al., 2015).

The regeneration of α -TO[•] is often done by reducing agents such as vitamin C (Scarpa et al., 1984; Liebler et al., 1986, 1992). Vitamin C itself is either regenerated by reduced glutathione, cysteine or dihydrolipoic acid as intermediates (Niki et al., 1982; Constantinescu et al., 1993, Traber et al., 1994). α -TO[•] can either be regenerated by nordehydroguaiaretic acid (NDGA) (Liebler and Burr, 1992), ubiquinols (Niki, 1997; Stoyanovsky et al. 1995) and bilirubin (Neuzil and Stocker 1994; Bowry et al., 1995), but at a slower rate than vitamin C. Moreover, *in vivo*, Vitamin E may also be regenerated via a continuous supply of food antioxidants such as polyphenolic compounds. If α -T is not regenerated, kinetic evidence

shows that it reacts with peroxy radical generating systems. This can be seen in vitro with a homodimeric thermolabile azometabolites, containing an N = N double bond, that may undergo a temperature-dependent homolysis through first-order kinetics in the presence of α -TO; thereby generating nitrogen and peroxyl radicals in aerobic systems. The most widely used azo compounds include 2,2'-azobis[2,4-dimethylvaleronitrile] (AMVN), 2,2'-azobis[2amidinopropane]hydrochloride (AAPH) (Yamauchi et al. 1997), 2,2-diphenyl-1picrylhydrazyl (DPPH) (Tsuchija et al., 1983; Musialik and Litwinienko, 2005) and 2,2'azobis(isobutyronitrile) (AIBN) (Skinner and Parkhurst, 1971; Mill et al., 1980). Unlike dialkylperoxides (ROOR') or alkylhydroperoxides (ROOH), these azometabolites do not react with themselves or with the solvent (Mill et al., 1980, Winterle et al., 1984). On the other hand, thermolysis or photolysis dissociation of dialkylperoxides or alkylhydroperoxides are also used as initiators and immediately lead to the formation of two oxyradicals with a very high affinity for hydrogens. This is often illustrated by di-t-butyl hydroperoxide (DTBP) and t-butyl hydroperoxide (TBHP). TBHP decomposed more readily in polar than in apolar solvents (Stannett and Mesrobian, 1950). In apolar solvents, polytocopherols such as dimers and trimers have been characterized in appreciable amounts in the autoxidation of α -T with unsaturated lipids (Csallany et al., 1970; Yamauchi et al., 1988). In polar protic solvents, TBHP could immediately oxidize α -T and solvolysis via a chromanoxylium cation led to the formation of 5a-ethoxymethyl-7,8dimethyltocol (XVI), α-TQ (V) as well as 5-formyl-7,8dimethyltocol (XVII). In addition, α -tocopherol spiro-dimers (XI) and trimers (XIII) were also observed but not as much as in apolar solvents (Suarna and Southwell-Keely, 1989; Suarna et al., 1992).

Furthermore, the reaction of α -T with less reactive peroxides such as ditertbutyl peroxy radicals leads mostly to a mixture of epoxytocopherones (Matsumoto et al., 1986; Matsuo et al., 1989; Liebler et al., 1990, 1992). Under aerobic conditions, Oxygen-centered peroxyl radicals (LOO⁻) derived from AMVN in hexane, acetonitrile or in liposomes, react respectively with α -TO⁻ at the C-8a position, to give 8a-(lipid-dioxy)- α -tocopherone (I), 8a-(hydroxy)- α -tocopherone (III), and their hydrolysis product α -TQ (V). Interestingly, the three systems also provide epoxytocopherones (VII and VIII) and their respective hydrolysis products 2,3-epoxy- α -tocopherolquinone (IX) and 5,6-epoxy- α -tocopherolquinone (X) along with a small amount of 8a-(1-cyano-1,3-dimethyl)butylperoxy- α -tocopherones is

dependent on the microenvironment of the medium although the yield of the α -TQ end product appears to be similar in the three different systems (Liebler et al., 1990, 1994, 1995, 1996). The reaction performed in hexane gave 8a-substituted tocopherone adducts in appreciable amounts compared to the reaction performed on liposome systems which were found to give higher amounts in epoxytocopherones (Liebler and Burr, 1995). In another report, α -T is oxidized in the presence of AMVN in polar protic solvents such as ethanol, and led to other epoxytocopherone stereoisomers such as 4a,5-epoxy-8a-ethoxy- α -tocopherone (XIX), 7,8-epoxy-8a-ethoxytocopherone (XX) and 8a-(1-cyano-1,3-dimethyl)butylperoxy- α tocopherone (XVIII) (Yamauchi et al., 1989).

Liebler et al. (1990, 1992) demonstrated two distinct pathways of different origins respectively for the formation of 8a-(lipidioxy)- α -tocopherone derivatives compared to the epoxytocopherone systems either in homogeneous systems or with liposomes. These two systems resulted from two competing reactions between α -TO and peroxy radicals. Moreover, unlike the formation of tocopherone diastereomers which were directly involved in the antioxidant activity of α -T, epoxytocopherones were not and may occur only by autoxidation of α -T probably by a four-electron oxidation.

In other reports, the oxidation of α -T by methyl linoleate hydroperoxide generating systems, entails the formation of stable products such as α -TQ, as well as the formation of dimers and trimers (Csallany et al, 1970; Yamauchi et al, 1988). In addition, with methyl linoleate-AMVN-derived peroxyl radicals, the primary products formed include 8a-(lipid-dioxy)- α -tocopherones, four stereoisomers of methyl-13-(8a-peroxy- α -tocopherone)-9(Z),11(E)-octadienoate and four others of methyl-9-(8a-peroxy- α -tocopherone)-10(E),12(Z)-octadienoate (an example of structure (XXI) is depicted in fig. 5) (Yamauchi et al., 1990).

The thermolytic incubation at 37 °C of liposomes containing α -T with AMVN as an initiator, led to the formation of 8a-(1-cyano-1,3-dimethyl)butylperoxy- α -tocopherone (Fig. 5, XVIII), 8a-(hydroperoxy)tocopherone (Fig. 5, IV), α -TQ (Fig. 5, V), 4a,5-epoxy-8a-hydroperoxytocopherone (Fig. 5, VII), 2,3-epoxy- α -tocopherol quinone (Fig. 5, IX), and 5,6-epoxy-a-tocopherol quinone (Fig. 5, X) (Liebler et al., 1991). Yamauchi et al. (1994, 1996, 1998), showed that α -T suppressed the formation of different hydroperoxides formed in liposomes using the lipophilic AMVN or the hydrophilic AAPH radicals as initiators. For example, multilamellar liposomes of dilinoleoyl phosphatidylcholine (DLPC) liposomes

containing small amounts of α -T (0.1 mol %) incubated with AMVN as an initiator, led to the mixture of 8a-alkyldioxy-α-tocopherones production of a as major products. Epoxytocopherones and their respective stable end-products were also detected. Amongst these products, α-TQ, epoxytocopherones 2,3 oxide and tocopherone 5,6 oxide, and DLPCderived 8a-(lipid-dioxy)- α -tocopherones were formed with the mechanism described above for the methyl linoleate model. Indeed, peroxyl radical liposomes react with the α tocopheroxy radical in position C8a. The central Sn-2- position of phospholipids was more subject to oxidation compared to the external Sn-1,3 positions of the glycerol moiety (Neff and ElAgaimy, 1996). In addition, the most labile allylic proton at C-11, in the Sn-2 position, generated a carbon-centered radical by transfer of a hydrogen in C-9 or C-13 respectively. As an example, one isomer formed is the 1-linoleoyl-2-[13-(8a-dioxy-(\alpha-tocopherone)-9(Z),11(E)-octadecadienoyl]-3-sn-phosphatidylcholine (DLPC-derived 8a-(lipid-dioxy)-αtocopherones (XXII)) (figure 5). No evidence for the formation of such a compound has been found in vivo. The 8a-(phospholipid-dioxy)-α-tocopherones were indeed deemed degraded to produce α -tocopherylquinone (Yamauchi, et al., 1994, 1996, 1998).

Lipid hydroperoxides may be decomposed into free radicals through a transition metal catalysis (Halliwell and Gatteridje, 1984; Sevanian & Hochstein, 1985). Iron III complex-catalyzed decomposition of methyl 13(S)-hydroperoxy-9(Z),11(E)- octadecadienoate with α -T in aerobic homogeneous solutions has been studied by Yamauchi et al., (1995). They report that the lipid alkoxyl radicals that are generated tend to rearrange into carbon-centered epoxyallylic radicals, which are then added to the 8a-carbon radical of α -T. The 8a-(epoxylipid-dioxy)- α -tocopherone products that are formed include 4a,5-epoxy8a-hydroperoxy- α -tocopherone)-(9Z,11E)-octadecadienoate, four stereoisomers of methyl-9-(8a-dioxy- α -tocopherone)-(12,13)-epoxy-(10E)-octadecenoate and four stereoisomers of methyl-11-(8a-dioxy- α -tocopherone)-(12,13)-epoxy-(9Z)-octadecenoate (an example of structure (12S, 13S, XXIII) is depicted in figure 5) (Yamauchi et al., 1995).

Although in human LDL, α -T does not provide any protection against oxidation of the cholesterol-esterified linoleate (Kim et al, 2005), the *in vitro* peroxidation of LDL lipids generates hydroperoxides mainly from cholesteryl linoleate (Ch18:2). 9- and 13-hydroperoxides with trans, cis conjugated diene were formed as the major oxidation products if endogenous α -T was present in the LDL (Horton and Fairhurst, 1987; Frei et al., 1988;

Kenar et al., 1996). Oxidation products of α -T with peroxyl radicals generated by ironcatalyzed decomposition of Ch18:2 hydroperoxides (Ch18:2-OOH) in homogeneous systems, have been investigated (Yamauchi et al., 2002). The results indicated that the peroxyl radicals from CH18:2-OOH react with the 8a-carbon radical of α -T to form addition products such as cholesteryl (8a-dioxy- α -tocopherone)-epoxyoctadecenoates (4 isomers) along with cholesteryl (8a-dioxy- α -tocopherone) octadecadienoates (2 isomers), these are illustrated by structures XXIV and XXV, depicted in figure 5 (Yamauchi et al., 2002).

During lipoperoxidation, research on other congeners (γ - and δ -), which were not fully methylated gave somewhat other insights into their oxidation products as well as their antioxidant potentials. Similar tocopherones were formed, albeit in smaller amounts than for the α-form, including 8a-(alkyl-dioxy)-γ-tocopherones (XXVI) and 8a-(alkyl-dioxy)-δtocopherones. Self recombinations of γ - and δ - tocopheroxy radicals led to the formation of other dimer types that still have potent antioxidant activities by means of their free hydroxy protons. More specifically, the emerging products from the γ -form include, in addition to 8a-(lipid-dioxy)-5-(γ -tocopheroxy)- γ -tocopherone (XXVII), the γ -tocopherol diphenylether dimer (γ -TED, XXVIII), 5-(γ -tocopheroxy-5-yl)- γ -tocopherol (γ -TBD, XXIX) along with γ tocored (XXX) and γ-tocopherylquinone (γ-TQ, XXXII) (Komoda & Harada, 1969; Fujitani & Yukagaku, 1984 ; Yamauchi et al., 1997). Tocored (XXX) is an intense bright orange-red metabolite, which may also be formed from the fully methylated chroman moiety of α -T due to the unusual cleavage at the 5a-methyl group site of α-T (John et al., 1939; Komoda and Harada, 1970). The exact mechanism responsible for its formation was elegantly deciphered by Rosenau et al. 1997. Compared to the γ -form, similar results have been reported with δ -T, however, no evidence on the formation of δ -TBD compared to γ -TBD, has been reported in the autoxidation of methyl linoleate with the AMVN peroxyl radical generating system (Yamauchi et al. 1997).

Vitamin E oxidation products with other radicals and oxidants

At a first glance, in the absence of other lipid co-substrates, tocol oxidometric assays have been achieved in strong acid media or using conventional reagents based on transition metals (3d) and lanthanides (4f) which may form colored compounds. Indeed, the oxidizability of the 6-hydroxychroman ring of α -T and δ -T with metal ions generates the corresponding 1,4- Benzoquinones (John et al., 1939; Frampton et al. 1954; 1960; Skinner & Parkhurst, 1971, Khallouki et al, 2016). When the oxidation was carried out in boiling alcohol, it gave tocored, amongst other minor metabolites including hydroxy-p-quinone (tocopurple, XXXI). The oxidation of α -T with ferric chloride, was earlier the basis for precise and simple reactions to carry out in clinical routine assays to help characterize tocopherols colorimetrically (Emmerie and Engel, 1939; Martinek, 1964). More interestingly, a mild oxidation of α -T with alkaline ferricyanide K₃Fe(CN)₆, a red crystalline and hydrophilic solid oxidant of α -T, caught the attention of several biochemists due to its probable resemblance with *in vivo* vitamin E oxidation, which generates α -T dimers and trimers (Nelan and Robeson, 1962; Schudel, 1963; Skinner and P. Alaupovic, 1963; and Nilsson et al., 1968b).

A metastable state of oxygen such as singlet oxygen confers it dienophilic properties. It can be either quenched physically or chemically by other species to return to its ground state, or react via 1,3-addition, as well as [4/2] cycloaddition in a similar manner to the Diels/Alder reaction. From a kinetic point of view, α-T reacts favorably with singlet oxygen, but to a lesser extent with oxygen superoxide. Singlet oxygen may also originate from multiple substrates including anion superoxide, ozone, hydrogen peroxide, enzymes and sensitizers amongst many others (Krinsky, 1989). When it reacts with α -T, it yields α -TQ and TQE (Grams, et al., 1972; Clough et al., 1979; Neely et al., 1988; Sies et al., 1994). The reaction of α -T with superoxide ion (O₂) in aprotic solvents was different from that observed under protic conditions (Kaiser et al., 1990; Ha and Csallany, 1992). In line with this, it may act either as a nucleophile (Dietz 1970) or as an electrogenerated base (EGB) (Sugawara et al., 1983). The reaction of α -T with superoxide anion O₂ in a protic solvent is very slow (Nishikimi and Machlin 1975). In aprotic solvents, it produced two unique tocopherone isomers, hydroxylated at the position C7, both were stereoisomers of 7-hydroxy-8,8a-epoxy- α -tocopherone (XXXIII). However, under protic conditions (10% water in acetonitrile), the reaction with α -T produced compounds such as α -TQ, α -tocopherol dimer, and α -tocopherylquinone-2,3-epoxide (Ha and Cssalany, 1992). In addition, Matsumoto and Matsuo (1977), used a rare oxidizing and drying salt of superoxide anion O_2^{-1} in a reaction with an analog of α -T (6-hydroxy-2,2,5,7,8-pentamethylchroman) in aprotic polar tetrahydrofuran. With this system, they were able to hydroxylate the C-5 of the chroman ring. The same behavior was described by oxidation with bromine of α -T inducing the formation of 5-bromomethyl- γ - tocopherol (XXXIV) (Rosenau and Habisher, 1995). The oxidation of α -T with organic oxidants such as N-bromosuccinimide or with quinone reagents, led to the formation of 8a-hydroxy- α -tocopherone (IV) (Durckheimer and Cohen, 1964). The same compound has been detected as the main product in a micellar system, in which α -T was dispersed in an aqueous media with deoxycholate as an emulsifier and oxidized by xanthine-xanthine oxidase, a system that mostly generated superoxide anion and hydroxyl radicals (Nishikimi et al., 1980).

All tocols except the fully methylated α -T and α -tocotrienol (α -T3) react with nitrous acid. γ -T forms 5-nitro- γ -tocopherol (tocoyellow) which is a yellow nitro compound (Brigelius and Traber, 1999; Cooney et al. 1993). Dimers γ -TED and γ -TBD have also been formed with 2% triethylamine oxide (TMAO) in a methyl linoleate system (Ishikawa et al., 1978).

Thermal oxidation of α -T in hexane may readily lead to α -TQ, 5- formyl- γ -tocopherol (5-F- γ -T), as well as spirodimers and spirotrimers and the formation of γ -T was also observed (Büsing and Ternes, 2011 ; Kreps et al., 2016). The thermal decomposition of other forms of tocols such as α -T3, which is the least thermostable Tocotrienol vitamin, with the highest rate of degradation (Piironen 1988; Ko et al., 2010), led to the formation of oxidation products similar to the α -T congener. These include 7-formyl- β -tocotrienol (XXXV) and 5-formyl- γ -tocotrienol (XXXVI) as well as α -tocotrienol dihydroxydimers (XXXVII) as major products alongside α -tocotrienol quinone (XXXIX), α -tocotrienol spiro-dimers (XXXVIII) and α -tocotrienol spiro-trimers (XL) (Busing and Ternes, 2011). More recent insights into the oxidation products of the eight forms of tocols thermally stressed in an apolar solvent such as hexane, have also been performed and comprehensively reported by Drotleff et al. (2015).

Vitamin E oxidation products in oils

Different findings as to the decomposition of tocols at high temperature in oils have been reported both in natural oils and in tocopherol-stripped oils.

The formation of TQ, Epoxy-tocopherylquinone and α -Tocotrienylquinone epoxides as well as tocored rather than Tocopherones, have often been detected (Murkovic et al., 1997; Verleyen, 2001; Nagy et al 2007; Büsing and Drotleff, 2012; Niki, 2019), whereas photoirradiation of extra virgin Olive Oil entailed the formation of tocopherone stereoisomers with no TQ observed (Tanno et al., 2020). Tocored was also reported to be a strong natural antioxidant useful for oil preservation and especially suitable for lipid based food substrates (Komoda and Harada, 1969; Zheng et al., 2020). Tocored was reported to be present for the first time in cottonseed oil (Golumbic, 1942), in germ oil (Swift et al., 1944; Komoda and Harada, 1969) as well as in soybean oil (Komoda et al., 1967). The concentration of tocored in soybean was found to be moisture-dependent, and could reach 102.2 mg kg⁻¹ (Komoda et al., 1967). Tocopherylquinone is a major oxidation metabolite present in oils. It may accumulate as the plant's response to biotic as well as abiotic stress including drought, thermal stress, and leaf age (Kruk et al., 1995, 2005; Munne-Bosch, 2005). At high thermal oxidation or cooking, α -TO⁻ undergoes a self-coupling to produce dimers and trimers in corn oil, and mixed dimers with two different tocopherols and tocotrienols have also been reported (Nilsson et al., 1968b). However, these products were not subsequently observed and this was probably due to the different dimerization kinetics observed for each tocol analog (Gutfinger and Letan, 1972; Niki, 2019).

Vitamin E oxidation products in biological samples

Oxidation products of vitamin E have also been detected in the urine and plasma of animals and humans, in cell cultures, in human atherosclerotic lesions amongst many other biological samples, and some are reported here (Csallany and Draper, 1962; Hughes and Tove, 1980; Vatassery et al., 1993; Wurzel et al. 1995; Jain et al., 1996; Yanagawa et al., 1999; Terentis et al., 2002; Mangialasche 2013a; Torquato et al., 2016). It is worth noting that numerous biological systems are able reduce tocopherylQuinone to to tocopherylhydroQuinone (TQH2) and this reaction may occur normally in vivo (Kohar et al., 1995). Moreover, α -T is not the sole precursor of α -TQ, there is also a proof of concept that α -TQ can also be biosynthesized even in the absence of α-T, in normal human plasma, and in animal tissues. The concentration of α -TQ remains smaller compared to the parent compound due, in part, to the recycling of α -TO into α -T. In vivo studies have shown that α -TQ and its epoxide derivatives did not alter the antioxidant status in rat liver tissues. This clearly indicates the presence of an efficient reductase that catalyzes α -TQ into α -TQH2 via the epoxide forms. The reductase was identified as the NAD(P)H:quinone oxidoreductase 1 (NQO1) (Siegel et al., 1997; Leray et al., 1998; Mayhoub et al., 2012), or as thioredoxin reductase with varying potencies (Fang et al., 2005; Gregor et al. 2006). α-TQ behaves like a redox-cycling agent. It may act as an antioxidant after its conversion in biological systems to its reduced form α -TQH2. α -TQH2 acts as a potent radical-scavenging agent and is more active than ubiquinol (a reduced form of coenzyme Q), or its parent molecule α -T (Kruk et al., 1993; Kohar et al., 1995; Neuzil et al., 1997; Shi et al., 1999; Niki, 2007; Shrader et al. 2012).

 α -TQH2 can be re-oxidized into α -TQ, hence constituting a quinone/hydroquinone antioxidant redox system as illustrated in figure 6 (Niki et al., 1984; Mukai et 1993; Shi et al., 1999; Itoh et al., 2007).

In experimental models of isolated rat liver mitochondria as well as in perfused rat liver, the reaction of α -T with AAPH or with tertbutylhydroperoxide, generated α -TQ, α -TQH2 and epoxyquinones, with no evidence of the formation of 8a-(lipid-dioxy)-atocopherones) (Ham & Liebler, 1992, 1997). In lipid bilayers, 8a-hydroperoxytocopherones were detected as very minor products throughout peroxyl radical-mediated oxidations (Matsuo et al., 1989). It has also been reported that in rat, chick and earthworm tissues, a rare 2,5,6-trimethyl-3- (farnesylgeranyl-geranyl)1,4-benzoquinone was formed following α -T side-chain oxidation and elongation (Martius and Purer (1963)). In bovine muscle microsome systems, as well as in chilled and frozen fish muscle, the presence of α -TQ along with epoxytocopherones as the main α -T oxidation products respectively was reported (Faustman et al. 1999; Pazos and Medina, 2005). In isolated LDL, the main oxidation product of α -T was α -TQ alongside 5,6-epoxy- α -tocopherylquinone (α -TQE1) and its hydrolytic product 2,3-epoxy-α-tocopherylquinone (α-TQE2) (Terentis, et al., 2002). The presence of a phosphorylated form of α -T, although present in small quantities in various biological samples (plasma, tissues), suggested the existence of an α -tocopherol kinase/phosphatase, which remains to be identified (Zingg et al., 2010).

Furthermore, from a nitrative stress point of view, in mammals, large quantities of Nitric Oxide (NO[•]), are generated through the oxidative deamination of arginine by iNos synthase catalysis (Marietta et al., 1988; Nathann 1992; Chiueh et al., 1999). NO[•] is a mixed hydrosoluble/liposoluble gas highly diffusible in cell membranes from the vascular system. At high concentrations, NO[•] quickly interacts with the superoxide anion radical to produce the toxic peroxynitrite (ONOO[–]) anion, which is a powerful oxidant of biological tissues (Radi et al., 1991; Ischiropoulos et al., 1992). This entails the formation of two radicals: a hydroxyl radical and a nitro radical, at physiological pH. Unlike the full methylated α -tocopherol, the 5th position in the γ -T is unoccupied on the chromanol ring, and may undergo facile electrophilic or nucleophilic substitution reactions, which explains why 5-nitro- γ -tocopherol

(5-NO2- γ -T, XLII, fig. 5) is produced (Cooney et al., 1993; Hoglen et al.,1997; Christen et al.,1997; Hensley et al., 2005). 5-NO₂- γ -T was not detected in human LDL possibly due to the regeneration of γ -T by α -T (Beckman and Koppenol, 1996; Umeno 2017; Morita et al., 2019), although it has been observed *in vitro* by the treatment of lipoproteins with peroxynitrite and in lipopolysaccharide-stimulated rat astrocytes (Christen et al., 1997, 2002). *In vivo*, 5-NO₂- γ -T and its probable metabolites are possible biomarkers of the formation of reactive nitrogen species. Indeed a number of studies have reported increasing levels of 5-NO₂- γ -T in smokers and sick individuals with metabolic syndromes associated with elevated nitrative stress (Christen et al., 1997; Morton et al., 2002; Williamson et al., 2002; Leonard et al., 2005; Devaraj et al., 2008). In addition, 5-chloro- γ -tocopherol may also be formed due to the action of Hypochlorous acid (HOCl), both products are considered as specific biomarkers of nitrative stress respectively. *In vivo*, HOCl, which is generated by stimulated neutrophils during inflammation and infection, may also react with α -T as well as γ -T to produce α -TQ and γ -TQ respectively (Eiserich et al. 1996; Nguyen and Southwell-Keely, 2007).

Although some studies showed no evidence of the formation of dimers or trimers (Plack and Bieri (1963, 1964)), other researchers succeeded in their isolation from mammalian livers and spleens (Csallany et al, 1963a,b; Mellors and Barnes, 1966; Draper et al., 1966; Strauch et al., 1969). In mouse skin irradiated by UV, the topical application of α -T induced the formation of α -T dimers as major photoproducts (Kramer-Stickland et al., 1999).

In vivo Vitamin E Catabolites

If tocols are oxidized at the level of their chroman cycles in vitro (see vide supra), their phytyl side chains still remain stable against chemical attacks (Rosenau et al., 2007a, 2009). However, in vivo vitamin E isoforms are catabolized at different rates in the liver to produce α -, β -, γ -, and δ -carboxyethylhydroxychromanol (CEHC). The formation of various tocol metabolites through the side chain oxidation pathway, has also been detected in plasma and cell cultures (Sontag and Parker, 2002; Jiang et al., 2007, 2015). This biotransformation is catalyzed by phase I enzymes, much like tocopherol ω -hydroxylase activity, which is associated with microsomal cytochrome CYP4F2 and CYP3A4. These enzymes catalyze the ω -hydroxylation of the methyl terminal, and susbsequently, a microsomal dehydrogenase oxidation step led to 13'-hydroxychromanol (13'-OH) and 13'-carboxychromanol (13'-

COOH) production (Birringer, 2001). The oxidative chain-shortening reactions leading to these products consists in five cycles of β -oxidation. Two steps occur in peroxisomes and three occur in mitochondria. Each β -oxidation cycle cleaves a two carbon moiety from the main side chain to give 3'-COOHs as end products, and mid or shorter-chain carboxychromanols such 11'-, 9'-, 7'- and 5'-COOHs (Birringer et al., 2001, 2002; Sontag and Parker, 2002; Mustacich et al., 2010; Jiang et al., 2015; Bartolini et al., 2021). These metabolites have intact ring structures illustrating their non participation in the antioxidant activity of tocols (Schultz et al. 1995; Galli et al., 2002, 2004; Freiser et al. 2009). Long chains of α -T metabolites are depicted in figure 7.

The enzyme kinetics necessary to form carboxy chromanol derivatives depend on the presence of their other isoforms as well as their respective concentrations (Devaraj et al., 2008). α -T is metabolized by Cyp3A4 (Birringer et et al., 2001), while Cyp4F2 preferentially oxidizes γ -T and δ -T (Sontag and Parker, 2002; Leonard et al., 2005). CEHC (3'-COOH) predominates in human plasma and stems essentially from γ -T oxidation (up to 10 μ M) (Burbank, 2017). Long chain carboxychromanol 11'-COOHs from δ -T and γ -T forms were found in the plasma of rodents (Jiang et al., 2015), while δ - and γ -13'COOH were found in mice feces (Jiang et al., 2013). In parallel, these compounds can be found in bioconjugated forms in plasma, bile, feces or urine. Sulfated, glucuronidated forms were found in animal and human urine (Chiku et al., 1984; Swanson et al., 1999; Schultz et al., 1995; Zhao et al., 2010; Li et al., 2008) as well as in human plasma (Jiang et al., 2007; Freiser et al., 2009). Glucosidated forms were detected in feces (Zhao, 2010; Pein et al., 2018).

Studies in humans using deuterium-labeled α - and γ -T demonstrated faster plasma γ -T disappearance and greater γ -metabolite production (Leonard et al 2005). γ -T is indeed rapidly converted by the liver in a cytochrome P450-dependent manner to its water-soluble metabolite γ -carboxyethyl hydroxychroman (γ -CEHC) in a free or bioconjugated form. These forms have been proposed to be those expected to exert beneficial biopotencies *in vivo* as well as at the cellular level.

Large dose α -T dietary supplementation in humans and animals gives rise to the production of sulfated or glucuronide derivatives that can be found in urine. These are known as "Simon" metabolites. These are yellow oils, considerably more polar than α -T or any of its

known oxidation products and are slightly soluble both in water and in lipophilic solvents. These metabolites were identified as α -Tocopheronic acid, α -tocopheronolactone and γ -tocopheronolactone (Simon, 1955; Pan et al., 2008). These metabolites were first thought to be artefacts formed under high dietary supplementation and only side-products under physiological conditions (Krishnamurthy and Bieri, 1963; Schultz et al., 1995). Interestingly, their is a certain analogy in the degradation of tocol side chains with the bile acid catabolism of cholesterol which leads to the formation of cholic acid (Bloch et al. 1943). Recent studies reported that α -TQ undergoes a similar ω -oxidation to that of α -T, catalyzed by the same Cyp enzymes (Shrader et al. 2012; Taylor et al., 2018). The catabolism of α -TQ is correlated with the human urine content of conjugated α -tocopheronolactone (Pope et al., 2002; Sharma et al., 2013). α -tocopheronolactone is the final metabolite from the α TQ- ω -oxidation pathway. The proposed pathway depicting the fate of α -TQ is shown in the figure 8.

In humans and mice, α -carboxyethylhydroxychroman (α -CEHC) glycine and its glucoronide form as well as α -CEHC taurine have also been characterized as urinary metabolites and α -CEHC glutamine has been detected in the urine of mice (Johnson et al., 2012). 5-(6-Hydroxy-2,5,7,8-tetramethyl-chroman-2-yl)-2-methyl-pentanoic acid (α -CMBHC, XLI, fig. 5) was also characterized in human urine as a minor metabolite (Pope et al., 2001).

Biological and Medical Significance of Vitamin E oxidation Metabolites

Vitamin E is proposed to act through a non-specific antioxidant mechanism via its catabolites. Studies on the biological significance of tocol catabolites have been reviewed in several reports. This includes anti-inflammatory, anti-atherogenic and chemopreventive activities as well as cytotoxicity, apoptosis and activation of several signaling pathways at the cellular and molecular level. These effects were found to be more potent with vitamin E catabolites than their unmetabolized precursors (Jiang et al., 2014; Galli et al., 2017; Schubert et al. 2018; Jiang et al., 2019).

In biological systems, the best surrogate indicators associated with oxidative and nitrative stress are α -TQ and 5-NO₂- γ -T (tocoyellow) as well as their ratios α -TQ/ α -T and 5-NO₂- γ -T/ γ -T which are also used as biomarkers and were found to be associated with some

debilitating conditions such as ischemia/reperfusion (Murphy et al., 1992), Alzheimer's disease (Ravaglia et al., 2008; Mangialasch et al., 2012, 2013a,b; Casati et al. 2020), hypercholesterolemia (Ballard et al. 2016), coronary diseases (Morton et al., 2002) and para-physiological states (Mottier et al., 2002). Other data showed that bioprenylquinones may monitor changes in the physical properties of the lipid bilayer (Cain et al., 1972; Spisni et al. 1978; Fato et al., 1986). Bioprenylquinones are produced by mitochondria and peroxysomes, which could mediate their effects since they are known to control cell cycle regulation, apoptosis, inflammation as well as cytotoxicity or cytoprotection.

 α -TQ was found to be the major tocopherylquinone *in vivo* compared to γ -TQ (Kiyose, 2001). This may be explained, as proposed by Cornwell's team, by an evolutionary approach. Indeed poor cellular uptake of γ -T allowed the generation of only a small amount of its mutagenic metabolite γ -TQ (Cornwell et al. 2002).

The exact biological roles of these bioprenylquinones have not yet been fully explored, although in plants, a number of studies have shown evidence that α -TQ participates in the photosynthetic electron transport and metabolism (Itoh et al., 2001). α -TQ has been identified as a major oxidation product of α -T in atherosclerotic plaques (Terentis et al., 2002).

In addition, different plasma concentrations of VEOP are observed in Alzheimer's disease (AD) and were related to cognitively healthy subjects. Humans exhibited a broad inter-individual fluctuation in leukocyte telomere length (LTL) that is strongly correlated with age, sex, heredity, as well as with lifespan. The levels of α -TQ/ α -T and 5-NO2- γ -T/ γ -T ratio, were significantly associated with AD in patients with small Leucocyte Telomers (Casati et al., 2020). Moreover, *in vitro*, α -TQ targets multiple pathogenic factors involved in Alzheimer's disease (AD). α -TQ inhibits α -amyloid aggregation, disaggregating preformed fibrils and decreases reactive oxygen species, NO and inflammatory cytokines levels (Yang et al., 2010; Mangialasche et al., 2012, 2013a).

The cytotoxicity of Vitamin E metabolites has been broadly studied *in vitro*. Tocopherylquinone cytotoxicity can be explained either by their redox cycling properties or by their interactions with specific protein targets. Indeed, due to its electrophilic character, γ -TQ can undergo "Michael" addition with amines and thiol residues present in proteins and nucleic acids. This leads to the formation of quinone-Nucleophile residues, which are

considered to be involved in γ -TQ cytotoxicity. These properties are not shared with the fully methylated non-arylating quinone α -TQ (Cornwell et al., 2003; Niki, 2007). Both γ -TQ and δ -TQ are highly cytotoxic arylating electrophiles. Both compounds were reported to be highly cytotoxic in leukemic cells independently of their P glycoprotein status and were more potent than anthracyclines (Thornton et al., 1995; Cornwell et al., 1998; Jones et al., 2002; Cornwell et al., 2002, 2003; Sachdeva et al. 2005). α -TQ is cytotoxic against human breast adenocarcinoma cells ZR-75-1 (Thornton et al., 1995; Cornwell et al., 1998; Jones et al., 2002). In another report, Wang et al. (2006) studied TQ cytotoxicity in neuroblastoma cell lines. They reported that unlike α -TQ or its precursor α -T, γ -TQ (10 mM) induced endoplasmic reticulum (ER) stress by activating the pancreatic ER kinase (PERK) signaling pathway. This pathway involves elF2 α , ATF4, and C/EBP homologous protein (CHOP). CHOP mediated the apoptosis signaling network which is involved in several human diseases such as diabetes, cancer and neurodegenerative disorders.

Androgen Receptors (AR) are members of the nuclear steroid receptor superfamily, which act as ligand-activated transcription factors. AR control the expression of genes involved in the growth, survival, and differentiation of prostate cells (Zhu and Kyprianou, 2008). α -TQ was reported to induce anti-androgenic effects on prostate cancer cells. α -TQ induces a down-regulation of the AR at the protein and at the mRNA level in LAPC4 and LNCaP cells. This effect was associated with a decrease of androgen-induced PSA release in LNCaP cells. In contrast, α -TQ was inefficient on the androgen-independent cell lines Du145 and PC3 (Thompson and MacKenzie 2008). Furthermore, Fajardo et al. (2016) reported a reduced prostate cancer incidence amongst male smokers, primarily associated with Vitamin E supplementation. This bioactivity of Vit E might also be related to the formation of α -TQ during chronic oxidative stress. Indeed, α -TQ but not α -T decreased the overexpression by 5-fold of human prostate gland genes such as TM4SF1, KLK2, and PSA.

 γ -TQ (20–50 mM) was reported to induce apoptosis in other cell lines such as human leukemia HL-60, colon adenocarcinoma WiDr cells and murine thymoma cells in a dose- and time-dependent manner (Calviello et al. 2003). Such a pro-apoptotic effect was associated with a modification of the mitochondrial transmembrane potential, the release of mitochondrial cytochrome c and the activation of caspase-9. In contrast α -T and α -TQ are weakly cytotoxic on Human colon cancer HCT-116 and HT-29 cells, whilst these cells are sensitive to γ -TQ and δ -TQ (Dolfi et al. 2013).

More recently TQ and its reduced forms were reported to control ferroptosis in cancer cells. Ferroptosis is an iron-dependant programmed cell death acting via the redox control of 15-lipoxygenase (15-LO) (Hinman et al., 2018), but the fine mechanism involved in this effect deserves further investigations. This effect may be controlled by multiple pathways that integrate both intra- and extracellular signals. Ferroptosis seems to play a role in critical adaptations to the redox metabolism in a wide array of diseases (Do Van et al., 2016; Stockwell et al., 2017; Wenzel et al., 2017 and Li et al., 2021). α -TQ is a more dynamic inhibitor of ferroptosis than its precursor α -T. α -TQ inhibits 15-LO through the reduction of its active non-heme Fe³⁺ center into the inactive Fe²⁺ state; hence inhibiting ferroptosis signals by blocking the formation of lipid peroxidation products (Hinman et al., 2018).

A janus facet have also been ascribed to γ -TQ. Indeed, γ -TQ was cytoprotective in PC12 cells and immature primary cortical cells, whilst pre-treatment of these cells at sublethal concentrations resulted in an increase in the levels of γ -TQH2 and glutathione. This effect was due to an increase of cysteine availability in an ATF4-dependent manner (Ogawa et al., 2008).

Altogether these effects highlight that the efficacy of TQ metabolites to kill cells depends on the TQ types, the concentrations used during treatments as well as the cellular context.

Apart from TQ metabolites, some studies have focused on the cytotoxicity of long chain metabolites of vitamin E. α -13'-COOH and δ -13'-COOH or δ -13'-OH at 20 μ M were found to be more cytotoxic than their tocopherol precursors or their short and mid–chain carboxychromanol oxidation products when tested on liver hepatoma Hep-G2 cells. These compounds induced both caspase-3 and caspase-9 activation, PARP-1 cleavage, a reduction of the mitochondrial membrane potential, and an increase in the intracellular and intramitochondrial reactive oxygen species levels (Birringer et al., 2010). δ -Tocotrienol-13'-COOH (Garcinoic acid), first isolated from an African bitter nut *Garcinia kola* (Mazzini et al., 2009), significantly suppressed the growth of human colon cancers (HCT-116, HT-29, Caco-2 and normal epithelial cells (CCD841CoN), and appeared to induce apoptosis and autophagy in human cancer cells. These effects were associated with a modulation of the sphingolipid metabolism. δ -Tocotrienol-13'-COOH induced an increase in intracellular dihydrosphingosin, dihydroceramide and ceramide levels and a decrease in sphingomyelins. This modulation of the lipid metabolism is associated with a rapid induction of apoptosis (Jang et al., 2016).

Moreover, Drotleff et al. (2015) reported that an oxidized γ -tocotrienol was cytotoxic in the human estrogen receptor positive breast cancer cell line MCF-7. In the human colon adenocarcinoma cell line LS180, α -CEHC, γ -CEHC and α -13'-COOH were found to stimulate the expression of P glycoprotein (Podszun et al. 2017). The cytotoxicity expressed as the percentage of growth inhibition of different cell lines leading to the IC50 values of vitamin E *in vivo* metabolites in previously studied cancer cell lines are summarized in table 2.

It is well established that the production of pro-inflammatory compounds are catalyzed by cyclooxygenases (COXs)- or 5-lipoxygenases, and several cytokines/chemokines and are associated with chronic inflammation in tumorigenesis (Wang et al. 2010; Ben-Neriah et al. 2011; Grivennikov et al., 2010). 5-lipoxygenase (5-LOX)-catalyzed leukotriene and cyclooxygenase (COX-1/COX-2)-catalyzed eicosanoids are key regulators of inflammation and both play a key role in inflammation-associated diseases. Theses enzymes are potent targets for vitamin E metabolites. Metabolites of vitamin E in their free or sulfated forms were detected in the plasma and urine of both animals and humans. Long chain metabolites (LCMs) are excreted via the bile into the intestine and are mainly found in the feces (Bardowell et al., 2012a, b; Jiang et al., 2013; Jiang et al. 2014). Importantly, LCMs are found in human plasma at nanomolar concentrations albeit with some substantial fluctuations (Wallert et al., 2014; Galli et al., 2017; Pein et al., 2018). Short chain metabolites (SCMs) are mainly found in glucoronidated forms in human urine (Swanson et al., 1999). Such compounds (LCMs) mediate immune functions and have been examined for their anti-inflammatory potentials. This field of research is a very dynamic one and deserves further investigations. Docking experiments suggested that 13'-carboxychromanol metabolites from all tocols bind to COX-2 and HMG-CoA reductase yielding specific biological activities (Sarkisyan et al., 2018). In COX-preinduced cells with 5 µM arachidonic acid as a substrate, long-chain carboxychromanols, but not their vitamin E sulfated analogs, reduced COX-2 activity. 9'- and 13'-carboxychromanol, both inhibited purified COX-2 with an IC50 of 6 or 4 µM, respectively. 13'-carboxychromanol was reported to be a competitive inhibitor of arachidonate on both COX-1 and COX-2. These compounds were found to be more potent than analogs with shorter side-chains and their tocopherol precursors (Jiang et al., 2008).

In human blood neutrophils or differentiated HL-60 cells, the long-chain metabolites of vitamin E derived from δ -tocopherol and δ -tocotrienol were both shown to be potent dual inhibitors of cyclooxygenase COX-2 and 5-Lipooxygenase. In these studies, δ -Tocotrienol-

13'-COOH (Garcinoic acid) appeared to be slightly stronger than δ -Tocopherol-13'-COOH in inhibiting 5-LOX with an IC50 of 2 and 0.5-1 µM respectively, but less potent in inhibiting COX-2 with an IC50 of 9.8 µM and 4 µM respectively (Jiang et al., 2011, 2014, 2019). Furthermore, δ -Tocopherol-13'-COOH decreased the cellular production of ionophorestimulated LTB4 in HL-60 cells (a leukotriene involved in inflammation) regardless of the different stimuli with an IC50 of 4-7 µM (Jiang et al., 2011). In another study, δ T-13'-COOH was found to display an anti-inflammatory activity close to that of ibuprofen. δ T-13'-COOH was found to be more potent than all other tested tocol analog metabolites (Grammas et al., 2004; Jiang et al., 2008, 2014).

More data have reported direct interactions of such vitamin E metabolites with 5lipoxygenase (5-LO) (Pein et al., 2018). The mechanism of α -T-13'-COOH anti-inflammatory potential was also revealed by Pein et al., (2018). They showed both by library screening (liver-on-chip) and *in vitro* and *in vivo* testing, that this compound was a potent allosteric inhibitor of 5-lipoxygenase in human leukocytes. α -T-13'-COOH efficiently suppressed inflammation within immune cells in mouse models of peritonitis and asthma.

5-LOX is involved in the biosynthesis of lipoxins, and resolvins (Serhan et al., 2014). Unlike zileuton, a synthetic leucotriene inhibitor (a 5-LOX inhibitor clinically used against asthma), α -T-13'-COOH was found to strongly increase systemic resolvin E3 levels in mice with less toxicity (Pein et al., 2018).

Apart from these bioactivities, LCMs appear to regulate lipid homeostasis and Longchain metabolites of α -tocopherol occur in human serum and inhibit macrophage foam cell formation *in vitro* which might strongly alter atherogenic processes (Wallert et al., 2014).

In a more recent report, α -13'-COOH revealed possible antiatherogenic effects via the modulation of the lipoprotein lipase system which reduced VLDL-induced foam cell formation in THP-1 macrophages (Kluge et al., 2021). These metabolites, including Garcinoic acid (δ -T3-13'-COOH), were also inhibitors of lipopolysaccharide-stimulated inducible nitric oxide synthase (iNos) expression and Cox 2 in murine RAW264.7 macrophages (Wallert et al., 2015; Ciffolilli et al., 2015; Schmölz et al., 2017; Wallert et al., 2019).

 α -13'-COOH and δ -13'-COOH analogs activated all three PPARs in a dose-dependent manner, exhibiting remarkable activity (Willems, 2021). δ -T3-13'-COOH (Garcinoic acid)

along with other LCMs were found to be peroxisome proliferator-activated receptor PPAR γ and pregnan X receptor (PXR) antagonists (Willems et al., 2021). δ -T3-13'-COOH is also a modulator of nuclear receptors involved in the β -amyloid metabolism and progression of Alzheimer's disease (Marinelli et al., 2020).

In vitro and animal (but not yet human) studies, identified γ -CEHC as a mild endogenous natriuretic factor distinct from α -CEHC. This observation may be of physiological importance in the regulation of the water-sodium balance by inhibiting the potassium channel and increasing the secretion of urinary sodium. In contrast, γ -T and α -T did not exhibit such properties (Wechter et al. 1996; Murray et al., 1997; Saito et al., 2003). In animal studies, γ -CEHC was shown to protect against metal-induced nephrotoxicity through various mechanisms such as an antioxidant-based mechanism (Appenroth et al., 2001), the down-regulation of COX-2 and the inhibition of the anti-apoptosis protein NF- κ B (Hensley et al., 2004; Jiang et al., 2008). γ -CEHC inhibited the expression of cyclin D1 which induced a cell cycle arrest in the G1 phase in prostate cancer cells (Galli et al., 2004). Moreover, γ -CEHC may also control the neutrophil oxidative burst through the negative modulation of PKC-related signaling (Varga et al., 2008). Li et al. (2016) showed that γ -CEHC also exerts vasoprotective effects which may preserve eNOS signaling in human aortic endothelial cells (HAECs) subjected to hyperglycemia-like conditions by decreasing the expression of VCAM, E-Selectin, and IL-8.

Along with these observations, Simon metabolites with open chroman rings were considered as biomarkers of the antioxidant potential of vitamin E (Simon et al. 1956). Although, they were first considered as artefacts formed by simple oxidation (Schultz et al., 1995), other reports illustrated by Pope et al. (2002) provided evidence that Simon metabolites may be native metabolites. More recent studies underlined the importance of the content of α -tocopheronolactone conjugates in the urine of children with type 1 diabetes compared to healthy children, the contents were fifteen times greater in diabetic individuals (Sharma et al. 2013).

Conclusion and future directions

Overall, this complex study created a scientific perspective on tocochromanol oxidation products which may be much more diverse. There remains a growing interest to fully clarify the physiological functions of vitamin E as well as its janus faced effects. We

have attempted to cover the research available to date. Evidence suggests that VEOP are good candidates to exert different biological properties according to their chemical structures and are more active than their metabolized precursors, which suggests that the physiological functions of vitamin E are still not yet fully understood.

The effect of TQ against cancer cell proliferation and the anti-inflammatory effects of tocol LCMs may be generated through several molecular mechanisms that deserve to be further investigated. Furthermore, the concentrations used for *in vitro* studies are far more elevated than those found in animal plasma and biological tissues. In addition, very little is known about the absorption, distribution and transport of VEOP and their putative receptors and other targets. The future challenge could also focus on studies of their specific bioavailabilities in rodents and humans and the eventual increase of their cellular uptake to try and improve their pharmacological properties. Furthermore, the toxicities of TQ must be taken into account as some compounds are electrophilic and alkylating. On the other hand, *in vivo*, if Tocopherones are formed, they might be reduced into tocopherols and thus neutralized through enzymatic systems that are not yet identified. Although the catabolism of tocopherylquinones has been analyzed *in vivo* and a cross-talk has been established with the long chains of α -tocopherol and Simon products, the human catabolites of 5-NO₂- γ -T do warrant further investigations.

More research is therefore needed to study the other tocopherol congeners, their respective metabolites formed in humans and the determination of their potentially beneficial role in health. Indeed, tocotrienol congeners are quite different from tocopherols. They differ in their chemical structures, their stereochemistry, their metabolisms and their biological activities. Tocotrienols have indeed the same reactivity *in vitro* towards free radicals as tocopherols, but may disseminate faster than tocopherols in biomembranes and cultured cells due to their unsaturated nature, their plasma levels in humans however have been much less studied compared to tocopherols (Hayes et al., 1993).

The "**vitaminEome**" (figure 9) includes a large diversity of products of transformation of vitamin E components, including oxidative self-condensation products, Simon metabolites, side-chain and chromanol oxidation products as well as conjugation products with lipids, phosphate and sulfate. The limitation of this study is that the "**vitaminEome**" was mainly characterized through *in vitro* using and requires validation studies in human.

A precise knowledge of the "**vitaminEome**" is thus important. The identification of actors controlling this metabolism will give pharmacogenomic data that will predict the impact of these dietary components on human health. Therefore, exploring and determining the "vitaminEome" in humans will be crucial not only in future randomized trials but also if we consider that vitamin E is widely used in dietary supplements.

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Figure captions

Figure 1: structural features of Tocols (Tocopherols and Tocotrienols). The natural α -T has a 2R, 4'R and 8'R configuration. Therefore, its systematic name is (2R, 4'R, 8'R)- α -tocopherol, formerly known as d- α -tocopherol, the abbreviation RRR- α -T is also used. It can be obtained by condensation of trimethylhydroquinone with phytol (DellaPenna and Pogson, 2006). A total racemic tocopherol mixture is then obtained, with 8 different stereoisomers, due to 3 chiral centers at C-2, C-4 ' and C-8. Each of the four tocopherols may be represented by the configurations RRR, RSR, RRS, RSS, SRR, SSR, SRS and SSS. Therefore 32 stereoisomers may be produced. The commercial forms of vitamin E are RRR- α -tocopherol which is the natural stereoisomer or a synthetic form, called all-racemic- α -tocopherol or all-rac- α -tocopherol, which is a mixture in approximately equal amounts of the 8 stereoisomers in the case of α -tocopherol (Lodge, 2005).

Figure 2: Possible initiation of bis allylic carbons and mechanism of formation of 9-Hydroperoxide and 13-Hydroperoxide in the autoxidation of linoleic acid

Figure 3: Mechanisms of α -tocopherol oxidation by: 1) hydrogen Atom transfer (HAT), 2) transfer of an electron and a proton single electron transfer (SET) or 3) sequential mechanism of loss of a proton and Electron transfer (SPLET).

Figure 4: α-tocopheroxyl radical and its resonance-stabilized forms

Figure 5: Investigated structures referred to in the text.

Figure 5bis: Investigated structures referred to in the text (continued).

Figure 6: Illustration using α -tocopherylquinone as an example of one and two electron reductions generating semiquinone and tocopherylhydroquinone. NQO1 : NADPH Quinone Oxidoreductase

Figure 7: *In vivo* α -tocopherol catabolite structures

Figure 8: Proposed pathway of the fate of α -TQ and Long chain Metabolites and their parent compound α -T as precursors of Simon metabolites (inspired and modified from Sharma et al., 2013).

Figure 9: Scheme showing the "VitaminEome"















13-(8a-peroxy-a-tocopherone)-9(Z),11(E)-octadecadienoate (XXI)

C₁₆H₃₃

1-linoleoyl-2-[13-(8a-dioxy-(a-tocopherone)-9(Z), 11(E)octadecadienoy]-3-sn-phosphatidylcholine (XXII)

ì

Figure 5 continued





methyl 9-(8a-dioxy-(α-tocopherone)-12,13epoxy-10(E)-octadecenoates (XXIII)









8a-(lipidi-dioxy)-5-(γ-tocopheroxy) -γ-tocopherone (XXVII)

 $cholesteryl\,(8a-dioxy-\alpha-to copherone)-octade cadieno ate isomers$ (XXV)







tocored (XXX)

В







7-formyl-β-tocotrienol (XXXV)



 α -tocotrienol quinone (XXXIX)



tocoyellow (XLII)



C

7-hydroxy-8,8a-epoxy-α-tocopherone (XXXIII)

0

OH

но

`C₁₆H₂₇

HO

С₁₆Н₃₃

O

5-bromomethyl-y-tocopherol (XXXIV)

`С₁₆Н₃₃





(XXXVIII)



α-CMBHC (XL)

γ-TQ (XXXII)

но、

C₁₆H₃₃

0





C₁₆H₂₇



C₁₆H₂₇

 α -tocotrienol spirotrimer (XL)



HO

C₁₆H₂₇ a-tocotrienol spirodimer





NAD(P)H quinone oxidoreductase









	R1	R2	R3	DESIGNATIONS	
tocopherols	Н	Н	Н	2-methyl-2- (4',8',12'-trimethyltridecyl) chroman-6-ol	
α-tocopherol	CH ₃	CH ₃	CH ₃	5,7,8-trimethyltocol.5,8-dimethyl-tocol7,8-dimethyltocol8-methyl-tocol.	
β-tocopherol	CH ₃	Н	CH ₃		
γ-tocopherol	Н	CH ₃	CH ₃		
δ-tocopherol	Н	Н	CH ₃		
tocotrienols	Η	Η	Η	2-methyl-2-(4',8',12'-trimethyltrideca-3',7',11' trienyl)chroman -6 -ol,	
α-tocotrienol	CH ₃	CH ₃	CH ₃	5,7,8-trimethyltocotrienol,	
β-tocotrienol	CH ₃	Н	CH ₃	5,8-dimethyltocotrienol,	
γ-tocotrienol	Н	CH ₃	CH ₃	7,8-dimethyltocotrienol,	
δ-tocotrienol	Н	Н	CH_3	8-methyltocotrienol,	

 Table 1: Designation of different Vitamin E structures

Vitamin E oxidation products	Vitamin E sources	Cancer cell lines	IC50 (μM)	
Chromanol ring oxidation		I	1	
Oxidized γ- tocotrienol	Thermal oxidation in hexane of each synthetic vitamer congeners along with a palm tocotrienol-rich fraction (TRF), characterization and purification by HPLC/UV/ESI/MS	Breast cancer MCF7	85	Results in tocotrien of individ most cyto cancer ce
γ-ΤQ	Purification from γ -tocopherol-rich mixture of tocopherols by flash chromatography and elution with a gradient of 0–5% ethyl acetate in hexane, γ -TQ is obtained by synthesis	Colon cancer HCT116	0.8	Apoptosis and PARF fragment
δ-ΤQ	Purification from δ -tocopherol-rich mixture of tocopherols by flash chromatography and elution with a gradient of 0–5% ethyl acetate in hexane, δ -TQ is obtained by synthesis	Colon cancer HCT116	2	Apoptosis and PARF fragment
γ-ΤQ	Synthetic γ-TQ	(MDR) leukemic cell HL-60, WiDr cells and murine ascites thymoma	-	Induction activatior
$\delta\text{-}TQ$ and $\gamma\text{-}TQ$	Synthetic of tocopheryl quinones	Acute lymphoblastic leukemia cell lines that are drug-sensitive (CEM) and multidrug-resistant (CEM/VLB100 CEM and multidrug- resistant cell line, CEM/VLB100	< 10	δ-TQ is m both wer other cor
γ-ΤQ	Synthetic γ-TQ	HL60 and MDR HL60/MX2 human promyelocytic leukemia, U937 human monocytic leukemia, and ZR-75-1 breast adenocarcinoma cells	-	Apoptosis Multidrug both P-gly proteins
γ-ΤQ	Synthetic γ-TQ	N2a (Neuroblastoma cells)	< 5	The role o

Table 2. Overview of cytotoxics activities of the vitamin E LCMs and tocopherylquinones

				via Endop
Side phytyl chain oxidation		L	1	
δ-13'-СООН	Synthetic δ-13'-COOH	HCT-116 HT-29	8.9 8.6	δ-13'-COC anticance by modul
				in preclin
Garcinoic acid	Natural Garcinoic acid purified from african	HCT-116	16	Garcinoic anticance by modula in preclini
	garcinia kola seeds	HT-29	17	
α-13'-COOH	Natural Garcinoic acid purified from	HepG2	13.5	long-chai
δ-13'-СООН	methanolic extract of african garcinia Kola seeds along with synthetic long chain		6.5	responsib propertie
α-13'-OH	metabolites		> 100	
δ-13'-ΟΗ			>50	
γ-CEHC <i>,</i>	Natural Garcinoic acid purified from	Glioma C6	-	Natural G
α-CEHC	seeds along with synthetic, γ -CEHC, α -			13'-Carbo
Garcinoic acid	CEHC, δ -13'-COOH and α -13'-COOH among			analogue
α-13'-COOH α-13'-COOH				
γ-CEHC <i>,</i>	Metabolites were a gift of Eisai, company,	PC3, HTB-82, HECV	-	Cytotoxic
α-CEHC	Japan with no indication of their origin			expressio
α-13'-ΟΗ	Blood of healthy men extracted with hexane/DCM, 5/2 v/v, and characterized by QTOF/LCMS	THP-1 macrophages	7.4	Modulatio via differe concentra
α-13'-COOH	Synthetic vitamin E and its analogues	Colorectal LS 180 adenocarcinoma cells	-	Activation l'expressi

- : not determined