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Chapter

Vitamin E in Human Health and Oxidative Stress Related Diseases

Israel Ehizuelen Ebhohimen, Taiwo Stephen Okanlawon, Augustine Ododo Osagie and Owen Norma Izevbigie

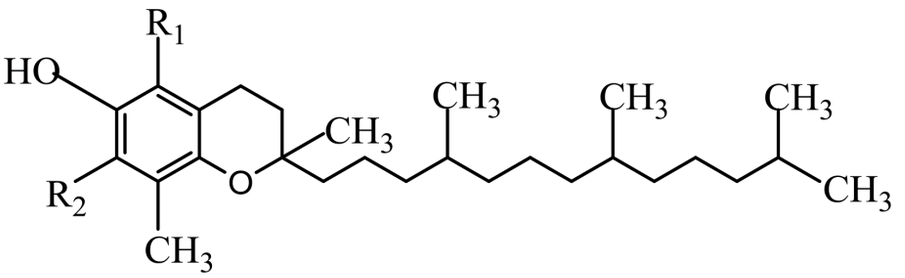
Abstract

Oxidative stress characterized by an imbalance in the production and degradation of radical species has been implicated in the onset and progression of several diseases. The efficacy of antioxidants acting via the inhibition of radical chain reactions, scavenging of free radicals, direct donation of electrons to radical species and chelation of metal ions have been reported to attenuate the oxidative process. Vitamin E is an effective antioxidant and its hydrophobic nature and membrane permeability offer some benefits to application and bioavailability. This chapter highlights the following; structural differences in the vitamin family, biosynthesis in plants and the native biological role, antioxidant mechanisms of vitamin E, an overview of the prophylactic action of vitamin E as well as the effect on the oxidative process in some diseases.

Keywords: vitamin E, antioxidant, bioactivity, tocopherol, tocotrienol

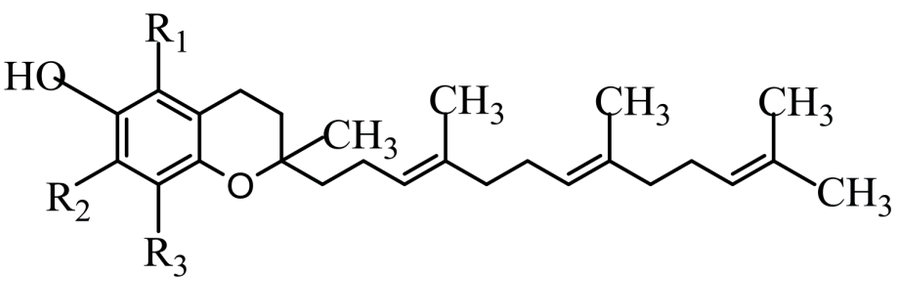
1. Introduction

The tocochromanols generally called the vitamin E family are amphipathic organic molecules with antioxidant capacity. They are categorized as tocopherols, tocotrienols and plastochromanol-8 (PC-8) [1]. All groups have a similar chemical structure comprising a polar chromanol head linked with a hydrophobic prenyl tail. The positive effect of tocopherols and tocotrienols on reproduction in animals called research attention to this family of organic compounds. Vitamin E was first described by Evans and Bishop in 1922 [2] as substance 'X' [3, 4]. The class of compounds was later called 'tocopherol' coined from the Greek words 'to'kos' meaning 'child birth', and 'phe'rein' meaning 'to bring forth'. The suffix '-ol' was included due to the presence of an alcohol functional group. The tocopherols have a saturated prenyl tail while the tocotrienols have unsaturated tails with carbon–carbon double bonds at 3′,7′ and 11′ positions. Each group comprises four molecular forms (α, β, γ and δ) that are differentiated by the methyl group substitutions in the chromanol head group (**Figures 1** and **2**) which strongly influence their antioxidant activity in various systems [3–5]. Plastochromanol-8 (PC-8), is also a natural component of plant tissues and was first discovered in the leaves of the rubber tree (*Hevea brasiliensis*), where its concentration exceeded that of α-tocopherol and plastoquinone [6]. Structural studies revealed that the compounds were identical to those of synthetic PC-8, a γ-tocotrienol homolog but had longer side chains [1].



$R_1 = R_2 = CH_3$ α-Tocopherol
$R_1 = CH_3, R_2 = H$ β-Tocopherol
$R_1 = H, R_2 = CH_3$ γ-Tocopherol
$R_1 = R_2 = H$ δ-Tocopherol

Figure 1.
Tocopherol.



$R_1 = R_2 = R_3 = H$ Tocotrienol
$R_1 = R_2 = R_3 = CH_3$ α-Tocotrienol
$R_1 = R_3 = CH_3, R_2 = H$ β-Tocopherol
$R_1 = H, R_2 = R_3 = CH_3$ γ-Tocopherol
$R_1 = R_2 = H, R_3 = CH_3$ δ-Tocotrienol

Figure 2.
Tocotrienol.

The human body tends to accumulate α-tocopherol due to the activity of the liver α-tocopherol transfer protein (α-TTP), which enriches plasma with a-tocopherol [7]. Besides α-TTP, which resides only in the liver, a system of tocopherol-binding proteins (TBPs) cause the localization of tocopherols in various human tissues where they are required [8].

The main dietary sources of vitamin E compounds include vegetable oils, nuts and seeds. The vitamin E family has been studied extensively due to their diverse biological functions and α-tocopherol is reported to have the highest biological activity [3]. Although α-tocopherol is universally distributed in the plant kingdom and is the predominant vitamin E form in photosynthetic tissues, γ-tocopherol and tocotrienols predominate in the seeds of several dicots and monocots [5].

1.1 Biological functions of vitamin E

The most notable biological function of this lipid-soluble is their antioxidant capacity. All vitamin E compounds meet the definition of an antioxidant moiety with the capacity to inhibit oxidative reactions *in vitro* [3]. Vitamin E is widely accepted as one of the most potent antioxidant in nature and the antioxidant property is based on the capacity to rapidly transfer its phenolic hydrogen atom to

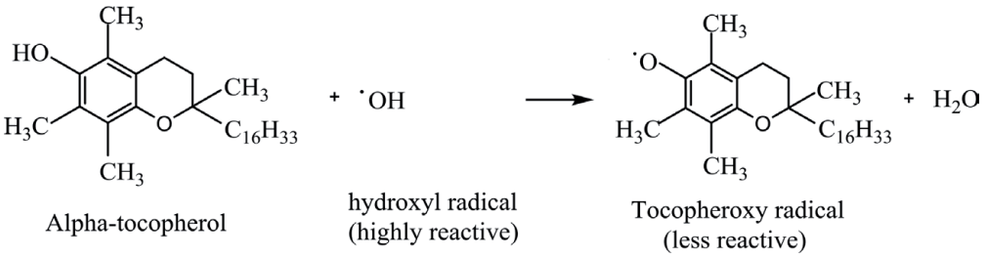


Figure 3.
Reaction of alpha-tocopherol with hydroxyl radical.

neutralize free radicals (**Figure 3**). The regeneration mechanism, mostly by vitamin C is essential for maintaining viability [9, 10].

The antioxidant capacity of α, β and γ isoforms of both tocopherol and tocotrienol are similar and the δ isoforms have weaker activity [11, 12]. As the main chain-breaking antioxidant in body tissues, the vitamin E isoforms inhibit lipid peroxidation especially in polyunsaturated fatty acid component of cell membranes. The in vivo antioxidant capacity of vitamin E is not completely clear. The suggested in vivo activity is based on the reported in vitro activity [3]. Based on the capacity to inhibit oxidation, vitamin E may help ameliorate or suppress the progression of oxidative stress related diseases [13].

Other reported biological functions of vitamin E include; regulation of inflammatory response, gene expression, cell proliferation, as well as modulation of cellular signaling and activity of membrane bound enzymes.

1.2 Biosynthesis of vitamin E

Tocochromanols are only synthesized by photosynthetic organisms. In plants, tocochromanol biosynthesis utilizes cytosolic aromatic amino acid pathway for head group synthesis while the tail is synthesized by the plastidic deoxyxylulose-5-phosphate pathway.

The formation of homogentisic acid (HGA) from p-hydroxyphenylpyruvic acid (HPP) by p-hydroxyphenylpyruvic acid dioxygenase (HPPD) is the rate-limiting step in the synthesis of the head group (**Figure 4**).

The biosynthesis of tocopherols and the tocotrienols follow the same pathway, each class requiring specific substrates and enzymes. HGA is prenylated with either phytyl-diphosphate (PDP) or geranylgeranyl diphosphate (GGDP) to yield the committed intermediates 2-methyl-6-phytylplastoquinol (MPBQ) and 2-methyl-6-geranylgeranylplastoquinol (MGGBQ) in tocopherol and tocotrienol synthesis respectively.

MPBQ methyltransferase (MPBQ MT) transfers a second methyl group to MPBQ to form 2,3-dimethyl-5-phytyl-1,4-benzoquinone (DMPBQ) and to MGGBQ to form 2,3-dimethyl-5-geranylgeranyl-1,4-benzoquinone (DMGGBQ) respctively. Tocopherol cyclase converts MPBQ and DMPBQ to δ- and γ-tocopherols, respectively, and the corresponding geranylgeranylated intermediates to δ- and γ-tocotrienols. Finally, γ-tocopherol methyltransferase (γ-TMT) adds a methyl group to C-6 of the chromanol ring, converting δ- and γ-tocopherols and tocotrienols to β- and α-tocopherols and tocotrienols, respectively [14].

Among the vitamin E family present in foods, α-tocopherol is the most important to human health [15]. Although all tocopherols are absorbed equally during digestion, only α-tocopherol is preferentially retained and distributed throughout the body [16]. The concentration of γ-tocopherol is far higher than that of α-tocopherol in oil seeds though the former is the biosynthetic precursor of the

latter. This suggests that the γ-tocopherol methyltansferase reaction is limited. One approach to increase α-tocopherol yield in these seeds is to increase the expression of γ-tocopherol methyltansferase gene [17].

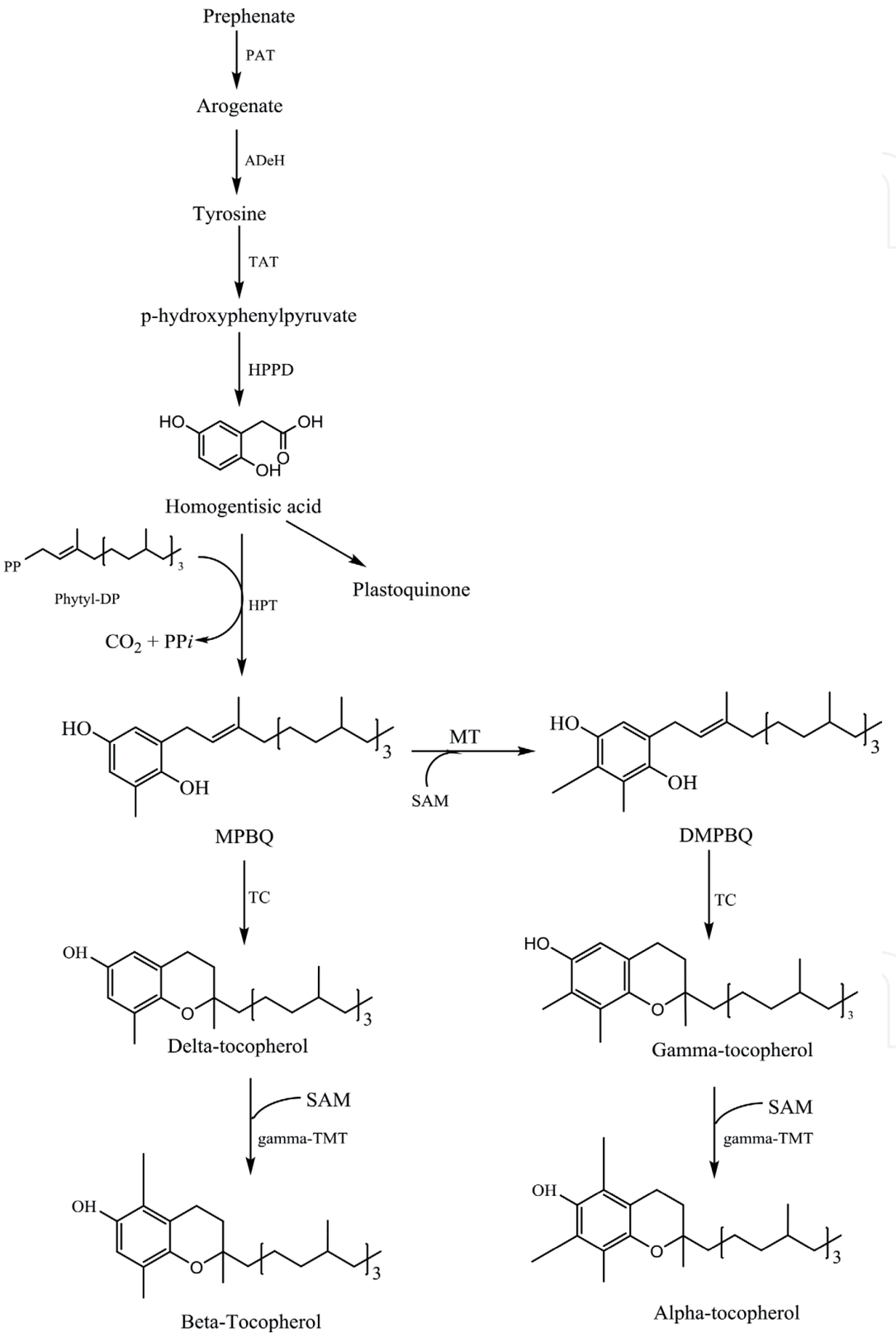


Figure 4.
Tocopherol biosynthesis [14]. Abbreviations: PAT, prephenate amino transferase; AdeH, arogenate dehydrogenase; TAT, tyrosine amino transferase; HPPD, p-hydroxyphenylpyruvate dioxygenase; HPT, homogentisate phytyltransferase; phytyl-DP, phytyl-diphosphate; MPBQ, 2-methyl-6-phytyl-1,4-benzoquinone; DMPBQ, 2,3-dimethyl-5-phytyl-1,4-benzoquinone; MT, methyltransferase; SAM, S-adenosyl methionine; TC, tocopherol cyclase; MPBQ MT, MPBQ methyltransferase; gamma-TMT, gamma-tocopherol methyltransferase.

2. Oxidative stress

The reactive oxygen species (ROS) represents the most important class of radical species generated in living systems formed from the partial reduction of molecular oxygen. Notable members of this family of radicals include superoxide anion (O_2^-), hydroxyl radical (OH•), hydrogen peroxide (H_2O_2), and singlet oxygen ($^1O_2$) which are generated by the respiratory chain in mitochondria, enzymatic reactions, exposure to UV light, ionizing radiation and heavy metal ions. The mitochondrial electron transport chain generates superoxide radicals through the single-electron leak at respiratory complexes I and III of the oxidative phosphorylation pathway. The flavin-dependent enzymes in the mitochondrial matrix also produce a considerable amount of reactive oxygen species.

The superoxide radical is readily dismutated to hydrogen peroxide. The reactivity of hydrogen peroxide as a molecule is low but it can penetrate cell membranes and generate hydroxyl radical via the Fenton's reaction [18].

The first step involves the reduction of ferric to ferrous ion:

$$Fe^{3+} + O_{2^{\bullet -}} \rightarrow Fe^{2+} + O_2 \tag{1}$$

The second step is the Fenton reaction:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO^- + HO^{\bullet} \tag{2}$$

Haber and Weiss reaction:

$$HO^{\bullet} + H_2O_2 \rightarrow H_2O + O_2^{\bullet -} + H^+ \tag{3}$$

$$O_2^{\bullet -} + H_2O_2 \rightarrow O_2 + HO^- + HO^{\bullet} \tag{4}$$

The chain termination reaction:

$$Fe^{2+} + HO^{\bullet} + H^+ \rightarrow Fe^{3+} + H_2O \tag{5}$$

The hydroxyl radical is regarded as the most reactive oxygen radical and can cause oxidative damage to cells by attacking biomolecules located a few nanometers from the site of generation [19].

Low levels of ROS production are required for important physiological functions, including proliferation, host defense, signal transduction, and gene expression [20]. There is a cellular balance between ROS generation and clearance in eukaryotic cells. This is achieved by the activity of several antioxidative defense mechanisms that comprise enzymes and antioxidants. The five main types of primary intracellular antioxidant enzymes are Cu/Zn-superoxide dismutase (Cu/Zn-SOD, SOD1) in the cytosol, manganese superoxide dismutase (Mn-SOD, SOD2) in the mitochondrial matrix, catalase, glutathione peroxidase (GPx), and glutathione reductase (GR). Small molecular weight and non-enzymatic antioxidants are also involved in the protection of the intracellular

components against the reactive oxygen species. However, when cellular production of ROS overwhelms these antioxidative mechanisms, oxidative stress occurs [18].

The use of the term 'oxidative stress' became frequent in the 1970s, but its origin dates back to the 1950s when researchers were studying the toxic effects of ionizing radiation and free radicals. Oxidative stress refers to a pathological state that arises from an imbalance between the production of free radicals and the ability to neutralize them by antioxidants. When the antioxidant capacity is reduced, prooxidants can react with surrounding biomolecules and the extent of the reaction is dependent on the susceptibility of the biomolecules [20–22].

2.1 Free radical reaction with biomolecules

Biological molecules, notably DNA, proteins and lipids, can be affected by free radicals. The reaction of reactive oxygen species (ROS) with these macromolecules if not checked generates additional free radicals thereby causing more damage. The incorporation of modified bases into a growing DNA molecule has serious phenotypic consequences [23]. Mitochondrial DNA is mainly vulnerable, because of its closeness to the site of metabolic ROS generation [24]. Telomeres are also vulnerable to ROS attack. ROS-accelerated reduction in telomere length hasten cell senescence [25].

Oxidation of proteins induce the formation of irreversible disulphide bridges, changes in secondary and tertiary structure and ultimately impaired function. The degree of the damage depends on the location of the proteins, their composition and structure [26]. Some amino acids (tryptophan, tyrosine, histidine and cysteine) are more susceptible to oxidation than others [24].

Damage to lipids is also of great significance because of the negative impact on membrane structure and function. The composition of biological membranes is very important to the membrane function but also influence susceptibility to oxidative damage. Polyunsaturated fatty acids (PUFAs) are much more prone to peroxidation than monounsaturated or saturated fatty acid acids. Oxidation of lipids can generate a wide range of reactive intermediates which can trigger complex chain reactions with widespread effects.

2.1.1 DNA oxidation

Technological advancement in analytical chemistry have provided sensitive and specific methods for identifying and quantifying DNA adducts. Application of these techniques to the analysis of nuclear DNA from human tissues has made it clear that the notion "human genome is pristine if there is no exposure to environmental carcinogens" is incorrect. Much damage is done to DNA molecules endogenously by intermediates of oxygen reduction that either attack the nitrogenous bases or the deoxyribosyl backbone of DNA (**Figure 5**) [28].

Hydroxyl radical ($HO^{\bullet}$) is a provable candidate in DNA oxidation because it is extremely reactive. Hydroxyl radicals cannot diffuse beyond two molecular diameters because of their high reactivity [29, 30]. It can add to DNA bases or abstract hydrogen atoms to produce DNA adducts in no specific order [28]. The effect on nuclear DNA can only be possible if H_2O_2 generate $HO^{\bullet}$ on reaction with a metal ion in the vicinity of a DNA molecule [31, 32].

Peroxinitrite, a product of the coupling of nitric oxide and superoxide ion (O_2-) has also been identified as an extremely strong DNA oxidant. Apart from its ability to generate $HO^{\bullet}$, its protonated form (peroxinitrous acid, ONOOH) is an extremely reactive oxidant [28].

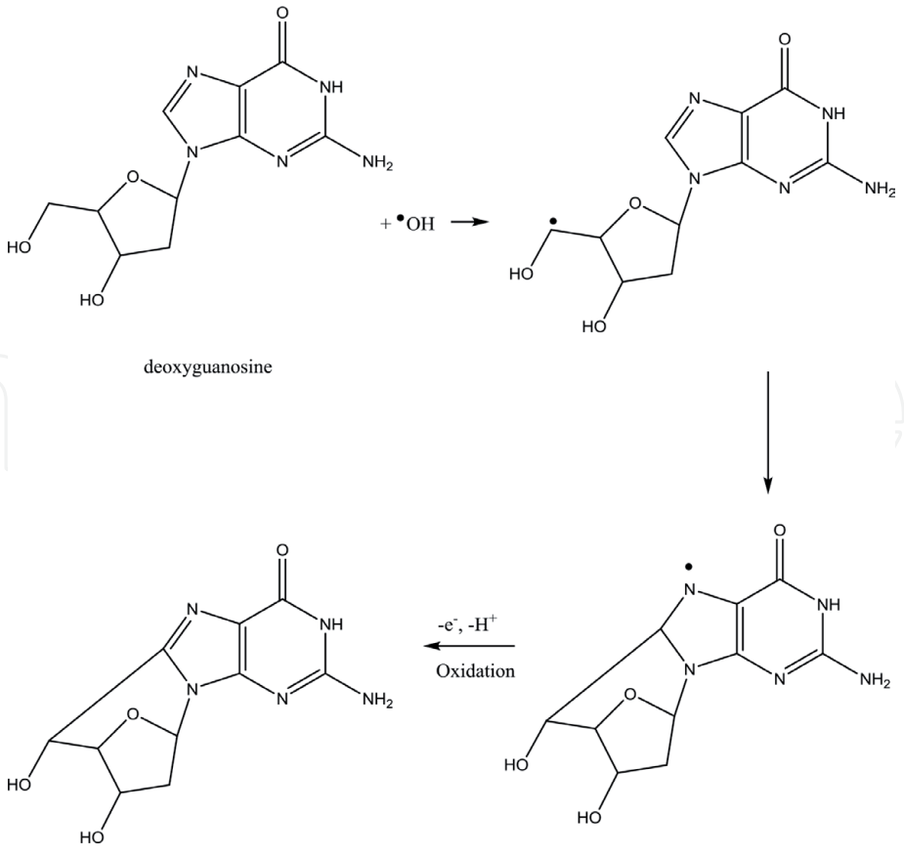


Figure 5.
Oxidation of deoxyribose in purines [27].

Secondary products of lipid peroxidation reactions are also culpably involved in DNA oxidation. Malondialdehyde and 4-hydroxylnonenal can oxidize DNA thereby generating several DNA adducts [30].

2.1.1.1 Mechanism of DNA oxidation

When a H-atom is abstracted from C5' carbon atom in the sugar moiety, the C5′-centered radical generated binds to the C8-position of the purine base in the same nucleoside. The products of this intramolecular cyclization are 8,5'-cyclopurine-2′-deoxynucleosides (**Figure 5**). The reactions of carbon-centered sugar radicals result in the DNA strand breaks [27].

The reaction of $HO^{\bullet}$ with purines in DNA produces a C-8-hydroxy-adduct radical of the purine base which can be converted to the 2,6-diamino-4-hydroxy-5-formamidopyrimidine by reduction that ultimately lead to ring opening. The oxidation of the C-8-hydroxy-adduct radical of purines yield 8-hydroxypurine $HO^{\bullet}$ can react also with the heterocyclic part of the pyrimidine bases to yield several base adducts. For example, the reaction of $HO^{\bullet}$ with cytosine and thymine at C5- and C6-positions, yields C5–OH and C6–OH adducts respectively. Further oxidation of these adducts by water and concomitant deprotonation results in the formation of the respective glycols.

2.1.2 Proteins

The interest in the study of protein oxidation started in the early 1990s with the aim to explain oxidative damage to specific purified enzymes or in oxidative stress processes involving proteins. The process of protein oxidation by free radicals is an important biochemical event in living cells and is implicated in a number of human diseases.

2.1.2.1 Oxidation of the protein backbone

The removal of one hydrogen atom from an amino acid residue in a polypeptide molecule by a free radical generates a carbon-centered radical. The reaction of the carbon-centered radical with O_2 forms an alkylperoxyl radical intermediate which can be converted to an alkylperoxide. The resulting alkoxyl radical may be converted to a hydroxyl protein. Steps in this pathway are mediated by interactions with $HO_2^{\bullet}$ and are catalyzed by Fe^{2+}. The radical intermediates generated can further react with other amino acid residues within the same or in different protein molecules thereby generating a new carbon-centered radical that can undergo similar reactions. However, when oxygen is absent, two carbon-centered radicals may react with each other to form a protein–protein cross-link (**Figure 6**) [33].

Peptide bond cleavage occurs by either the diamide or α-amidation pathways. ROS attack on glutamyl, aspartyl and prolyl side chains of polypeptide residues lead to peptide bond cleavage via a different pathway. Oxalic acid is formed and the N-terminal amino acid of the peptide derived from the C-terminal portion of the protein will exist as an N-pyruvyl derivative. The involvement of proline oxidation is linked to the observation that the number of peptides formed during radiolysis of proteins is approximately equal to the number of prolyl residues. It was thus proposed that oxidation of prolyl residues would lead to peptide bond cleavage. This was verified by Uchida et al. [34] who showed that the oxidation of proline residues leads to the formation of 2-pyrrolidone and concomitant peptide bond cleavage. The hydrolysis of 2-pyrrolidone by an acid yields 4-aminobutyric acid. The observation of 4-aminobutyric acid in protein hydrolysates serve as reasonable evidence of the involvement of proline oxidation in peptide bond cleavage.

2.1.3 Lipid peroxidation

The adverse effects of lipid peroxidation in biological systems gained attention in the 1960's and it is now known that this reaction is a relevant event in biology and medicine [35].

Lipid peroxidation is a chain reaction, catalyzed by transition metals ultimately resulting in the breakdown of membrane phospholipids that contain polyunsaturated fatty acids (PUFAs). The severity of the resulting damage depends on the nature and concentration of the oxidant and it may range from reductions in membrane fluidity to full disruption of bilayer integrity [30]. The two most dominant ROS that can affect lipids profoundly are; hydroxyl radical ($^{\bullet}OH$) and hydroperoxyl radical ($HO_2\bullet$), a protonated form of O_2^{-}. The hydroxyl radical ($^{\bullet}OH$) attack biomolecules located a few nanometers from the site of generation [36]. H_2O_2 generated from $HO_2\bullet$ can react with redox active metals to generate $^{\bullet}OH$ through Fenton or Haber-Weiss reactions. The $HO_2\bullet$ can also directly initiate the oxidation of polyunsaturated phospholipids in cell membrane [37].

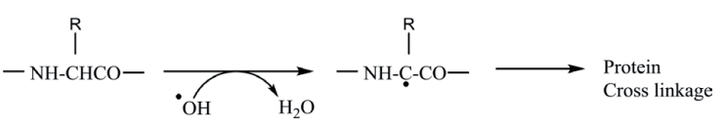


Figure 6.
Formation of carbon-centered radicals during protein oxidation [33].

2.1.3.1 Lipid peroxidation process

Lipid peroxidation reactions involve the abstraction of hydrogen from a carbon in a lipid molecule followed by the insertion of oxygen to form lipid peroxyl radicals and hydroperoxides. Glycolipids, phospholipids, and cholesterol are susceptible to these damaging and possibly lethal peroxidative alterations. The enzymes; lipoxygenase, cyclooxygenase and cytochrome P450 can also oxidize lipids.

Lipid peroxidation reactions are categorized into three phases: initiation, propagation, and termination. In the initiation step, pro-oxidants like hydroxyl radical removes an allylic hydrogen forming a carbon-centered lipid radical (L•). During the propagation phase, the lipid radical (L•) rapidly reacts with oxygen to form a lipid peroxyl radical (LOO•). The LOO• can react with neighboring lipid molecules form a new L• and lipid hydroperoxide (LOOH) (**Figure 7**).

The reaction process can be terminated by antioxidants that donate hydrogen atom(s) to the lipid peroxyl radical species resulting in the formation of non-radical products. For example, vitamin E donate hydrogen atom to the LOO• species. The resulting 'oxidized' vitamin E radical reacts with another LOO• forming non-radical products. The chain reaction continues in the absence of antioxidants [38].

2.1.3.2 Lipid peroxidation products

Lipid peroxidation produces a number of oxidation products categorized as primary and secondary products. Lipid hydroperoxides (LOOH) are the main primary products of lipid peroxidation. Several aldehydes are formed as secondary products from the hydroperoxides including; malondialdehyde (MDA), propanal, hexanal, and 4-hydroxynonenal (4-HNE) [39, 40]. 4-HNE and MDA have been reported to be the most toxic and most mutagenic product of lipid peroxidation respectively [41].

The decomposition of arachidonic acid (AA) and larger PUFAs as well as enzymatic processes during the biosynthesis of thromboxane A_2 (TXA_2) and 12-l-hydroxy-5,8,10-heptadecatrienoic acid (HHT), or the non-enzymatic processes

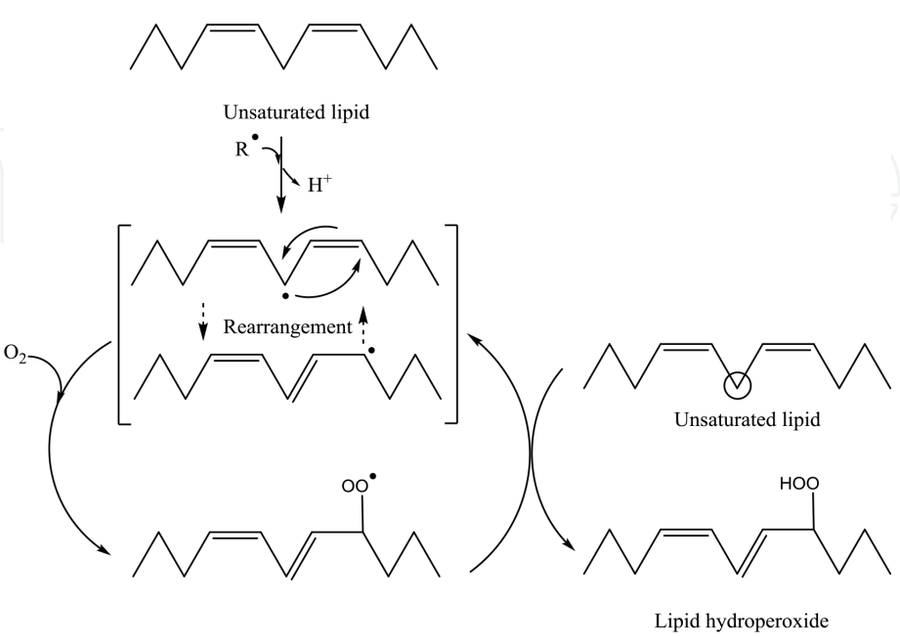


Figure 7.
Lipid peroxidation process [30].

by bicyclic endoperoxides produced during lipid peroxidation, can generate MDA in vivo. MDA generated by these processes can be enzymatically metabolized or form adducts with biomolecules [30].

2.2 Oxidative stress and human diseases

Oxidative stress has been implicated in the onset and progression of pathological conditions such as cancer, cardiovascular disease, neurological disorders, diabetes as well as aging [42–44]. The negative impact of oxidative stress is due to the damaging consequences of free radicals on important biological molecules [45]. Free radical mediated oxidative stress increases with age and may overwhelm natural repair systems [46]. A review of the mechanism of human diseases resulting from oxidative stress was published by Rahman [47]. The influence of oxidative stress on aging is now established and the associated diseases include; cardiovascular diseases, Huntington's disease, Alzheimer's disease, stroke, Parkinson's disease and cancer [47, 48].

The use of oxidative stress biomarkers for the diagnosis of acute and chronic diseases indicate the involvement of oxidative stress in such pathological conditions. This is confirmed by the difference in the concentration of these biomarkers in healthy and ill subjects evaluated for long periods. Representative biomarkers of oxidative damage associated with some human diseases were summarized by Valko et al. [20] and are presented in **Table 1**.

3. Roles of vitamin E in human health and disease

Natural antioxidants including vitamin E have gained relevance in combating oxidative stress [49]. The vitamin E required by humans is solely acquired from diet. The lipohilic nature of vitamin E support the theory of high antioxidant capacity in cell membranes [47]. The capacity to be replenished by other antioxidants such as ascorbic acid is another important factor [9, 10]. Vitamin E has been reported to slow down the progression of oxidative assaults on biomolecules thus suppressing diseases [13]. The remaining sections of this chapter shall focus on the roles of vitamin E in the management of some illnesses and human wellbeing.

Oxidation products used as biomarkers for oxidative stress	Disease
MDA, GSH/GSSG ratio, NO_2-Tyr, 8-OH-dG	Cancer
HNE, GSH/GSSG ratio, acrolein, NO_2-Tyr, F2-isoprostanes	Cardiovascular disease
F_2-isoprostanes, GSH/GSSG ratio	Rheumatoid arthritis
MDA, HNE, GSH/GSSG ratio, F_2-isoprostanes, NO_2-Tyr, AGE	Alzheimer's disease
HNE, GSH/GSSG ratio, carbonylated proteins, Fe-level	Parkinson's disease
F_2-isoprostanes, GSH/GSSG ratio	Ischemia and reperfusion
MDA, HNE, Acrolein, NO_2-Tyr, F_2-isoprostanes	Atherosclerosis
MDA, GSH/GSSG ratio, F_2-isoprostanes, NO_2-Tyr, AGE, S-gluathionylated proteins	Diabetes mellitus

Abbreviations: MDA, malondialdehyde; HNE, 4-hydroxy-2-nonenal; AGE, advanced glycation end products; 8-OH-dG, 8-hydroxy-20-deoxyguanosine; GSH, reduced glutathione; GSSG, oxidized glutathione; NO_2-Tyr, 3-nitro-tyrosine.

Table 1.
Oxidative stress biomarkers associated with some human diseases [20].

3.1 Vitamin E in disease prophylaxis

Epidemiological studies and observational surveys link populations that consume a high amount of vitamin E to a reduced incidence of chronic diseases. This disease preventing capacity is largely linked to the antioxidant capacity of the vitamin E family. The antioxidant property is based on the capacity of vitamin E to donate hydrogen to free radicals and its lipid membrane solubility. The resulting tocopheroxyl radical is far less reactive compared to free radicals so does not propagate the oxidative chain reaction. The tocopheroxyl radical can be reduced by ascorbic acid or react with another tocopheroxyl radical to form stable products [50].

Vitamin E is an immune booster which may play an essential role in the observed prophylactic action. The vitamin E family have been reported to regulate cell growth and induce apoptosis in tumor cells. Several other anticarcinogenic mechanisms have been reported for the vitamin E family including the stimulation of the migration of macrophages and lymphocytes that contain tumor necrosis factor to tumor sites [51] and modulation of the expression of oncogenes. Additional studies have revealed that vitamin E succinate, a modified product can specifically induce apoptosis in tumor and cancer cells but not normal epithelial cells in mammary and prostatic glands [50, 52].

The hypothesis that atherosclerosis may be prevented by blocking the oxidative modification of LDL cholesterol, a key process in the onset and progression of atherosclerosis renewed interest in vitamin E. Research outcomes have documented beneficial effects of vitamin E on several stages of the atherosclerotic process [53].

3.2 The role of vitamin E in cardiovascular disease

The development of atherosclerosis depends on the pro- and anti-inflammatory as well as pro- and anti-oxidant balance [54]. The oxidation of LDL is a principal component of atherosclerosis and is implicated in the onset of cardiovascular diseases via several mechanisms. At low concentrations, oxidized LDL can stimulate the production of inflammatory markers such as cell adhesion molecules and macrophage colony stimulating factor by endothelial cells. The resulting endothelial dysfunction can result in either cell growth or apoptotic cell death that can cause vasoconstriction.

At high concentrations, oxidized LDL are recognized by scavenger receptors and they are phagocytosed by macrophages resulting in the formation of lipid-laden foam cells. The cytotoxic property of oxidized LDL in cultured endothelial cells, the ability to inhibit macrophage motility and the inhibitory effect on nitric oxide-induced vasodilation are other potential atherogenic possibilities. Experimental evidence also back the involvement of free radicals in congestive heart failure (CHF), vascular injury and organ dysfunction [55, 56].

The vitamin E family has received considerable attention in atherosclerosis research based on the capacity to inhibit LDL oxidation and decrease uptake of oxidized LDL by macrophages in human arterial lesions. The vitamin E compounds are reported to be favorable modulators of the atherogenic process at the molecular and cellular levels [57, 58]. Other potential mechanisms of action include; reduction of endothelial injury, reduction in the expression of adhesion molecules, reduction in endothelial cell adhesion, inhibition of inflammatory cytokines and chemokines synthesis, inhibition of smooth muscle cell proliferation, inhibition of platelet aggregation, increased NO production and arterial dilation.

An in vitro study on the effect of vitamin E on LDL oxidation in the blood plasma of healthy volunteers revealed that enrichment with vitamin E increased resistance to LDL-oxidation in a dose-dependent manner [59] and decreased uptake

of oxidized LDL by macrophages in human arterial lesions. In another study, vitamin E enrichment increased LDL vitamin E concentration by approximately 2.5 folds and the susceptibility to oxidation was reduced by 30–40% [60].

The results obtained from in vitro studies have not been replicated exactly in clinical trials.

3.3 The role of vitamin E in cancer

Cancer is a complicated disease condition characterized by the inability to control cell growth. Carcinogenesis has been categorized into three stages; initiation, promotion, progression and the action of free radicals have been implicated in all stages due to their capacity to react with all components of DNA. The concentration of oxidized DNA adducts is directly linked to the size of benign tumors and can directly affect the transformation to malignancy [47].

The vitamin E compounds are powerful antioxidants thus can inhibit DNA oxidation. The natural forms of vitamin E have been reported as effective agents for cancer therapy [61]. The result of the selenium and vitamin E cancer prevention trial (SELECT) revealed that dietary supplementation of α-tocopherol at 400 IU/d increased the risk of prostate cancer [62]. The anticancer properties of α-tocopherol have been studied the most among the vitamin E compounds and available results reveal that the anticancer property of the compound is not very promising.

However, the vitamin E forms; γ-tocopherol, δ-tocopherol, γ-tocotrienol and δ-tocotrienol have been reported to have higher anticancer property compared to α-tocopherol. These vitamin E forms are able to inhibit multiple cancer promoting pathways by inhibiting the formation of eicosanoids. In conjunction with their metabolic product; 13′-carboxycromanol, they inhibit the cyclooxygenases (COX-1 and -2) and 5-lipoxgenase (5-LOX). Gamma- and δ-tocotrienols also suppress the activation of *nuclear factor kappa B* (NF-kB) and signal transducer and activator of transcription factor 3 (STAT3). These activities neutralize pro-inflammatory tumor microenvironments that favor cancer development, invasiveness, and resistance to treatment. These vitamin E compounds also target cancer cells and cancer stem cells by promoting apoptosis, antiangiogenesis, and antiproliferation partially via modulating epigenetic events and other signaling pathways. The modulatory effect of tocotrienols on immunity may also contribute to cancer prevention [61].

The anti-inflammatory mechanism of vitamin E compounds and their metabolites is based on their capacity to inhibit the cycloxogenases and the lipoxygenase involved in eicosanoid synthesis. Reduced synthesis of prostaglandins and leukotrienes have been reported to slow down tumorigenesis, angiogenesis and metastasis. The activity of COX-2 and 5-LOX as well as the concentration of Prostaglandin E_2 (PGE_2) are increased in tumor cells. These events promote angiogenesis and resistance to apoptosis via PGE_2 receptor-mediated signaling in cancer cells [61, 63, 64].

The non-steroidal anti-inflammatory drugs (NSAIDs) that inhibit inflammation via the inhibition of COX and 5-LOX have been shown to inhibit tumor development in various cancer models [65, 66]. Studies have revealed that γ-tocopherol, δ-tocopherol and γ-tocotrienol as well as their metabolites can inhibit COX- and 5-LOX at physiological concentrations [61].

Pro-inflammatory cytokines secreted by macrophages associated with tumor and cancer cells also promote tumor growth and invasiveness. The cytokines (interleukin-1 (IL-1), interleukin-6 (IL-6)) and *tumor necrosis factor alpha* (TNF-α), activate NF-kB and STAT3 in cancer cells. The activation of NF-kB and STAT3 increase the expression of genes that promote cell survival, proliferation, angiogenesis and

invasiveness [67]. The inhibition of NF-kB and STAT3 as well as their regulatory cytokines is a potent target to suppress tumor development and progression.

Vitamin E compounds have been shown to block NF-kB and STAT3 activation and their regulated genes in macrophages and cancer cells [68]. The inability to express survival genes following the inhibition of NF-kB and STAT3 sensitizes the cancer cells to therapeutic drugs. γ- and δ-Tocotrienols have been reported to be active inhibitors of NF-kB and STAT3 [69].

The immune system play an important role in the defense against cancer by detecting and killing tumor cells [68]. A combination of tocotrienols as supplements have been reported to modulate immune response and has a higher anticancer activity than α-tocopherol alone [70]. Tocotrienol supplementation enhanced lymphocyte proliferation without affecting major cytokines in old mice but not young ones, suggesting an age-dependent immune modulatory function [71]. The supplementation with the vitamin E compounds increase interferon gamma (IFN-γ) and interleukin 4 (IL-4), thus enhancing antibody production while suppressing TNF-α in stimulated splenocytes. This activity observed in response to tetanus toxoid vaccination suggest anticancer activity via immune modulation [68].

The vitamin E forms have been reported to directly target cancer cells. γ-Tocopherol, δ-tocopherol, γ-totrienol, δ-tocotrienol and 13′-carboxychromanol have been reported to induce the arrest of cancer cell growth, apoptosis and autophagy in several types of cancer cells [72]. The preferential accumulation of γ-totrienol, δ-tocotrienol and 13′-carboxychromanol in cancer cells may be responsible for the observed higher anticancer activity compared to the tocopherol counterparts [73].

The capacity of these vitamin E forms to induce pathways associated with antiproliferation [74], elevation of mitochondria apoptotic proteins [73], autophagy marker LC3II and endoplasmic reticulum stress markers such as c-Jun N-Terminal kinase (JNK) phosphorylation and death receptor-5 (DR5) pro-apoptotic pathway [75] may contribute to the reported anticancer activity. The anticancer activity has also been linked with the capacity of the vitamin E forms and 13′-carboxylchromanol to modulate sphingolipid metabolism. At elevated concentrations, sphingolipids such as dihydroceramide, dihydroshpingosine and ceramides induce stress and apoptosis as well as inhibit cell growth [76]. This has been shown in prostate, colon, pancreatic and breast cancer cells were an elevation of the sphingolipids precede or happen simultaneously with cell death [74]. Suppressing de novo synthesis of sphingolipids reverses the anticancer activity of the vitamin E forms. Research is still ongoing to completely unravel the interactions and effect of sphingolipid modulation in vivo [61].

3.4 The role of vitamin E in cataracts

Cataracts are one of the commonest reasons for critical vision distress in adult humans. They essentially happen because of the aggregation of proteins oxidized by free radicals. A few observational examinations have uncovered a likely connection between vitamin E supplements and the danger of cataracts development. Leske et al. [77] reported that lens clarity was higher in individuals receiving vitamin E supplements and those with higher plasma concentrations of the vitamin. In another investigation, vitamin E supplementation was related with reduced opacification of the lens. However, in a randomized Age-Related Eye Illness Study (AREDS), vitamin E had no clear impact [78]. Like in other disease conditions, the exact mechanism of the observed positive effects of vitamin in the reduction of cataract formation in vivo is in progress [79].

3.5 Roles of vitamin E in other diseases

The role of vitamin E gas been studied in several other diseases conditions linked to oxidative stress. For example, stroke has been linked with free radical reactions arising from xanthine oxidase, cyclooxygenase and inflammation [80]. These free radical reactions can cause neuronal death [81]. The oxidative assault is increased by the biochemical processes associated with stroke.

Oxidative stress is also implicated in the onset and progression of the neurological disorders; Alzheimer's disease and Parkinson's disease. In both conditions, logarithmic age-dependent increase in the oxidation of proteins, lipids and DNA as well as decreased in vivo antioxidant activity has been reported [47]. In Alzheimer's disease, oxidation induce protein cross linking and aggregation of β-amyloid protein which in turn induce the oxidation of carbohydrate side chains of membrane lipids leading to neuronal membrane breakdown [82]. Oxidation of lipids also accompany the process and has been quantitatively assessed by increased concentration of 4-hydroxyl-2-nonenal-glutathione conjugates in the brain [83].

In diabetes, free radical-induced OS has been reported to play a significant role in the development of insulin resistance, β-cell dysfunction and impaired glucose tolerance. Hyperglycemia worsens the oxidative burden following the formation of advanced glycation end products (AGEs).

The biochemical importance of oxidative stress in the onset and progression of disease conditions underscores the relevance of vitamin E in prevention and management.

In HIV infection, it is not exactly clear if vitamin E supplementation has the same effect at all stages of the disease. However, high serum concentration of vitamins A and E have been reported to affect disease progression. Vitamin E concentrations higher than 23.5 μM reduced the risk of progression of HIV-1. Vitamin E has also been shown to normalize immune system parameters in murine acquired immunodeficiency syndrome as well as protect against bone marrow toxicity of azidothymidine. Protection against azidothymidine toxicity was confirmed in stage IV HIV patients on alpha-tocopherol supplementation. High doses have also been reported to restore delayed skin hypersensitivity, stimulate interleukin-2 production and T-helper (CD4 T-cell) proliferation [79].

4. Discussion

The in vitro antioxidant activity of vitamin E compounds are well documented. However in vivo studies on prevention and treatment of oxidative stress-related diseases have been disappointing. Till date, there is no approval for the clinical use of vitamin E as a drug even though vitamin E consumption has been reported to boost immunity, improve skin health and vision. Vitamin E remains a popular supplement and is generally regarded as safe by the FDA.

Vitamin E is the main lipid soluble antioxidant [79] in the cell membrane thus will always attract research attention considering the relevance of membrane lipid oxidation [84]. The bioactivity of vitamin E in the cell membrane may be a direct approach to limit oxidation of other biomolecules that can form conjugates with oxidized lipids.

Emerging research outputs are shedding light on the disparity between in vitro and in vivo antioxidant capacity of vitamin E [85]. In macrophages, the oxidation of lipids occur in the lysosomes. Alboaklah and Leake [85] conducted an experiment on LDL oxidation at lysosomal pH (about 4.5). In their experiment, LDL enriched with vitamin E was oxidized by Cu^{2+} more slowly compared to control LDL. At

pH 4.5, the enriched LDL was not protected against oxidation by low concentrations of Cu^{2+} or Fe^{3+}. They observed that the enriched LDL reduced the Cu^{2+} and Fe^{3+} to the more pro-oxidant Cu^{+} and Fe^{2+} at a faster rate than control LDL at lysosomal pH. This may partly be responsible for the observed reduction in the bioactivity of vitamin E compounds in vivo.

The bioavailability of vitamin E has been another complication in clinical applications. Recent data indicate that the absorption of vitamin E is far more complex than previously thought. Details about the digestion, absorption and transport of vitamin E are presented in a review by Reboul [86]. The author concluded that the process is only partly understood and suggested further studies to decipher the molecular mechanisms [86].

The poor water solubility of vitamin E has been implicated in the low oral bioavailability [87]. Recently, nanoformulations such as nanovesicles, solid-lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, and polymeric nanoparticles have shown promising outcomes in improving the efficacy and bioavailability of vitamin E.

Lipid-based nanovesicles such as niosomes and liposomes are highly promising for the delivery of lipophilic drugs and active compounds. Although niosomes and liposomes have similar physicochemical properties, niosomes have a higher permeability to small solutes and ions than liposomes. The application of these nanovesicles as drug delivery vehicles is suitable because they are non-toxic and stable.

In a study to enhance the tumor-suppressing effect of tocotrienols in vivo, Fu et al. [88] first developed a D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS)-based noisome [88, 89]. This system appeared to significantly increase tocotrienol uptake in vitro using A431, B16F10 and T98G cell lines and hence improved the therapeutic efficacy. TPGS can be functionalized as an excellent solubilizer, emulsifier, permeation and bioavailability enhancer for hydrophobic drugs [90]. TPGS has demonstrated capacity to selectively induce apoptogenic activity against many cancer types by targeting the activation of mitochondrial mediators of apoptosis [91]. Another 6-*O*-palmitoyl-ascorbic acid (PA) based niosomes (comprising AP, TPGS, cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[carboxy(polyethylene glycol)-2000] (DSPE-PEG (2000)-carboxylic acid)) was developed by Tan et al. [92] targeting transferrin receptors for intravenous administration of γ-tocotrienol aimed at treating breast cancer. Both in vitro and in vivo studies have proven that tumor-targeted niosomes significantly improve the therapeutic efficacy of γ-tocotrienol. These studies suggests that nanovesicles can be suitable carriers for improved delivery and enhanced efficacy of vitamin E [93].

5. Conclusion

Although the antioxidant and antiproliferative properties of vitamin E against oxidative stress related diseases have been reported, there is currently no approval for clinical application. A modified product, TPGS has been approved by the FDA as a safe pharmaceutical adjuvant with high biocompatibility. Despite the reported bioactivity of the tocotrienols, studies so far are inconclusive. The reported in vitro biochemical properties of the vitamin E family will continually call the attention of researchers since they are natural and can play essential roles in ameliorating the impact of oxidative assault in biological membranes. To maximize the prophylactic and curative properties of vitamin E, further research on absorption, cellular uptake, solubility, and stability is required to improve bioavailabilty and efficacy in vivo.

Conflict of interest

The authors declare no conflict of interest.

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