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Vitamin E: Regulatory role in the cardiovascular system

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Abstract
Cardiovascular diseases (CVD) has a considerable impact on global health, resulting in elevated rates of illness and mortality. Vitamin E is essential for regulating cellular processes and gene activity that are critical for avoiding cardiovascular disease (CVD). Studies utilizing cell cultures and animal models have provided insights into the impact of vitamin E on signaling pathways associated with inflammation, lipid regulation, and the stability of atherosclerotic plaques. While several advantages of vitamin E have been validated through human trials, not all favorable results seen in initial investigations have been replicated in larger population-based studies.
Recent studies have also investigated the impact of vitamin E's physiological byproducts, such as those generated by the liver and its phosphorylated forms, on cardiovascular disease (CVD). These findings provide novel insights into the potential impact of vitamin E and its derivatives on cardiovascular health. This information is anticipated to provide guidance for future research in animal and clinical environments with the goal of mitigating cardiovascular disease (CVD) risks. This review focuses on the contribution of vitamin E to preventing cardiovascular disease and presents recent discoveries about the role of its metabolites in the management of CVD.

Keywords: Vitamin E, α-tocopherol, long-chain metabolites, tocopheryl phosphate, cardiovascular disease

Introduction
Cardiovascular disease (CVD) is a collection of illnesses that affect the functioning of the heart and blood vessels, including conditions like heart attack, heart failure, and atherosclerosis. Cardiovascular disease (CVD) has the highest rates of both mortality and morbidity, making it the leading cause of death globally. The World Health Organization data states that around 17.5 million individuals succumbed to cardiovascular disease (CVD) in 2012, accounting for 31% of all worldwide fatalities [1]. Cardiovascular disease (CVD) claims the lives of around 4 million individuals annually in European nations. The global incidence of cardiovascular disease (CVD) is projected to result in about 23.6 million deaths by 2030 [2].
Numerous risk factors linked to the development of cardiovascular illnesses have been extensively discovered by epidemiological investigations [3]. Blood pressure, dietary practices, smoking, and cholesterol levels are the main research topics in studies that look for the main risk factors for cardiovascular disease (CVD). High blood cholesterol, defined as 240 mg/dL or more, is thought to be the cause of 18% of strokes and 56% of instances of ischemic heart disease, translating into an estimated 4.4 million deaths annually. Every year [4], Of those diagnosed with heart failure, 75% had preexisting hypertension [5]. Of the deaths that can be directly linked to a cause, 1.6 million deaths from cardiovascular disease (or 9% of all deaths from cardiovascular disease) are attributable to tobacco use. Obesity (5%), excessive blood sugar (6%), and physical inactivity (6%), in that order [6]. A number of research investigations have also demonstrated an inverse relationship between the risk of cardiovascular disease (CVD) and vitamin E supplementation [7-9].
There are four analogues for each of the two forms of vitamin E, tocopherols and tocotrienols: α, β, γ, and δ [10]. It has been demonstrated that vitamin E's non-antioxidant qualities are important in disease prevention, even though it is thought to help prevent damage from free radicals.

Non-antioxidant actions of vitamin E and its metabolites on cells include signaling pathway regulation, namely affecting transcription factors and signal transduction proteins/enzymes [11]. Numerous cellular responses, such as migration, immunology, survival, inflammation, and secretion, have been seen to be impacted by vitamin E. It accomplishes this via affecting enzymes that are involved in signal transduction pathways, including lipoxygenases, phosphoinositide 3-kinase, protein tyrosine phosphatase, protein kinase B, protein kinase C, protein phosphatase 2A, and protein tyrosine phosphatase. Furthermore, it controls the actions of certain transcription factors such as peroxisome proliferator-activated receptor gamma [12], nuclear factor erythroid 2-related factor 2, and nuclear factor kappa B. However, the inconsistent outcomes from several clinical trials failed to show beneficial benefits in humans. Novel and unexpected molecular insights into the role of vitamin E metabolites generated by hepatic metabolism in the regulation of cardiovascular disease (CVD) have been revealed by recent research [13]. There isn't any text available. An overview of the role of vitamin E and its metabolites in preventing cardiovascular disease (CVD) is given in this paper. Research carried out *in vitro* (in laboratory settings) and *in vivo* (live creatures) as well as clinical studies have demonstrated the efficacy of these substances. The cellular and molecular findings that bolster vitamin E's protective effects against CVD are also highlighted in the study.

Vitamin E against CVD

Vitamin E is a lipid-soluble vitamin that is essential for the emergence and advancement of certain diseases. The most physiologically active form of vitamin E, α-tocopherol, has been used in numerous *in vitro*, *in vivo*, and clinical studies. The results of those studies showed that vitamin E controls the expression of genes, cell division, and signal transmission, among other cellular processes. An overview of vitamin E's effects on cardiovascular disease (CVD) is given in this section, with particular attention on how it affects atherosclerosis, ischemia/reperfusion, and heart failure.

In vitro and *In vivo* Experiments

α-tocopherol has been shown to have a preventive effect on cardiovascular disease (CVD) in a number of studies using cell cultures and animals because of its large influence on the regulation of gene expression and signaling pathways (Table 1). The first information about the effects of α-tocopherol comes from the study group of Azzi. This data relates to its capacity to inhibit PKC activity, which in turn causes a reduction in the proliferation of smooth muscle cells (SMCs) in human smooth muscle (HAI) cell lines [14-16] as well as rat aorta smooth muscle (A7r5). It has been demonstrated that alpha-tocopherol inhibits the production of superoxide in human adherent monocytes by interfering with NADPH-oxidase synthesis and lowering p47 motility and activation on the cell membrane. Because of its capacity to inhibit PKC, this occurs. Reference [17] provides support for this information. α-tocopherol did not reduce lipid peroxidation in cardiovascular disease (CVD) lesions, as demonstrated by Upston *et al*. [31]. Further noteworthy data, released by Azzi's team, shows that giving α-tocopherol to HL-60 macrophages, THP-1 monocytes, and human smooth muscle cells (SMCs) effectively suppressed the absorption of oxidized low-density lipoprotein (oxLDL) by reducing the expression of CD36 [18, 19]. According to further research, α-tocopherol inhibits P-selectin production in U937 macrophage cell line [20] and NFkB activation, which in turn lowers the formation of foam cells produced by oxLDL. Simultaneously, it was shown that when exposed to oxLDL 32, murine macrophage RAW264.7 cell line may produce less foam cells, experience oxidative stress, and undergo apoptosis when HDL enhanced with vitamin E.

Table 1: Regulatory effects of vitamin E against cardiovascular diseases tested by *in vitro*/*in vivo* experiments

Mechanism of Action	Cell Type or Animal Model	References
control of PKC activity in conjunction with p47 phosphorylation to inhibit cell division and LDL oxidation	Rat aorta smooth muscle (A7r5), Human monocyte cells and human smooth muscle (HAI) originally	[14-17]
suppression of oxLDL uptake by CD36 downregulation	HL-60 differentiated macrophages, THP-1 monocytes, and macrophage cells in human aortic smooth muscle	[18, 19]
reduction of inflammatory response and fat buildup by NFkB signaling pathway inhibition	U937 macrophage	[20]
defense against the development of atherosclerotic lesions and aortic damage	$LDLR^{-/-}$ mice and Wistar rats	[21, 22]
reduction of atherosclerotic lesions caused by cholesterol via phosphorylating c-jun, blocking CD36, PKC signaling, MMP-1 and -9, and increasing Nrf2, PPARγ, LXRα, and ABCA-1 levels	$ApoE^{-/-}$ mice and hypercholesterolemic rabbits	[23-28]
decrease of death after a sudden myocardial infarction or heart failure	Rat	[29, 30]

Animal models have been used to assess vitamin E's atheroprotective qualities. It has been demonstrated that consuming vitamin E through meals enhanced with sunflower, olive, or palm oil is linked to a reduction in the severity of atherosclerotic lesions in mice's aorta [33]. Furthermore, animals treated with vitamin E and Coenzyme Q10 showed a decrease in the progression of atherosclerosis in the descending thoracic aorta, aortic root, and arch 34. Another study found that supplementing with vitamin E effectively reduced atherosclerotic lesions in mice who lacked the LDL receptor (LDLR−/−) [21]. Vitamin E was found to have a positive impact on reducing aorta damage in a rat model of atherosclerosis caused by homocysteine and cholesterol. This was confirmed using morphological measurements of collagen buildup and dissociation of elastic fibers [35].

The formation of macrophage foam cells is a clearly recognized and distinctive characteristic of the early stages of atherosclerosis advancement. Scavenger receptors are a collection of receptors that are attached to the membrane of macrophages. They are primarily responsible for recognizing and attaching to certain molecules called ligands. These ligands include oxidized phospholipids/lipoproteins and modified lipid particles [22].

Studies conducted in living organisms indicate that CD36, which is widely regarded as the primary scavenger receptor in the setting of cardiovascular disease (CVD), has a crucial role in the development of atherosclerosis, particularly in the creation of foam cells. CD36 is found in several cell types including monocytes/macrophages, endothelial cells, and smooth muscle cells (SMCs) [36]. Studies have demonstrated that the addition of α-tocopherol decreases the expression of CD36 mRNA, while simultaneously boosting the expression of PPARγ, LXRα, and ABCA1 mRNA in ApoE−/− mice [23].

One of the main risk factors for atherosclerosis and ischemic conditions, such as cerebral and myocardial infarction, is hypercholesterolemia. Our team has shown that vitamin E slows the progression of atherosclerosis in a model of rabbits fed a diet rich in cholesterol. Previous *in vivo* studies have demonstrated that α-tocopherol reduces PKC activity by 24 units, hence inhibiting the formation of atherosclerotic lesions generated by cholesterol. Our *in vitro* studies have shown that α-tocopherol significantly lowers CD36 mRNA expression by 25% and successfully prevents the development of atherosclerotic lesions brought on by cholesterol. In this rabbit model 26, the study found a connection between the inhibitory impact of vitamin E on CD36 mRNA expression in aortic tissue and peripheral blood mononuclear cells.

Oxidized low-density lipoprotein (oxLDL), which is a source of cholesterol, sets off a chain of events that leads to the development of atherosclerosis. A signaling cascade involving the CD36 receptor is one example of this, since it triggers the activation of matrix metalloproteinase (MMP), c-jun N-terminal kinase-1 (JNK1), and mitogen-activated protein kinase (MAPK). These chemicals draw monocytes to the afflicted location and encourage inflammation. According to our research, α-tocopherol prevents MMP-9 synthesis and proteasome activity in atherosclerosis caused by hypercholesterolemia 27 via lowering JNK1-mediated c-jun phosphorylation. By raising the levels of Nrf2 and PPARγ, which in turn increased the synthesis of GSTα and ABCA1, respectively, vitamin E reduced the development of atherosclerosis. It also decreased MMP-1 levels in a rabbit model of hypercholesterolemia 28. In our lab, we have effectively identified proteins that have differential expression in the aortic tissues of fed vitamin E-treated hypercholesterolemic rabbits. This is done through the use of proteomic analysis. Seventy-three proteins with differential expression were found in the investigation. Apolipoproteins A-I and E are two of these proteins that are involved in lipid metabolism. The antioxidant system include thioredoxin, peroxiredoxin 1, and peroxiredoxin 2. Cell signaling is mediated by 14-3-3 protein beta alpha and 14-3-3 protein zeta delta. The structural and contractile proteins biglycan, smooth muscle α-actin, tropomyosin, and vimentin are particularly significant in atherosclerosis [37].

Research on vitamin E is also concerned with inflammation. The anti-inflammatory properties of α-tocopherol have also been demonstrated in experiments on animals and cell cultures. By inhibiting NFκB 38, lowering PKC activity [17, 39], and lowering the synthesis of adhesion molecules such as vascular cell adhesion molecule-1, intercellular adhesion molecule 1, and E-selectin 40, it functions as an anti-inflammatory primarily. It has been established that α-tocopherol modulates pro-inflammatory cytokine release during inflammation, including interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and IL-8. It is possible that PKC [41], NF-κB activation, and 5-lipoxygenase inhibition will result in this effect. According to the latest research, vitamin E may prevent atherosclerosis by controlling the expression of genes and the activity of inflammatory-related enzymes, as well as the absorption of oxidized low-density lipoprotein (oxLDL) and the formation of foam cells. Both in animal models and at the cellular level, this impact is demonstrated.

A number of *in vitro* and *in vivo* models have been used to study the effects of vitamin E on cardiovascular diseases, including atherosclerosis, ischemic heart disease, and heart failure. It has been demonstrated that giving C57Bl/6 mice a daily dosage of a dietary combination that includes vitamin E, vitamin C, docosahexaenoic acid, eicosapentaenoic acid, and L-arginine reduces risk factors in cardiovascular disease (CVD) caused by a high-fat diet [42]. A common cardiovascular disease called ischemic heart disease is associated with a number of clinical problems, including myocardial infarction. Sethi and associates 29 we evaluated the theory that protective vitamin E against acute myocardial infarction (Acute myocardial infarction produced by closure of the left anterior descending coronary artery) lowers mortality. A reduction in the body's metabolic energy reserve and the activation of several molecular pathways leading to cardiac hypertrophy, inflammation, fibrosis, angiogenesis, and apoptosis characterize heart failure, a kind of cardiovascular disease (CVD) [43]. Heart failure may arise from the loss of cardiomyocyte cell function in extreme stress conditions, which may set off pathways leading to necrotic or apoptotic death. Previous studies have demonstrated that vitamin E has a beneficial effect by reducing cardiomyocyte apoptotic activity [44]. 30 Hamblin *et al*. According to a study, feeding rats with diabetic heart failure caused by streptozotocin a meal supplemented with 2000 IU of vitamin E/kg for eight weeks showed a cardioprotective effect. Our earlier studies have shown that adding α-tocopherol prevented cholesterol-induced damage to cardiac muscle cells by reducing the expression of scavenger receptors and LXRα. In a rabbit model with elevated cholesterol, it concurrently raised the levels of ABCA1 and 27-hydroxycholesterol [45].

Additional variations of vitamin E, such as tocotrienols, have been shown to decrease the likelihood of cardiovascular disease (CVD) by reducing levels of cholesterol and triglyceride in the bloodstream. These substances are the primary risk factors for CVD [46]. Tocotrienols may affect cholesterol metabolism by decreasing the oxidation of LDL and inhibiting the expression of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, an important enzyme involved in cholesterol production [47]. These results, together with research conducted on animals, provide more evidence for the preventative effect of tocotrienols on the advancement of atherosclerosis [48, 49]. In addition to this information, several research have indicated that tocotrienols has cardioprotective properties because they can activate proteasomes and enhance myocardial health [50].

Clinical Studies

Several laboratory and animal studies have discovered the controlling influence of vitamin E on the process of cholesterol metabolism, transmission of signals within cells, inflammation, and the stability of plaque in the arteries, as

previously indicated. Based on these findings, vitamin E was found to have a preventive effect against the development of cardiovascular disease (CVD) in several long-term clinical studies [51]. In this section of our study, we provide a concise overview of the role of vitamin E, namely α-tocopherol, in combating cardiovascular disease (CVD). We also discuss the significant human intervention studies conducted in pursuit of this objective.

The association between the risk of cardiovascular disease (CVD) and vitamin E intake from diet and/or supplements has been investigated in cohort studies. Studies such as the Nurses' Health Study (NHS) 7, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study [52], and the Health Professionals Follow-up Study 8, [53], are highlighted. This list of studies includes the Iowa Women's Health Study (IWHS), Physician Health Study, Cancer Prevention Study II (CPS-II), Finnish Cohort Study (FS), Zutphen Study, and Scottish Heart Health Study. When vitamin E was consumed through supplements or food, the first large-scale research revealed positive results for lowering the risk of coronary heart disease. Studies [58, 59, 55, 56] showed a 5% decline in males, a 40% drop in men in the HPFS study, a 34% decrease in women in the NHS study, a 62% decrease in women in the IWHS study, and a 32% fall in men and a 65% decrease in women in the FS study.

In addition to its positive impact on decreasing the incidence of coronary heart disease, vitamin E has also demonstrated protective effects against various cardiovascular problems. The CPS-II study found that women who used vitamin E, vitamin C, and/or vitamin A without multivitamins, or with multivitamins, saw a decrease in the incidence of ischemic heart disease by 10-14%. In a separate trial, patients who took vitamin E supplements for a duration exceeding 4 years exhibited a 59% decrease in death caused by coronary heart disease. The Cambridge Heart Antioxidant Study found that administering α-tocopherol (At a dosage of 400-800 mg/dL) decreased the likelihood of myocardial infarction in individuals with coronary atherosclerosis [9]. The study on secondary prevention of cardiovascular disease in end-stage renal disease demonstrated that the administration of α-tocopherol at a dosage of 800 mg/dL significantly reduced the occurrence of myocardial infarction (both fatal and nonfatal) and ischemic stroke in patients with chronic kidney disease. The number is 61. The Multi-Ethnic Study of Atherosclerosis examined the risk variables linked to subclinical cardiovascular disease (CVD) and discovered that consuming vitamin E through food has positive effects on people [62].

Several clinical studies have also examined the impact of γ-tocopherol, which has been found to have an inverse relationship with coronary heart disease either taken alone or in combination with other analogs. Research conducted on the use of γ-tocopherol supplementation, both on its own and in combination with α-tocopherol, shown a decrease in indicators of oxidative stress in individuals with metabolic syndrome. Additionally, it was found that γ-tocopherol supplementation was more effective than α-tocopherol alone in reducing exercise-induced coagulation and platelet aggregation. In contrast, Stonehouse *et al.* [67] conducted a randomized controlled experiment to investigate the impact of palm-tocotrienols on vascular function and cardiovascular disease (CVD) risk factors. However, they did not find any significant changes in any of these areas.

Additional research has also examined the impact of vitamin E supplementation in comparison to food consumption. In a study conducted by Ehab *et al.* [68], it was shown that a greater consumption of fat-soluble vitamins (namely vitamins K, E, and D) in the diet was linked to a decreased likelihood of death from heart failure in Japanese women, but not in men. In a separate trial, women who took vitamin E supplements for a duration exceeding 2 years saw a 41% decrease in the occurrence of coronary disease when compared to those who did not take the supplements [69]. Loffredo *et al.* [70] Studies have found that vitamin E supplementation alone lowers the occurrence of myocardial infarction in interventional studies. However, when combined with other antioxidants, it seems to be ineffective.

Many clinical investigations provided contradictory information that did not explicitly highlight the beneficial effects of vitamin E consumption, despite good results regarding the prevention of cardiovascular diseases. Hercberg *et al.* [71] looked at the Supplementation en Vitamines et Mineraux Antioxydants experiment to see if a combination of vitamins and minerals may reduce the risk of cancer and ischemic cardiovascular disease (CVD) in the general population. The incidence of ischemic cardiovascular disease (CVD) in the groups and vitamin E supplementation were not shown to be significantly correlated. Similarly, vitamin A and E consumption was shown to have no significant relationship with the risk of mortality from total stroke, coronary heart disease, or cardiovascular disease in Japanese men and women, according to the Japan Collaborative Cohort Study [72]. Myung *et al*. conducted a study which concluded that there is no evidence to substantiate the efficacy of vitamin and antioxidant supplements in preventing cardiovascular disease (CVD). The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico conducted a study to examine the impact of combining α-tocopherol and n-3 polyunsaturated fatty acids (PUFA) on patients with myocardial infarction. Although dietary supplementation with n-3 PUFA has been shown to have a positive impact on cardiovascular events, the group that received vitamin E supplementation did not see any benefit [74]. There is no text provided. The Heart Outcomes Prevention Evaluation research demonstrated that the daily administration of 400 IU of α-tocopherol over a period of 4-6 years did not provide any favorable benefits on cardiovascular outcomes in a cohort of elderly patients at high risk [75]. The recently released PREvención with DIeta MEDiterránea research found no significant correlation between vitamin E and overall mortality in those with a high risk of cardiovascular disease. A separate research conducted a randomized trial on women who were originally healthy and received long-term vitamin E treatment. This study did not find any meaningful alteration in the overall risk of developing heart failure [77].

A collection of controversial findings from clinical research is shown in Table 2. There are a number of reasons for the inconsistent outcomes shown in vitamin E supplementation clinical studies. These consist of the selection criteria that were applied, the group sizes that were being studied, the amount and duration of the supplementation, the presence of other nutrients in the diets of the participants, the type of vitamin E that was used in relation to the baseline levels that were already present, and the existence of

pathophysiological conditions like infection, inflammation, and tobacco use that can affect vitamin E levels. 78. Additionally, it has been proposed that differences in the genes that control the uptake and transport of vitamin E, such as α-tocopherol transfer protein, CD36, SR-BI, human tocopherol-associated protein 1, ABCA1, and ABCG1, may be a major factor in the lack of any protective effect by altering the amounts of vitamin E in the blood and body tissues. 79-81. The vitamin E-related signaling pathways and gene expressions that explain vitamin E sensitivity and thus raise the risk of cardiovascular disease (CVD), including atherosclerosis, may also be regulated by these genetic variants. 82, 83. Simultaneously, genetic differences in specific enzymes, such as catechol-O-methyltransferase or cytokines, or in genes associated with inflammation may account for the different responses seen following vitamin E treatment. 84, 85In light of these findings, genetic differences as well as other factors affecting vitamin E's absorption, distribution, and transportation as well as its efficiency may make gathering solid information about its association with cardiovascular disease more difficult.

Table 2: Controversial effects of vitamin E against cardiovascular disease tested by clinical studies

Beneficial effect		Non-beneficial effect	
Associated disease	**References**	**Associated disease**	**References**
lowering coronary heart disease risk by vitamin E supplementation or diet	[7, 8, 55, 56, 58, 59, 69]	No change on the incidence of ischemic CVDs by the use of vitamin mix which include vitamin E	[71, 73]
Decreased risk of myocardial infarction after α-tocopherol therapy	[9, 61, 70]	α-tocopherol has no favorable impact on cardiovascular outcomes or myocardial infarction patients.	[74, 75]
Protection against coronary heart disease with γ-tocopherol	[63, 65]	Prolonged vitamin E intake does not appear to be associated with an increased risk of heart failure generally.	[77]
Decreased chance of dying from heart failure after consuming fat-soluble vitamins (K, E, and D) in food	[68]		

Although the aforementioned responses have been provided, the issue remains as to why vitamin E demonstrates positive effects in *in vitro* and *in vivo* investigations, whereas clinical trials provide unsatisfactory results. The clinical trials are presenting conflicting findings about the determination of selection criteria, such as the identification of particular biomarkers, to predict the individuals who are most likely to have positive effects from vitamin E intake. We anticipate that conducting comparative pharmacokinetic and clinical studies will enhance the scientific validity and therapeutic applicability by identifying specific side effects and bad outcomes. In addition, vitamin E supplementation can be personalized by targeting certain subpopulations with a particular genotype, such as people with type-2 diabetes and the haptoglobin 2-2 genotype [86]. Will be a beneficial approach in future academic pursuits.

Vitamin E metabolism and its function in CVD

The potential biological impacts of α-tocopherol metabolites, such as α-tocopheryl phosphate (α-TP), a phosphoric acid ester of α-tocopherol, and long- and short-chain breakdown products, have also been highlighted by recent research. It has been found that these metabolites control pathophysiological processes as inflammation, fat metabolism, cell proliferation, and cell death 13, [87]. ω-hydroxylation and α-oxidation, mediated by CYP3A4, are the two mechanisms involved in the hepatic metabolism of α-tocopherol. The endoplasmic reticulum is the site of these processes, which produce alpha long-chain metabolites including alpha-13′-hydroxychromanol and alpha-13′-carboxychromanol. Short-chain metabolites are produced in the mitochondria by the β-oxidation process, namely α-carboxyethyl hydroxychromans (α-CEHCs) [88]. Apart from its potential as a preventive measure, studies have demonstrated that α-tocopherol metabolites influence cardiovascular disease (CVD) through different mechanisms and at lower concentrations than its precursor, α-tocopherol. In this portion of our review, we offer a succinct overview of studies that demonstrate the benefits of α-TP and long- and short-chain α-tocopherol metabolites in the prevention of cardiovascular disease (CVD).

Together with γ- and δ-CEHCs, the byproducts of γ- and δ-tocopherol metabolism, the α-tocopherol metabolite α-CEHC is excreted in urine and is mostly used as a marker of tocopherol consumption [89]. Furthermore, it has been discovered that CEHCs work as bioactive substances by binding to nuclear receptors, transcription factors, and enzyme [90] and controlling their activity. Additionally, studies have shown that α-CEHC can function as an antioxidant [92] and has anti-inflammatory qualities [91]. It has also been shown to inhibit PKC signaling 94 and the formation of oxLDL [93]. Extensive study on the involvement of these long-chain metabolites has been hampered by the low availability of pure α-13′-hydroxychromanol and α-13′-carboxychromanol molecules. According to preliminary studies, alpha long-chain metabolites, as opposed to its precursor α-tocopherol, may have different effects on many pathways implicated in the prevention of atherosclerosis development. Wallert *et al.* (1995) discovered that by upregulating CD36 expression in human macrophage cultures, alpha long-chain metabolites inhibited the growth of foam cells produced by oxLDL. This outcome was not consistent with the α-tocopherol's inhibitory effect. New research has demonstrated the beneficial effects of long-chain metabolites. The rise in PLIN2, a well-studied protein associated with lipid droplets, might be the cause of this impact. Consequently, there is defense against stearic acid 96-induced lipotoxicity. According to references [97, 98], alpha long-chain metabolites may play a part in controlling the inflammatory response by reducing the release of pro-inflammatory cytokines and LPS-mediated nitric oxide production. It has been discovered that alpha long-chain metabolites, namely α-13′-carboxychromanol, contribute to the reduction of acute inflammation and bronchial hyperreactivity. By building up at the sites of inflammation and blocking 5-lipoxygenase-which is in charge of generating lipid mediators produced from 5-lipoxygenase-they are able to do this [99].

Apart from side chain oxidation, the phosphorylated version of α-tocopherol, or α-TP, could be more active and unique than α-tocopherol in terms of regulating cellular functions including growth, survival/apoptosis, enzyme translocation,

and lipid transport. This is because of its ability to control protein-membrane interactions and its similarity to phosphorylated messenger lipids. Prior studies have made considerable use of THP-1 monocytes, which are incapable of hydrolyzing α-TP. In this system, α-TP showed that it could slow down THP-1 monocyte development, whereas α-tocopherol had no discernible effect [102]. Wu *et al.* [103] showed that in endothelial progenitor cells exposed to high glucose/hypoxic circumstances, α-TP is more effective than α-tocopherol in inhibiting apoptosis and encouraging migration and the creation of capillary tube architectures. A different study discovered that α-TP was more effective than α-tocopherol [104] in raising the promoter activity of human vascular endothelial growth factor. This suggests that angiogenesis and vasculogenesis may involve α-TP [105]. Additionally, studies carried out by our group and other researchers on apoE mutant mice and hypercholesterolemic rabbits have demonstrated the preventive impact of α-TP in halting the formation of atherosclerotic plaques. Reducing the amounts of CD36 scavenger receptors and proinflammatory cytokines (IL-1β, IL-6, IL-8, CRP, PAI1, and TNF-α) produces this effect 106-109. Supplementing with α-TP led to the increase of cell survival and the reduction of cell death in a rat model of ischemia/reperfusion. This was accomplished by raising the amount of NFκB binding to DNA, decreasing the amounts of proapoptotic proteins p38 MAPKα, JNK, and phosphorylated c-Src 110, and boosting the activity of anti-apoptotic p42/44 ERK kinase and p38 MAPKβ signaling pathways.

Conclusion

Cardiovascular disease (CVD) is the leading cause of death, accounting for 31% of all fatalities in 2012 and having the highest rates of both morbidity and mortality. Vascular diseases are made worse by the high incidence of important risk factors, such diabetes and obesity, in both developed and developing countries. A number of studies have revealed a negative correlation between vitamin E levels and conditions such as cardiovascular disease (CVD), despite vitamin E being an important nutrient. Research using cell culture and animal models has demonstrated the possible molecular pathways that are impacted by vitamin E and its metabolites in many illnesses, as fully reviewed by Azzi *et al*. 11 and Galli *et al*. 13. Predicted on promising results from *in vitro* and *in vivo* research, several large-scale human trials were carried out and observed over years. Apart from studies that have demonstrated the beneficial effects of vitamin E in lowering the risk of cardiovascular disease, there are also studies that have yielded negative outcomes.

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