

**Review Article**

**A REVIEW ON NOVEL USES OF VITAMIN E**

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**ABSTRACT**

Vitamin E is a major lipid-soluble antioxidant which exclusively obtained from the diet. It has numerous functions within the body because of its antioxidant activity. Generally, oxidation has been linked to numerous possible conditions and diseases, including cancer, ageing, arthritis, and cataracts, etc.; and this lipid-soluble component has been shown to be effective against these conditions. So it can be used for the treatment in such disease conditions as a vitamin supplement. The general mechanism includes the prevention of the propagation of free-radical damage and contributes the membrane stability. Recent studies indicate; that vitamin E may have a structure-specific role in addition to its antioxidant function. Vitamin E supplementation can also have an important role in the reduction of cardiovascular complications, skin diseases (photo-protective effects), osteoporosis (beneficial effects of bone structure changes), and in glycemic control. The aim of this review to explore the uses of vitamin E in the human body and their beneficial actions in various disease conditions.

**Keywords:** Vitamin E, Free-radical, Photo-protectives, Antioxidant activity

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**INTRODUCTION**

Vitamin E is an important lipid-soluble antioxidant which was found in 1922 by Evans and Bishop, and its antioxidant activities play a fundamental part in the functioning of the body [1]. It is generally seen in foods that containing fat [2], and its fat-soluble property allows it to be stored in the fatty tissues of animals and humans, so it doesn't need to be expended each day. The vitamin E group (i.e. chroman-6-ols), gather altogether named tocopherols which include tocopherols and tocotrienols of which  $\alpha$ -tocopherol found to have high biological action. Among them, tocopherols have the potent antioxidant properties [3]. The  $\alpha$ -tocopherol has flagging capacities in vascular smooth muscle cells, which can't be exhibited by various types of tocopherols [4]. Aside from this since the tocopherols are nucleophiles,  $\gamma$ -tocopherol can trap electrophilic mutagens in lipophilic compartments and creates a metabolite that encourages natriuresis. The  $\alpha$ -tocopherols get converted into  $\alpha$ -CEHC and eliminated via the urine when it becomes excess in the body. Tocopherols, like  $\gamma$ - and  $\delta$ -tocopherol, are degraded and eliminated through urine [5, 6]. Vitamin E functions in the human body are not clearly established, but it is recognized to be an essential component in some vertebrate species, especially in

humans [7]. This review mainly focuses on the recent developments in the uses of vitamin E in improving the human health-related problems and also their prevention. The data obtained from a survey of clinical trials or systematic reviews have been included hereto describe the evidence-based results.

**Search criteria**

Articles related to the uses of Vitamin E were reviewed for the study; most of them were from Pubmed databases. Articles between the years of 1999 and 2017 were selected for reviewing and the points were extracted. Primary resources were given the first preference for reviewing.

**Sources of vitamin E**

Vitamin E is a vital micronutrient which obtained through fruits, Nuts, seeds, vegetable oils such as sunflower, wheat germ, safflower, corn and soybean oils and green leafy vegetables contain high amounts of alpha-tocopherol. Vitamin E capsules are also available as supplements on the market. Following is the richest sources of vitamin E, along with their tocopherol content were given in table 1.

**Table 1: Sources of vitamin E**

Oil	Alpha tocopherols	G-tocopherols	D-tocopherols	A-Tocotrienol
in mg of tocopherol per 100 g				
Coconut	0.5	0	0.6	0.5
Palm	25.6	31.6	7.0	14.3
Olive	5.1	Trace amounts	0	0
Peanut	13.0	21.4	2.1	0
Wheatgerm	133.0	26.0	27.1	2.6
Soybean	10.1	59.3	26.4	0
Maize	11.2	60.2	1.8	0
Sunflower	48.7	5.1	0.8	0

Source: Slover HT. Tocopherols in foods and fats [8]

**Recommended dose of vitamin E**

The recommended intake (6–10 mg of  $\alpha$ -tocopherol) is based upon the estimation of an amount of tocopherol the person consumes, which was given in table 2.

**Functions of vitamin E**

Vitamin E functions in an antioxidant it protects the cells, tissues, and organs from the damage by free radicals that are the main reason for ageing and, which can also lead to various health

issues such as cardiovascular diseases, inflammatory conditions, cancer, stroke, Alzheimer's disease, liver disease, etc. But further studies still required for explaining and emphasizing the actual role of vitamin E in these diseased conditions. The actions of vitamin E in various disease conditions are described below.

### Prevention of oxidative stress

Vitamin E (alpha tocopherols) is an antioxidant which thought to have a protective effect by either reducing or preventing oxidative damage, and it inhibits reactive oxygen species (ROS) molecules production, during fat oxidation and propagation of free radical reactions [10, 11]. It is primarily situated within the cell and organelle membranes where it can exhibit its maximum protective effect, even when its concentration ratio may be only one molecule for each 2,000 phospholipid molecule. It acts as the first-line agent for defending

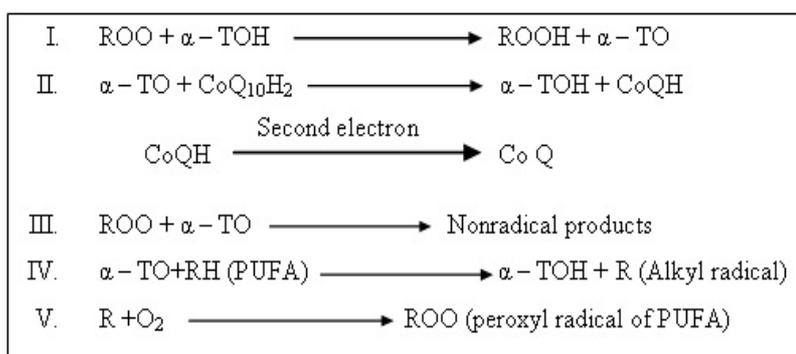
against lipid peroxidation, protects the cell membranes from free-radical attack. The mechanism of vitamin E free radical attack and lipid peroxidation was given in fig. 1. Tocopherols have a strong inhibitory action on lipid peroxidation occurred in human erythrocytes when comparing with alpha-tocopherol [12], as it can damage peroxy radical [13]. The tocopheryl radicals can lead to: (1) lipid oxidation; (2) tocopheryl quinone production; (3) formation of non-reactive tocopherol dimers by the reaction with other tocopheroxyl radical.

Certain studies were shown that alpha-tocopherols can involve in the inhibition of the new free-radical production, while gamma-tocopherol traps and neutralizes the existing free-radicals. Oxidation is usually linked to many disease conditions, including cancer, ageing, arthritis and cataracts. Thus, vitamin E can help in the prevention or delaying of chronic diseases, which are occurred by the oxidative damage and reactive oxygen species (ROS) molecules.

**Table 2: Recommended intake of vitamin E in various age groups**

AGE	RDA in mg (IU)	
	MALES	FEMALES
0-6 mo	4 (6)	4 (6)
7-12 mo	5 (7.5)	5 (7.5)
1-3 y	6 (9)	6 (9)
4-8 y	7 (10.4)	7 (10.4)
9-13 y	11 (16.4)	11 (16.4)
>14 y	15 (22.4)	15 (22.4)
In pregnancy		15 (22.4)
If lactating		19 (28.4)

Source: Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes: Vitamin C, Vitamin E, Selenium, and Carotenoids [9]



**Fig. 1: The mechanism of vitamin E mediated lipid peroxidation**

Source: Rathore GS, Suthar M, Pareek A, Gupta RN. Nutritional antioxidants: A battle for better health [14]

### Cardiovascular diseases

Complications generally occur due to the oxidation of low-density lipoproteins present on the body and the consequent inflammation [15]. Gamma-tocopherols can improve the cardiovascular functions by enhancing nitric oxide synthase activity, which leads to the production of vessel-relaxing nitric oxide [16]. It acts by inhibiting the reactive nitrogen species (peroxynitrite) molecules and thus enhancing the endothelial function. Researchers showed that gamma-tocopherol supplementation in the dose of 100 mg/d in humans has a capacity in reducing the risk factors for arterial clottings, such as platelet aggregation and cholesterol [17]. A study conducted by Singh *et al.*, stated that mixed tocopherols exert a strong inhibitory action on lipid peroxidation and in the inhibition of human platelet aggregation than individual tocopherols alone [18]. Tocotrienols also have the ability to reduce cholesterol biosynthesis by acting against 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, resulting in the reduction in cholesterol synthesis [19]. Contradictory to this, most of the current large interventional clinical trials showed that there are no beneficial effects were found in patients with cardiovascular disease while taking vitamin E and reported that, the vitamin E use was related with a significant increase in the risk of a hemorrhagic stroke in the participants [20].

A raise in the alpha-tocopherol concentration in the endothelial cells have the ability to inhibit platelet aggregation and results in the release of prostacyclin from the endothelium. This occurs as a result of down-regulation of the intracellular cell adhesion molecule (ICAM-1) and the vascular cell adhesion molecule (VCAM-1), thereby reducing the endothelial adhesion of blood cell components [21]. A few other studies suggest that tocopherols appear to inhibit platelet aggregation by the inhibition of protein kinase C (PKC) [22] and the increased action of nitric oxide synthase [23]. It was also found that; vitamin E supplementation is effective in reduction of atherosclerosis progression in patients with previous coronary artery bypass graft, who are not beneath antihyperlipidemic treatment. Thus, it was recommended that proper awareness about the uses of vitamin E in preventing coronary heart disease might demand further large studies with younger subjects.

### Cancer

Present developments in vitamin E studies distinctly indicated that tocotrienols possess apoptotic and antiproliferative activities on normal and cancer human cells [24]. The mechanism is strongly allied with the induction of apoptosis via a mitochondria-mediated pathway and to cell cycle arrest due to suppression of cyclin D by

tocotrienols [25]. Tocotrienols also suppress the vascularisation and malignant proliferation [26]. There are several mechanisms that explained the beneficial and protective actions of vitamin E in cancer which includes; inhibition of cancer formation by preventing free radical propagation; controlling the tumor growth through induction of differentiation; cell cycle inhibition or induction of apoptosis; and tumor cells elimination by increased efficacy of antitumor actions by the immune system [27, 28]. Certain studies were reported that vitamin E succinate (VES) compounds are the most powerful apoptotic inducers of numerous human cancer cells of both lymphoid and epithelial origin [29]. It enhances apoptosis in a concentration-dependent and a time-dependent manner, and also it never induces normal epithelial cell apoptosis [25]. So, VES has a major effect on the tumorigenic phenotype, restoring pro-death TGF- $\beta$  and Fas; the two signalling pathways, which are involved in the regulatory control of tumour cell's elimination and cellular proliferation [30].

### Alzheimer's disease

It is proposed that oxidative stress is the underlying mechanism of Alzheimer's disease (AD) which mainly occurs due to the lipid peroxidation and oxidation of protein by the free-radical mechanism, where the beta-amyloid protein induces cytotoxicity leads to neuronal loss. Vitamin E can hinder the production of hydrogen peroxide and the associated cytotoxicity. It decreases beta-amyloid-induced cell death and thereby reduces the excitatory amino acid potentiated toxicity to the neuroblastoma cells [31, 32]. The amyloid  $\beta$  (Ab) deposition is the major characteristic in the patients with AD, which can enhance production of free radicals and also indirectly stimulates the inflammatory cells (microglia) to produce pro-oxidant species, including reactive nitrogen intermediates. Generally, vitamin E can inhibit the lipid peroxidation and also exhibit anti-inflammatory properties ie; it inhibits the pro-inflammatory cytokines, for example, IL-1, IL-6, and TNF alpha, etc., which are found in higher concentration in the cerebrospinal fluid and brain of patients with AD [33]. So it is a reasonable hypothesis that vitamin E can reduce the probability of development of AD or slowing the progression of the disease. A study performed by Block *et al.*, showed that vitamin E and related tocopherols and tocotrienols can suppress the action of several AD-relevant enzymes (eg: COX2) which are mainly involved in the oxidative damage, neuroinflammation, and AD pathology development [34]. Vitamin E can also activate PP2A, a phosphatase which maintains the tau homeostasis and has been shown to be down-regulated in human AD brains. Vitamin E also has certain structure specific roles in the modulation of signal transduction pathways and participation in biochemical processes, which involves the synthesis of neurotransmitters [35]. Thus it is clear that both preventive and therapeutic effects are exerted by vitamin E in the Alzheimer's disease.

### Glycaemic control

Type 2 diabetes mellitus (T2DM) is a world medical issue characterized by high blood glucose in the body [36]. Long-term health-related problems in patients with DM, including microvascular and macro-vascular complications, such as cardiovascular events, renal failure, diabetic neuropathy and peripheral neuropathy are the complications of poor glycaemic control [37]. It was observed that there is a direct relationship between oxidative stress and T2DM, which is based on the observation that hyperglycemia, hyperinsulinemia, and insulin resistance can enhance the free radical generation and finally result in oxidative stress [38]. Oxidative stress will impair insulin signalling, beta cell insulin secretion and enhances the haemoglobin glycation in T2DM [39]. Thus, the beneficial effect of antioxidants, such as vitamin E should be taken into consideration for the effective glycaemic control in patients with T2DM. Certain studies revealed the possible mechanisms underlying the connection between vitamin E and glucose metabolism they include, prevention of haemoglobin glycosylation by blocking the development of advanced glycosylation end products (AGEs) and mitigation of long-term pancreatic  $\beta$ -cell dysfunction, which caused by oxidative stress in T2DM [40], but with less considerable biological evidence. So large-scale investigations are required to explore the efficacy of vitamin E supplementation for the effective glycaemic control.

### Dermatologic uses

#### Yellow nail syndrome

It characterized by gradually developing, opaque yellow nails with lymphedema and respiratory disorders like chronic sinusitis and bronchitis [41]. Vitamin E is the drug of choice for yellow nail syndrome, with a once-daily dose of 1000 IU for 6 mo [42].

#### Dapsone-induced hemolysis and headache

Certain studies were indicated that vitamin E has a protective effect in hemolysis related with dapsone treatment, and it (dl- $\alpha$ -tocopheryl acetate) is effective when it has given in 800 IU/d, mainly in the treatment of dapsone-induced hemolysis [43, 44]. Vitamin E can also relieve headache associated with this [45], which is generally characterized by methemoglobinemia, vitamin acts by reducing the previously elevated methemoglobin concentration and thereby improves the related symptoms. The improvement in the methemoglobin concentration is considered as the major and reliable laboratory parameter in studies of vitamin E for protection against dapsone side effects [43].

#### Subcorneal pustular dermatoses

Vitamin E generally used in patients who are not responded to conventional medications [46]. It (d- $\alpha$ -tocopheryl acetate) can be given at the dose of 100 IU/d and gradually increased to 400 IU/d for 4 w, mainly for therapeutic modalities in subcorneal pustular dermatoses.

#### Cutaneous amyloidosis

A study conducted for the evaluation on the effects of topical tocotrienol on macular amyloidosis and lichen amyloidosis has shown that it can reduce the associated signs and symptoms of macular amyloidosis and lichen [47].

#### Cataracts

Cataracts is the major contributing factor for significant visual loss in elderly. They basically occur when the proteins get damaged and accumulated, and this damage is caused by unstable molecules called free-radicals. The free-radicals also break down the healthy eye tissue, and this will result in the increased risk of age-dependent macular degeneration and cataract development. Vitamin E has a potential antioxidant property to block the free-radical formation and thereby reduces the risk of cataract. Certain studies have to describe the potential connection between vitamin E and the risk of cataract development. A study conducted by Leske *et al.*, they included participants who are taking vitamin E and who are not taking supplements, and they finally concluded that lens clarity was better in participants who have taken vitamin E as compared to others. A long-term use of vitamin E was linked with the delayed development of age-dependent lens opacification [48]. However, no noticeable effect on cataract formation or progression according to randomized Age-Related Eye Disease Study is indicated for vitamin E [49]. Vitamin E is mainly located in lens membranes and fibers, and it may prevent cataract development by the reduction of Photo-oxidation in lens lipids and stabilizes the lens cell membrane [50]. Generally, the existing evidence was not sufficient to conclude that vitamin E taking alone or in combination with other antioxidants, can prevent the hazard of cataract development; so further researchers are expected to clarify its efficacy.

#### Osteoporosis

Osteoporosis is a gradually developing skeletal disorder which characterized by the slow reduction in bone mineral density (BMD) with advancing age. It's also characterized by micro-architecture decaying of bone tissue, and fracture susceptibility by bone resorption [51]. When the osteoclast cells generate free radicals, like reactive oxygen species (ROS) it will damage calcified bone tissue [52]. Vitamin E performs as a beneficial agent against osteoporosis by improving bone density. It increases the trabecular bone, stops bone calcium loss by the neutralization of antioxidants. By scavenging free-radicals vitamin E supplement protects bone from oxidative damage in humans [53] and could maintain bone matrix

trophism and stimulate the formation of trabecular bone [54]. Earlier studies showed that vitamin E supplements secure against bone loss occurred by oxidative stress that may be due to the oxygen-derived free-radicals or sex hormone's deficiency [55]. Calcium has an important role in bone metabolism and remodelling, and vitamin E-deficiency may lead to bone damage, due to impaired calcium absorption, which finally leads to a state of calcium deficiency and increased free radical activity. Bone resorption may also cause after menopause by a rise in bone-resorbing cytokines level, mainly interleukin1 and 6 (IL-1 and IL-6) [54]. The monocytes secrete IL-1 in an estrogen insufficient state that will lead osteoblast to secrete IL-6, and this IL-6 will stimulate osteoclast production and in this manner, bone resorption is increased. Vitamin E, particularly tocotrienol which is more powerful than tocopherol, can prevent the serum IL-1 and undesirable effects of free radicals on trabecular bone structure [53].

#### Human immunodeficiency virus and acquired immune deficiency syndrome

Vitamin E is an essential anti-inflammatory agent which usually found to be lower in human immunodeficiency virus (HIV) positive individuals; however, it is not identified whether it is beneficial either at every or any phase of HIV infection. Certain studies indicated that vitamin E can re-establish delayed skin hypersensitivity reactions and interleukin-2 production at the dose of 400 IU, and it can also stimulate T helper cell (CD4T-cell) proliferation at high doses [55]. In 1997, Tang *et al.* studied the relationship of both serum vitamin E and A in the progression of HIV infection. They found that high concentration of serum vitamin E (above 23.5  $\mu\text{m}/\text{l}$ ) can slow down the further worsening of the condition [56]. A study on murine acquired immunodeficiency syndrome (AIDS) affected patients were given vitamin E in the 15-fold increase in dietary intake, and the study results showed that immune parameters that are altered in HIV/AIDS have become normalised after the trial. Aside from this, an enhance in dietary vitamin E has also been appeared to ensure against bone marrow toxicity, which is the side-effects of azidothymidine [55]. A study conducted on bone marrow cultures of phase IV AIDS patients who are taking d-alpha-tocopherol revealed comparable results as that of the present findings. Thus, further studies are expected to clarify the part vitamin E plays in the pathogenesis of HIV-1 [56].

#### Immunity

There are certain studies found that vitamin E can enhance the body's defences, cell immune responses and also increases phagocytic functions. It has a pronounced impact in infectious diseases where immune phagocytosis is involved, however, is less effective in the case of cell-mediated immune safeguards. Vitamin E supplementation considerably increases both humoral and cell-mediated immunity in humans, particularly in the geriatrics. A daily intake of 200 mg of vitamin E improves the antibody response to different immunizations in healthy subjects who showed no adverse side effects to vitamin E supplementation [57]. Vitamin E is resistant to geriatric viral diseases, where higher plasma vitamin E levels is in connection with a decrease in a number of infections over a 3 y period [58]. A current report by Kutty *et al.* showed that a daily supplementation of vitamin E can enhance the immune response to a particular antigen [59]. Apart from this, vitamin E assumes a helpful part in different conditions like menstrual pain/dysmenorrhea, photodermatitis, tardive dyskinesia and pre-eclampsia when it is given with vitamin C [60].

#### CONCLUSION

The study presumed that vitamin E is an important nutrient in the treatment of different illnesses, for example, cancer, cataract, AD, atherosclerosis, oxidative stress, osteoporosis, etc.; it has various beneficial impacts in the body functioning and had a significant role in the treatment context. Therefore, raising public alertness about the function of dietary antioxidants in keeping up better well being is essential. There are many conflicting reports of positive and negative results on the same biological activities of vitamin E in the literature. The present writing seems to help the view that the advantages exceed the side-effects. Even so, there are fewer

numbers of human studies in the view of utilizations and useful impact of vitamin E as compared to others so, further studies should be needed to explore the beneficial impacts of vitamin E to human health.

#### AUTHORS CONTRIBUTIONS

All the author have contributed equally

#### CONFLICTS OF INTERESTS

All authors have none to declare

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