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Vitamin E and human health: An update

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ABSTRACT

Vitamin E, a fat-soluble vitamin, has an immense role and is the main constituent of defense due to its antioxidant and anti-inflammatory properties. It performs many actions in the body, such as protecting the body from metabolic syndromes such as cancer, diabetes, and hypertension due to its antioxidant property. Once the Vitamin E is absorbed by the small intestine, it is absorbed by the liver, and it is stored in the liver until it is required. Fruits, vegetables, cereals, chicken, and eggs are the best sources of Vitamin E. Human red blood cells and serum contain alpha- and gamma-tocopherols, whereas alpha-tocopherol is present in the highest quantity. In this chapter, we tried to focus on the beneficial roles of Vitamin E, its synthesis, its types, etc.

Keywords: Anticytokine agent, Antisterility vitamin, Chromanol rings, Interlukin 6 osteoarthritis, Knee society scores and randomized control trial, Osteoporosis, Prospective case control study, Reactive nitrogen species, Toxicity, Vitamin E

INTRODUCTION

Vitamin E is a fat-soluble vitamin whose molecular structure consists of chromanol and isoprenoid rings with a side chain in the C2 position. The chromanol ring is the hydrophilic part of the molecule, while the isoprenoid side chain makes Vitamin E a fat-soluble vitamin. It can therefore be said that Vitamin E is an amphipathic vitamin and is mainly located in the membrane due to its amphipathic property.[1,2] Vitamin E is insoluble in water, but it is soluble in organic solvents and vegetable oils.[2] Vitamin E has a light yellow to amber color, but in its purest form, it is a colorless, oily, clear liquid that darkens by oxidation when exposed to air or light.

Due to its lipophilic nature, Vitamin E, especially alpha-tocopherol, is localized in the cell membrane, plasma membrane, and plasma lipoproteins, where it interferes with the chain reactions of lipid peroxidation, especially in polyunsaturated fatty acids (PUFAs). Defects in the α-tocopherol transfer protein (α-TTP) lead to a genetic disorder called "ataxia with Vitamin E deficiency."[3]

Since humans cannot synthesize Vitamin E themselves, they are primarily dependent on food sources for Vitamin E, and its absorption depends on the intake of lipids.

In the bloodstream, it is transported in the form of lipoproteins. Hydrolysis of the lipoprotein leads to the release of Vitamin E and its subsequent uptake into the cells. Of the various forms of Vitamin E absorbed by the body, only α-tocopherol is recognized and utilized. This is due to the presence of a hepatic 32 kDa α-TTP and tocopherol-associated proteins that selectively bind α-tocopherol.[1]

Vitamin E is only synthesized by photosynthetic organisms. Plants, fruits, green leafy vegetables, and seeds are the richest sources of Vitamin E. Due to its antioxidant properties, this vitamin protects cells from damage caused by reactive oxygen species [Tables 1-3].

In 1922, Vitamin E was discovered as a substance necessary for reproduction. Vitamin E is an important micronutrient for the human body as it maintains various biological functions of the body due to its antioxidant properties [Table 4].

Since its significance for reproduction was studied eight decades ago, it is referred to as the antisterility vitamin. Another name for it is a protective vitamin. For adults, the recommended daily intake of Vitamin E in natural forms is 1500 IU, while the recommended daily intake of Vitamin E in synthetic or artificial forms is 1000 IU.

Pregnant women who are Vitamin E deficient experience miscarriages. Vitamin E was discovered in 1922 and given the moniker X-factor by Evan and Bishops. Four tocopherols and four tocotrienols that are present in food are collectively referred to as Vitamin E.

According to certain research, the amount of Vitamin E in breast milk drops as nursing duration increases, meaning that colostrum gives babies the most Vitamin E. Vitamin E's two primary functions are anti-inflammatory and antioxidant. Due to a lack of this vitamin, people with human immunodeficiency syndrome have extremely weakened immune systems. Vitamin E was formally acknowledged as the fifth vitamin in 1925 [Figure 1].[4]

This vitamin is found in lipid compartments like the cell membrane due to its hydrophobic nature. In this case, Vitamin E's primary role is to stop lipid peroxidation, which keeps membrane stability. Due to its many benefits, Vitamin E also contains anti-cancer potential. Heat-shock proteins are activated by Vitamin E, which also downregulates mutant p53 protein and promotes the p53 tumor suppressor gene.

Alpha-, beta-, and gamma-tocopherols and alpha-, beta-, and gamma-tocotrienols are the eight distinct isoforms of natural Vitamin E. In their cross-sectional study of 232 early postmenopausal women, Mata-Granados *et al.*[5] looked into the relationship between low Vitamin E levels and low bone mineral density. As a result, they found that low Vitamin E levels may be a risk factor for osteoporosis in these women. A similar study by Holvik *et al.*[6] investigated that low serum alpha-tocopherol levels are associated with an increased risk of hip fractures in the elderly Norwegian population. In animal and human studies, VE has shown its anti-inflammatory properties by suppressing levels of C-reactive protein and tumor necrosis factor-alpha. Podila *et al.*[7] investigated that Vitamin E is very beneficial for liver health. One of the most common metabolic syndromes, known as non-alcoholic fatty liver disease (NAFLD), is

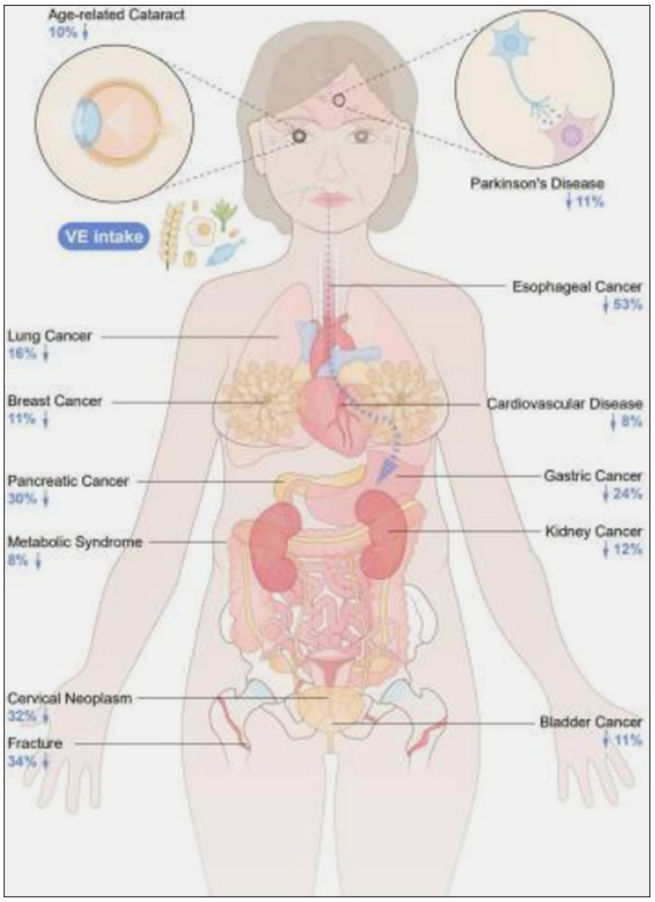

Figure 1: Diagrammatic Representation of Vitamin E in different diseases (Source: Zhang *et al.*, 2023) Vitamin E intake and multiple health outcomes: An umbrella review. Frontiers in Public Health.

the most common liver disease worldwide today, and due to the prevalence of obesity and type 2 diabetes, which are related to lifestyle and diet, the incidence of NAFLD is rapidly increasing. NAFLD is characterized by excessive accumulation of fat, particularly triglycerides, in the liver and encompasses a broad spectrum from benign steatosis to non-alcoholic steatohepatitis (NASH), cirrhosis, liver failure, and hepatocellular carcinoma.

Study by Yoshida *et al.*,[8] investigated in a mouse model that mice with a knockout of the α-TTP, when fed a VE-deficient diet for 28 weeks, had elevated levels of lipid peroxidation markers due to severe Vitamin E deficiency.

Sanyal *et al.*[9] conducted a randomized clinical trial with 247 adults with NASH and without diabetes. The participants were randomly assigned to three groups based on the study criteria after obtaining informed consent. The study lasted 96 weeks, with Group 1 receiving 30 mg pioglitazone and a Vitamin E placebo daily, Group 2 receiving 800 IU of Vitamin E and a pioglitazone placebo daily, and Group 3 receiving placebos for both drugs. The drugs were stopped after biopsy, and the subjects

Table 1: Different food sources of Vitamin E.

Sources	Plant parts	Usable product name	Vitamin E content, g/kg
Wheat	Kerne	Germ	1500
Sunflower	Seed	Oil, Kernel	610/351
Almond	Kernel	Oil	392
Safflower	Kernel	Oil	450
Canola	Seed	Oil	270
Walnut	Fruit	Oil	200
Peanut	Seed	Edible nut	172
Palm	Kernel	Oil	150
Olive Oil	Seed	Oil	120
Soybean	Kernel	Oil	116
Maize	Seed	Entire grain	20
Oat	Seed	Kernel	15
Coconut	Seed/Fruit	Oil	10
Asparagus	Shoot Young	Shoot	15
Spinach	Leaf, Leaf	Raw leaf, Cooked leaf	20/21
Tomato	Fruit	Raw fruit	9
Carrot	Root	Taproot	6
Tobacco	Leaf, Leaf	Young leaf, Old leaf	57/180

were followed for 24 weeks. The results showed that the Vitamin E-treated groups had significant improvements compared to the placebo group. Both the pioglitazone and Vitamin E-treated groups showed reduced levels of serum alanine and aspartate aminotransferase compared to the placebo group.

PHYSIOCHEMICAL PROPERTIES OF VITAMIN E

The International unit of pure and applied chemistry (IUPAC) name and molecular formula of Vitamin E are (2R)-2,5,7,8-Tetramethyl-2-([4R, 8R]-4,8,12-trimethyltridecyl]-3,4-dihydrochromen-6-ol and C29H50O2, respectively. It has a molecular weight of 430.7 g/mol and a melting point of 3°C and boiling point of 235°C.[1,2] As it is a fat-soluble vitamin, it is insoluble (1.9×10^{-6} mg/L at 25°C) in water but slightly soluble in ethanol, with a density of 0.950 g/cm^{-3} at 25°C and a partition coefficient log P = 12.2. It is unstable under ultraviolet (UV) light, and its bond dissociation energy is 77.1 kcal/mol. The optical rotation of tocopherols is very small and depends on the nature of the solvent. In ethanol, the UV absorption spectra of tocopherols and tocotrienols show maximum absorption at 292–298 nm, whereas in a hydrophobic solution, α-Tocopherol is fluorescent with an emission maximum at about 325 nm.

Vitamin E is non-polar. Among the eight different isomers of Vitamin E, alpha-tocopherol is the most active and important

Table 2: Different sources of Vitamin E.

Food (100 g/100 mL)	Amount of Vitamin E (mg)
Hazelnut oil	47.2
Sunflower oil	41.08
Almond oil	39.2
Almond	23.75
Roasted sunflower seeds	38.33
Roasted sesame seeds	36.33
Safflower oil	34.1
Hazelnut	23
Canola oil	17.46
Peanut oil	15.69
Corn oil	14.3
Olive oil	11.42
Soybean oil	8.18
Brazil nuts	7.14
Palm oil	3.81
Egg yolk	2.58
Avocado	2.07
Walnuts	1.8
Sesame oil	1.4
Cashew nuts	0.92
Chilli powder	47.74 mg
Red pepper/cayenne pepper	29.83 mg
Linseed oil	0.71
Coconut oil	0.09
Peanut/groundnuts	6.94

Table 3: Recommended dietry allowance of Vitamin E at different stages of life.

Life stage	Recommended amount
Birth till 6 months	4 mg/day
7–12 months infants	5 mg/day
1–3 years children	6 mg/day
4–8 years children	7 mg/day
9–13 years children	11 mg/day
14–18 years of teen	15 mg/day
Adults	15 mg/day
Pregnant women	15 mg/day
Breastfeeding women	19 mg/day

form. Tocopherols are easily oxidized but can be destroyed by peroxide ozone and permanganate in a process catalyzed by light and accelerated by PUFAs and metal salts. Due to the presence of tocotrienols and tocopherols, Vitamin E is a fat-soluble vitamin as these two groups possess hydrophobic character, but the presence of a hydroxyl substituent confers

Table 4: The Numerous biological activity of Vitamin E Supplementation.

Serial No	Biological functions of Vitamin E
1.	Healthy skin
2.	Antioxidant
3.	Anti-inflammation
4.	Anti-aging
5.	Anti-cancer
6.	Enhanced cell-mediated immunity
7.	Enhanced innate immunity
8.	Development of skeletal muscles

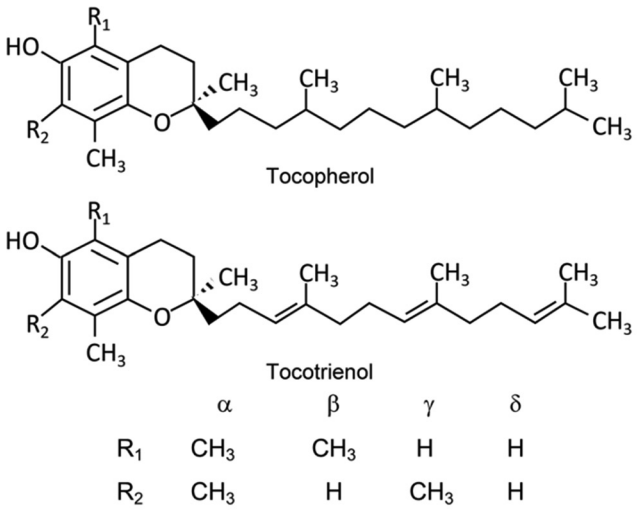

Figure 2: Showing chemical structure of Vitamin E

its amphipathic nature. The CAS number of Vitamin E is 59-02-09. Another naturally occurring form of Vitamin E in food sources is alpha tocopherol also known as d-alpha-tocopherol [Figure 2].

Once absorbed by the small intestine, Vitamin E is readily stored in the liver until needed. It is secreted by the liver as alpha-tocopherol, which is recognized by the body. Deficiency or insufficiency of Vitamin E during pregnancy can lead to the birth of premature infants with low birth weight. The best dietary sources of Vitamin E are edible vegetable oils, as they have the highest concentration of all the different homologues of Vitamin E. Alpha-tocopherol and gamma-tocopherols are present in red blood cells and serum, with the highest concentration of alpha-tocopherol between the two homologues. In plasma, trace quantities of gamma-tocopherol and delta-tocopherol are present. Vitamin E is a powerful antioxidant because it has the capacity to react with singlet oxygen and Peroxyl radical (HOH•), favoring lipid peroxidation.[10]

STRUCTURE OF VITAMIN E

As discussed above, Vitamin E is a plant-derived, lipid-soluble substance. Its molecular structure consists of chromanol rings with a side chain at the C2 position.[1] There are eight different isoforms of Vitamin E: alpha, beta, gamma, delta tocopherols, and four corresponding tocotrienols. A fully saturated phytyl-derived side chain is present in all forms of tocopherols, while a geranylgeranyl-derived side chain with three double bonds at positions C3', C7', and C11 is present in tocotrienols. Tocotrienols have an unsaturated isoprenyl side chain.

The isoforms of Vitamin E, alpha, beta, gamma, delta forms of tocopherols, and tocotrienols differ from each other due to the position and number of methyl groups in the chromanol ring. The alpha forms of tocopherol and tocotrienol have three methyl groups at the C5, C7, and C8 positions of the chromanol ring, while the beta and gamma forms have two methyl groups, and the delta form has one methyl group. Natural occurring tocopherols have three asymmetric carbon atoms at the C2 position of the chromanol ring and C4 and C8 of the side chain. The double bonds of tocotrienols' side chains at C3' and C7' positions possess a trans configuration. Chiral carbon atoms are present in tocopherols at the C2 position in the chromanol ring and two in the side chain at C4' and C8.

Two other isomers of Vitamin E besides tocopherol and tocotrienol are tocomonoenols and tocodienols, having a single and two double bond unsaturations, respectively, are found in natural sources. Tocomonoenol, which contains a single bond at carbon 11', 2,5,7,8-tetramethyl-2-(4',8',12'-trimethyltrideca-11'-enyl)-6-chromanol, has been isolated from palm and rice bran oils. Tocomonoenol has been detected in plants and plant foods such as palm oil, pumpkin seed oil, sunflower oil, and delta-tocomonoenol in kiwi fruit. Beta, gamma, and delta tocomonoenols were detected in the leaves of *Kalanchoe daigremontiana* and *Phaseolus coccineus*.

The chromanol ring present in the structure of Vitamin E plays a crucial role in detoxifying reactive nitrogen species and reactive oxygen species. The reaction of radicals that are scavenged by tocopherol leads to the formation of tocopheroxyl radicals. This radical is then reduced back to tocopherols by ascorbic acid, ubiquinol, plastoquinol, or phenolic compounds. Scavenging of singlet oxygen (1 O_2) by α-tocopherol leads to the formation of an unstable compound known as 8a-hydroperoxy-α-tocopherone, which is again reduced back to α-tocopherol by ascorbic acid, or may be oxidized into α-tocopheryloquinone, which is one of the stable forms.

BIO SYNTHESIS OF VITAMIN E

In most cyanobacteria, the biosynthetic pathway of tocopherols occurs. Homologues (HGA) and phytyl pyrophosphate (PPP) are the direct biosynthetic precursors of tocopherols. Homogentisate (HGA) is derived from tyrosine in higher plants, whereas PPP is a product formed by the reduction of geranylgeranyl pyrophosphate (GGPP), catalyzed by geranylgeranyl reductase. GGPP is synthesized due to the condensation of two carbon precursors, dimethylallyl diphosphate, and isopentenyl diphosphate. There are two known pathways for the synthesis of these compounds: The 1-deoxy-D-xylulose-5-phosphate (DXP) pathway, also known as the methylerythritol phosphate pathway, is used by cyanobacteria for the synthesis of isoprenoid precursors. The enzymes of the DXP pathway occur in the plastids of higher plants, while the mevalonate pathway is found in the cytoplasm of higher plants. Tocochromanol biosynthesis starts with the condensation of homogentisate (HGA) and PPP. Another key reaction that takes place is cyclization, leading to the formation of the chromanol ring.[1] Vitamin E is highly dependent on vitamin C, vitamin B3, selenium, and glutathione. Vitamin E enriched diet cannot have an optimal effect unless it is also rich in food that provides these three nutrients also.

VITAMIN E AS AN ANTICYTOKINE AGENT

Vitamin E acts as an anticytokine agent by helping to suppress bone resorption markers, which, in turn, prevents osteoporosis. One study involving a rat model showed that when the rats were injected with ferric nitrilotriacetate, an oxidizing agent that produces free radicals through the Fenton reaction, oxidative stress markers such as interleukin (IL)-6 and IL-1 were generated, leading to inflammation in various organs. When these rats were supplemented with Vitamin E in the forms of tocotrienols and α-tocopherol, the levels of inflammatory cytokine markers were significantly suppressed. This suggests that Vitamin E serves as a potent antioxidant, helping to reduce the levels of inflammatory cytokines and thereby protecting bones from osteoporosis. The transcription factor nuclear factor-kappa B (NF-κB) is activated by free radicals, which leads to the production of bone-resorbing cytokines such as IL-1 and IL-6. These inflammatory cytokines are responsible for causing inflammation, contributing to the fragility and weakness of bones. Consequently, it has been investigated that Vitamin E supplementation is very effective, as it can scavenge and neutralize free radicals before they activate the transcription factor NF-κB.[11]

In addition, Vitamin E supplementation helps elevate the levels of antioxidant enzymes, such as superoxide dismutase (SOD) and catalase, within the bone. A study by Maniam *et al*. demonstrated that Vitamin E supplementation is highly effective in reducing femoral thiobarbituric acid-reactive substances and in increasing the activity of glutathione peroxidase, an important antioxidant enzyme.[12] In a cross-sectional study conducted by Zhuang *et al*., which involved data from 9 years to 5,800 older adult women aged over 50, it was concluded that a high intake of Vitamin E is associated with a reduced risk of osteoporosis, based on the study's inclusion and exclusion criteria [Table 5].[13-20]

VITAMIN E AND JOINT HEALTH RELATIONSHIP

Several studies have demonstrated the positive effects of Vitamin E supplementation on cartilage health. In a case–control study by Surapaneni and Venkataramana,[14] which included an Indian population of 20 patients aged between 35 and 60 years, it was found that osteoarthritis (OA) patients have lower levels of Vitamin E compared to healthy controls. Similar findings were reported by Bhattacharya *et al*.[21] in a study involving 40 osteoarthritic patients aged between 40 and 70 years. Along with the lower levels of Vitamin E, this study also identified elevated levels of inflammatory cytokines such as IL-6, C-reactive protein, and ceruloplasmin in these patients. Another case–control study conducted on a Thai population by Sutipornpalangkul *et al*.[22] examined Vitamin E levels in the synovial fluid of 32 primary knee OA patients with severe cartilage damage undergoing knee replacement. The study found that Vitamin E levels were lower in comparison to those of injured knee joint patients with intact cartilage undergoing knee arthroscopy. Thus, this study concluded that Vitamin E is very beneficial in managing OA patients.

In a study by Angthong *et al*.,[23] focused on OA, it was found that the concentration of Vitamin E in the synovial fluid of knee OA patients is a prognostic factor that suggests treatment directions. This study recruited 23 patients with primary knee OA and divided them into two groups based on their pre-treatment knee society scores (KSS). Group 1 consisted of 9 severe knee OA patients with a KSS ≤ 46, while Group 2 included 14 patients with mild to moderate knee OA having a KSS > 46. The study revealed that the mean concentration of Vitamin E is inversely related to the severity of knee OA (mild-moderate > severe, $P = 0.006$), along with a significant positive correlation between KSS grade and Vitamin E concentration ($r = 0.43$, $P = 0.04$).[21-24]

Li *et al*. suggest that Vitamin E has an important impact on reproductive health. Lipid peroxidation is caused by free radicals and reactive oxygen species, such as hydroxyl radicals, superoxide, and hydrogen peroxide. Vitamin E, often referred to as the "antisterility vitamin," plays a crucial role in reproductive health. Its deficiency can lead to damage to the reproductive system, resulting in testicular

Table 5: Role of Vitamin E in different diseases.

Study title	Type of study	Number of participants	Conclusion
Interrelation between plasma concentrations of Vitamins C and E along the trajectory of ageing in consideration of lifestyle and body composition: A longitudinal study over two decades	Observational study	399 subjects recruited from both the genders, 121 men and 278 women, above aged 60 years.	Stable positive interrelation was shown between plasma concentrations of VC and VE with aging[15]
A controlled clinical trial of Vitamin E supplementation in patients with congestive heart failure	Double-blinded randomized control clinical trial	Fifty-six patients with advance heart failure disease were recruited in the trial according to inclusion and exclusion criteria of the study, recruited Subjects were followed for 3 months, that is, at baseline, 3 and 12 weeks and they were randomly assigned in two groups that were supplemented with either 500 IU alpha-tocopherol or placebo and at each follow-up 25 mL blood was also collected for routine investigation and measurement of oxidative stress markers	Vitamin E supplementation significantly elevated Vitamin E plasma concentration but have no impact on quality of life and levels of oxidative stress markers. Similarly, levels of atrial naturetic peptide neurohormonal-cytokine markers of prognosis, tumor necrosis factor, epinephrine, and norepinephrine were also remain unchanged even after supplementation[16]
Effect of supplementation with tomato juice, Vitamin E, and Vitamin C on LDL oxidation and products of inflammatory activity in type 2 diabetes	A randomized placebo-controlled parallel trial	Fifty-seven patients with type 2 diabetes who were under the age of 75 years and having n HbA1c level <10% and a fasting plasma glucose level <11% were recruited in the study and were continuously given placebo for 4 weeks after that they were randomly assigned and were supplemented with tomato juice without added sugar (500 mL/day), Vitamin E (800 U/day), vitamin C (500 mg/day), or continued with placebo for 4 weeks, Levels of Vitamin C, E, CRP, vascular cell adhesion molecule 1, and intercellular adhesion molecule 1, Susceptibility of LDL to oxidation (lag time) were measured 3 times during the study, that is, at the beginning of the study, after the placebo phase and after the end of the study.	Lycopene levels were increased nearly 3 folds (P=0.001), and the lag time in isolated LDL oxidation by copper ions increased by 42% (*P*=0.001) in patients who were consuming tomato juice, CRP levels were significantly decreased in patients who were consuming Vitamin E whereas. Circulating levels of cell adhesion molecules and plasma glucose did not change significantly during the study. Thus the finding of the study indicates that Vitamin E and Tomato juice supplementation is effective in reducing the risk factor of myocardial infarction in diabetic patients.[17]
Combined supplementation with α-tocopherol and vitamin C improves the blood pressure of pediatric idiopathic nephrotic syndrome patients	Prospective case–control study	Forty-two pediatric idiopathic nephrotic syndrome patients having age 1–15 years were recruited in the study according to the Inclusion and exclusion criteria of the study after obtaining informed consent, subjects were divided into two groups, group 1 is control group who were only on standard treatment and placebo, group 2 were standard treatment, placebo, Vitamin C and Vitamin E having dose 10–15 mg/kg/day for 12 weeks.	The combined treatment of Vitamin C and Vitamin E is very effective in improving blood pressure in pediatric idiopathic nephrotic patients[18]

(*Contd...*)

Table 5: Role of Vitamin E in different diseases (*Continued*).

Study title	Type of study	Number of participants	Conclusion
Vitamin E modulation of CRP in smokers with acute coronary syndromes	Double-blind, placebo controlled trial	One hundred and ten acute coronary syndrome patients were enrolled in the study who were above 18 years of age according to the inclusion criteria of the study, they were divide in two groups, Group 1 was supplemented with 400 IU of Vitamin E for 6 months, serum samples were collected at baseline, 2, 4, and at 6 month. Group 2 was supplemented with placebo and were also followed for 6 months and serum sample was collected at baseline, 2, 4, and at 6 month.	Over 6 months supplementation with Vitamin E was effective in reducing the CRP levels in smokers in comparison to smokers on placebo treatment.[19]
Marked decrease in plasma antioxidants in aged osteoporotic women: Results of a cross-sectional study	Cross-sectional study	1100 women were recruited in the study for screening for osteoporosis from Geriatric Division of Perugia University Hospital according to the inclusion and exclusion criteria of the study, 150 women were willingly participated in the study (75 Osteoporotic, 75 Control). Study variables of the study include age, years since menopause, BMI, self-reported fractures, smoking habit, nutritional status, etc. Duration of the study was 1 year.	In osteoporotic women, Vitamin C, Vitamin E, Vitamin A, and uric acid plasma level were lower in comparison to control group. Similarly, levels of antioxidant enzymes such as SOD and GPx in plasma and erythrocytes (only SOD) were significantly lower in osteoporotic women in comparison to non-osteoporotic women. MDA a lipid peroxidation marker showed no significant damage in both groups.[20]

CRP: C-reactive protein, GPx: Glutathione peroxidase, SOD: Superoxide dismutase, HbA1c: Hemoglobin A1C, BMI: Body mass index, LDL: Low density lipoprotein, MDA: Malondialdehyde

damage, degenerative spermatogonia, and degeneration of the seminiferous tubules. Vitamin E supplementation has been shown to improve the weight of the epididymis, the density and diameter of convoluted seminiferous tubules, spermatogenic cell density, and the diameters of epididymal ductules when administered at dosages of 80 and 320 IU/day in goats.[24-26]

Another Indian study by Rao *et al.*[25] on mice has shown that Vitamin E proves to be very effective against toxicity caused by nickel and chromium metals in the ovary of a mouse by preventing lipid peroxidation and protecting the antioxidant system.[25]

VITAMIN E REGULATES MICRO RIBONUCLEIC ACIDS (MIRNAS)

miRNAs are small, non-coding (22 nucleotides long), single-stranded in their mature form. They post-transcriptionally influence gene expression by binding to the 3' untranslated region of mRNA, thereby affecting its translation into proteins. miRNAs have different target mRNAs. To investigate the role of one of the analogues of Vitamin E, namely, RRR-α-tocopherol, in the expression of microRNAs in the liver, rats were fed a diet containing either sufficient or insufficient Vitamin E for 6 months. After 6 months, it was investigated that a diet containing insufficient Vitamin E downregulated the levels of miR-122a and miR-125b, which have been linked to important functions such as lipid metabolism, carcinogenesis, and inflammation.[27]

In their study, Tili *et al.* investigated that the expression of miR-125b is downregulated in cancer and chronic inflammation so that the decrease in the expression of miR-125b is directly related to the upregulation of the inflammatory cytokine tumor necrosis factor-alpha (TNF-α) after lipopolysaccharide stimulation. From the above discussion, it can be hypothesized that the down-regulated expression of miRNA-125b in the liver of Vitamin E-deficient rats may enhance the inflammatory response.[27]

Tang *et al.* 2013 showed in his study that Vitamin E plays a very important role as an antioxidant in the immune system of fish. To confirm the role of Vitamin E as an antioxidant and as protection against oxidative stress, juvenile Nile tilapia fish were fed with VE at three different doses, that is, 50 and 2500 mg/kg. After an 8-week growth experiment, the

expression level of eight miRNAs (miR-21, miR-223, miR-146a, miR-125b, miR-181a, miR-16, miR-155, and miR-122) was detected in the liver of tilapia fish, and it was found that a VE-deficient diet, fed fish exhibited suppressed SOD activity and decreased expression of miR-223, miR-146a, miR-16, and miR-122, whereas fish fed a Vitamin E-rich diet also exhibited decreased activity of the SOD enzyme, but expression of all eight miRNAs was increased. This study could open up a new avenue for research into molecular nutrition.[28]

According to Ara *et al*. 2023, the antioxidant property of Vitamin E is very beneficial and promotes axonal regeneration after acute spinal cord injury, low plasma Vitamin E levels in pregnant women lead to miscarriages.[29]

A case cohort study by Shamim *et al*. 2015 in Bangladesh of 1605 pregnant women from rural areas found that low plasma alpha-tocopherol levels were associated with increased odds of miscarriage in these women, while low gamma-alpha-tocopherol levels were associated with lower odds of miscarriage. Maternal Vitamin E status in the first trimester may influence the risk of early miscarriage.[30]

Rapid metabolism, increased production of free radicals, and increased lipid peroxidation are more common in pregnant women. Thus, if they have low plasma Vitamin E levels, there may be excessive production of free radicals leading to placental aging and endothelial vascular damage, which increases the incidence of high-risk infections in pregnancy. Fetal cell membrane lining also get damage due to low Vitamin E levels during pregnancy that increase the chances of premature ruptures of the embryo, In men, recurrent miscarriage occurs due to elevation in the levels of reactive oxygen species and suppression in the levels of antioxidant, thus to improve sperm quality and its parameters; nowadays, antioxidants therapy has been more focused.

Pourmasumi *et al*. 2018 included 60 or more couples with recurrent miscarriages in their randomized control trial. They were asked to take 1 tablet of VE and 1 tablet of selenium daily for 3 months, and sperm samples were collected and analyzed before and after treatment and after analysis they investigated that antioxidant therapy can improve sperm parameters and chromatin condensation in recurrent miscarriage male partners.[31]

In polycystic ovary syndrome (PCOS), Vitamin E has proven to be very beneficial. Studies have shown that while Vitamin E is not a hormone, it acts similarly to hormones by mimicking the effects of progesterone in the body. Furthermore, it helps to reduce the side effects associated with high levels of androgens, such as testosterone and estrogen. The consumption of omega-3 fatty acids alongside Vitamin E, along with lifestyle changes, can effectively reduce inflammation and improve insulin sensitivity. Therefore, this combination presents an effective treatment approach for individuals with PCOS. Given its antioxidant and anti-inflammatory properties, Vitamin E may serve as a cost-effective supplement for PCOS patients, potentially improving their quality of life.[32,33]

Wong *et al*. have investigated the benefits of Vitamin E in relation to hypertension. As we know, oxidative stress is a key factor in the pathogenesis of hypertension. To mitigate the effects of oxidative stress, Vitamin E has been found to be very beneficial.[33]

The tocotrienol-rich fraction (TRF) of palm oil was utilized in a randomized double-blind, placebo-controlled clinical experiment to examine its potential to reduce pregnancy-induced hypertension in healthy primigravida. It was determined that TRF from palm oil does not statistically significantly lower the risk of developing pregnancy-induced hypertension in the population under study, although there was a tendency toward a lower incidence of pregnancy induced hypertension (PIH) in the TRF arm compared to the placebo arm. Of the 299 healthy women, 151 were randomized to receive oral TRF 100 mg daily from the early second trimester until delivery, while 148 were on placebo.[34]

Pinto *et al*.,[10] states that Vitamin E is a powerful antioxidant that has the ability to suppress collagen degradation by suppressing the action of matrix metalloprotein 1, involved in the initial process of collagen hydrolysis. Vitamin E can be found in deeper layers of the skin, that minimize the photocarcinogenesis process. Due to its antioxidant activity in skin, it is classified as an early and very sensitive marker for oxidative damage promoted by the environment. Lipoperoxidation of cell membranes and the degradation of fatty acids in the skin and body is prevented by Vitamin E for their proper functioning.[10]

Vitamin E has the ability to eliminate free radicals induced by UV radiation, thus protects endogenous antioxidants from degrading processes, prevents lipid peroxidation, and reduces immunosuppression caused by UV rays in the skin. Combination of Vitamin E and C is very effective in protecting skin from sunburn and erythema. These two combinations of Vitamins E and C are a very potential agent against skin aging and skin cancer. Applying Vitamin E topically on skin before sun exposure prevents the formation of cyclobutane pyrimidine dimer induced by harmful UV B.[34]

CONCLUSION

Researchers attention on nutraceuticals supplementation on various metabolic syndrome treatment, metabolic bone disorders, and various other communicable and non-communicable diseases are an emerging field of interest as nutraceutical like Vitamin E is cost effective and easy to consume and have various beneficial properties as

antioxidant, anti-inflammatory, neuroprotectective, etc., as proved by different animal and human studies. In 1922, Vitamin E was identified as essential component that's why it is known as antisterility vitamin. It is a lipid soluble vitamin mostly available in its two forms known as tocopherol (TF) and tocotrienol (T3). It is also another aspect that more focus on tocotrienol in comparison to tocopherol due to its anticancer and cholesterol lowering property since decades. Studies have also proven that T3 is a very strong class of antioxidant than TF. In metabolic syndromes, major role is played by oxidative stress and inflammation. In case of obesity and dyslipidemia, there is abnormal growth of adipose tissue that contributes in the overproduction of inflammatory mediators such as TNF-α, IL-6, and IL-1 beta and activates the NF-κB. Due to increased production of AGEs in hyperglycemia leads to the production of pro-inflammatory cytokines in monocytes and macrophages. In hyperglycemia, high glucose levels also promote stimulation of increased production of reactive oxygen species and superoxide anion (O-2O_2-) through activation of glycolysis. Similarly, there is an inverse relationship between blood pressure and activity of antioxidant enzymes SOD and glutathione peroxidase that promotes in the production of oxidative stress, thus from above mentioned details, it is confirmed that inflammation and oxidative stress are closely related to metabolic syndromes; therefore, Vitamin E is the best nutraceutical that has potential in regulating metabolic syndromes because it possess both anti-inflammatory and anti-oxidative properties. However, more human clinical trials need to be conducted to confirm these findings. In addition, many animal studies and human clinical trials also confirm the dissimilarity in the biological properties between TF and T3.

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