Vitamin E

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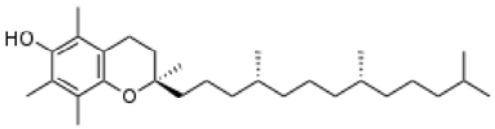
Vitamin E refers to a group of compounds that include both tocopherols and tocotrienols.[1][2] Of the many different forms of vitamin E, γ-tocopherol is the most common form found in the North American diet.[3] γ-Tocopherol can be found in corn oil, soybean oil, margarine, and dressings.[4][5] α-tocopherol, the most biologically active form of vitamin E, is the second-most common form of vitamin E in the diet. This variant can be found most abundantly in wheat germ oil, sunflower, and safflower oils.[5][6] As a fat-soluble antioxidant, it interrupts the propagation of reactive oxygen species that spread through biological membranes or through a fat when its lipid content undergoes oxidation by reacting with more-reactive lipid radicals to form more stable products.[7][8][9][10] Regular consumption of more than 1,000 mg (1,500 IU) of tocopherols per day[1] may be expected to cause hypervitaminosis E, with an associated risk of vitamin K deficiency and consequently of bleeding problems.

Vitamin E

Drug class



The α-tocopherol form of vitamin E

Class identifiers	
Use	Vitamin E deficiency, antioxidant
ATC code	A11H
Biological target	Reactive oxygen species
Clinical data	
Drugs.com	MedFacts Natural Products (https://www.drugs.com/npp/vitamin-e.html)
External links	
MeSH	D014810

In Wikidata

Contents

Forms

The nutritional content of vitamin E is defined by α-tocopherol activity. The molecules that contribute α-tocopherol activity are four tocopherols and four tocotrienols, identified by the prefixes alpha- (α-), beta- (β-), gamma- (γ-), and delta- (δ-).[11] Natural tocopherols occur in the RRR-configuration only. The synthetic form contains eight different stereoisomers and is called 'all-rac'-α-tocopherol.[12] Water-soluble forms such as d-alpha-tocopheryl succinate are used as food additive.

α-Tocopherol

alpha-Tocopherol is an important lipid-soluble antioxidant. It performs its functions as antioxidant in the glutathione peroxidase pathway,[13] and it protects cell membranes from oxidation by reacting with lipid radicals produced in the lipid peroxidation chain reaction.[9][14] This removes the free radical intermediates and prevents the oxidation reaction from continuing. The oxidized α-tocopheroxyl radicals produced in this process may be recycled back to the active reduced form through reduction by other antioxidants, such as ascorbate, retinol or ubiquinol.[15] Other forms of vitamin E have their own unique properties; for example, γ-tocopherol is a nucleophile that can react with electrophilic mutagens.[16]

Sample of α-tocopherol, one of the various forms of vitamin E

Tocotrienols

Compared with tocopherols, tocotrienols are sparsely studied.[17][18]

Functions

Vitamin E has many biological functions, including its role as a fat-soluble antioxidant.[1]

- As an antioxidant, vitamin E acts as a peroxyl radical scavenger, disabling the production of damaging free radicals in tissues, by reacting with them to form a tocopheryl radical, which will then be reduced by a hydrogen donor (such as vitamin C) and thus return to its reduced state.[19] As it is fat-soluble, it is incorporated into cell membranes, which protects them from oxidative damage. Vitamin E has also found use as a commercial antioxidant in ultra high molecular weight polyethylene (UHMWPE) used in hip and knee implants to replace faulty joints, to help resist oxidation.[20]
- As an enzymatic activity regulator, for instance, protein kinase C (PKC), which plays a role in smooth muscle growth, can be inhibited by α-tocopherol. α-Tocopherol has a stimulatory effect on the dephosphorylation enzyme, protein phosphatase 2A, which in turn, cleaves phosphate groups from PKC, leading to its deactivation, bringing the smooth muscle growth to a halt.[21]
- Vitamin E also has an effect on gene expression. Macrophages rich in cholesterol are found in the atherogenetic tissue. Scavenger receptor CD36 is a class B scavenger receptor found to be up-regulated by oxidized low density lipoprotein (LDL) and binds it.[22] Treatment with α-tocopherol was found to downregulate the expression of the CD36 scavenger receptor gene and the scavenger receptor class A (SR-A) [22] and modulates expression of the connective tissue growth factor (*CTGF*).[23][24] The *CTGF* gene, when expressed, is responsible for the repair of wounds and regeneration of the extracellular tissue lost or damaged during atherosclerosis.[24]

- Vitamin E also plays a role in eye and neurological functions,[1][25] and inhibition of platelet coagulation.[26][27][28]
- Vitamin E also protects lipids and prevents the oxidation of polyunsaturated fatty acids.[29]

So far, most human supplementation studies about vitamin E have used only α-tocopherol. This can affect levels of other forms of vitamin E, e.g. reducing serum γ- and δ-tocopherol concentrations. Moreover, a 2007 clinical study involving α-tocopherol concluded supplementation did not reduce the risk of major cardiovascular events in middle-aged and older men.[30]

Deficiency

Vitamin E deficiency can cause:

- spinocerebellar ataxia[14]
- myopathies[5]
- peripheral neuropathy[8][31][32]
- ataxia[8][31][32]
- skeletal myopathy[8][31][32]
- retinopathy[8][31][32]
- impairment of the immune response[8][31][32]
- red blood cell destruction[29]

Supplementation

Vitamin E supplementation has not been shown to have significant benefit for people who are healthy, and appears to be harmful.[33][34] It does not improve blood sugar control in an unselected group of people with diabetes mellitus [35] or decrease the risk of stroke.[36] Daily supplementation of vitamin E does not decrease the risk of prostate cancer, and may increase it.[1][37] Studies on its role in age-related macular degeneration are ongoing, though if it is of a combination of dietary antioxidants used to treat the condition it may increase the risk.[38] Routine supplementation with vitamin E during pregnancy has been shown to offer no benefit to the mother or the child. Vitamin E has been reported to cause more side effects, such as abdominal pain in pregnant women, and also the increased risk of having early rupture of membranes at term.[39]

Vitamin E, along with β-carotene and vitamin C, has no protective effect on reducing the risk of cataract, cataract extraction, progression of cataract, and slowing the loss of visual acuity.[40]

Clinical applications

Vitamin E and its analogs are used to prevent and repair cell and tissue damage during radiation therapy. Vitamin E with adjuvant Evening Primrose Oil may reduce breast pain.[41]

The use of vitamin E in the treatment of some cancers is beneficial. Vitamin E and its derivatives promote tumor susceptibility of ionizing radiation during cancer treatment.[42]

Toxicity

The LD_{50}, or the toxic dose required to kill 50% of group of rats and mice, respectively is 4000 mg of VitaminE E/kg of rat and 4000 mg of Vitamin E/kg of mouse.[43] Comparatively speaking, and at lethal doses, Vitamin E is less toxic than table salt and acetaminophen and it is more toxic than ethanol and Vitamin C. Vitamin E can act as an anticoagulant, increasing the risk of bleeding problems. As a result, many agencies have set a tolerable upper intake levels (UL) at 1,000 mg (1,500 IU) per day.[1] In combination with certain other drugs such as aspirin, hypervitaminosis E can be life-threatening. Hypervitaminosis E may also counteract vitamin K, leading to a vitamin K deficiency.

Dietary sources

mg/ (100 g) [note 1]		Some foods with vitamin E content[8]
low	high	
150		Wheat germ oil
44		Canola/rapeseed oil
41		Sunflower oil
95		Almond oil
34		Safflower oil
26		Almonds
19		Wheat germ
15		Palm oil[44]
15		Hazelnuts
14		Olive oil
12.2		Common purslane[45]
8.33		Peanut
1.5	3.4	High-value green, leafy vegetables: spinach, turnip, beet greens, collard greens, and dandelion greens[note 2]
2.32		Butter
2		Avocados[46]
1.8		Cocoa butter
1.4		Sesame oil[47]
1.1	1.5	Asparagus[note 3]
1.5		Kiwifruit (green)
0.90		Cashew nuts
0.78	1.5	Broccoli[note 4]
0.8	1	Pumpkin[note 5]
0.26	0.94	Sweet potato[note 6]
0.9		Mangoes
0.7		Walnuts
0.54	0.56	Tomatoes[note 7]
0.36	0.44	Rockfish[note 8]
0.3		Papayas
0.25		Tahini
0.13	0.22	Low-value green, leafy vegetables: lettuce[note 9]

Dietary Reference Intake

The Food and Nutrition Board (FNB) of the U.S. Institute of Medicine updated Estimated Average Requirements (EARs) and Recommended Dietary Allowances (RDAs) for vitamin E in 2000. The current EAR for vitamin E for women and men ages 14 and up is 12 mg/day. The RDA is 15 mg/day. RDAs are higher than EARs so as to identify amounts that will cover people with higher than average requirements. RDA for pregnancy equals 15 mg/day. RDA for lactation equals 19 mg/day. For infants up to 12 months the Adequate Intake (AI) is 4–5 mg/day and for children ages 1–13 years the RDA increases with age from 6 to 11 mg/day. The FNB also sets Tolerable Upper Intake Levels (ULs) for vitamins and minerals when evidence is sufficient. In the case of vitamin E the UL is 1,000 mg/day.[48] Collectively the EARs, RDAs and ULs are referred to as Dietary Reference Intakes. The European Food Safety Authority reviewed the same safety question and set a UL at 300 mg/day.[49]

For U.S. food and dietary supplement labeling purposes the amount in a serving is expressed as a percent of Daily Value (%DV). For vitamin E labeling purposes 100% of the Daily Value was 30 mg, but as of May 2016 it has been revised to 15 mg. A table of the pre-change adult Daily Values is provided at Reference Daily Intake. Food and supplement companies have until July 28, 2018 to comply with the change.

History

Vitamin E was discovered in 1922 by Herbert McLean Evans and Katharine Scott Bishop[50] and first isolated in a pure form by Gladys Anderson Emerson in 1935 at the University of California, Berkeley.[51] Erhard Fernholz elucidated its structure in 1938 and shortly afterwards the same year, Paul Karrer and his team first synthesized it.[52]

The first use for vitamin E as a therapeutic agent was conducted in 1938 by Widenbauer, who used wheat germ oil supplement on 17 premature newborn infants suffering from growth failure. Eleven of the original 17 patients recovered and were able to resume normal growth rates.[53]

In 1945, Drs. Evan V. Shute and Wilfred E. Shute, siblings from Ontario, Canada, published the first monograph arguing that megadoses of vitamin E can slow down and even reverse the development of atherosclerosis.[54] Peer-reviewed publications soon followed.[55][56] The same research team also demonstrated, in 1946, that α-tocopherol improved impaired capillary permeability and low platelet counts in experimental and clinical thrombocytopenic purpura.[57]

Later, in 1948, while conducting experiments on alloxan effects on rats, Gyorge and Rose noted rats receiving tocopherol supplements suffered from less hemolysis than those that did not receive tocopherol.[58] In 1949, Gerloczy administered all-rac-α-tocopheryl acetate to prevent and cure edema.[59][60] Methods of administration used were both oral, that showed positive response, and intramuscular, which did not show a response.[53] This early investigative work on the benefits of vitamin E supplementation was the gateway to curing the vitamin E deficiency-caused hemolytic anemia described during the 1960s. Since then, supplementation of infant formulas with vitamin E has eradicated this vitamin's deficiency as a cause for hemolytic anemia.[53]

Vitamin E supplementation and cardiovascular disease

Vitamin E and atherosclerosis

Atherosclerosis is a disease condition refer to the buildup of plaque, which is a substance containing lipid and cholesterol (mainly the low-density lipoprotein or LDL cholesterol) on the inner layer of the arterial lumen.[61] With the existing plaque, instead of being smooth and elastic, the layers become thickened and irregular and the lumen of the artery become narrower. This vessel-narrowing effect lead to a reduction of blood circulation and can lead to or worsen the condition of hypertension.[62]

There are currently multiple theories explaining factors causing and affecting the cholesterol plaque build up within arteries with the most popular theory indicating that the rate of build up is affected by the oxidation of the LDL cholesterol. LDL cholesterol is one of the five major groups of lipoproteins with one of the physiological roles being lipid transportation. A typical LDL particle contain 2,700 fatty acid molecules and half of them are poly-unsaturated fatty acids, which are very oxidation sensitive.[63] Once the oxidation of LDL occur, it will start a series of undesirable effects starting from the increase production of inflammatory cytokines by stimulating the endothelial cells and monocytes, followed by increased production of tissue factors, production of macrophages and monocytes, which eventually lead to the formation of foam cells and accelerated development of atherosclerosis. With the presence of adequate concentration of vitamin E, which is a very potent fat-soluble antioxidant, it can inhibit the oxidation of LDL, and this inhibition contributes protection against the development of atherosclerosis and can stabilize the existing plaque.[63]

Critical evaluation of current related literature

Interpreting the science jargon of the following paragraphs: If human trials are similar enough in design and measurements, a statistical analysis can be conducted on the combined results. This is called a meta-analysis. Controversies arise when different authors disagree on the criteria to use to include or exclude trials. An odds ratio (OR) indicates whether a treatment helped or harmed compared to control. In the first example below, an OR = 0.74 means that the risk of cardiovascular disease was reduced by 26%. An inverse association (the next referenced example) means that the higher the dose, the lower the risk. Odds ratio and relative risk sort of mean the same thing (unless you are a statistician). The paragraphs below are in conflict. The first reports on observing how much vitamin E subjects chose to consume, and their disease outcome. The second describes RCTs, i.e., randomized clinical trials, in which subjects are assigned to get or not get vitamin E, without knowing which group they are in, and tracking results. The conclusion of observational studies is a benefit; the conclusion of RCTs is no benefit. (As indicated by the ORs being close to 1.00, meaning no effect. An OR higher than 1.00 indicates harm.)

According to Asplund (2002)'s [64] meta-analysis, nine cohort studies showed that high intake of tocopherol was associated with a lower risk of CVD events compared with lower intake. The odds ratio (OR) was 0.74 (95% confidential interval (CI): 0.66-0.83). In this study, higher dietary, supplementation and combined vitamin E intake was also associated with lower CHD incidents, as presented in Appendix II. A large cohort study conducted by Rimm et al.[65] in 1993 included 39,919 male health professionals aged between 40 and 75 showed that consumption of more than 60 IU of vitamin E (any form) per day was associated with a lower incidence of CHD compared with less than 7.5 IU/day intake. This study also showed an inverse association between vitamin E supplementation and the incidence of CHD. The relative risk (RR) of at least 100 IU/day for at least two years was 0.63 (95% CI: 0.47-0.84). A European cohort study was conducted by Knekt et al. in 1994. This study also found an inverse relationship between higher vitamin E (any form) intake and lower CHD risk in men and women. In addition, Kushi et al. (1996) discovered an inverse relationship between vitamin E intake and CHD mortality among 34,486 postmenopausal women (RR=0.38, 95% CI: 0.18-0.8; trend: P=0.014).

For the result of RCTs, as mentioned previously, it was controversy. A meta-analysis of 6 RCTs showed no significant association between vitamin E supplementation and CVD mortality; the pooled OR (95% CI) was 1.0 (0.94-1.06) (Vivekananthan et al., 2003). Another meta-analysis of 7 RCTs also showed similar results, with the pooled ORs (95% CI) of cardiovascular events, non-fatal MI, non-fatal stroke, and CVD deaths being 0.98 (0.94-1.03), 1.00 (0.92-1.09), 1.03 (0.93-1.14), and 1.00 (0.94-1.05), respectively [66]

Notes

1. "USDA Nutrient Data Laboratory". In notes 2–11, USDA NDL Release 24 numbers are given as mg/(100 g). Low and high values vary some by raw versus cooked and by variety.
2. Spinach (2.0 raw, 2.1 cooked), turnip (2.9 raw, 1.9 cooked), beet (1.5 raw, 1.8 cooked), collard (2.3 raw, 0.88 cooked), and dandelion greens (3.4 raw, 2.4 cooked)

3. 1.1 raw, 1.5 cooked
4. 0.78 raw, 1.5 cooked
5. 1. raw, 0.8 cooked
6. 0.26 raw, 0.94 boiled
7. 0.54 raw, 0.56 cooked
8. 0.36 raw, 0.44 cooked
9. Lettuce (0.18 iceberg, 0.22 green leaf, 0.13 romaine, 0.15 red leaf, 0.18 butterhead)

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Further reading

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