Graphical Review

Tocopherols, tocotrienols and tocomonoenols: Many similar molecules but only one vitamin E

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A B S T R A C T

The aim of this article is to correct a very general error in scientific articles, in textbooks and in the Internet that has become an accepted fact. In this literature, the term “vitamin E” is used for several similar molecules (both tocopherols and tocotrienols) that have never been shown to have vitamin property, i.e. a protective effect against the human deficiency disease. In fact, the name “vitamin E” should only be used to define molecules that prevent the human deficiency disease “Ataxia with Vitamin E Deficiency” (AVED). Only one such molecule is known, α-tocopherol. This error may confuse consumers as well as medical doctors, who prescribe vitamin E without realizing that the current use of the name includes molecules of unknown, if not unwanted functions.

According to most scientific and popular publications (see for instance [1,2] and https://pli.oregonstate.edu/mic/vitamins/vitamin-E) “vitamin E includes eight fat-soluble isoforms: α, β, γ, and δ-tocopherol and α, β, γ, and δ-tocotrienol”. (Fig. 1).

In addition, more recently, very similar molecules have been described, the tocomonoenols, with only one double bond in the sidechain (Fig. 2)

Do all those molecules, tocopherols, tocotrienols and tocomonoenols act in the human body in a way that they can be called vitamins?

Vitamins are organic substances essential in small quantities to normal metabolism, found in minute amounts in natural foodstuffs or sometimes produced synthetically: deficiencies of vitamins produce specific disorders which can be prevented by the administration of the missing vitamin. https://www.dictionary.com/browse/vitamin.

According to this definition, molecules such as essential fatty acids or essential amino acids cannot be called vitamins being needed not in minute amounts. Also trace metals, like zinc, copper, iron and molybdenum cannot be called vitamins, given their nature of inorganic compounds. In addition, vitamins are compounds whose deficiency results in a disease.

Are the molecular structures of vitamins specific?

Scurvy is a disease caused by deficiency of vitamin C, historically famous because it affected sailors until the end of the 18th century, whose diets were lacking fresh fruits and vegetables. The disease can be prevented by l-ascorbic acid but not by the enantiomer d-ascorbic acid and only l-ascorbic acid can be called vitamin C (Fig. 3).

l-Ascorbic acid but not the enantiomer d-ascorbic acid prevents the deficiency disease. Only l-Ascorbic acid is called vitamin C.

Another example is given by rickets prevention by vitamin D (Fig. 4). Are all tocopherols and tocotrienols vitamins?

Tocopherols and tocotrienols act as free radical scavengers in membranes and lipoproteins[3]. They quench fatty acid peroxyl radicals by becoming tocopheroxyl radicals. Tocopheroxyl radicals potential damage would be avoided via reduction by an appropriate reducing agent (Fig. 5).

Different tocopherols have gene regulatory functions, not related to their radical scavenging capacity.

In addition to their radical scavenging action, non-antioxidant functions of tocopherols have been shown, both in vivo and in vitro [8,9]. In T cells from mouse spleen, α-tocopherol affects signal transduction, transcriptional regulation, apoptosis pathways and other genes associated with the regulation of cell cycle. The modulation of gene expression is dependent on the fine molecular structure of α-tocopherol: S and R isomers of the molecule side chain act differentily and marker genes respond uniquely to natural vitamin E (RRR-α-tocopherol) and not to the SSS isomers, that have identical radical scavenging properties [10]. The two vitamins α and γ tocopherols differ only by a methyl group on the chromane ring and have essentially the same antioxidant properties certain genes uniquely respond to either α-tocopherol or γ tocopherol [11].

Different tocopherols and tocotrienols have largely different cellular effects.

β-Tocopherol has similar antioxidant properties as α-tocopherol but does not inhibit protein kinase C activity, cell proliferation and gene expression, and it is 10-fold less active than α-tocopherol in inhibiting thrombin-induced PKC activity. β-Tocopherol, has no effect on IL-1β release in monocytes, in endothelial cells, β-tocopherol, contrary to α-
tocopherol has no effect on caspase-3 activity. β-Tocopherol and γ-tocopherol but not α-tocopherol strongly inhibit intracellular tyrosinase [12].

γ-Tocopherol, and its metabolite γ-CEHC, exhibit activities different from α-tocopherol such as natriuretic, anti-inflammatory, antitumoral, and more. α-Tocopherol does not exhibit anticancer properties, but it reduces anticancer actions of γ-tocopherol in vivo. δ-Tocopherol is responsible for a proinflammatory response promoted by reactive oxygen species, it prevents hormone-dependent breast cancer progression, colon carcinogenesis, lung tumorigenesis and prostate cancer cell growth. δ-Tocopherol reduces lipid accumulation, has antiangiogenic effects and elevates L-type calcium channel activity to increase neuronal differentiation [12]. In summary, the activities of β-, γ-, and δ-tocopherols do not correspond to their radical scavenging behavior: they reflect anti-inflammatory, antineoplastic, and natriuretic actions probably mediated through specific binding interactions and have no property suggesting a protective effect against AVED.

In vitro studies with tocotrienols indicate effects against cancer (mostly due to suppression of angiogenesis), cardiovascular and neurodegenerative diseases (ability to suppress glutamate-induced activation of c-Src kinase) [2]. It has been concluded that tocotrienols are more potent than tocopherols and that the different tocotrienols, which differ in their number of methyl groups and their position on the chromanol ring, also differ in their biological activities. While various studies have indicated that α-tocotrienol is neuroprotective, δ- and γ-tocotrienol have been shown to exhibit the greatest anticancer effects. However, none of these molecules has been tested for an effect on AVED and only α-tocopherol has been shown to protect against AVED, the
Conclusions

Only human disease associated with vitamin E deficiency.

Since it is known that small structural changes can eliminate the vitamin effect of a molecule and since only α-tocopherol, and none of the other tocopherols, have been shown to protect against the human deficiency disease, only α-tocopherol can be called *bona fide* vitamin E. Why the other seven fat-soluble tocopherols and tocotrienols, that have never shown any protective effect against a human deficiency disease, should be called (and sold as) vitamin E? The recently described α-tocomoenoel should also be called “vitamin E”?

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