Tocopherols and tocotrienols as vitamin E

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Introduction

Vitamins are chemical compounds which are components of coenzymes and non-protein ingredients of enzymes. They are essential for life and normal functioning of the body. Vitamins are supplied with food as they cannot be synthesised by the body [1]. Bad diet, impaired vitamin absorption or the use of substances such as caffeine, nicotine and medicines may lead to hypovitaminosis, that is vitamin deficiency. This causes weakness, lowered immunity, muscular and joint pains, fragility of blood vessels, apathy and skin lesions. It also speeds up the ageing process. One of the most effective antioxidants which slow down the ageing of cells is vitamin E. It can penetrate the skin and is absorbed by the intercellular cement, thus protecting against epidermal damage and decreasing the sensitivity of epidermis to UV radiation [1, 2]. The term vitamin E describes a group of α-tocopherol derivatives exhibiting similar physiological activity [2].

The history of vitamin E

The existence of vitamin E was first confirmed at the beginning of the 20th century. It happened as a result of studies on the impact of various factors on animal reproduction. Soon the compound gained a name of a fat soluble nutrient [3]. Vitamin E (α-tocopherol, α-T) was isolated from wheat germ oil by a research team led by Evans in 1936 [4]. The name “tocopherol” is derived from Greek words: tocos (birth) andpherein (to carry) which were to emphasise the essential role of this compound for the life of young rats [5]. The ending “-ol” signifies its status as a chemical alcohol [6]. In 1937 β- and γ-tocopherol were isolated from vegetable oil (β-, γ-T) [7]. The following year the structure of α-tocopherol was determined [8, 9], followed by defining the process of its synthesis [10] and it was confirmed that it is the most effective of the known tocopherols in the prevention of vitamin E deficiency [11]. In 1947 δ-tocopherol (δ-T) was isolated from soy oil [12]. In the same year the scientists identified four naturally occurring tocotrienols (α-T3, β-T3, γ-T3, δ-T3) [13, 14].

Structure and chemical properties

Vitamin E is the term for a group of organic chemical compounds soluble in lipids, which include tocopherols (T) and tocotrienols (T3). Their common characteristic is the presence of a 6-chromanol ring and a side chain made of three isoprene units. The basic unit for vitamin E family is tocotol, the chemical name of which is 2-methyl-2-(4',8',12'-trimethyltridecyl)chroman-6-ol [15] (Fig. 1). This nomenclature has been adopted by the IUPAC (International Union of Pure and Applied Chemistry) [16-18].

![Fig. 1. Chemical structure of tocotol: 2-methyl-2-(4',8',12'-trimethyltridecyl)-chroman-6-ol; (R1=R2=R3=H)](image)

There are eight known naturally occurring homologues which belong to the vitamin E family. They include α-, β-, γ-, δ-tocopherols which are characterised by a saturated carbon side chain and made up of three isoprenoid units and their counterparts in the form of unsaturated α-, β-, γ-, δ-tocotrienols [15]. Tocotrienols have double bonds at positions 3’, 7’ and 11’ in the side chain (Fig. 2). The mutual structural relations of tocopherols and tocotrienols are presented in the tables (Tab. 1, 2).

![Fig. 2. Chemical structure of tocotrienol: 2-methyl-2-(4',8',12'-trimethyltrideca-3',7',11'-tri-enyl)-chroman-6-ol; (R1=R2=R3=H)](image)

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<thead>
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<th>Table of tocopherols</th>
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<td><strong>Trivial name</strong></td>
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<td><strong>Trivial name</strong></td>
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<td>δ-tocotrienol</td>
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Tocopherol and tocotrienol homologues differ structurally in terms of the number and position of methyl groups on the chromanol ring. α-homologues contain three methyl groups, β- and γ-homologues are mutual isomers with two methyl groups, whereas α-tocopherol...
(α-T) and δ-tocotrienol (δ-T) have one methyl group. Tocopherols have three asymmetric carbons (chiral centres) at position 2’ of the chromanol ring and at positions 4’ and 8’ of the saturated phytol side chain. Synthetic α-T (all-rac-α-T) is a racemic mixture of identical parts of individual stereoisomers. Therefore, each of the tocopherols has eight (2⁴) optical isomers. For example, for α-tocopherol all eight isomers, so called all-rac-α-T, are as follows: RRR-, RSR-, RRS-, RRR-, SSR-, SSS- and SSS-. Only RRR-tocopherols occur naturally [15]. Tocotrienols derived from 2-methyl-2-(4,8,12-trimethyltrideca-3,7,11-tri-enyloxy)chroman-6-ol, unmethylated ring structure, have only one chiral centre at position 2’. As a result it is possible to make two stereoisomers: 2R and 2S. The unsaturated phytyl chain at 3’ and 7’ positions makes it possible to create four geometric cis-trans isomers. Eight potential tocotrienol isomers are presented in the table (Tab. 3). Only 2R, 3’-trans and 7’-trans isomers occur naturally [15]. All forms of tocotrienols were isolated and their structural properties explained in 1960 by Penncoock and co-workers and the research group led by Isler [16-20].

Table 3
The eight possible RS, cis-trans isomers of the tocotrienols [15]

<table>
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<tr>
<th>2R configuration position</th>
<th>2S configuration position</th>
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<tr>
<td>2R, 3'cis, 7'cis</td>
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<td>2R, 3'cis, 7'trans</td>
<td>2S, 3'cis, 7'trans</td>
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<td>2R, 3'trans, 7'cis</td>
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Vitamin E compounds are the most important natural antioxidants. They occur most commonly in raw plant materials and plant products. Their antioxidant properties are a result of the presence of hydroxy group in the chromanol ring (6’ position). The antioxidative activity of tocopherols in vivo is created in the following order: α-T > β-T > γ-T > δ-T. Their activity in vitro is exactly opposite: δ-T > γ-T > β-T > α-T [21]. The activity of homologues β-, γ- and δ-tocopherol in a human body is limited, as they are immediately metabolised in the liver and excreted in bile and urine [21]. Moreover, it was found that α-T is characterised by a significantly higher anti-oxidative activity than α-T [21]. All forms of vitamin E resemble colourless or light yellow, viscous oils and they are soluble in lipids or organic lipid solvents [15].

Principles of nomenclature
Due to a complex nomenclature for tocopherols and tocotrienols, the principles of nomenclature presented by the IUPAC-IUB Joint Commission on Biochemical Nomenclature have been used since 1981 [15-18]. The term vitamin E should be used in reference to general nomenclature of all tocols and tocotrienols and their derivatives exhibiting similarity to α-tocopherol, both in qualitative terms and in terms of biological activity. The term tocopherol is a simplified designation for 2-methyl-2-(4,8,12-trimethyltrideca-3,7,11-tri-enyloxy)chroman-6-ol (Fig. 1) in which R₁ = R₂ = R₃ = R₄ = H. The term tocopherol(s) should be used as a generic descriptor for all mono, di, and trimethyltocopherols. Thus, this term is not synonymous with the term vitamin E. The compound in Figure 2, where R₁ = R₂ = R₃ = R₄ = H, i.e. 2-methyl-2-(4,8,12-trimethyltrideca-3,7,11-tri-enyloxy)chroman-6-ol is designated as tocotrienol [only all-trans-(E,E)-tocotrienol has been found occurring in nature]. The only naturally occurring stereoisomer of α-tocopherol discovered so far has the configuration 2R,4'R,8'R according to the sequence-rule system. Its systematic name is therefore (2R,4'R,8'R)-α-tocopherol. The same system can be applied to all other individual stereoisomers of tocopherols. Simplified designations are recommended to indicate briefly the configuration of important stereoisomers of α-tocopherol and especially of mixtures of such stereoisomers. For example: α-tocopherol (α-T) referred to above, with the configuration 2R,4'R,8'R, previously known as d-α-tocopherol, should be designated as RRR-α-T. Esters of tocopherols and esters of tocotrienols are called e.g. α-tocopheryl acetate, α-tocotrienyl acetate.

The significance of vitamin E for health and beauty
Vitamin E is a strong antioxidant of polyunsaturated fatty acids and phospholipids which are found in cell membranes. It also takes part in metabolic processes [2, 22]. Its deficiency may cause neurological disorders resulting from peroxidation of neuronal membranes and degenerative processes in the brain which intensify in the ageing process [5, 15, 19]. Vitamin E deficiency in adults is usually caused by disrupted tocopherol absorption, e.g. in case of fatty diarrhoea or removal of part of the small intestine [11, 15]. Its endogenous deficiency may occur in type III hyperlipoproteinemia (a hereditary disease), as well as during secretion of lipoproteins, transporting tocopherols from liver to other tissues [19]. Vitamin E deficiency is particularly dangerous for children, in particular newborns, as it may lead to the development of anaemia, visual disorders (retinopathy, fibroplasia), bronchopulmonary dysplasia, and sudden death [15]. In vitamin E deficiency there is an increased risk of infectious diseases, cardiovascular diseases and inflammatory processes [22]. On the other hand, the presence of tocopherols and tocotrienols in the form of vitamin E protects the body from ageing, as these compounds can effectively neutralise free radicals [6, 13]. It is worth knowing that a particularly rich sources of tocopherols are vegetable oils and fish, but also wheat germs, wholegrain cereals, seeds, green peas [15]. Vitamin E is used in treatment of muscle disorders and heart disorders. Moreover, it lowers the risk of angina pectoris and cardiac infarction, and administering it shortly after a cardiac infarction can prevent the spreading of the area of heart damage. It was also found that the compound prevents the development of atherosclerosis and prevents the development of cancers [19]. Vitamin E lowers degradation of erythrocytes facilitating the supply of oxygen contained in them to all cells of the body [15, 19]. Additionally, it strengthens blood vessels and improves their elasticity and lowers blood clotting. Interestingly, the concentration of vitamin E in blood plasma in people ranges from 0.8 to 2 mg/dl (on average 1 mg/dl). The symptoms of deficiency appear usually with tocopherol concentration below 0.5 mg/dl [15]. Vitamin E is not synthesised in human body, therefore tocopherols supplied with food are mainly stored in fat tissue. The absorption of vitamin E in intestines is determined by the content of fats in food. This process is disturbed in case of an insufficient bile secretion [15]. The biological activity of vitamin E is measured in micrograms of RRR-α-tocopherol or in international units, hence 1 i.u. corresponds to activity of 1 mg of D-L-α-tocopheryl acetate, administered orally in a test preventing fetal resorption in rats that were vitamin E deficient [5-7, 15].

In cosmetic products vitamin E is an excellent antioxidant stabilising the structure of unsaturated fats [2]. Thanks to physicochemical interactions between the isoprenoid side chain of a tocopherol molecule and a hydrocarbon chain of polyunsaturated fatty acids which make up the membrane phospholipids, a stabilising effect of tocopherols on biological membranes is possible [2]. Vitamin E is used together with vitamin A in treatment of common acne and eczema [2]. It should be noted that vitamin E is resistant to high temperatures, but breaks down under the influence of light and oxygen [21, 22]. However, a compound in the tocopherol family which is most resistant to both of these factors is a vitamin E ester – tocopheryl acetate, which is an active commonly used in sunscreens. It provides an effective protection against oxidation and degradation of epidermal lipids [6, 22]. Vitamin E soothes skin irritation and burns caused by solar radiation. Additionally, it has anti-inflammatory and anti-oedematous properties. It penetrates epidermis well and...
is absorbed by the intercellular cement, nourishing the skin and improving its elasticity. As an active ingredient of cosmeceuticals vitamin E not only soothes, moisturises, smooths and firms the skin, but also helps in the treatment of discolouration and relieves the symptoms of contact dermatitis [1-3].

Tocopherol derivatives are also extremely effective, including α-tocopherol linolate which is absorbed by the lipids of the epidermis, exhibiting a long-term moisturising and UV absorbing effect. Another frequently used tocopherol derivative is tocopheryl acetate, referred to above. This compound is an active resistant to light and oxygen. Sunscreen products increasingly often use tocopheryl acetylsalicylate, which is easily absorbed both by skin and hair [1, 6, 22].

The content of vitamin E is determined by establishing the concentration of tocopherols in blood serum and plasma. This is performed using spectrophotometric methods, which involve oxidation of tocopherols with iron (III) chloride and then determining the amount of obtained Fe**⁺** in the form of coloured complex with 2,2'-bipyridine or 3-phenanthroline. In recent years spectrophotometric methods have been used which are characterised by a higher sensitivity and allow for determining tocopherol concentration in 0.1 ml of blood serum. Additionally, in order to detect potential vitamin E deficiency, the amount of keratin excreted in urine and the sensitivity of erythrocytes to hemolysis in an isotonic environment are tested. Both these indicators increase significantly in vitamin E deficiency. In recent years it has been proposed to test the content of pentane and ethane in exhaled air using gas chromatography. In vitamin E deficiency the amount of both compounds increases as a result of peroxidation of unsaturated fatty acids [15, 19].

Summary

Tocopherols (α-T, β-T, γ-T, δ-T) and their tocotrienol counterparts (α-T3, β-T3, γ-T3, δ-T3) are members of the vitamin E family. In living organisms these compounds act as biological antioxidants which inactivate free radicals and thus impair the development of unsaturated lipid peroxidation. Due to the fact that unsaturated lipids are some of more important components of biological membranes this function of tocopherols is significant for maintaining structural coherence and functional activity of lipidprotein cell membranes and cell organelles. Because of their beneficial qualities tocopherols and tocotrienols have wide applications in medicine. For example, they support treatment of muscular disorders and heart diseases, as well as prevent the development of atherosclerosis and cancers. Additionally, α-, β-, γ-, δ-tocopherols gained recognition in cosmetic industry where they are used as very strong antioxidants. These compounds known mainly as vitamin E ("vitamin of youth") exhibit soothing, moisturising, elasticity improving, protective and anti-aging effects. Therefore, they are typically used in sunscreens, in moisturising and regenerating creams and in hair care products.

Literature


*Aleksandra ZIELIŃSKA, M.Sc., is a first year student of the Ph.D. studies in Chemistry Department at Adam Mickiewicz University in Poznań. She obtained the Master’s degree in 2013, specialisation: cosmetic chemistry. Her scientific interests are focused on physical and chemical properties of vegetable and essential oils, as well as applications of nanotechnology for medical and cosmetic purposes.

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