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Review

Novel and rare prenyllipids – Occurrence and biological activity

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ABSTRACT

The data presented indicate that there is a variety of unique prenyllipids, often of very limited taxonomic distribution, whose origin, biosynthesis, metabolism and biological function deserves to be elucidated. These compounds include tocoenols, tocochromanol esters, tocochromanol acids, plastoquinones and ubiquinones. Additionally, based on the available data, it can be assumed that there are still unrecognized prenyllipids, like prenylquinols fatty acid esters of the hydroquinone ring, including prenylquinol phosphates, and others, whose biological function might be of great importance. Our knowledge of these compounds is not only important from the scientific point of view, but may also be of practical significance to medicine, pharmacy or cosmetics.

1. Introduction

Prenyllipids, such as plastoquinone, ubiquinones, menaquinones, phylloquinone, are a group of lipoliphilic compounds which are mainly known as antioxidants, as well as electron and proton carriers in electron transport chains of bacteria, plants and animals (Nowicka and Kruk, 2010).

The prenyl side-chains of plastoquinone and ubiquinone are assembled by specific isoprenyl diphosphate synthases from isopentenyl diphosphate (IPP) within chloroplasts and mitochondria, respectively (Bouvier et al., 2005; Block et al., 2013). Homogentisate, the precursor of the head group of plastoquinone and tocochromanols, is synthesizes in plants from tyrosine in cytosol (Falk et al., 2005) and subsequent biosynthetic steps of plastoquinone, as well as of tocochromanols, take place within chloroplasts at the inner chloroplast envelope and plastoglobules (van Wijk and Kessler, 2017). On the other hand, the head group precursor of ubiquinone, 4-hydroxybenzoate is synthesized in plants from phenylalanine in the cytosol and afterwards in peroxisomes (Block et al., 2014). After import of 4-hydroxybenzoate into mitochondria, further biosynthetic steps of ubiquinone take place in mitochondria at the inner mitochondrial membrane (Tran and Clarke, 2007). Besides, it was found that the ubiquinone ring is formed in plants independently from tyrosine by a still not recognized pathway (Block et al., 2014).

Tocochromanols (vitamin E complex), whose biosynthesis, metabolism and function is relatively well recognized (Dörmann, 2007; Mene-Saffrane and DellaPenna, 2010; Mene-Saffrane et al., 2010; Piller et al., 2012; Almeida et al., 2016; van Wijk and Kessler, 2017), are a group of lipid-soluble antioxidants that encompass at least eight compounds, differing in terms of their chromanol ring structure and the saturation of a side-chain – tocopherols with a fully saturated side-chain or tocotrienols where three double bonds are present. In leaves of green plants, α-tocopherol is a predominant tocochromanol (DellaPenna, 2005; Lichtenthaler, 2007; Szymanska and Kruk, 2008a), but there are some exceptions where γ-tocopherol (Szymanska and Kruk, 2008b) or even δ-tocopherol dominates (van der Kooij et al., 2005; Szymanska and Kruk, 2008a). On the other hand, in seeds and seeds oils mainly γ-tocopherol is found, although other tocopherols may be also present in various proportions (DellaPenna, 2005; Gruszka and Kruk, 2007; Szymanska and Kruk, 2008a). In contrast to tocopherols, which are ubiquitous in the plant kingdom, the occurrence of tocotrienols is limited only to the non-photosynthetic organs of some groups of higher plants, mainly monocots (Ong, 1993; Zielinski, 2008).

Despite the fact that most of these compounds have been known for many years, new prenyllipids and their derivatives are still being discovered. Moreover, their origin, biosynthesis and biological activity are being revealed. One example may be plastochromanol-8, discovered over 50 years ago, but its biosynthesis and antioxidant functions have only been revealed recently (Szymanska and Kruk, 2010a, 2010b; Kruk et al., 2014).

Some data in the literature indicate that there are prenyllipids of unknown function and origin, such as tocopherol phosphate, plastochromanol-8 esters, tocotrienol esters, plastoquinone side-chain homologues, as well as solanochromene and ubichromenol. Moreover,

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a number of other compounds that have not been identified yet probably occur in plants, such as tocopherol esters, plastoquinol esters and phosphates or plastoquinone carboxylates. It is interesting to note that rare vitamin E forms usually show higher biological activity than the parent compounds (Qureshi et al., 2000; Yamamoto et al., 2001). It turned out that tocotrienols and plastochromanol, beyond their stronger antioxidant activity, play many other physiological roles, not shared with tocopherols. For example, tocotrienols are very efficient in the lowering of cholesterol and thus can be used as a preventive agents in atherosclerosis and cardiovascular diseases (Nesaretnam et al., 2012). In nanomolar concentrations, tocotrienols display neuroprotective activity (Riccioni et al., 2007), anticancer properties (McIntyre et al., 2000; Ji et al., 2012), anti-inflammatory activity (as inhibitors of cyclooxygenase and lipoxygenase-dependent eicosanoids) (Jiang, 2014) as well as hepatoprotective effects, much stronger than those of α-tocopherol (Patel et al., 2012). All these results indicate that non-tocopherol forms of vitamin E have high therapeutic potential, especially in high-mortality index diseases (diseases of affluence) treatments, such as cancers or cardiovascular disease.

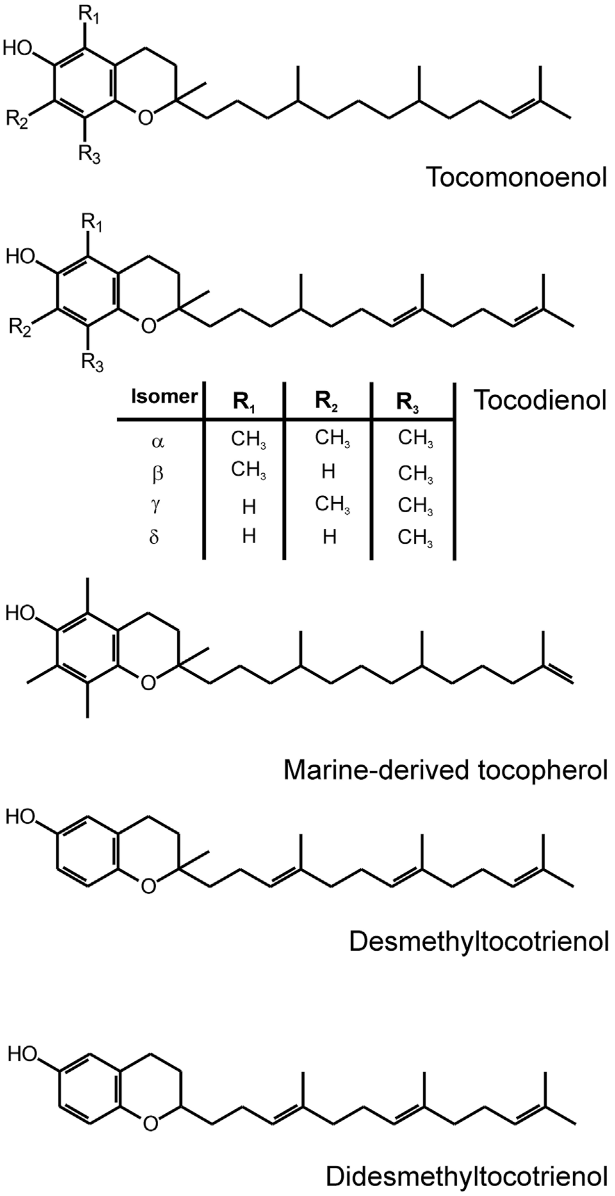
2. Tocoenols

Rare representatives of this group include tocomonoenols, tocodienols and desmethyltocotrienols (Fig. 1), which are usually found in small amounts in some seed oils, fruits, leaves and even animals.

Tocomonoenols (α- and γ-dehydrotocopherols) (Fig. 1) were first identified in etiolated maize and barley shoots (Threlfall and Whistance, 1977), together with dehydrophylloquinone and α-dehydrotocopherolquinone, in comparable amounts to the corresponding tocopherols. Subsequently, tocomonoenols were found e.g. in palm seed oil (Matsumoto et al., 1995; Strohschein et al., 1999), kiwi fruit (Fiorentiono et al., 2009), pumpkin seed oil (Butinar et al., 2011), etiolated runner bean leaves and leaves of *Kalanchoe daigremontiana* (Kruk et al., 2011), as well as in *Arabidopsis* seeds (Pellaud et al., 2017). α-Tocomonoenol found in crude palm oil constitutes about 3–4% of the vitaminE fraction and 40 ± 5 ppm of the palm oil, whereas its content in palm fiber oil was about 11% and 430 ± 6 ppm, respectively (Ng et al., 2004).

In our studies, we found β-, γ-, and δ-tocomonoenols in *Kalanchoe daigremontiana* and γ-tocomonoenol in etiolated leaves of runner bean (*Phaseolus coccineus*) (Fig. 1) (Kruk et al., 2011). The level of γ-tocomonoenol in etiolated bean leaves increased gradually with the age of seedlings, reaching 50% of the γ-tocopherol level in 40-day-old plants. The γ-tocomonoenol content also increased as a result of short illumination (500 μmol photons/m^2/s) of etiolated plants. Moreover, an increase in the level of this compound was observed after the addition of homogentisic acid (HGA) – a biosynthetic precursor of tocopherols, which indicated that γ-tocomonoenol is synthesized *de novo* from HGA and tetrahydro-geranylgeraniol diphosphate (a phytol precursor) (Kruk et al., 2011). Tocoenols may also be tocopherol precursors, where the double bond in the side chain is reduced by geranylgeraniol reductase (Kruk et al., 2011).

Yamamoto et al. (1999) have found a novel antioxidant in the eggs of the fish chum salmon (*Oncorhynchus keta*). GC-MS, ^{1}H NMR and ^{13}C NMR measurements resulted in the structure of 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyl-12-tridecenyl)-2H-1-benzopyran-6-ol, which corresponded to α-tocomonoenol with an unusual methylene unsaturation at the isoprenoid-chain terminus (Yamamoto et al., 1999). The level of α-tocomonoenol from chum salmon eggs was estimated as 25% of the α-tocopherol content. The antioxidant properties of this compound were identical to those of the corresponding tocopherol. As this compound was found in fish it was called "marine-derived tocopherol" by the authors (MDT) (Fig. 1). The presence of α-tocomonoenol in fish eggs was explained by the exposition to higher levels of oxygen, thus oxidative stress (pO$_2$ = 150 mmHg at air saturation) and chronic environmental challenge. The demand for additional antioxidants in eggs may also be connected to the respiratory burst during fertilization and reactive oxygen species production (Shapiro, 1991). MDT was further found in a wide range of marine organisms (Dunlap et al., 2002; Yamamoto et al., 2001). The highest level of this prenyllipid was detected in the muscles of marine fish living in cold water. Further measurements have shown that MDT co-exists with α-tocopherol in numerous Antarctic organisms (fish, krill, phytoplankton) ranging from 2.8% to 22.3% of the total vitamin E content (Dunlap et al., 2002). The high content of MDT in Antarctic species suggests its adaptive functions in cold-water resistance and adaptation. Furthermore, MDT was found in human plasma (Yamamoto et al., 2001). This indicate that this compound is recognized by the α-tocopherol transfer protein and distributed within the body (Gotoh et al., 2009). The source of MDT in human plasma is a variety of marine organisms (Franke et al., 2007; Navarro-García et al., 2004). Gotoh et al. (2011) revealed that the heat-resistance of MDT is similar to that of α-tocopherol and its content in processed food (boiled, grilled, frying) is diminished.



Isomer	R$_1$	R$_2$	R$_3$
α	CH$_3$	CH$_3$	CH$_3$
β	CH$_3$	H	CH$_3$
γ	H	CH$_3$	CH$_3$
δ	H	H	CH$_3$

Fig. 1. The chemical structure of tocomonoenols, tocodienols, marine-derived tocopherol, desmethyltocotrienol and didesmethyltocotrienol.

Another tocoenol, namely δ-tocomonoenol, was isolated from kiwi fruit (*Actinidia chinensis*) (Fig. 1) (Fiorentiono et al., 2009). This