Tocotrienols molecular aspect beyond its antioxidant activity biology essay

Science, Biology

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Abstract

Tocotrienols are newer components of the vitamin E family. Vitamin E family represent eight different isomers that belong to two classes α, β, γ, and δ tocopherols and α, β, γ, and δ tocotrienols. Numerous studies compare the properties of tocotrienols with those of tocopherols. However, some biological activities were demonstrated to be unique for tocotrienols. Tocotrienols are the active components of many plants including annatto, rice bran, and palm. Since its discovery, mostly antioxidant and cell signaling activities of tocopherols and tocotrienols have been examined. Although the antioxidant functionality of tocotrienols is higher than that of tocopherols, tocotrienols show a lower bioavailability after oral administration. In this review, we will summarize recent developments in the understanding of the molecular targets of the tocotrienols beyond their antioxidant, anti-proliferative, anti-survival, anti-inflammatory, anti-angiogenic and anti-apoptotic activities. Key words: tocopherols, tocotrienols, cell signaling.

1. Introduction

Vitamin E, which display antioxidant activities, is a generic name refers to a family of eight fat soluble compounds that can be fall into two classes called tocopherols (TP) and tocotrienols (T3) (1). Both tocopherols and tocotrienols are structurally identical compounds in that they have chromanol ring and a side chain at the C-2 position with tocotrienol possesses an unsaturated isoprenoid side chain (2). Tocopherol and tocotrienol are further subgrouped

into alpha, beta, gamma and delta tocopherols and alpha, beta, gamma and delta tocotrienols, depends on their number and location of methyl substitutions on the chromanol ring (3). Each of these isoforms of vitamin E has a demonstrated different biopotency (4). Tocotrienols are distributed throughout the body via the bloodstream and accumulates in various tissues of rats, particularly adipose tissues, heart, and skin, after oral gavage, suggesting that tocotrienols are absorbed and distributed in vivo (5). Tocotrienols and tocopherols are metabolized identically by omega oxidation accompanied by beta oxidation of the side chain, omega oxidation is achieved by cytochrome P450 (CYP450) enzymes which are often regulated by their substrates themselves, however tocotrienols were found to be degraded to a larger amount than tocopherols (6). The plasma levels of tocotrienols were reported to reach 1 μmol/L in humans and between 3 and 20 μmol/L in different animal species (7, 8). The mean apparent elimination half-life of α, γ, and δ-tocotrienols when given as a single dose of 300 mg of mixed tocotrienols is valued to be 4. 4, 4. 3, and 2. 3 hours, respectively, between 4. 5- to 8. 7-fold shorter than that identified for α-tocopherol (9). Products of lipid-rich plant and vegetable oils are the essential natural sources of vitamin E, whereas tocopherol is found in the leaves and seeds of most plants including corn, olive, soybean, sesame, peanut, and sun flow (10), tocotrienols is less abundant, present at most in rice bran, annatto, and palm oils (11). Palm oil is one of the most plentiful natural sources of tocotrienols, with frank palm oil (tocotrienol-rich fraction (TFT)) containing around 800 mg/kg weight of α- and γ-tocotrienol isoforms. The content of vitamin E in palm oil is 70% tocotrienols and 30% tocopherols (10). Other

natural sources of tocotrienol are walnut, hazelnut, rye, amaranth, poppy, safflower, maize, and the seeds of grape, flax, and pumpkin. Furthermore, tocotrienols were also found in eggs and meat (2). The chemical structure of tocopherols and tocotrienols are very similar and many investigators have obviously demonstrated that each individual isoforms exhibit significant differences in their biological activity and health benefits (12). Until recently, tocotrienol derivatives did not attract much attention, however during the past decade a growing body of information has accumulated concerning the health-related biological functionality of tocotrienols. Studies have clearly established that tocotrienol, in compare to tocopherols, exhibit strong anticancer activity (13). Evidence now suggests that tocotrienol affects diverse pathways linked with tumorigenesis and therefore has prospect in both the prevention and the treatment of cancer (14).

2. Antioxidant Activity of Tocotrienols

Vitamin E is well known for its strong antioxidant activities and has been suggested as the most important lipid soluble antioxidant in the human blood plasma and circulating lipoproteins (15). Researchers have suggested that tocotrienols possess superior antioxidants in compare to tocopherols at preventing cardiovascular diseases (16) and cancer (17). Results obviously indicated that d-α-tocotrienol have 40-60 times higher antioxidant potency than conventional d-α-tocopherol, although their absorption and distribution after oral intake are less than that of α-tocopherol (18). Two factors must be considered when comparing the effectiveness of various vitamin E homologues, the substituents on the chromanol nucleus and the properties

of the side chain (19). Kamat et al. identified that tocotrienol rich fraction (TRF) was significantly more efficient than α-tocopherol against lipid peroxidation and protein oxidation in rat brain mitochondria (20). When oxidative lipid hydroperoxides are created, the hydroxyl group of α-tocopherol reacts with the lipid peroxyl radical, this results in forming lipid hydroperoxide and an α-tocopheroxyl radical which can be recycled back to the active reduced form through reduction by other antioxidants, such as retinol, ascorbate, or ubiquinol. Interestingly, lipid peroxyl radicals interact with vitamin E faster than with poly unsaturated fatty acids by 1000 times, therefore, preventing autoxidation of lipids and additional propagation of free radicals (21). The higher antioxidant efficiency of d-α-tocotrienol were shown to be due to the combined effects of three properties displayed by d-alpha-tocotrienol in contrast to d-alpha-tocopherol includes; its higher recycling efficiency from chromanoxyl radicals, its more constant distribution in the membrane lipid bilayer, and its more effective interaction of the chromanol ring with lipid radicals, these properties make the interaction of chromanols with lipids radicals more efficient (22).

3. Molecular target and signaling pathways of tocotrienols

Tocotrienols have attract many attention in the last few years not just as secondary forms of vitamin E but also as unique nutritional compounds with unique antioxidant properties. These properties mediated by modulation of various targets which may occur indirect at the transcriptional, translational, or post-translational levels, or by direct interactions with cellular targets (14). The consumption of vitamin E for prevention and treatment of human

diseases is well documented. Various studies revels that tocotrienols exhibit chemopreventive activity. For instance, tocotrienols from TRF suppressed the proliferation of human breast cancer cell lines in vitro (23) Tocotrienols have been identified to possess diverse specific activities, such as antioxidant (24), anti-proliferative (25), anti-survival (26), anti-inflammatory (27), anti-angiogenic (28) and anti-apoptotic activities (29). The molecular mechanisms behind these beneficial effects are still scarcely understood. Reporters clearly point out the antioxidant functionality of tocotrienols are executed through induction of phase II antioxidant enzymes such as; glutathione peroxidise (30), NADPH: quinone oxidoreductase (31), and superoxide dismutase (32), which results in free radicals such as superoxide radicals (33). Induction of phase II enzymes provide protection against free radical damage and reduce the incidence of the radical derived degenerative diseases such as cancer (2). However, researchers have recently linked the antioxidant activities of tocotrienols with nuclear factor-erythroid 2-related factor 2 (Nrf2), a member of the Cap 'n' collar (CNC) family of basic region-leucine zipper transcription factors (34). Results shows that tocotrienol were able to affect activates of Nrf2 regulated enzymes such as UDP-Glucuronyltranferase (UDP-GT), γ-glutamyltransferase (GGT) and glutathione S- transferase (GST) (35). Palm oil tocotrienols have been shown to inhibit proliferation and growth of many cancer cells including the breast, prostate and colon cancer cells both in vivo and in vitro (36). It is suggested that tocotrienols might exert anti-proliferative effect by interfering with signal transduction events at physiologically attainable concentrations (37). Tocotrienol-mediated growth suppression is attributed to cell cycle arrest,

mostly at the G1 phase of cell cycle, and apoptosis (38). Signaling activities associated with enhancing cell cycle growth, and survival e, g; vascular endothelial growth factor(VEGF) (39), mitogen-activated protein kinases (MAPK) such as p38 MAPK, ERK and JNK, c-Jun, c-myc, FLIP (40, 41, 42), Cyclin-dependent kinases (CDK2, CDK4, CDK6) (43, 25), , protein kinase C (48), PIK, Akt, IκB kinase, nuclear factor κ B (39), telomerase (37), Bcl-2, Bcl-xL, COX-2, and matrix metalloproteinases (MMP) (42), are suppressed by tocotrienols. On other hand, signaling pathways promoting cell growth arrest and apoptosis, including transforming growth factor-β(TGF-b) (44), Cyclin-dependent kinases inhibitors such as p21, p27 and p53 (43, 25), activation of caspase-8, which results to caspase-3 activation (45), up-regulation of Bax, cleavage of Bid (46), Apaf-1, Fas (44), caspases (47), DNA fragmentation (48), and release of cytochrome C (43), are activated by tocotrienols. Inhibition of the phosphotidyl- inositol-3-kinase (PI3K)/AKT pathway by tocotrienols was capable to abolish mitogen-dependent growth and survival in various types of cancer cells (49). Reporters, however, linked the ability of tocotrienols to suppress 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase to its antitumor activity (35). Moreover, inhibiting cell survival proteins expression such as XIAP, IAP-1, IAP-2, bcl-2, bcl-xl, c-FLIP, TRAF-1(42), and down-regulation of the telomerase, c-myc, and raf–ERK signaling pathways has also been attributed to tocotrienol’s ability to block cell survival and growth (40). It’s well documented that tocotrienols exhibit anti-angiogenic activity in both in vitro and in vivo experimental systems (17). Angiogenesis plays an important role in the progression of cancer and has been the major focus area for developing cancer treatment strategies.

Tocotrienols suppress angiogenesis by inhibiting proliferation, migration, and tube formation of endothelial cells in vitro (17). Studies demonstrate that tocotrienols promote inhibition of vascular endothelial growth factor (VEGF) expression (39) and VEGF receptor signaling (50). These results suggested the possibility that tocotrienols inhibit angiogenesis via regulation of growth factor receptor on cell surface. Further, inhibition of fibroblast growth factors (FGF) (51), interleukin-8 (IL-8) (52), tumour necrosis factor-alpha (TNF-α) (53), matrix metalloproteinase (MMP)-9 gene, and angiopoietin-1 (42) also linked to the angiogenesis-suppressive activity of tocotrienols. Numerous studies have suggest that tocotrienols possess strong anti-inflammatory activity, mostly by activation of transcription factors NF-kB (42) and STAT3 (54), the two major pathways for inflammation, and most gene products linked to inflammation are regulated by NF-kB and STAT3. Suppression of NF-kB and STAT3 inhibits the proliferation and invasion of tumors and therefore, inhibition of these pro-inflammatory pathways may give opportunity for both prevention and treatment of cancer (55). Furthermore, suppress the expression of Hypoxia-induced factor-1 (52), inducible nitric oxide synthase (iNOS), cyclo-oxygenase 2 (COX-2) (26), prostaglandin E2, TNF (53), IL-1 (56), IL-6 (57), IL-8 (52), by tocotrienols also plays an axial role in the anti-inflammatory activity of this Vitamin. Tocotrienols belong to a phytochemical group of isoprenoid molecules which has shown to exhibit anticarcinogenic activities. Studies however, clearly reported that tocotrienols suppress proliferation and induce apoptosis in various types of tumor cells including those of the skin (47), breast (44), lung (61), stomach (40), colon (62), liver (46), pancreases (63) and prostate (64). Numerous mechanisms have been

suggested by which tocotrienols induce apoptosis in these cancer cells, as described earlier. Further, the anticancer effects of tocotrienols have been demonstrated in both in vivo and in vitro. For instance; Guthrie et al. suggested that tocotrienols are effective inhibitor of both estrogen receptor negative and estrogen receptor positive cells. Meanwhile, Iqbal et al. showed that giving tocotrienol-rich fraction to DMBA-administered rats suppressed mammary carcinogenesis.

4. Conclusion

Tocotrienols constitutes a great part of total vitamin E in variety of food sources. Evidence continues to accumulate regarding how tocotrienols mediates its antioxidant activities. Experimental studies both in vivo and in vitro obviously stated that tocotrienols exhibit enhanced antioxidant activities compared with tocopherols. They have shown to inhibit proliferation and growth of many cancer cells including those of the skin, breast, lung, stomach, colon, liver, pancreases and prostate. In addition, they have shown to possess strong anti-inflammatory activity. However, these properties that exhibited by tocotrienols are mediated by targeting multiple cell singling pathways linked to its activities toward many health aspects, importantly cancer, cardiovascular and neurodegenerative diseases. Additional studies are required to clarify how tocotrienols mediated its antioxidant effects by activates Nrf2.