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Vitamin E: An Anti-Carcinogen Agent

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Abstract. Today, one of the major diseases causing high levels of morbidity and mortality globally is the cancer pandemic. Subsequently, according to the world health organization data, the incidence of cancer is one of the major causes of downward trends in global economy, including western economies. Since most of the causes of the cancer pandemic are related to events in body systems, organs and tissues nutrition has been factored in or identified as one of the strategies to control, reduce cancer incidence and possibly prevent the cancer pandemic. From nutrition standpoint therefore, most anti-oxidants molecules have been recognized as parts of the antidotes to the condition. Amongst the anti-oxidants molecules identified, such as vitamins C and D the anti-oxidant vitamins E are speculated to be more promising as anti-cancer agent compared to others. Vitamin E discovered in 1922, as at that time was thought to be a dietary factor important for reproduction in the rat. At present, vitamin E being the most potent anti-oxidant vitamin has been demonstrated to be the most promising as an anti-carcinogen agent. In the same vein, the tocotrienols' groups of vitamin E are more successful and thus showed more beneficial inclinations in the control and prevention of the cancer epidemic. This paper is tailored to bring to the limelight some of the studies that support the above stated assertions in respect to vitamin E being an anti-carcinogen agent. This is truly so with the tocotrienols than with the tocopherols as highlighted below in a literature-based fashion using different animal cell lines.

Key words: Vitamin E, Tocotrienols, Anti-Carcinogen and Animal Cell Lines

Introduction

Vitamin E was discovered in 1922 by Evans and Bishop (1922). As at that time vitamin E was thought to be a dietary factor essential for reproduction mostly in the rat. However, at present our understanding of the vitamin has expanded such that today it is used as a dietary supplement because of the belief that its potent antioxidant properties may aid to attenuate morbidity and mortality in animals, including humans. Plants normally synthesize eight different molecules with vitamin E antioxidant activity. These include: *α-, β-, γ-* and *δ-*tocopherols and their corresponding four tocotrienols. The *α-, β-, γ-* and *δ-*forms differ with respect to the number and position of the methyl groups on their chromanol ring. Furthermore, the tocotrienols have an unsaturated tail containing three double bonds, whereas the four tocopherols have a phytyl tail. The *RRR-α*-Tocopherol is the naturally occurring form of *α*-tocopherol, containing chiral carbons in the *R*-conformation at positions 2, 4' and 8' (Birringer et al., 2002).

The synthetic vitamin E is known as all-*rac*-α-tocopherol. Position 2 is very critical for in vivo α-tocopherol activity and only the 2*R*-forms are recognized to meet human requirements (Food and Nutrition Board and Institute of Medicine, 2000). Vitamin E functions *in vivo* as a very potent peroxyl radical scavenger (Burton et al., 1983). Peroxyl radicals (ROO-) react 1,000 times more favorably with α-tocopherol (Vitamin E-OH) than with polyunsaturated fatty acids (RH). The tocopherol's phenolic hydroxyl group reacts with an organic peroxyl radical to form the corresponding organic hydroperoxide (ROOH) and the tocopheroxyl radical (Vitamin E-O.) (Burton et al., 1985).

Due to the fact that vitamin E is a known potent antioxidant most of its biological and biomedical investigations had been in the areas of antioxidant activities. However, further studies of vitamin E has demonstrated that vitamin E is also an anti-cancer agent. This

deposition is principally premised on the fact that isoprenoids exhibit anti-carcinogenic characteristics (Marantz et al., 1994). The anti-carcinogenic status of vitamin E is framed around two major theories, namely: vitamin E inhibits lipid peroxidation as well as formation of reactive intermediates that are capable to binding DNA and possibly causing its damage. Secondly, it is involved in the inhibition and formation of mutagenic reactive nitrogen species, including peroxy-nitrite and nitroso-amines that are capable of reacting with DNA and other biological molecules (Ames, Gold &Willet, 1995). Therefore, in this paper, the implications of vitamin E as an anti-carcinogenic agent would be highlighted. Furthermore, where tocopherol or tocotrienol is used would be clearly specified to properly position this paper in addressing its set out objectives.

Vitamin E as an Anti-Carcinogen Agent

In the rat, studies have shown that the long-term intake of tocotrienol rich fraction reduced cancer risk by the prevention of hepatic lipid peroxidation and protein oxidation damage principally due to its potent antioxidant ability (Iqbal, Minhajuddin & Beg, 2004). Again, there are studies that demonstrated growth inhibition of human, mouse and rat tumor cell lines when they were exposed to tocotrienol (Nesaretnam et al., 1995; Nesaretnam et al., 1998). In recent times, the area of research involving tocotrienol in its role in cell growth regulation and its application as potential anticancer agent have evolved. To this extent, tocotrienols have proven to be better than tocopherols as anti-cancer agent in both *in vitro* and *in vivo* studies. As stated earlier, tocotrienols from tocotrienol rich fraction inhibited the proliferation of human breast cancer cell lines (Nesaretnam et al., 1995; Nesaretnam et al., 1998; Guthrie et al., 1997). In the studies of He et al. (1997), both γ- and δ-tocotrienols were potently effective in the inhibition of mouse growth derived melanoma cancer cell cultures. It is also worthy of note that the unsaturation of the hydrocarbon chain and the degree of methylation of the chromanol ring is essential for effecting these anti-cancer impacts of tocotrienols as shown in the studies of Elson and Yu (1994). Furthermore, Yu et al. (1999) reported that tocotrienols induced cell-cycle arrest in the G-1 phase and apoptosis in human and murine tumor cells.

Conte et al. (2004) investigated the anti-proliferative impact and metabolism of tocotrienol in prostate cancer cells. The cell lines transformed tocopherols and tocotrienols in the corresponding carboxyethyl-hydroxychromans metabolites. The inhibitory impact of this metabolism on cell growth mimicked the order of magnitude of α-tocopherol < α-tocotrienol < γ-tocopherol < γ-tocotrienol. Tocotrienols acted on cell proliferation in a dose-dependent manner and induced programmed cell death. δ-Tocotrienol had the most potent in inducing apoptosis in estrogen-responsive and estrogen-non-responsive human breast cancer cells. This might be related to the ability of tocotrienols to upregulate apoptosis in these lines. Furthermore, another possible mechanism might be related to tocotrienols' post-transcriptional suppression of HMG-CoA reductase. Tocotrienol exhibited cytotoxicity against A549 cells (a human lung adenocarcinoma cell line with a ras gene mutation) in a dose-dependent pattern (0 - 40 μM). Tocotrienol cytotoxicity was related to the accumulation of cells in the G1-phase of the cell-cycle and the subsequent induction of apoptosis. Accordingly, therefore, 24-hr treatment of A549 cells with 40 μM tocotrienol inhibited Ras farnesylation and subsequently decreased levels of cyclin D (required for G1/S progression in the cell-cycle and Bcl-xL (a key anti-apoptotic molecule) (Yano et al., 2005).

In another independent study by Wada et al. (2005) that investigated the anti-tumor effect of tocotrienols in both in vivo and in vitro studies in mice showed that liver and lung carcinogenesis was significantly suppressed on oral administration of tocotrienols. In human hepatocellular carcinoma HepG2 cells, δ-tocotrienol exerted a more significant anti-proliferative effect than α, β and γ-tocotrienols. Gene expression analysis revealed that δ-

tocotrienol increased CYP1A1 gene, a phase 1 enzyme. These data put together support the fact that vitamin E, particularly the tocotrienols are promising anti-carcinogen agents.

Conclusions

From the fore-presented data, vitamin E and more so, the tocotrienols are clearly one of the anti-carcinogens extensively studied and found to be promising potent anti-carcinogen agents.

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