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Potential Anticancer Activity of Tocotrienols

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Abstract

Natural compounds of plant origin are being used in cancer research since several decades. More than treatment, they hold promise in cancer prevention. Besides cancer, they are also used in other health disorders. Interest in natural compounds mediated treatment is increasing due to their low toxicity, wide variety of health benefits and natural abundance. They can be easily obtained from nature and can be taken in diet without doctor consulting based upon their availability. As they do not result in significant health problems, a little change in dietary habits can give us benefit against various diseases including cancer. Tocotrienols are vitamin E groups of compounds obtained from Pam oil in high concentrations. In this review, we describe the anticancer activities of Tocotrienols in various cancer types. Tocotrienols have shown potential *in vitro* and *in vivo* activity and are being tested in several clinical studies.

Keywords: Tocotrienol; Cancer; Natural compounds

Introduction

Cancer is characterized by uncontrolled proliferation of the cells in the body that are able to metastasize to secondary sites. Cancer is one of the burdensome diseases worldwide and diagnosed in millions of people [1]. Majority of those people are diagnosed when the disease is already at advanced stages and treatment is becoming challenging due to aggressiveness of the tumour [2]. It occurs mainly due to genetic, epigenetic modifications in the cell, dietary habits, pathological conditions due to other disease states, and environmental factors. Cancer incidence is varying at different parts of the globe and can be attributed to socioeconomic state, lifestyle and environmental factors at the particular regions [3,4]. Advance stage of the cancer is characterized by metastasis where the tumour cells disseminate from the primary site and enter the systemic circulation which is driven by mutations of the cell. Cancer spread can be targeted at various stages including invasion, angiogenesis, cell proliferation, growth and metastasis. Metastasis remains the major cause of death in cancer patients [5,6]. Genomic and epigenetic prolife of cancers is studied to observe the drivers and co drivers in the patient [7,8]. Cellular and molecular mediators that lead the cancer cells to distant organs for reseeding of the same is key factor to identify. When tumour size is increased beyond a certain level, the core region of tumour become hypoxic as blood vessels are not fully formed at that site. Hypoxia leads to the stabilization of hypoxia inducible factor (HIF-1) and further activation of genes responsible for angiogenesis, anaerobic metabolism, cell survival, and invasion [9,10]. Tumour microenvironment plays a crucial role in generation of more resistant tumour cells with aggressiveness and favourable to metastasis. Inflammatory and immune signalling in tumour microenvironment are altered during cancer growth in favour of the same [11-14].

Even many chemotherapy and radiotherapy options are available to treat the cancer at certain extent, still they are not enough as they cannot completely eradicate the cancer [15]. During treatment, small proportion of quiescent cancer cells that have stemness and resistant characteristics generated leading to cancer regrowth after certain period of time [16,17]. Moreover, these treatments have significant unwanted side effects in the patient. Hence it is important to prevent cancer [18] or treat with natural compounds which have low toxicity towards normal cells of the body [19]. Several studies are conducted to administer the natural compounds in diet which showed that the specific diet can delay the cancer occurrence or treat the condition [20]. However, factors such as availability, oral administration limitations, identifying the target, reaching the bio therapeutic concentrations in the blood should be estimated [21]. Potential natural compounds include vitamin derivatives, phenolic and flavonoid agents, organic sulphur compounds, isothiocyanates, curcumins, fatty acids and d-limonene. Several vitamins including Vitamin D, E, C and A are already tested *in vitro* and *in vivo* for their anticancer activity [22-24]. Structural modifications of the parent natural compounds led to increase in anticancer activity [25,26].

In the review, we will discuss anticancer activities of Tocotrienols against various cancers. Tocotrienols belong to the Vitamin E family of compounds. While the Tocopherol sub group of Vitamin E are associated with anti-oxidant properties, tocotrienols are responsible for anti-proliferative activity against tumour cells [27].

Anticancer Activities of Tocotrienols in Cancer

Prostate cancer

Prostate cancer begins in the prostate glands or male reproductive system. It grows very slowly and is not diagnosed in many of the cases at early stages. According to reports, prostate cancer is present in majority of the men without being diagnosed [28,29]. So, it is very important to identify and classify it based upon the site of initiation, number of lymph nodes involved, and stage of metastasis. It helps in identifying the right treatment and estimate the disease prognosis. It

can be a result of age, diet, genetics, obesity or sexually transmitted diseases [30,31]. Mostly prostate cancers are the mixtures of androgen dependent and androgen independent cells.

Androgen deprivation therapy (ADT) is highly recommended method of treating prostate cancer [32]. ADT can induce cell apoptosis in prostate cancers by acting on the androgen dependent cell population. However, ADT is not successful as there is a chance of recurrence due to resistant cells that survive or generate in the treatment [33-35]. ADT can lead to the development of stem cell population in prostate cancers which is a major concern due to their ability to metastasis and recurrence after few years [36]. Moreover, ADT can cause cardiovascular problems due to possible alteration of metabolic state in the body [35].

Cancer stem cells express elevated Akt signaling and expression of bcl-2. Akt signaling implies increased cell survival and resistance to apoptosis, while bcl-2 indicates reduced apoptosis in cancer cells [37-39]. γ-Tocotrienol is used in combination with ADT, as it has shown to downregulate Akt signaling and decreases bcl-2 expression [36]. Development of alternative treatment strategy is needed for the treatment of prostate cancer and other cancer types to overcome the problems associated with treatment [40]. When γ-tocotrienol is used along with docetaxel, γ tocotrienol is sensitizing the tumour cells to docetaxel for effective growth control in androgen independent prostate cancer tumours [41]. γ-Tocotrienol was shown to deposit in the androgen independent prostate cancer cells and decreased cell proliferation markers and increased apoptotic markers including cleaved caspase 3 and poly(ADP-ribose) polymerase [41].

Ideal anti-cancer agent should selectively remove the malignant cells and at the same time should not cause unwanted harmful effect on normal cells. Tocotrienol rich fraction (TRF) consists of various concentrations of tocopherols and tocotrienols [42-44]. TRF has growth inhibitory action and can also induce apoptosis when tested on prostate cancer cell lines (LNCaP, DU 145, and PC-3). It is not showing significant unwanted effects on regular human prostate epithelial cells [42]. TRF is also decreasing the anchorage independent growth of these prostate cancer lines. This shows that the TRF is reducing the malignant transformation of cancer cells. Cancer cells exposure to TRF cause DNA fragmentation and further results in apoptosis. Cancer cell cycle progression is also inhibited at G0/G1 phase [42].

γ-Tocotrienol suppresses NF-κβ activity and also down regulates bcl-2. This causes activation of caspases and further leads to apoptosis [45]. It's been also shown that γ-tocotrienol induces apoptosis through JNK pathway. C-Jun and ATf-2 are intermediates in JNK pathway, and are up regulated by γ- tocotrienol treatment. One more target of the γ-tocotrienol in prostate cancer cells is the de novo synthesis of sphingolipids. γ-Tocotrienol increases the accumulation of dihydrosphingosine and dihydroceramide (intermediates in the de novo synthesis) in the cells, leading to apoptosis when tested on human prostate PC3 and LNCaP cancer cell lines [46]. It is shown that the accumulation of the sphingolipids is associated with cancer cell death due to decreased phosphorylation of Akt and activity of PI3kinase by γ-tocotrienol. γ-Tocotrienol decrease the tumour growth by 53% when tested in LNCaP xenograft models [46]. Feeding of transgenic mouse model of prostate cancer (TRAMP) with mixed tocotrienols lower the incidence of prostate carcinogenesis [47]. And the level of high grade neoplastic lesions is less in tocotrienol feeding group. This effect is mediated by increased expression of proapoptotic proteins BAD and cleaved caspase-3 and cell cycle progression inhibitors, CDK inhibitors p21 and p27. At the same time, expression of cyclin A and cyclin E is decreased showing that the action of tocotrienols is mediated by cell cycle regulation. The direct cellular targets and mechanism of action of γ-tocotrienol are still need to be identified.

In another study, γ-Tocotrienol sensitized prostate cancer cells to irradiation therapy [48].

When nude BALB/c mice were injected with PC-3 cells, they developed prostate tumours. Subcutaneous injection of γ-tocotrienol, followed by irradiation therapy resulted in increased lipid peroxidation in tumour cells. Tocotrienols themselves have ability to peroxidase the lipids in the cell membrane. Tocotrienols are converted to corresponding quinones because of free radical scavenging action [49]. Being pro-oxidative in nature, accumulation of quinones in tumour cells results in lipid peroxidation in cell wall and lead to tumour destruction. When γ- tocotrienol is used along with irradiation therapy, tocotrienol sensitized the cells to radiation and tumour size was reduced by 40% [48]. γ-Tocotrienol has inhibitory effect on prostate cancer stem cells (prostate CSC). When PC-3 cells were exposed to γ-tocotrienol, stem cell markers, CD44 and CD 133, were down regulated [50]. γ-Tocotrienol reduced expression of β-catenin and ID-1 proteins, which are essential for stem cell maintenance. Stem cells are very important for recurrence in cancers [51]. γ-Tocotrienol pre-treated PC-3 cells were injected into mice, and observed that tumours appeared relatively late when compared to the not pre-treated PC-3 cells. Further, spheroid formation ability of the cells (key characteristic of stem cells) is inhibited with γ-tocotrienol treatment [50]. This data suggests that γ-tocotrienol is effective against cancer stem cells.

γ-Tocotrienol regulates the invasion capabilities of the prostate cancer cells. E-cadherin together with γ-catenin is essential for inhibiting epithelial-mesenchymal transition. γ-Tocotrienol is up-regulating both E-cadherin and γ-catenin [45]. γ-Tocotrienol is essential for the prevention of advancement of prostate cancer during ADT therapy. ADT therapy results in progression of resistant prostate cancer in individuals by favouring the growth of androgen independent cells in tumour. NF-κβ is essential for the conversion of androgen dependent cells to androgen independent cells [52]. And TGFβ2 expression results in up-regulation of NF-κβ. Tocotrienol mediated down regulation of NF-κβ resulted in decreased survival of PC-3 cells [53]. When γ- tocotrienol is used in prostate cancer PC-3 cells, it caused the down regulation of NF-κβ, p38α, TAK-1, TAB-1, and MMK3/6 all corroborating the NF-κβ down-regulation. In this way, γ- tocotrienol is inhibiting the transformation of androgen dependent cell into androgen independent cells and further decreasing the prevention of cancer advancement [54].

Pancreatic cancer

Pancreatic cancer is the fifth leading cause of death in the United States. Ras pathway plays an important role in proliferation of pancreatic cancer cells. Ras activation needs farnesyl pyrophosphate [55,56]. γ-Tocotrienol has a farnesylated tail and inhibits HMG-CoA reductase enzyme resulting in down regulation of farnesyl pyrophosphate and further Ras protein. Gamma tocotrienol is not toxic to the normal cells. Tocotrienols act against pancreatic cancer by Ras mediated raf/MEK/ERK pathway in K-ras mutated cancer cells. ERK pathway is needed for proliferation, differentiation and survival of cells. When ERK pathway is activated, apoptosis is inhibited [57]. γ-Tocotrienol reduces both ERK and phosphorylated ERK, down regulates ErbB2 and p-Akt expression [58]. γ-Tocotrienol inhibits

phosphorylation of ErbB2 at tyrosine 1248 residue and also downregulates ErbB2 at messenger RNA level. Moreover, tocotrienols can increase phosphorylation of c-Jun protein and favour the apoptosis in cancer cells.

Downstream signalling molecules of Akt are p-mTOR, p-70 S6 kinase and p-GSK-3β. mTOR is present upstream of p-70 S6 kinase and helpful in maintenance of cell homeostasis by autophagy [59-61]. One more protein activated by p-Akt is Fox03a. It is phosphorylated by p-Akt and degraded in cytoplasm [62,63]. When p-Akt is inhibited by the tocotrienol, it is resulting in phosphorylation, activation and cellular transportation of Foxo3a [58]. Fox03a is a tumour suppressor, induces cell cycle arrest and apoptosis.

In combination treatment consisting of γ-Tocotrienol and gemcitabine, tocotrienol sensitized pancreatic cancer cells towards Gemcitabine induced apoptosis through NF-kB regulated protein [64]. Pancreatic tumours were induced in nude mice by orthotropic injection and this combination inhibited tumour growth by 50%. The anti-proliferative action against cancer cells is mediated by down regulation of cyclin D1, c-myc and COX-2. γ-Tocotrienol alone inhibited activation of NF-kB and suppressed the expression of invasion biomarker MMP-9, angiogenic biomarker VEGF in cancer tissues. These effects are increases synergistically with Gemcitabine [64].

Colon cancer

Similar to other cancer types, colon cancer is the result of accumulation genetic and epigenetic modified/altered cells in the colon. It is considered very aggressive due to the high prevalence and mortality rates. γ-Tocotrienol has anti-cancer activity in colon cancer lines evident by *in vitro* and *in vivo* studies. When tested the activity in human colon carcinoma cell lines (HT-29 cells), it has growth inhibitory activity against them [65]. The proposed mechanism of γ-tocotrienol is by increasing the caspase-3 activity in colon carcinoma cells and increasing Bax/Bcl2 ratio. The growth inhibitory activity of gamma tocotrienol is also accompanied by the cell cycle arrest at G0/G1 phase [65].

It has previously shown that, γ-tocotrienol works synergistically with other drugs and reduces the cancer cell growth in various cancers. In same way when γ-tocotrienol is given in combination with Atorvastatin, cell cycle arrest and apoptosis were observed at lower dose levels in HT-29 and HCT116 cells [66]. Atorvastatin is HMGCoA reductase inhibitor, and further reduces the isoprenylation of many proteins (required for cell proliferation and cell cycle regulation). When given alone, atorvastatin is decreasing the enzymatic activity of HMGCoA reductase and so the protein isoprenylation is inhibited. Long term use of Atorvastatin increased HMGCoA reductase levels due to compensatory pathways. When used along with γ-tocotrienol, the latter is decreasing the levels of HMGCoA reductase and action is synergized. Further triple combination of γ-tocotrienol with Atorvastatin and celecoxib showed much more response in HT29 cell lines [66].

Chromosomes consist of telomere caps on their both ends. Upon continuous cell divisions in the body, the length of telomeres is decreased and cells enter into replication silent state. This happens usually in aging. Telomerase is a RNA dependent DNA polymerase which works by increasing the length of telomeres in the cell thereby preventing its shortening [67,68]. Hence, suppressing or inactivation of telomerases is the new target in cancer therapy. Tocotrienols have the ability to decrease telomerase activity by downregulation of human telomerase reverse transcriptase (hTERT) expression in DLD-1 human colorectal carcinoma cells. This was shown to be coincided by inhibiting protein kinase C activity and c-myc downregulation [67].

Gastric cancer

γ- Tocotrienol inhibited proliferation and induced apoptosis in gastric cancer cells. When 60 μmol/L of γ-tocotrienol is added to SGC-7901 (Human gastric carcinoma cells) cells, it showed strong anti-proliferative activity and induced apoptosis [69]. They found that apoptosis is mediated through the up-regulation of Bax, down regulation of Bcl-2 proteins and further activation of caspase-3, poly (ADP-ribose) polymerase (PARP) cleavage. PARP is responsible for DNA damage triggered signalling cascade. γ-Tocotrienol is able to cleave the PARP by activation of caspase-3 and the cell is not able to detect the DNA damage during apoptosis. γ- Tocotrienol is showing its anti-proliferative activity in SGC-7901 cells by influencing the Raf/MEK/ERK pathway [69]. It is one of the MAPK pathways needed for cell cycle progression and proliferation. γ- Tocotrienol is able to down-regulate the Raf-1 and phosphorylation of ERK1/2. This inhibits the downstream target gene expression of c-Myc, an oncogene expressed in many cancers. Another group of scientists suggested that apoptosis is induced in gastric cancer cells (SGC-7901) by mitochondria dependent cascades [70]. This is supported by the finding of caspase-9 (apical caspase involved in mitochondria mediated apoptosis) activation and further caspase-3 activation in SGC-7901 cells. They have also shown that cell cycle arrest is occurred at G0/G1 phase and cell proliferation is decreased in time dependent and dose dependent manner. γ- Tocotrienol has the ability to inhibit the invasion and metastasis of gastric cancers. Metastatic cells will have the ability to invade extracellular matrix and basement membrane components like LN, FN and type I collagen. γ-Tocotrienol successfully inhibited the adhesion of SGC-7901 cells to matrigel, FN or LN [71]. Matrix metalloproteinases (MMPs) are released by invasive cancer cells to digest the extra cellular membrane and favour the cell motility [72]. The important MMPs are MMP-2 and MMP-9. γ-Tocotrienol decrease mRNA levels of MMP-2 and MMP-9 but did not control the activation of MMP-9. This is supported by up-regulation TIMP-1 (Tissue inhibitor of metalloproteinase-1) and TIMP-2 at mRNA levels and increasing the expression of nm23-H1 (anti-oncogene) by treatment with γ-tocotrienol [71]. With this we can say that γ-tocotrienol inhibits invasion of gastric cancer cells. γ-Tocotrienol also inhibits angiogenesis and metastasis in gastric cancer cells as it inhibited the accumulation of HIF-1α and paracrine secretion of VEGF in hypoxia induced SGC-7901 cells. Cobalt(II) chloride at 150 μmol/L concentration is used to induce hypoxia in these cells [73].

γ-Tocotrienol is showing potent *in vitro* and *in vivo* anti-cancer activity when used alone or in combination with other anticancer drugs. Capecitabine is the chemotherapeutic drug used in treatment of gastric cancer patients. But it causes development of resistance in patients. γ- tocotrienol along with Capecitabine in xenograft mouse model of gastric cancer [74] is enhancing the apoptotic activity of Capecitabine synergistically and inhibited NF-kβ expression. NF-kβ is the main culprit which supports development of cancer resistance, decreased apoptosis and increased cell proliferation in gastric cancers [75,76]. γ-Tocotrienol reduced the gastric tumor growth when given alone and in combination with Capecitabine. This combination synergistically downregulated the expression of ICAM-1, MMP-9,

CXCR4 and VEGF which are essential for invasion, metastasis and angiogenesis.

Conclusions

At this point, we can conclude that tocotrienols exert anticancer activity in different cancer types. They have anti-proliferative, anti-angiogenic, anti-migratory, anti-hypoxic and anti-metastatic properties in cancer cells evident by *in vitro* and *in vivo* data. However, data suggests that they have limitations with poor oral absorption, and poor bioavailability. Human studies also indicated their potential anticancer activity and limitations. Hence further research is needed to overcome the limitations for better treatment and improved patient prognosis.

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