REVIEW ARTICLE

Vitamin E: An Antioxidant With Anticancer Properties?

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ABSTRACT

More studies are now focusing on vitamin E as an anticancer agent for its good effects in many in-vitro studies. Current studies proposed that vitamin E might be a suitable candidate as an alternative treatment for cancer due to its antioxidant properties. Vitamin E act as an antioxidant by their long-chain polyunsaturated fatty acids, and thus the integrity of membranes in the cells is maintained and consequently retain the bioactivity of the cells. This mini review will focus on the activity of vitamin E as an antioxidant to protect against cancer in in-vitro, in-vivo, and clinical studies. Although most studies reported great outcomes for the anticancer activity of vitamin E, there were some conflicting data. To date, studies on effects of vitamin E are still undergoing where researchers are still debating on the positive and negative effects of vitamin E as an anticancer therapeutic action.

Keywords: Vitamin E, Antioxidant, Anticancer, Tocopherol, Tocotrienol

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INTRODUCTION

Evans and Bishop has discovered vitamin E in 1922 and it is declared as a factor that could not be identified in vegetable oil. This factor is known to be essential in female rodents for their reproduction process (1). They found out that the laboratory rats were unable to reproduce after being fed with only lard as a source of food fat. Subsequently, the addition of wheat germ and lettuce to the diet adjusted the problem, and the compound responsible for the adjustment was termed 'factor X' at that time (2). In 1925, Evans renamed the compound as vitamin E, as the last vitamin to be discovered prior to that is vitamin D. It is then became known as an important, fat-soluble nutrient with antioxidant ability in our body system (3).

Two types of vitamin E make up the eight different compounds, which include alpha (α), beta (β), gamma (γ), and delta (δ) classes of tocopherol or tocotrienol. Together, both tocopherols and tocotrienols are called the tocochromanols (4). High levels of tocopherols are found in soybeans, nuts, sunflower seeds, safflower, cottonseed, and vegetable oils. On the other hand, tocotrienols is normally available in cereal grain, palm oil, coconut oil, barley, tobacco, Apiaceae species, and rice bran (5). Amongst all classes of vitamin E, alpha-tocopherol is the most active biologically, and it efficiently transfers hydrogen atoms to lipid-free radicals, giving an alpha-tocopheroxyl radical to the corresponding non-radical product of the lipid. In terms of chemical structure, both types of vitamin E have identical basic structure which is characterized by a long isoprenoid side chain that attached to two positions of the 6-chromanol ring (6). Tocotrienols contradict with tocopherols in the sense that they occupy a farnesyl side chain compared to tocopherols that possess a side chain of saturated isoprenoid C16 (7). Fig. 1 shows the molecular structures of vitamin E (3).

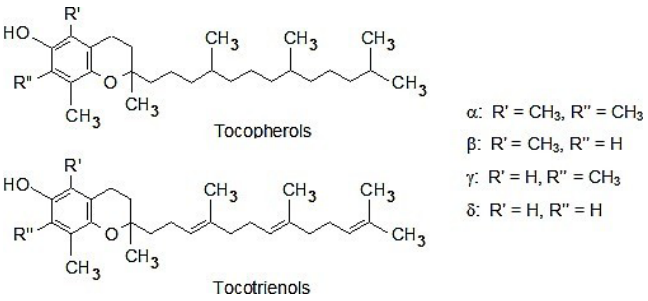

Figure 1: Molecular structure of tocopherols and tocotrienols

Human and animal body is not able to synthesize Vitamin E, thus it has to be consumed through food or other supplements due to the fact that it is considered to be an essential nutrient (8). Nonetheless, deficiency of vitamin E is rarely occurs, usually happens in individuals who could not absorb vitamin E due to abnormalities (9). The intake recommendations for vitamin E is listed in the Dietary Reference Intakes (DRIs) established by the Food and Nutrition Board (FNB). DRI contain a set of reference values of nutrient intakes in healthy individuals. FNB recommendation on daily intake of vitamin for humans is shown in Table I (9).

Table I: Recommended daily intake of vitamin E by gender and age

Age	Males	Females	Pregnancy	Lactation
0–6 months	4 mg (6 IU)	4 mg (6 IU)		
7–12 months	5 mg (7.5 IU)	5 mg (7.5 IU)		
1–3 years	6 mg (9 IU)	6 mg (9 IU)		
4–8 years	7 mg (10.4 IU)	7 mg (10.4 IU)		
9–13 years	11 mg (16.4 IU)	11 mg (16.4 IU)		
14+ years	15 mg (22.4 IU)	15 mg (22.4 IU)	15 mg (22.4 IU)	19 mg (28.4 IU)

There is no recommendation regarding consumption of vitamin E supplements have been made so far. In fact, the ideal dosage is still speculative as there is no specific dosage that is too high or too low to provide benefit to the human body. Few previous studies on human reported that vitamin in high dosage supplementation (> 400 IU/day) specifically increased mortality, including from cardiovascular diseases and cancer (10), and increases the risk of prostate cancer incidents (11). Other study confirms that vitamin E taken in high dose (> 400 IU/day) showed no effects on cardiovascular events (12) and did not affect muscle training or exercise (13). Vitamin E supplementation has been linked to pro-oxidant damage at dosages of > 1000 mg/day or 1100 IU, but there is no evidence of toxicity has been observed following its consumption from food sources at equal doses (7). Vitamin E was also found not to give effect to any site-specific cancer, including lung, bladder, prostate, and pancreatic cancer in a research by Wang et al. where supplementations of vitamin E were given at a dose of 400 IU on alternating days for 11 years among 10,000 men (14).

Six years study on Vitamin E supplementation on 29,133 male smokers found out that vitamin E consumption gives no positive or negative effects on primary lung cancer, but the prevalence of prostate cancer was decreased by 34% (15). Another continuous study for eight years found out that supplementation of vitamin E at 75 IU/day reduces the incidence of lung cancer cases among smokers (16).

The purpose of this mini review is to outline the vitamin E activity whether to provide benefits or harmful effect of as an alternative medicine in cancer treatment. Many studies linked the antioxidant ability of vitamin E with cancer (17–19), thus this mini review focuses mainly on the antioxidant ability of vitamin E in cancer treatment. Antioxidants which contains in vitamin E is an ultimate free radical buster, that prevents the production of reactive oxygen species (ROS) molecules. It acts as defense mechanism by protecting cell membrane from free radicals attack (20,21). The studies that we discuss in this article were summarized in Table II and Table III.

Table II: Summary of Vitamin E study on Antioxidant Activity

Dosage of Vitamin E	Study Subjects	Diseases	Outcome	Citation number
Vitamin E succinate 400 IU/day	Healthy human	Cardiovascular event	No effect	12
		Muscle training		13
Alpha tocopherol 1.5 mg/kg	Disease-free albino rats	Superoxide activity	Reduced oxidative stress compared to normal	56
400/IU/day Alpha tocopherol	Male smoker (urine)	Superoxide activity	Reduced oxidative stress	57
	Fat-1 transgenic mice	Lipid peroxidation	Inhibit oxidative stress	58
	Rat liver microsome			59
Alpha tocopherol (30,60,100 mg/kg) Tocotrienol rich fraction (10, 30, 60, 100 mg/kg)	Male wistar Rats	Free radical activity via Ferric nitrilotriacetate (FeNTA)	Tocotrienol able to prevent free radical activation at low dose compared to tocopherol	60

Antioxidants action on free radicals

Antioxidants can be categorized as water- or lipid-soluble. Water-soluble antioxidants, vitamin C for example, located in cellular fluids, while lipid-soluble ones such as vitamin E located predominantly in cell membranes (3). Antioxidant activity can be grouped as enzymatic and non-enzymatic. Antioxidants neutralizes free radicals through interactions between them. The defend mechanism of our body against free radicals involves enzymatic antioxidants that reduces the level of lipid hyperoxide (22).

Free radical is defined as an oxygen-containing molecule with one or more unpaired electrons, which is extremely reactive towards other molecules (23,24). Conditions such as stress as well as environmental toxins from pollutants, chemicals, foods, alcohol, and tobacco leads to free radicals formation (19,25,26). Problem arise when free radicals react chemically with cell components which include proteins, DNA, and lipids, and steal their electrons to become stabilized (25). Consequently, this activity of free radicals can play an extensive role in the advancement of diseases such as cancers, neurodegenerative disorders, and arthritis (27). Free radicals are principally and enormously generated during the aerobic production of ATP from the mitochondrial electron transport chain which then

Table III: Summary of Vitamin E study on Anticancer Activity

Dosage of Vitamin E	Study Subjects	Diseases	Outcome	Citation number
Vitamin E succinate 400 IU/day	Healthy human	Cancer	Increased mortality	10
		Prostate cancer	Increased Risk	11
		Site-specific cancer	No effect	14
Vitamin E succinate (2-20 μM)	Murine mammary tumor cell (66cl-4-GFP) in BALB/cfc3H mouse	Tumor burden and metastasis	Effective in reducing tumor burden	64
Vitamin E succinate 20 μg/ml	MDA-MB-435 Human breast cancer cells, MCF-7 cell line	Apoptosis study	Vitamin E succinate induces apoptosis involving TGF-□ pathway	72
Vitamin E succinate 1.5 – 3.0 mg/kg	Noble rats	Prostate carcinogenesis	Induced inflammation in the rats	92
Vitamin E succinate In-vivo study (2 mg/kg) In-vitro study (25-50μM)	In-vivo study (E7 expressing murine tumor model) In-vitro study (TC-1 cells)	Antitumor activity	Treatment significantly diminished tumor volume in TC-1 tumor bearing mice and the treatment able to induce necrosis in TC-1 cells	79
Vitamin E Succinate 150 mg/kg	A549 lung cancer was injected into right submammary fat in athymic nude mice	Lung cancer	Tumor growth was reduced however pulmonary metastasis were spotted	82
	AT6.1 prostate cancer cell line was injected subcutaneously in right flank of male SCID mice	Prostate cancer	The growth of tumor is suppressed and the metastatic spread is also reduced	90
Vitamin E succinate 330 mg per day	Risk factor for cancer in both women and men	Lung, prostate, stomach and colon cancer	Low level of vitamin E related to increased level of lung and prostate cancer	94
Alpha tocopherol succinate 10 mmol/L	MDA-MB-231 Breast cancer cell line	Neoangiogenesis, tumor development and progression	VEGF (Vascular endothelial growth factor) was inhibited suggesting a mechanism for mammary cancer prevention	73
Alpha tocopherol 75 IU/day	Male smoker	Primary lung cancer	No effect	15
		Prostate cancer	Prevalence decreased by 34%	
		Secondary lung cancer	Reduce incidence of the cancer	16
Alpha tocopherol 100 mg/ml	Human oral squamous carcinoma cell line (ORL-48)	Oral squamous carcinoma cells	Alpha tocopherol showed an anti-proliferative activity and showed cell death and apoptosis activity	80
Alpha tocopherol In-vivo study (3.3 mg/kg) In-vitro study (40 mg)	In-vivo study (BALB/c mice) In-vitro study (4T1 mammary cell)	Metastatic murine breast cancer	The growth of tumor was inhibited and the spreads of metastatic to lung also reduced	81
Alpha tocopherol acetate 0.1 and 0.5 g/kg	K-RAS induced and B-RAF induced lung cancer model (Trp53)	Lung cancer	The treatment increased the proliferation of human lung cancer	89
Vitamin E analogue Alpha tocopherol (500 – 1250 mg/kg)	MDA-MB-435 was injected at mammary spot in female out breed of NU/NU immumodeficient mice	Breast cancer burden and metastasis	The treatment reduced tumor burden and also reducing visible macroscopic lung metastasis	86
DL Alpha Tocopherol acetate 30 mg/kg	Wistar-unilever rats administer with carcinogen	Chemopreventive effects	No reduction in prostate cancer treatment	91
Alpha tocopherol 50 mg/kg	Male smokers 50 -69 years old	Prostate cancer	Little or no effect on total mortality of prostate cancer	16
Tocopherol (Alpha, Beta, Gamma, Delta) 50 mg/kg			Supplementation of tocopherol lower the risk of prostate cancer especially in Gamma Tocotrienol	93
Vitamin E (from food and vegetable in high vitamin E content)	Head and Neck cancer patients	Head and Neck cancer	Vitamin E had a protective role in cancer of oral cavity and pharynx	95
Alpha tocopherol 400 IU/day for 6.5 years			The treatment increased in all-cause mortality	97
Alpha tocopherol 400 IU/day	Prostate cancer patient (men) 55-70 years old	Prostate cancer	Treatment does not reduced prostate cancer mortality	98
	Colorectal adenoma patient	Prostate cancer	Vitamin E does not reduce the risk of prostate cancer in colorectal cancer patient	103
Alpha tocopherol 50 mg/kg per day for 8 years	Male smoker 50 – 69 years old	Pancreatic cancer	The supplement increased the rate of prostate cancer incidence	100
	Male smoker (cancer patient) 50 – 69 years old	Upper aerodigestive tract cancer	The supplement had no effect on the Upper aerodigestive tract cancer	101
		Colorectal cancer	Treatment may had a modest preventive effect on colorectal cancer	102
Alpha tocopherol 30 mg/kg per day for 7 years	Healthy women (35-60 years old) Healthy men (45-60) years old)	Skin cancer	Lower incidence of skin cancer in men but not women	104
Alpha tocopherol 0.1 mg per head	MDA-MB-231 was injected into the cardiac of BALB/c nude mice	Breast cancer	Tumor burden is reduced	110
Tocopherol and Tocotrienol (Alpha, Beta, Gamma, Delta) 0-100 μM	Human pancreatic cancer cell line (MIA PaCa-2)	Pancreatic cancer	Delta-tocotrienol act as pro-apoptotic factor in pancreatic cells	63

continue.....

Table III: Summary of Vitamin E study on Anticancer Activity (*continued.....*)

Dosage of Vitamin E	Study Subjects	Diseases	Outcome	Citation number
Tocopherol and Tocotrienol (Alpha and Gamma) 0-20 µM	Malignant mouse mammary epithelial cell	Anti-proliferative and apoptotic effects	Tocotrineol induced apoptosis compared to the Tocopherol	65
Alpha tocopherol and Tocotrienol Rich Fraction (32 mg/ml)	Mice cell line (BNL CL.2 and BNL 1ME A.7R.1)	Liver cancer	Tocotrienol initiated apoptosis in liver cancer cells	84
Tocopherol and Tocotrineol (Alpha, Beta, Gamma and Delta) 5-35 µM	Bovine aortic endothelial cells	Anti-angiogenic activity	Tocotrineol inhibited the proliferation and had significant anti-angiogenic effect compared to tocopherol	88
Gamma Tocotrienol 10 µg/ml	Prostate cancer cell line (LNCaP, DU145 and PC-3)	Prostate cancer	Gamma Tocotrienol has a therapeutic potential to treat advanced prostate cancer	74
Gamma Tocotrienol from Rice-Bran 10.3 mg/day	Implantation of DLD-1 cells in dorsal region of male athymic nude mice	Colorectal cancer	The tumor volume was inhibited and the growth was reduced compared to normal mice	77
Gamma tocotrienol 30 µmol/L	MDA-MB-231 breast cancer cell line	Breast cancer	Gamma tocotrienol had an anti-cancer effect	107
Gamma tocotrienol 40 µM/L				108
Gamma tocotrienol 50 µg/L				109
Delta Tocotrienol 20 µM	Human colorectal adenocarcinoma cells	Colorectal cancer	Treatment of delta tocotrienol induces apoptosis and inhibit angiogenesis	77
Delta Tocotrienol 10 µM	Human pancreatic normal epithelial cells with empty vector (HPNE-V) and Kras-transformed HPNE cells	Pancreatic cancer metastasis	The supplement significantly inhibited growth and metastasis of the cells	76
Tocotrienol Rich Fraction (100 µg/ml)	Metastatic prostate cancer LNCaP (from lymph node) PC-3 (from bone) DU145 (from brain)	Prostate cancer	The treatment shows a selective effect in all cancer cell line in causing apoptosis without affecting normal cells	85
Tocotrienol Rich Fraction 200 mg per capsule	Breast cancer patients (women) 40 -60 years old	Breast cancer	The treatment showed a lower mortality rate however the data is not significant	99

attributed to leakage of electrons. Superoxide anion (O^{2-}) and hydroxyl radicals (OH) are the major free radical species propagated. These highly reactive molecules production will cause hydrogen peroxide (H_2O_2) formation. This may be potentially be the source of additional hydroxyl radicals through the reaction of Fenton-type, involving metal ions transition (e.g., Fe2+) (28).

Hydroxyl radical (OH), hydrogen peroxide (H2O2), superoxide anion radical (O^{2-}), and peroxynitrite radical ($ONOO^-$) are the most highly reactive free radical species (28–30). Among them, OH is the most active oxygen species, which cause biological disturbance and lipid peroxidation, whereas O^{2-} reacts harmfully with cellular components (31). H2O2 is a weak oxidizing agent with high diffusion rate and a long life span; and is able to inactivate some enzymes and attack mitochondrial DNA (32). Compared to other free radicals, peroxynitrite ($ONOO^-$) is stable, however, if protonated, highly reactive peroxynitrous acid (ONOOH) will be formed, which can lead to oxidative damage and tissue injury (33).

Free radicals predominantly attack polyunsaturated fatty acids (PUFAs) of cell membranes, and this oxidative damage is called lipid peroxidation. PUFA molecules can be further oxidized by peroxyl radicals and this will cause a new chain reaction that can produce more radical species such as aldehydes (34). Aldehydes have an ability to raid other cells, and their association with cancer and tissue injuries is widely accepted (35). Lipids oxidation process is initiated by a chain process mediated by free radicals, where lipid peroxyl radical acts as the chain carrier. During the initial step of chain propagation, peroxyl radicals separate hydrogen atom from the target lipid. In this regard, tocopherols are known to prevent the propagation of lipid peroxidation (36).

Alpha-tocopherol's main function is to scavenge lipid peroxyl radical before it reacts with lipid substrate. This reaction forms 8α-substituted tocopherones, and it is readily hydrolyzed to 8α- hydroxy tocopherones. These compounds spontaneously rearranged, forming alpha-tocopherol quinones (34,37,38), which play important roles in both signaling and antioxidant function (39). Tocotrienol on the other hand, is more effective in scavenging superoxide radicals produced by xanthine oxidase/ hypoxanthine when compared to tocopherols. Palm oil extract containing predominantly tocotrienols with some tocopherols were found to be effective in improving endothelium-dependent relaxation in the condition of oxidant stress (40). Fig. 2 shows the reaction scheme of alpha-tocopherol during unsaturated lipids autoxidation (41).

Oxidative Stress Causes Cancer

Findings from studies in in-vitro and in-vivo models have demonstrated that the damage induced by free radicals can be prevented by antioxidants, although researchers are still investigating whether dietary supplementation with antioxidants can help in reducing cancer risk or cancer prevention. Most observational studies in human have yielded mixed results due to factors such as

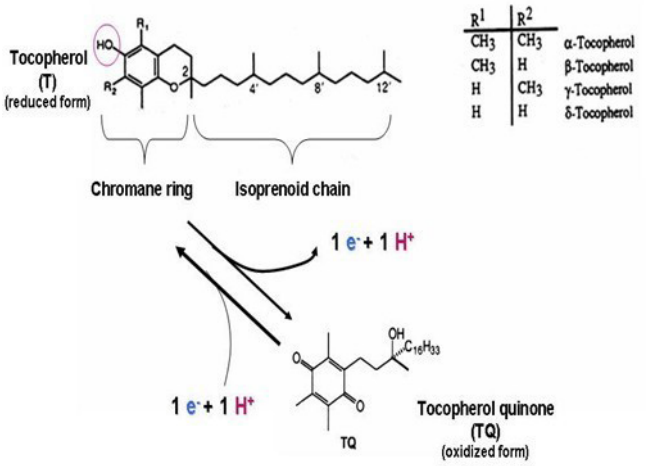

Figure 2: Reaction of alpha-tocopherol during autoxidation of unsaturated lipids in cell membranes

genetics, overall health, and biochemistry of the body itself (42); whereas controlled clinical trial studies limit the reliability of these studies due to biases where only the healthy model organism is being used.

Cancer progression and side effects of cancer treatment which include chemotherapy and radiation, is always been associated with oxidative stress (21), and, oxidative stress has always been associated with many diseases, including cancer (43–45). Oxidative stress can activate certain signaling pathways and thereby contribute to tumour development through deregulation of cellular proliferation, angiogenesis, and metastasis (21). Tobacco consumption was shown to increases oxidative stress, subsequently increases cancer cases by mutations, oxidations of lipid and proteins and also by alteration of signal transduction pathways that causes cell damage. Furthermore, nutritional quality value may be affected in alcohol consumers due to malnutrition; and in turn, the deficiency of vitamins and minerals may lead to alcohol-associated carcinogenesis (46). Fortunately, based on an inferred relationship between oxidative stress and cancer, it has been postulated that a diet containing antioxidants, vitamins C and E for example, is useful in the prevention of carcinogenesis (47–50).

Other known antioxidants, such as that found in grape seed, are known to serve as chemo-protectants against three stages of cancer. Bagchi et al. (51) found that proanthocyanidins of grape seed selectively protected against genomic integrity, oxidative stress, and cell death patterns in in-vivo liver carcinogenesis, thereby illustrating the antioxidants role as a novel therapeutic agents against carcinogenesis. An interview and questionnaire study showed that the consumption of high antioxidant diet are related with a decreased breast cancer due to the antioxidant capacity contains in a food (52).

Antioxidant Activity of Vitamin E

Antioxidants such as vitamin E confer a protective effect through neutralization by donating one of their own electrons. However, this action will not cause the antioxidant themselves to be a free radicals due to the fact that they are stable in both forms (53). Vitamin E reduces free radical activity by preventing electron leakage and thus directly mediating the generation of superoxide (54). Radical scavenging operates by removing excessive amount of free radicals and vitamin E is known to be as the most abundant antioxidant, an important lipophilic radical-scavenging antioxidant, and efficiently scavenge peroxyl radicals (55).

Administration of vitamin E in disease-free albino rats showed that superoxide activity was reduced significantly compared to that in the control rats (56). Guertin et al. (57) studied oxidative stress by measuring biomarkers of lipid peroxidation (8-iso-prostaglandin F2–alpha) in smokers' urine. One group of smokers was given vitamin E for a period of time, and the finding showed that the vitamin E supplementation reduced oxidative stress among the subjects. Another study by Fu et al. (58) showed that vitamin E efficiently inhibit elevated levels of lipid peroxidation in Fat-1 transgenic mice.

Alpha-tocotrienol is generally considered as a better radical scavenger than alpha-tocopherol. A lipid peroxidation study using rat liver microsome via incubation system (Fe2+ + ascorbate and Fe2+ + NADPH) concluded that alpha-tocotrienol scavenged peroxyl radicals more efficiently than alpha tocopherol in liposomes (59). Another study also reported that alpha tocotrienol being more potent compared to alpha-tocopherol in which the tocotrienols mixture was capable to prevent the activation of free radical of monocytes which mainly produces Interleukin-6 (IL-6) (60). In this study, the oxygen-derived free radicals was generated via intraperitoneal injection of induced Ferric nitrilotriacetate (FeNTA) into male Wistar rats and the rats were supplemented with both alpha-tocopherol and alpha- tocotrienol throughout the study. Their results showed that alpha- tocotrienol was able to prevent free radical activation even at low doses compared to alpha-tocopherol (60).

In-Vitro and In-vivo Studies of Vitamin E in Primary Cancer

Vitamin E has been used widely due to its potential medicinal properties. It acts as antioxidant (61,62) and anticancer (63–65) in in-vitro studies. However, nutritional requirements for vitamins in animal studies have not been determined (66,67). Some factors which may affect vitamin E in the biological system include hepatic discrimination where tocopherol are more favorable; as well as preferential metabolism of vitamin E in rats (68). Although both subgroups share similar molecular structure, both of them have different absorption rate in which the tocopherol possess an alpha-tocopherol transport protein (69). Route of absorption for tocopherol is mainly through lymphatic

system and from there, tocopherol passes the systemic circulation and is taken up by liver (70). However, in tocotrienol, the absorption rate is poor, inconsistent and is highly dependent on the presence of food in the gut (71). Although these studies were done in rodents, they can be considered as a basis to establish the health benefits of vitamin E in human.

Vitamin E mainly tocotrienol is shown to not only inhibit the growth of cancer cells, but it also triggered apoptosis in cancer cells. They exert anticancer effect on cancer cells by inhibiting angiogenesis and also inhibiting tumour cell progression (72–74). An in-vitro study of the effect of delta-tocotrienol on HCT-116 and SW-620 of human colon cancer cells and metastatic colon cancer cells respectively showed that delta-tocotrienol significantly inhibit cancer cell growth and induced apoptosis (20).

Similarly, delta-tocotrienol showed a reduced colon cancer formation and also induced apoptosis compared to the vehicle and untreated groups using colon cancer-induced Fisher-344 rats (75). Delta-tocotrienol has also been proven to inhibit the proliferation rates of transformed pancreatic cells without disturbing normal cells (76). It also has been shown that delta-tocotrienol also demonstrated the growth of human colorectal adenocarcinoma (DLD-1) cells was inhibited under normal and low oxygen (hypoxic) conditions. This study has proceeded with in-vivo studies using nude mice fed with rice bran supplemented with tocotrienol, which revealed inhibition of tumor growth (77). Stem cell cancer study also showed that delta-tocotrienol play a potential effective therapeutic target in the treatment of melanoma. It is also demonstrated the antitumour activity of delta-tocotrienol against cancer stem cells (78). Tocotrienol given as a supplement has displayed encouraging data specifically from in-vitro and in-vivo models and has shown to suppress and inhibit mammary tumour cells growth. Nevertheless, tocotrienols might be used to enhanced therapeutic activity with other combination drug as a potential anticancer agent to enhance responsiveness of cancer patients towards their treatments.

Other types of vitamin E, tocopherol, are mostly studied on tumour progression, apoptosis and cancer invasion. There are few evidences to support that tocopherol can induce or suppress tumour development which is mostly done in animal study. In a study using E7-expressing murine tumour model in in vitro, Kang et al. (79) found that supplementation of tocopherol causes apoptosis and cell necrosis towards the TC-1 cells, and it significantly reduced tumour volume in tumour-bearing mice. Alpha-tocopherol also shown an anti-tumour activity on squamous oral cancer cells and also displayed a nontoxic property to normal human keratinocytes (80). Similar study also reported that cell induction by alpha-tocopherol occurred much earlier compared to chemotherapeutic drug. Furthermore, tumour-bearing mice supplemented with vitamin E showed a greater accumulation of T cells in the tumour area, resulting in a potent anti-tumour effect (79,81–83).

The possible anti-cancer activities of alpha-tocopherol involved multiple mechanisms for instance, through apoptotic, anti-angiogenesis and anti-migration. Several studies reported that vitamin E can induce apoptosis preferentially in cancer cells, especially mammary epithelial cells (65,84,85). In-vitro study on anticancer properties of vitamin E analog against mouse mammary tumour cells interpreted that apoptosis occurred at 38% against the treatment of camptothecin, which causes apoptosis at around 2 to 7% (86). It is generally accepted that the higher apoptosis rate will slow tumour growth, and thus, a better anti-tumour properties (87). Inokuchi et al. (88) reported that there is no adverse effect of vitamin E on the growth or function of normal cells and that it had a potent anti-angiogenic function in the signaling of endothelial cells. Another study testing the effects of vitamin E d-α-tocopherol also detected anti-angiogenesis and anti-migration of overexpressing MDA-MB-231 tumour in xenograft mice models (49). Vitamin E succinate, which is a natural tocopherol also has demonstrated to activate multiple apoptosis pathway and also able to inhibit the growth of prostate cancer in in-vivo model (83).

Despite the well-documented beneficial anticancer properties of vitamin E, supplementation of the antioxidant could not offer consistent result for cancer prevention and treatment. A contrasting result from animal study of vitamin E found that when the supplement was administered in chow pellet to the animal models of K-RAS- and B-RAF- induced lung cancer, it increases tumour progression and tumour cell proliferation by disrupting the ROS-p53 axis (89). An intraperitoneal injection of vitamin E succinate into nude mice that has been induced with lung tumour via sub-mammary fat pads showed a reduction of tumour growth, however, all of the induced mice displayed pulmonary metastasis in vitamin E succinate treatment group (90). Animals induced with androgen dependent prostate tumour and then treated with alpha-tocopherol were shown to have a slight increase in incidence of prostate cancer (91), and also animals induced with sex hormone oxidative mechanisms and treated with alpha-tocopherol acetate shows a significant decrease in survival rates and a significant increase in cancer incidence (92).

Clinical study on Vitamin E in Primary Cancer

The data from clinical studies of vitamin E in cancer is inconsistent and few studies shows contradictory findings compared to animal studies. However, a few promising results from clinical studies have been observed where supplementation of vitamin E decreased cancer incidence in cancer patients and in daily cigarette smoker who have a higher risk in developing lung and

prostate cancers. A study conducted in Finland where 29,133 male smokers received alpha-tocopherol (50 mg/kg) daily for six years has reported decreased prevalence of prostate cancer by 32% and decreased mortality by 41% (16). In addition, Weinstein et al. (93) has shown that supplementation of tocopherol in diet for 6 years may reduce cancer incidence and delay the progression of cancer in patients diagnosed with prostate cancer. A study also linked the high risk of prostate cancer mortality with low plasma levels of vitamin E in smokers and also linked the plasma levels with high frequency of lung cancer mortality (94).

Serum level of alpha-tocopherol were also related to few other cancers which include breast cancer, oropharyngeal cancer and pancreatic cancer, however, the data were inconsistent. Vitamin E intake mainly from food and natural sources showed that it may lower the head and neck cancer incidence (95), and intake of vitamin E significantly reduces the risk of bladder cancer (96).

The inconsistency between findings in animal study and clinical trials causes problems in which a drug that seems safe in animal turns out to be harmful in human. Increased mortality were seen in cancer patients receiving large doses of alpha-tocopherol (10,97,98). Women with early breast cancer supplemented with tocotrienol-rich fraction showed no relation on treatment and cancer survival rate (99). Similarly, a randomized controlled study has also been conducted in Finland using male participants aged 50 to 69 to investigate the incidences of urinary tract cancer, pancreatic cancer, colorectal cancer, and upper aero digestive tract after supplementation with alpha-tocopherol at 50 mg/kg per day for up to eight years. Their results indicated that supplementation with alpha-tocopherol was not significantly affected by the incidence rate of pancreatic cancer (100). Another study also reported the same incidence of negative effects on cancer treatment by supplementation of alpha-tocopherol which had no preventive effect on urinary tract cancer and on the upper aero digestive tract (101), but it may have had some modest preventive effect on colorectal cancer (102). Daily supplementation of vitamin E showed that it did not reduce the risk of incidence of prostate cancer (11,48,103). A randomized, placebo-controlled study in France showed no association between the supplementation of daily vitamin (ascorbic acid, vitamin E, beta carotene, selenium and zinc) and the incidence of skin cancer. It was found that the supplementation affected men and women differently, with a lower incidence of skin cancer found among men but not in women (104).

Vitamin E Supplementation in Metastatic Cancer

Metastasis is a process where a primary cancer spreads to other body parts via lymphatic system. The process starts by detachment of epithelial cells from the extracellular matrix. Under normal condition, detached epithelial cells undergo programmed cell death as a result of incorrect cell attachment and oxidative stress (105). However, during progression of metastasis, the detached epithelial cells might survive and undergone oncogenic signaling which generates NADPH and thus induced antioxidant response (106). A study on delta-tocotrienol supplementation was shown to inhibit pancreatic cancer metastasis in both in-vitro and in-vivo models using L3.6pl human pancreatic cancer cells and nude mice respectively. The study also confirmed that delta-tocotrienol induced apoptosis in pancreatic cancer stem-like cells, as well as inhibited the metastatic environment (76). Other tocotrienol such as gamma-tocotrienol also has shown an inhibited response in in-vitro study towards MDA-MB-231 cell lines, a highly malignant triple negative breast cancer cell line (107–109).

Alpha-tocopherol is widely studied on their anti-metastatic activity and has not shown a consistent result in both in-vitro and animal study. Tocopherol reported to inhibit the cell growth of MDA-MB-231 cells, a breast cancer cell line, and it is demonstrated that serum-induced cell migration of MDA-MB-231 cells was inhibited significantly by alpha-tocopherol in dose-dependent manner. In the study of a cardiac injection mouse model to express the metastatic model, showed that alpha-tocopherol effectively inhibited the cancer metastasis (110). The size of primary mammary tumour determines metastasis. A study of mammary tumour metastasis in rodents administered with vitamin E orally showed a reduced size of the primary tumour (111) and subcutaneous tumour burden and also lower the metastasis rate to lung and lymph nodes (86). Similarly, cell line of MDA-MB-435-FL-GFP, a human breast cancer xenograft in nude mice, showed that analog of vitamin E which administered in diet significantly reduced the tumour volume and macroscopic lung metastasis. The treatment also had enhanced apoptosis and significantly decreased cell proliferation rates (86).

A study in xenograft models showed that the progression of metastasis is detected by the size of the primary mammary tumour, where in a melanoma cancer model, the higher sensitivity rate to apoptosis, causes decreased tumour growth and progression of metastasis. Another study on MMTV-PymT mice fed with antioxidant diet also consistently reported that mammary tumour progression reduction is may be related to the decreased in mitosis activity and increased in apoptosis activity in the tumour cells, and thus resulted in a down-size of primary mammary tumour (112).

Metastasis is a dynamic process which is regulated by numerous mechanisms via molecular and cellular basis of cancer progression causing inconsistency in its treatment. An animal model of metastasis using metastasizing melanoma which were xenografted into Non-obese

diabetic/Severe combined immunodeficiency (NOD-Scid) mouse found out that antioxidant promotes diseases progression and thus further promotes metastasis (113). In an in-vitro study, administration of Trolox, a vitamin E analog on a cultured melanoma cells showed that it did not affected the proliferation rate but rather promotes the migration and other invasive properties of the cells (114).

Once cancer cells metastasize to bone, it can cause pain and broken bones and its treatment would only help in reducing the pain (115). Thus, an urgent therapeutic approach to relieve the pain from bone metastasis could be an alternative option in improving patient's quality of life. Suppressing the osteoclastic activity by slowing the expansion of osteolytic bone metastasis via antioxidants might be another potential way to treat bone metastasis. Bone remodeling process is also related to the changes in antioxidant system which then might influenced the mechanism of bone loss. Reactive oxygen species induces apoptosis of osteoblast and osteocyte which then stimulates osteoclastogenesis (116).

CONCLUSION

Since its discovery, vitamin E has been pharmacologically studied extensively for its therapeutics effects. However, data from epidemiology and laboratory reports showed no definitive effects of vitamin E on health. In addition, a few studies reported harmful effects of vitamin E, thus the benefit of using vitamin E as an alternative medicine for cancer treatment remains unclear. To date, the only clear benefit of consuming vitamin E supplements is for those who have an actual vitamin E deficiency. Nevertheless, the myths about vitamin E being a super antioxidant that can cure diseases which include heart-related diseases, diabetes and its complications, cancer, brain and nervous system diseases, aging conditions, and also hormone related disease have been circulating for years.

In conclusion, despite numerous in-vitro, animal, and epidemiological studies of vitamin E benefits in cancer treatment, results remain inconclusive whether it is beneficial, ineffective or harmful. Most epidemiological studies have yielded negative results, with vitamin E having no effect on reducing tumour incidence or progression. Low solubility in aqueous solvents might also further complicated the use of vitamin E as medicine. Although in-vitro and animal studies have shown anti-tumour activity of vitamin E, the amount that needs to be ingested to achieve the preventive or treatment in cancer has yet to be elucidated.

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