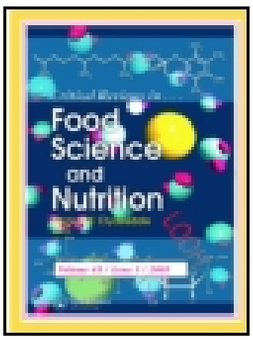

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Vitamin E and its anticancer effects

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Abstract

Vitamin E is a lipid soluble vitamin comprising of eight natural isoforms, namely, α, β, δ, γ isoforms of tocopherol and α, β, δ, γ isoforms of tocotrienol. Many studies have been performed to elucidate its role in cancer. Until last decade, major focus was on alpha tocopherol and its anticancer effects. However, major clinical trials using alpha-tocopherol like SELECT trial and ATBC trial did not yield meaningful results. Hence there was a shift of focus to gamma-tocopherol, delta-tocopherol and tocotrienol. Unlike alpha-tocopherol, gamma-tocopherol and delta-tocopherol can scavenge reactive nitrogen species in addition to reactive oxygen species. Antiangiogenic effect, inhibition of HMG CoA reductase enzyme and inhibition of NF-κB pathway make the anti-cancer effects of tocotrienols unique compared to other vitamin E isoforms. Preclinical research on non-alpha tocopherol isoforms of vitamin E showed promising data on their anticancer effects. In this review, we deal with the current understanding on the potential mechanisms involved in the anticancer effects of vitamin E and the controversies in this field over last three decades. We also highlight the need to conduct further research on the anticancer effects of non-alpha-tocopherol isoforms in larger population and clinical setting.

Keywords: Vitamin E and cancer, tocopherol, tocotrienol, tocopherol and cancer, anticancer mechanisms

Introduction

Vitamin E and its anticancer effects is an area of research over last three decades. Multiple trials have been conducted using α-tocopherol, which is a major isoform of vitamin E, to evaluate its anticancer properties, based on the hypothesis that there is intense oxidative stress in many cancers (1). However, large clinical trials with α-tocopherol, a chain-breaking anti-oxidant, did not yield meaningful results. This led to serious consideration of other isoforms of vitamin E, especially γ-tocopherol, and tocotrienols. Here, we summarize current understanding of the potential mechanisms involved in the anticancer effects of vitamin E, and the emerging role of tocotrienols.

Structure and Sources of Vitamin E

Vitamin E, a lipid soluble vitamin, was discovered in green leafy vegetables in 1922 (2). Vitamin E is a family of 8 natural isoforms, namely, α, β, γ, δ isoforms of tocopherol and α, β, γ, δ isoforms of tocotrienol. Tocopherols and tocotrienols have a chromanol ring in common. The 16 carbon hydrophobic phytyl side chain is fully saturated in tocopherols while it has 3 trans double bonds in tocotrienols. Four isoforms each of tocopherols and tocotrienols differ in the degree of methylation and the position of methyl group attached to the chromanol ring (Figure 1) (3).

Major dietary sources of vitamin E are nuts and edible vegetable oils. α and γ tocopherols constitute 60-70% and 20-25 % of consumed vitamin E, respectively. These are mainly found in corn, soybean and peanut oils. Sources of tocotrienols are palm oil, barley and cereal grains.(1, 4) Until recently, major focus in terms to anti-oxidant use was on α-tocopherol as vitamin E and the role of other isoforms of tocopherols and tocotrienols were dismissed.

The absorption and metabolism of tocopherols and tocotrienols takes place via the same pathway. Absorption takes place along with dietary fat and reach peripheral tissues like adipose tissue, skin, muscle, bone marrow via lymphatics. α-tocopherol is protected by α tocopherol transfer protein (α-TTP) in liver and hence is least metabolized.(5) The isoforms of vitamin E other than α-tocopherol are catabolized via CYP450 mediated ω-hydroxylation or oxidation of side chain, to yield the final metabolite 3'-carboxychromanol or 2'-carboxyethyl-6-hydroxychromans (CEHCs). A portion of vitamin E is metabolized via sulfation. Due to the high affinity of α-TTP for α-tocopherol and ω-hydroxylation of other isoforms, α tocopherol has the highest bioavailability.(1, 6) Tocotrienols, are largely degraded and thus have very low bioavailability.(7) Nonetheless, recent work has shown that this low plasma concentration of tocotrienols is sufficient for exerting its therapeutic effects.(3)

Possible anticancer effects of vitamin E

The relationship between cancer risk and vitamin E has been studied in various epidemiological studies. The anticancer effects of vitamin E has been attributed mainly to its anti-oxidant, anti-inflammatory, anti-proliferative, anti-angiogenic, immune modulatory mechanisms and the inhibition of HMG CoA reductase enzyme (Figure 1).(3)

1. Anti-oxidant effect

Oxidative stress has been implied in the pathogenesis of various cancers, especially skin and gastrointestinal cancers. All isoforms of vitamin E scavenge reactive oxygen species due to the presence of phenolic hydrogen in their chromanol ring.(1) In the human body as well as in experimental animals, free radical chain reactions take place causing lipid peroxidation under oxidative stress. Vitamin E plays an important role in breaking the free radical chain reaction and preventing lipid peroxidation and protecting biological membrane.(8, 9) Nrf2 is a transcription factor

that regulates induction of antioxidant enzymes. Vitamin E isoforms, especially γ-tocopherol, and to some extent α-tocopherol induce Nrf2 which stimulate gene expression of various antioxidant enzymes like superoxide dismutase (SOD), catalase, glutathione peroxidase and phase II detoxifying enzymes.(10, 11) Among the tocopherol isoforms, γ-tocopherol and δ-tocopherol are more potent as they have unmethylated C-5 position on chromanol ring. These isoforms can detoxify reactive nitrogen species like NO_2 and peroxynitrite by forming 5 nitro-γ-tocopherol.(10) The metabolites of vitamin E like CEHCs also inhibit lipid peroxidation and exhibit a stronger free radical scavenging than vitamin E isoforms. Among the metabolites of vitamin E isoforms, γ-tocopheryl quinone is more efficient than α-tocopheryl quinone in inducing antioxidant response by increasing levels of glutathione, increasing transcription of activating transcription factor 4.(12, 13) Due to even distribution of tocotrienols in phospholipid bilayer, they can scavenge lipid peroxyl radicals better than tocopherols.(1) Tocotrienol also exert antioxidant effect by inducing various antioxidant enzymes like SOD and catalase.(14)

2. Anti-inflammatory effect

All isoforms of vitamin E exert anti-inflammatory action by inhibiting a variety of inflammatory mediators. Isoforms, especially γ-tocopherol, δ-tocopherol and tocotrienols inhibit cyclooxygenase-2 (COX-2)-mediated production of prostaglandin E2 (PGE2), as well as 5-lipooxygenase (LOX)-mediated production of leukotrienes - LTB4, LTC4, LTD4.(15) The metabolite of vitamin E, 13'-COOH also suppresses COX-2 and LOX pathway.(16) Eicosanoids from COX-2 and 5-LOX pathway are known to be involved in colon cancer pathogenesis. Hence, the suppression of these pathways by vitamin E helps in inhibiting inflammation in the colon and carcinogenesis.(17) Tocotrienols are found to block NF-κB (nuclear factor-kappa B) and JAK-STAT3 (Janus kinase-signals transduction and activation of transcription) signaling pathways that mediate expression of various proinflammatory cytokines like IL-1, IL-6, and TNF.(18) γ-tocotrienol is the most potent vitamin E isoform in this regard. Shibata et al showed that hypoxia inducible factor-1 (HIF-1)-

modulated inflammatory pathway is also suppressed by tocotrienols.(19) Peroxisome proliferator activated receptors (PPAR-α, γ, and δ) are ligand mediated transcription factors that modulate inflammatory pathways by inhibiting COX-2. PPARs are also linked with various pathways like PI3k-Akt and NF-κB signaling. In in-vitro and in-vivo studies, δ-tocopherol was shown to activate PPARγ in various cell lines, suppress inflammation as well as inhibit cell cycle progression and induce apoptosis.(10, 20)

3. Anti-proliferative effect

Vitamin E exerts anti-proliferative effect by inducing apoptosis and cell cycle arrest.

Apoptosis takes place through extrinsic pathway mediated by death receptor signaling or intrinsic pathway mediated by mitochondrial disruption and release of cytochrome c into cytosol. Both pathways finally lead to the activation of execution caspases, especially caspase-3, followed by cleavage of poly-ADP-ribose-polymerase (PARP). Among tocopherols, δ-tocopherol and γ-tocopherol are more potent than α-tocopherol in induction of apoptosis.(17) These compounds act mainly via caspase-9 and -3 activation.(17) Of note, Jian et al (21) identified a caspase-independent mechanism in androgen responsive LNCaP cells; this pathway was inhibited by γ-tocopherol.(21) Tocotrienols induce apoptosis via different mechanisms involving, death receptor or by increasing Bax/Bcl-2 ratio or activating p53 leading to caspase 9 activation.(22, 23) Enhanced caspase expression was observed when malignant human liver cells were incubated with various forms of tocotrienols in a dose and time dependent manner.(24) Nuclear factor-kappa B (NF-κB) is a major transcription factor involved in cancer pathogenesis. Downstream of this pathway lie Bcl-2 and Bcl-xl, proliferative proteins like cyclin D1 and various angiogenic proteins. Cyclin D1 activation leads to cell cycle progression from G1 to S phase. Tocotrienols inhibit NF-κB signaling pathway resulting in induction of apoptosis and G1 cell cycle arrest.(25-28) Phosphatidylinositol-3-kinase (PI3k)/PI3K-dependent kinase-1 (PDK-1)/Akt signaling pathway is shown to be involved in cancer cell growth and

survival. γ-tocotrienol was found to block PI3k/PDK-1/Akt mitogenic signaling upstream at the level of epidermal growth factor receptor (EGF-receptor) ErbB3.(29) It was shown that, in human breast cancer cell line, δ-tocotrienol and α-tocopheryl succinate induce apoptosis by activation of Transforming Growth Factor-β (TGF-β) and Fas apoptotic pathway leading to activation of transcription factor c-Jun and movement of Bax into mitochondria causing release of cytochrome c and apoptosis.(30)

4. Anti-angiogenic effect

Angiogenesis is a crucial step in growth of tumor as well as tumor metastasis. It involves proliferation and migration of endothelial cells. Inhibition of angiogenesis by vitamin E isoforms especially tocotrienols have been shown in both in vitro and in vivo studies. Among tocotrienols, δ isoform is the most potent inhibitor of angiogenesis.(RW.ERROR - Unable to find reference:doc:5959c470e4b0ea004a7b38d4) Other tocopherols do not exhibit this property.(2) Tocotrienols, invitro in bovine aortic endothelial cells (BAEC) and human umbilical vein endothelial cells (HUVEC) inhibits proliferation, migration and tube formation. Tocotrienols display antiangiogenic property by downregulating vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), epidermal growth factor (EGF).(14) In addition, tocotrienols were also found to downregulate VEGF receptor expression. Hypoxia inducible factor (HIF-1) is a transcription factor that activates VEGF expression and result in angiogenesis in response to hypoxia. In a study on human colorectal adenocarcinoma cells by shibata et al, tocotrienol treatment was found to suppress HIF-1 and thus inhibit secretion of angiogenic factors.(19) IL-6 and IL-8 are proangiogenic cytokines that act by upregulating VEGF levels. In HUVEC cells treated with tocotrienols, the levels of IL-6 and IL-8 were found to be lowered.(32) Tocotrienols inhibit phosphorylation of PI3k/AkT signaling pathway and downregulate its signals like endothelial nitric oxide synthase (eNOS), glycogen synthase kinase 3 (GSK3) and extracellular signal regulated kinase (ESRK). This pathway plays a role in angiogenesis by inducing binding of VEGF to its receptor.(RW.ERROR - Unable to find

reference:doc:5959c470e4b0ea004a7b38d4) Suppression of angiogenesis is also mediated through matrix metalloproteinase (MMP-9) gene suppression which is essential for tumor invasion and angiogenesis.(33)

5. Anti-platelet effect

α-tocopherol and γ-tocopherol inhibit platelet aggregation. γ-tocopherol is more potent than α-tocopherol in this effect.(34) Studies have shown that vitamin E especially α-tocopherol potentiate the antiplatelet effect of aspirin.(35) Chang et al, demonstrated that α-tocopherol inhibit platelet aggregation by downregulating Gp-IIb expression in human erythroleukemia cells.(36) Platelets play a vital role in cancer progression. Platelets protect the circulating tumor cells (CTC) in blood stream by forming platelet clots around them. CTC in turn activate platelets to release various pro-angiogenic factors like vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF). Platelets also protect CTC from natural killer-cell recognition, enhancing its survival in blood. Transforming growth factor TGF-β and PDGF released from activated platelets induce epithelial mesenchymal transition (EMT) that aids in cancer cell invasion.(37, 38) Hence the anti-platelet action of various isoforms of vitamin E is thought to decrease the pro-angiogenic effects of CTCs, enhance CTC recognition by immune cells and negatively influence metastasis.

6. Inhibition of HMG CoA reductase.

Inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA reductase) to lower cholesterol is a property unique to tocotrienols. In certain tumor cells, this enzyme is found to be dysregulated, and metabolites of this pathway contribute to malignant cell proliferation. Tocotrienols, especially γ-tocotrienol, lower the activity of HMG-CoA reductase and thus exert anti-tumor effect.(28, 39) Interestingly, α-tocopherol was found to attenuate this activity of tocotrienols when given in combination with other tocopherols.(40) Tocotrienols exhibit synergistic effect with

other HMG CoA reductase inhibitors, such as statins.(41) Wali et al showed that although γ-tocotrienol lowered HMG CoA reductase enzyme levels, addition of mevalonate (product of HMG CoA reductase pathway) to the system did not reverse γ-tocotrienol-induced apoptosis. This suggests that the anti-tumor activity of tocotrienols may not be linked with inhibition of HMG CoA reductase.(42) Further studies need to be performed to clarify this link.

Vitamin E and Cancer - Controversies.

We evaluated the trends in research in studies on vitamin E and cancer over the last three decades. Studies from 1980s showed an inverse correlation between vitamin E intake and cancer risk. Since tocopherols were known as the potent anti-oxidants and α-tocopherol being the predominant form, this finding was attributed to α-tocopherol. The human case-control and cohort studies that analyzed the relationship between tocopherols and cancer showed inconsistent results.(17) For example, in Iowa women's health study, there was reduced risk of colorectal cancer with high intake of vitamin E, especially in age under 65 years.(43) Breast cancer risk was found to be unrelated to the intake of vitamin E, A and C.(44) A case-control study on plasma tocopherol and prevalence of colorectal adenoma in multiethnic population showed no protective effect of tocopherol. (45) Based on the results of observational studies, various interventional studies were designed to examine in depth the effect of Vitamin E supplementation on cancer risk. The prominent studies and their results are listed in Table 1.

The ATBC trial analyzed the effect of α-tocopherol and β-carotene on the incidence of lung cancer and other cancers in male smokers. In this primary prevention trial, there was no association between α-tocopherol and lung cancer, but there was a statistically significant negative correlation between α-tocopherol levels and incidence of prostate cancer.(46, 47) Stolzenberg et al was able to show evidence supporting the hypothesis that a higher α-tocopherol concentrations may play a protective role in pancreatic cancer in male smokers.(48) 18 year - follow up of ATBC trial did not

show any late effects on cancer incidence with α-tocopherol and beta-carotene. However, the preventive effects on prostate cancer continued resulting in a lower prostate cancer related mortality in the α-tocopherol group.(49)

Another groundbreaking interventional study was the SELECT trial which was launched in 427 states across the U.S, Canada and Puerto Rico between 2001 and 2004. It was a randomized double blind placebo controlled trial that looked at the effects of selenium and α-tocopherol on the risk of developing cancer.(50) The trial did not find a protective effect of α-tocopherol supplementation but showed a non-significant increase in the risk of prostate cancer risk with α-tocopherol ($p=0.06$). In a follow up report, Klein et al reported a significantly increased risk of prostate cancer after vitamin E supplementation.(51) Kristal et al conducted a survey (Prostate Cancer Prevention Trial) assessing the nutritional risk factors for prostate cancer and concluded that dietary supplementation with vitamin E did not prevent prostate cancer.(52)

The findings of the interventional studies on Vitamin E and cancer risk were also inconsistent and conflicting.(53, 54) The conflicting results in these studies paved way for the serious consideration of other isoforms of tocopherol and tocotrienol. A tocopherol mixture rich in γ-tocopherol, γ-tocopherol-rich mixture of Tocopherol (γ-TmT), displayed a potential in inhibiting cancerous growth in lung, colon, breast and prostate cell lines. γ-TmT contains 568mg γ-tocopherol, 243 δ-tocopherol, 130mg α-tocopherol and 15mg β-tocopherol per gram.(54) Lu et al (55) used A/J mice with chemically induced lung tumors and showed that treatment with 0.3% γ-TmT resulted in a significant reduction in tumor multiplicity, tumor volume and tumor burden (30%, 50% and 55% respectively; $p<0.05$). Further, treatment with γ-TmT enhanced apoptotic index (from 0.09% to 0.25%), lowered levels of 8-hydroxydeoxyguanine (marker of oxidative DNA damage) and γ-H2AX (marker of double stranded break induced DNA repair). The authors also observed reduced microvessel density in the periphery of lung adenoma and decreased plasma levels of prostaglandin E2 and leukotriene B4 in γ-TmT treated mice. These findings suggest proapoptotic, antioxidative, antiangiogenic and anti-inflammatory activities of γ-TmT in this animal model. These investigators also studied the effect of

various isoforms of tocopherol on the growth of H1299 human lung carcinoma cells. They observed that δ-tocopherol and γ-tocopherol inhibited cell growth, while α-tocopherol did not, δ-tocopherol being the most potent inhibitor. Studies in transgenic rat for prostate adenocarcinoma (TRAP) suggested that γ-tocopherol activated caspase-3 and -7 and significantly suppressed progression from prostate intraepithelial neoplasia (PIN) to adenocarcinoma.(56) This potential of γ and δ tocopherol could be due to their ability to scavenge reactive nitrogen species, a property unique to γ and δ-tocopherol.(53, 54) Further, Akt signaling involved in cancer cell growth was suppressed by γ-tocopherol and δ –tocopherol. It is possible that higher dose α-tocopherol supplementation would compete with δ and γ –tocopherols for binding to relevant proteins and decrease the anticancer properties δ and γ –tocopherols.(53, 57) This may explain the disappointing results of SELECT study.

Tocotrienols have not been fully explored in anticancer research, but there are in vitro and in vivo studies in this area.(14, 58, 59) Nesaretnam et al demonstrated that benign breast lumps contained higher tocotrienol (α, γ and δ-tocotrienol) than the malignant breast lumps, and proposed that tocotrienols may have a role in scavenging free radicals.(60, 61) In spite of the accumulating evidence suggesting the potential of tocotrienols as anti-cancer agents, very few clinical trials have so far been conducted on their anticancer effects. A double blinded placebo controlled pilot trial evaluated the effectiveness of tocotrienol combined with tamoxifene in 240 women with early breast cancer showed 60% reduction in mortality ($p=0.27$). The major limitation of this study, which was the first experimental study on the use of tocotrienol, was its small sample size and lack of randomization.(62) Of note, tocotrienol rich fraction used in the study contained mostly α-tocopherol which might have influenced the results. Springett et al conducted a clinical trial in which δ-tocotrienol was given in escalating doses to patients with pancreatic ductal neoplasia for 2 weeks before surgery. This study demonstrated significant apoptotic changes as measured by increased caspase-3 levels in patients who received doses 400-1600mg. The authors asserted that δ-tocotrienol is a well-tolerated compound with no drug related toxicities with doses up to 1600mg daily. This dose resulted in plasma concentrations that demonstrated bioactivity in preclinical models.(63) Surprisingly, no major clinical trial has yet fully explored the potential of tocotrienol in cancer.

Recent advances

Tocotrienols were found to display a unique property of sensitizing cancer cells to the action of various chemotherapeutic agents.(26) A combination of γ-tocotrienol with ErbB receptor inhibitors like erlotinib was found to be highly effective than monotherapy in inhibiting tumor cell growth in highly malignant mouse mammary epithelial cells.(64) Abubakar et al recently showed that combination of γ-tocotrienol with jerantinine, an alkaloid with proven anticancer activity, induces potent cytotoxic effects on brain cancer cells.(65) Synergistic effect of γ-tocotrienol is seen with a number of chemotherapeutic agents like EGFR tyrosine kinase inhibitors, HMG-CoA reductase inhibitors, cyclooxygenase (COX-2) inhibitor, a Met inhibitor, PPARγ antagonists, autophagy inducer, and arylhydrocarbon receptor (AhR) modulator.(41, 64, 66-72)

In recent years, research on vitamin E has expanded into new realms. Vitamin E isoforms can effectively deliver anticancer agents to target tumor tissue using novel drug delivery systems. Tocopheryl succinate-nanovesicles (TS-NV) were the first ones to be developed. Later, for better stability TS-NV was combined with egg phosphatidyl choline (TS-EPC-NV).(73) D-α-tocopheryl polyethylene glycolsuccinate (TPGS) which was developed by esterifying α-tocopheryl succinate with polyethylene glycol was found to inhibit growth of prostate and lung cancer cells.(74) Tocotrienol drug delivery systems include multilamellar transferrin bearing vesicles encapsulating tocotrienol. They bind to transferrin receptors overexpressed in cancer cells.(75) The importance of these systems lies in the fact that they result in enhanced uptake into tumor cells and in combination with other chemotherapeutic agents is thought to decrease effective therapeutic dose and limit toxicity. These novel nano carriers are unique in that it has inherent anticancer effect. The efficacy of these systems has been demonstrated in preclinical models.

Conclusion

It is clear that studies on γ- and δ- tocopherol and tocotrienol have provided initial promising data on their anticancer effects. Anti-angiogenic effect, STAT3 activation and inhibition of HMG-CoA reductase enzyme and NF-κB pathway are properties that distinguishes tocotrienol from other isoforms. The accumulating evidence on anticancer properties of tocotrienol in preclinical models warrants future research on clinical setting and larger population. Recent advances in the realm of vitamin E based nanomedicines for drug delivery needs to be tested in clinical trials. Vitamin E isoforms are very well tolerated natural compounds. Hence fully realizing the anti-cancer potential of them will go a long way in revolutionizing cancer research.

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Figure legends

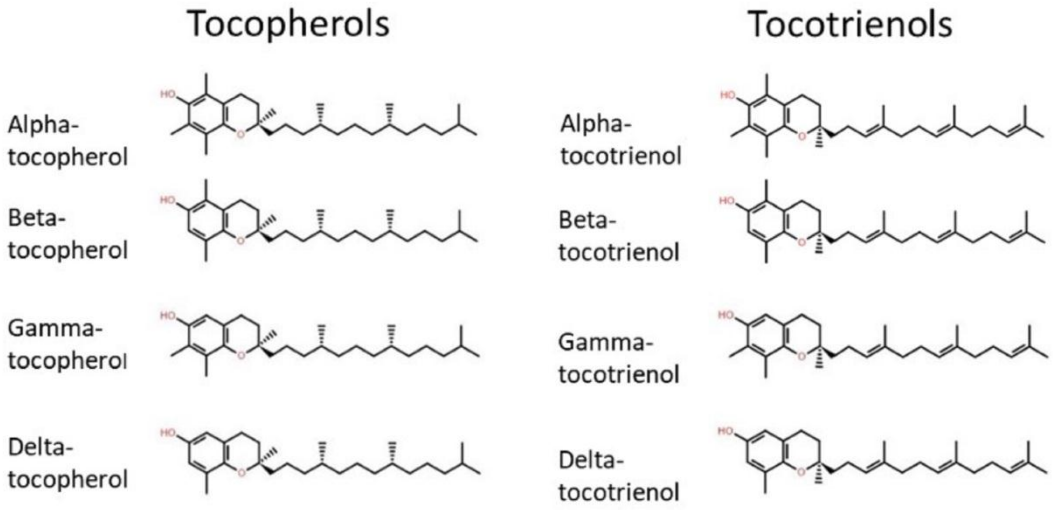

Figure 1: Chemical structure of vitamin E isoforms.

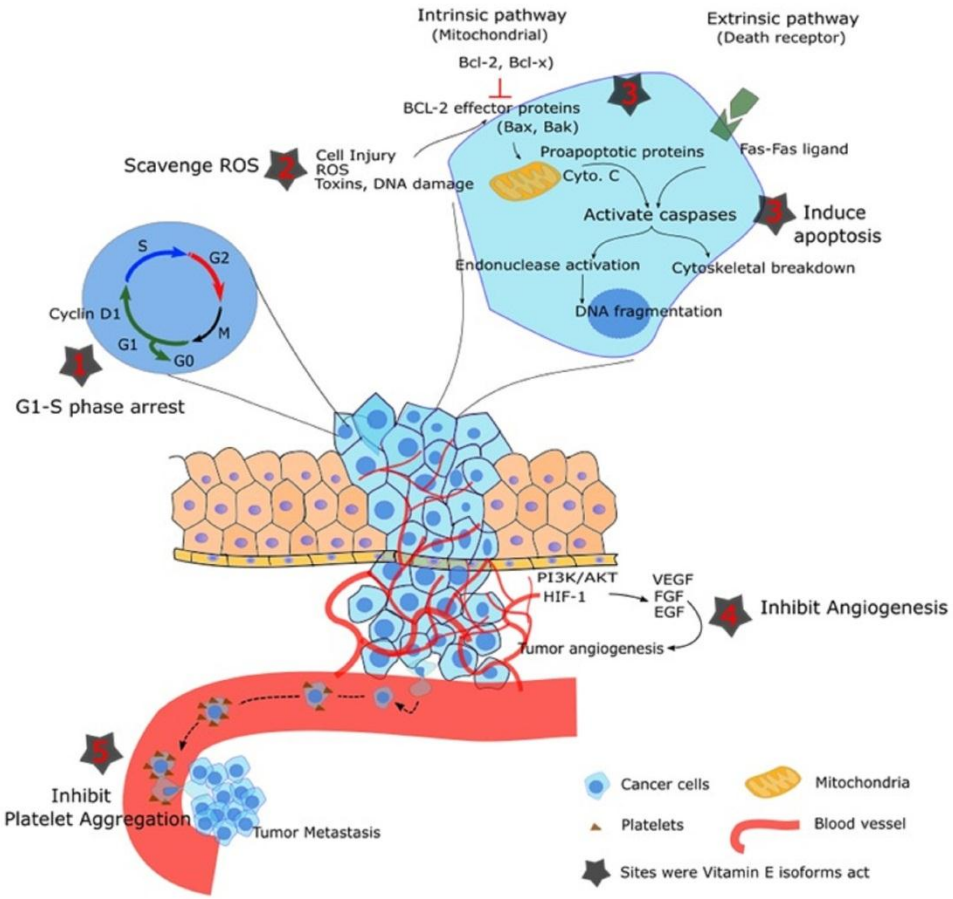

Figure 2: Postulated mechanisms of anti-cancer effects of vitamin E – 1. Anti-proliferation by cell cycle arrest 2. Antioxidant effect 3. Antiproliferation by inducing apoptosis by promotion of caspase activation and Bcl-2 proteins 4.Anti-angiogenic effect by inhibition of angiogenic factors 5.Anti-platelet effect by inhibiting platelet aggregation

Table 1: Clinical trials evaluating the anti-cancer effects of vitamin E.

Study author, year	Sample size (n), study population	Study duration	Intervention	Results
Blot WJ et al, 1993	29584 adults	5 yrs	Factorial design - Either of the 4 combinations - Zinc + retinol or Niacin + riboflavin or Vitamin C + molybdenum or α-tocopherol + selenium + beta carotene.	Significantly lower mortality occurred among vitamin E + selenium + beta carotene group (RR= 0.91; 95% CI 0.64-0.99, p=0.03)
Alpha-Tocopherol Beta-Carotene Cancer Prevention Study Group,(ATBC trial), 1994	29133, male smokers	5-8 yrs	50mg/day α-Tocopherol Vs. β- carotene 20mg/day Vs. combined Vs. placebo	No reduction lung cancer incidence with α-Tocopherol. Decreased prostate cancer in α-Tocopherol group.
Lippman SM et al - SELECT trial, 2009	32400, men	4-7 yrs	α-tocopheryl acetate Vs. selinium Vs. combined Vs. placebo	Non-significant ↑ risk of prostate cancer with vitamin E (HR=1.13; 99% CI 0.95-1.35, p=0.06)
Gaziano JM et al- The Physician's Health Study II 2009	14641 Male physicians in US, >50 yrs	~8 yrs	α-tocopherol + Vitamin C q.o.d Vs. placebo	No difference in incidence of prostate cancer (HR=0.97; 95% CI, 0.85-1.09, p=0.58)
Springett et al, 2009	25, Patients with pancreatic ductal	Phase 1 study – 2 weeks	δ –tocotrienol at escalating doses from 200mg to 3200mg daily given for 13 days	Significantly increased apoptotic changes and increased caspase 3 levels in intervention group.

	neoplasia >18yrs		before surgery.	δ –tocotrienol is safe and tolerated well.
Nesaretnam et al, 2010	240, Women, 40-60 yrs, with TNM stage 1 or 2 breast cancer – ER+	5 yrs	Tocotrienol rich fraction + tamoxifene Vs Placebo + tamoxifene	Non significant reduction in mortality by 60% in intervention group (HR=0.40' 95% CI 0.08-2.05, p=0.27)
Fleshner et al, 2011	303 Men with High-grade prostatic intraepithelial neoplasia	3 yrs	Vitamin E*+ soy + selenium Vs placebo	No reduction in progression to prostate cancer. (HR=1.03; 95% CI 0.67-1.60, p=0.88)

*-study does not mention the type of vitamin E isoform used.