PL3

Targeting Inflammation for Prevention and Treatment of Cancer by Tocotrienols : Food for Thought

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ABSTRACT

Tocotrienols are the active components of wide variety of plants including palm, rice bran, coconut, oats, and wheat. Unlike the tocopherols, the tocotrienols, also members of the vitamin E family, have an unsaturated isoprenoid side chain. In contrast to extensive studies on tocopherol, very little is known about tocotrienols. We present evidence that tocotrienols may have a potential in treatment of cancer, cardiovascular diseases, bone loss, arthritis and other proinflammatory diseases through the suppression of NF-κB pathway.

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INTRODUCTION

While both tocopherols and tocotrienols exist as alpha, beta, gamma, and delta forms and are members of the Vitamin E family, the two differ structurally in that tocopherols contain a saturated phytyl chain whereas tocotrienols possess an unsaturated side chain (see Fig. 1). The source of these vitamins also differ: tocopherols are components of nuts and common vegetable oils whereas tocotrienols are primarily derived from oat, wheat germ, barley, rye, rice bran, and palm oil (Kamal-Eldin and Appelqvist, 1996) (see Fig. 2). The unsaturated side chain present in tocotrienols facilitates its entry through the membrane bilayer more efficiently than the saturated chain of tocopherol (Birringer *et al.*, 2002; Hayes *et al.*, 1993; Suzuki *et al.*, 1993). In spite of this advantage and some reports that tocotrienols are better antioxidants (Kamal-Eldin and Appelqvist, 1996), there are 11,900 Pubmed citations on tocopherol and less than 300 on tocotrienols.

Besides its activity against atherosclerosis (Black *et al.*, 2000; Qureshi *et al.*, 1991a; Qureshi *et al.*, 1991b), there are reports to suggest that tocotrienols may have potential against cancer. For instance, tocotrienols have been shown to suppress the proliferation of a wide variety of tumor cells in culture including breast (Guthrie *et al.*, 1997; Nesaretnam *et al.*, 2000; Shun *et al.*, 2004; Sylvester and Shah, 2005; Yu *et al.*, 1999), prostate (Galli *et al.*, 2004; Srivastava and Gupta, 2006), and colon (Eitsuka *et al.*, 2006) (see Table 1). Animal studies have shown that tocotrienols can suppress the growth of breast tumor (Goh *et al.*, 1994; Gould *et al.*, 1991; Iqbal *et al.*, 2004) and melanoma (He *et al.*, 1997) and inhibit liver and lung carcinogenesis (Ngah *et al.*, 1991; Wada *et al.*, 2005) (see Table 2).

Tocotrienols possess powerful neuroprotective, anti-cancer, and cholesterol-lowering properties that are often not exhibited by tocopherols (Sen *et al.*, 2006). When mammary tumors were induced by 7,12-dimethylbenz(α)anthracene, only mice given tocotrienol had a significant increase in tumor latency; tocopherol had no effect (Gould et al., 1991). Similarly, only tocotrienol, not tocopherol, blocked the stress-induced changes in gastric acidity and gastrin level (Azlina *et al.*, 2005). Also, in contrast to tocotrienol, tocopherol showed very weak telomerase inhibition (Eitsuka et al., 2006). A recent study has shown the ability of tocotrienols to preferentially sensitize prostate cancer to γ-radiation in nude mice (Kumar *et al.*, 2006).

How tocotrienols mediate their effects is not fully understood, but their abilities to induce cell cycle arrest (Wada et al., 2005), regulate HMG-COA reductase (Parker *et al.*, 1993), activate p53 (Agarwal *et al.*, 2004), activate caspase-8 (Shah and Sylvester, 2004), suppress adhesion molecules (Naito *et al.*, 2005; Noguchi *et al.*, 2003; Theriault *et al.*, 2002), downregulate c-myc and telomerase (Eitsuka et al., 2006), and inhibit angiogenesis (Miyazawa *et al.*, 2004) have been established (see Fig. 3). Because of the critical role of NF-κB pathway in tumorigenesis, radiosensitization, apoptosis, cell adhesion, expression of c-myc and human telomerase reverse transcriptase (hTERT), and cell cycle arrest (Aggarwal, 2004), we postulated that γ-tocotrienol must modulate this pathway. Our results indeed demonstrate that γ-tocotrienol can suppress NF-κB activated by inflammatory cytokines, growth factors, and tumor promoters through the inhibition of IκBα kinase, leading to suppression of NF-κB-regulated gene products and potentiation of apoptosis.

Moreover, we found that while γ-tocotrienol completely abolished TNF-induced NF-κB activation, a similar dose of γ-tocopherol had no effect. Besides TNF, γ-tocotrienol also abolished NF-κB activation induced by PMA, okadaic acid, lipopolysaccharide, cigarette smoke, interleukin-1β, and EGF. Constitutive NF-κB activation expressed by certain tumor cells, was also abrogated by γ-tocotrienol. Reducing agent had no effect on the γ-tocotrienol-induced on the downregulation of NF-κB. Mevalonate reversed the NF-κB-inhibitory effect of γ-tocotrienol, indicating the role of HMG-CoA reductase. γ-Tocotrienol blocked TNF-induced phosphorylation and degradation of IκBα through the inhibition of IκBα kinase (IKK) activation; thus leading to the suppression of the phosphorylation and nuclear translocation of p65. γ-Tocotrienol also suppressed NF-κB-dependent reporter gene transcription induced by TNF, TNFR1, TRADD, TRAF2, TAK1, RIP, NIK, and IKK but not that activated by p65. Additionally, the expression of NF-κB-regulated gene products associated with antiapoptosis (IAP1, IAP2, Bcl-xL, Bcl-2, cFLIP, XIAP, Bfl-1/A1, TRAF1, and survivin), proliferation (cyclin D1, COX2, and c-myc), invasion (MMP-9 and ICAM-1), and angiogenesis (VEGF) were downregulated by γ-tocotrienol. This correlated with potentiation of apoptosis induced by TNF, paclitaxel, and doxorubicin. These results demonstrate that γ-tocotrienol inhibited the NF-κB activation pathway, leading to downregulation of various gene products and potentiation of apoptosis.

Our report is the first to investigate the effect of γ-tocotrienol on NF-κB activation by a variety of stimuli. Besides inducible NF-κB activation, we found that γ-tocotrienol also inhibited constitutive NF-κB activation. Constitutively active NF-κB has been found in a wide variety of leukemic and tumor epithelial cells (Jackson-Bernitsas *et al.*, 2007), and it is needed for the proliferation of those cells (Bharti *et al.*, 2003; Shishodia *et al.*, 2005). The inhibition of the proliferation of neoplastic mammary epithelial cells by tocotrienols has been suggested to correlate with inhibition of NF-κB activity (Shah and Sylvester, 2005). Why tumor cells express constitutively active NF-κB is not fully understood, but the role of IKK has been implicated (Bharti et al., 2003; Shishodia et al., 2005). Thus it is possible that inhibition of IKK in tumor cells is linked to the ability of tocotrienol to suppress constitutive NF-κB activation. Src-transformed fibroblasts have been shown to express constitutive NF-κB (Shain *et al.*, 1999). Because tocotrienols have been shown to inhibit c-Src (Sen *et al.*, 2000), this may be another mechanism by which tocotrienols suppress constitutive NF-κB activation.

We found that γ-tocotrienol inhibits RIP induced NF-κB dependent reporter gene expression. One of the mechanisms by which γ-tocotrienols could mediate its effects on NF-κB pathway is through its ability to induce the posttranscriptional suppression of HMG-CoA reductase that involves controlled degradation of the enzyme (Parker et al., 1993). Recent studies indicated that tocotrienols stimulate ubiquitination and degradation of the reductase (Ahn *et al.*, 2007). These results are consistent with a recent report from our laboratory that inhibitors of HMG-CoA reductase (statins) can suppress TNF-induced NF-κB activation (Ahn et al., 2007). Thus these results provide a link between the reductase that controls cholesterol biosynthesis and NF-κB activation. Cardiovascular diseases linked with elevated cholesterol have been found to have constitutively active NF-κB (Cominacini *et al.*, 2005).

We found that the expression of NF-κB–regulated gene products involved in invasion (e.g, COX-2, MMP-9, and ICAM-1) and proliferation (e.g., cyclin D1 and c-Myc) were abrogated by γ-tocotrienol. Further, our results showing that γ-tocotrienol suppresses NF-κB–regulated COX-2 and ICAM-1 expression are in agreement with a previous report involving human neoplastic mammary epithelial cells and human umbilical vein endothelial cells (Shah and Sylvester, 2004; Theriault et al., 2002). Similarly, our findings that γ-tocotrienol downregulates cyclin D1 expression are in agreement with previous reports (Galli et al., 2004) that showed that downregulation of cyclin D1 is responsible for cell cycle arrest at the G0/G1 phase. Our report, however, is the first to show that γ-tocotrienol suppresses TNF-induced MMP-9 expression, which plays a crucial role in tumor invasion and angiogenesis by mediating the degradation of the extracellular matrix (John and Tuszynski, 2001).

NF-κB is known to regulate the expression of survivin, IAPs, Bcl-2, Bcl-xL, Bfl-1/A1, cFLIP and TRAF1, and their overexpression in numerous tumors has been associated with tumor survival, chemoresistance, and radioresistance. We showed that γ-tocotrienol downregulates most of these gene products. These results are in agreement with recent findings that tocotrienol-rich fraction induce apoptosis through the modulation of Bax/Bcl-2 in colon carcinoma cells (Agarwal et al., 2004). The cytotoxic effects of TNF, paclitaxel, and doxorubicin are enhanced by γ-tocotrienol. These effects suggested that γ-tocotrienol potentiates apoptosis by cytokine and chemotherapeutic agents.

We found that under the conditions in which γ-tocotrienol suppressed NF-κB activation, γ-tocopherol had no effect. Our data are in agreement with other published reports that tocotrienol is a superior molecule among the members of the family of Vitamin E (Mcintyre *et al.*, 2000; Shah *et al.*, 2003; Song and Debose-Boyd, 2006). Four different homologues of tocotrienols have been identified viz; α, β, γ, and δ. Under the conditions γ-tocotrienol completely suppressed TNF-induced NF-κB activation, other forms were found to have minimal effect. Published reports indicate that δ-tocotrienol is at least as active as γ-tocotrienol for inducing apoptosis (He et al., 1997; Mcintyre et al., 2000). The differences between our results and those previously reported could be due to the difference in purity of the tocotrienols employed or difference in the assays used.

Overall, our results demonstrate that γ-tocotrienol is a potent inhibitor of NF-κB activation, which may explain its anti-angiogenic, anti-proliferative, proapoptotic, anti-metastatic, anti-inflammatory, and immunomodulatory effects. Only 1% of all papers published on vitamin E have explored tocotrienols. Therefore, further studies are needed to explore its potential against cancer and cardiovascular and neurological diseases.

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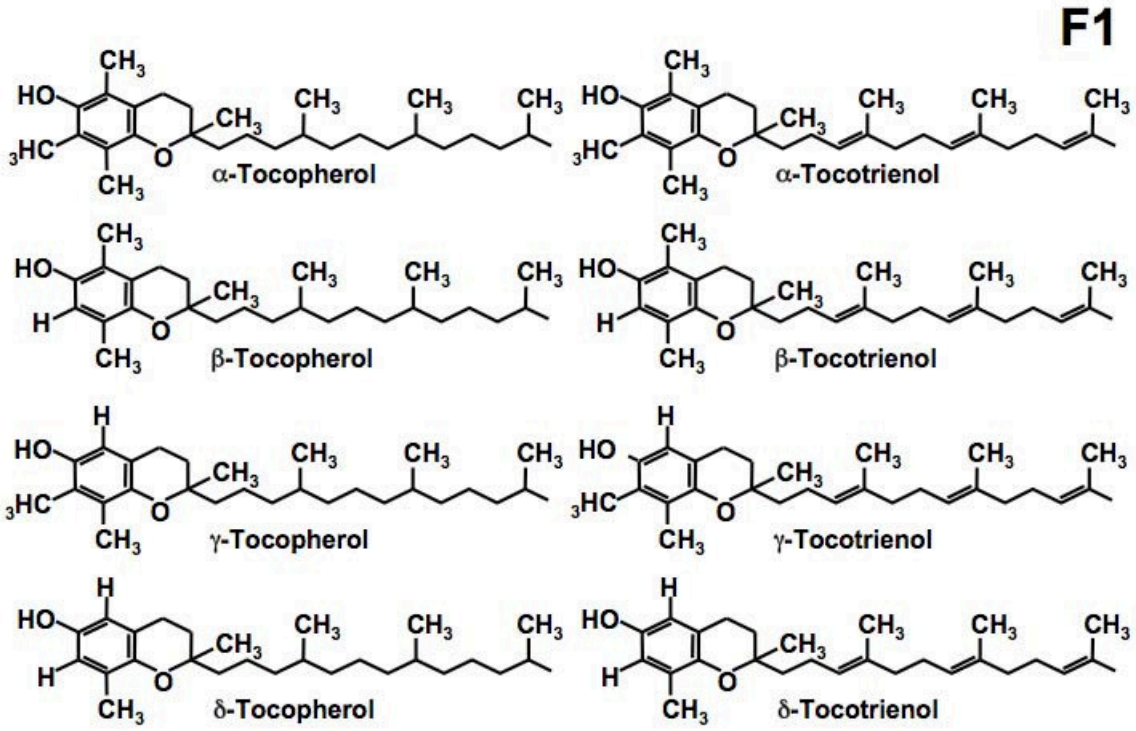
F1
α-Tocopherol
α-Tocotrienol
β-Tocopherol
β-Tocotrienol
γ-Tocopherol
γ-Tocotrienol
δ-Tocopherol
δ-Tocotrienol
Structures of Tocopherol and Tocotrienols

Figure 1,

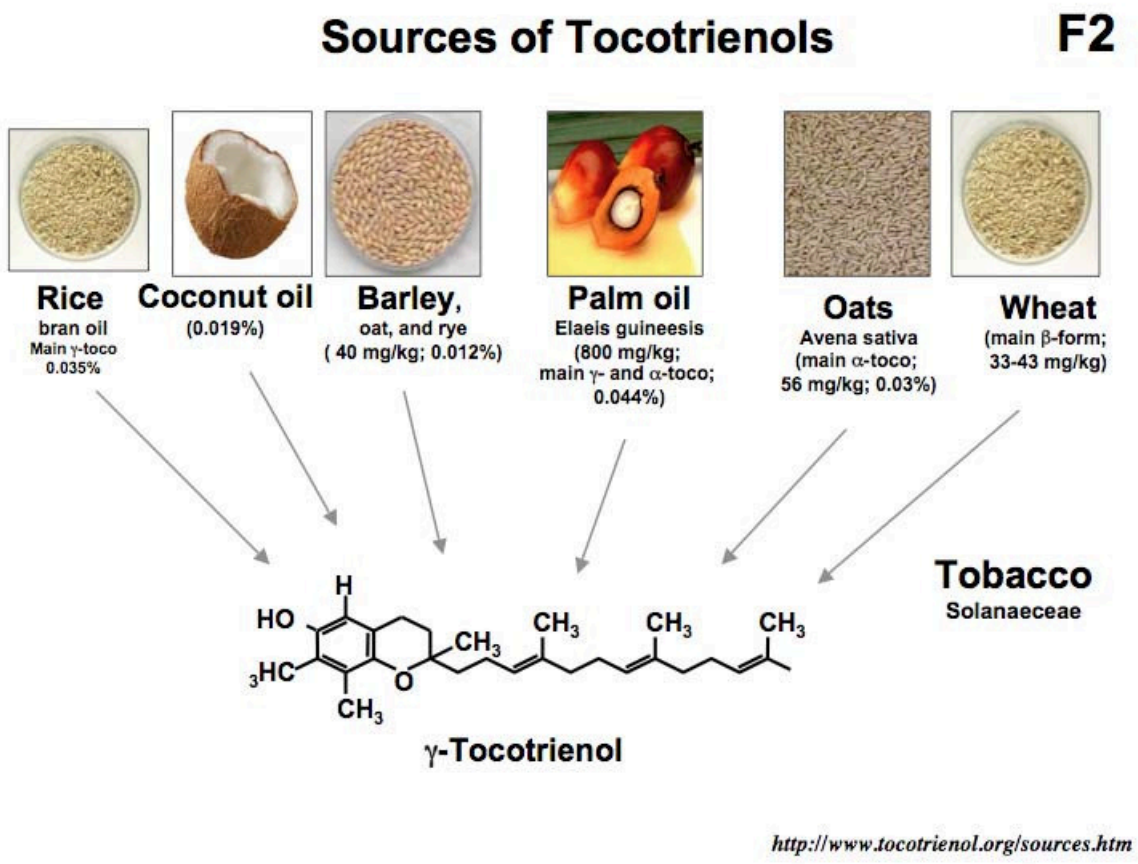
Sources of Tocotrienols
F2
Rice
bran oil
Main γ-toco
0.035%
Coconut oil
(0.019%)
Barley,
oat, and rye
(40 mg/kg; 0.012%)
Palm oil
Elaeis guineesis
(800 mg/kg;
main γ- and α-toco;
0.044%)
Oats
Avena sativa
(main α-toco;
56 mg/kg; 0.03%)
Wheat
(main β-form;
33-43 mg/kg)
Tobacco
Solanaceae
γ-Tocotrienol
http://www.tocotrienol.org/sources.htm

Figure 2,

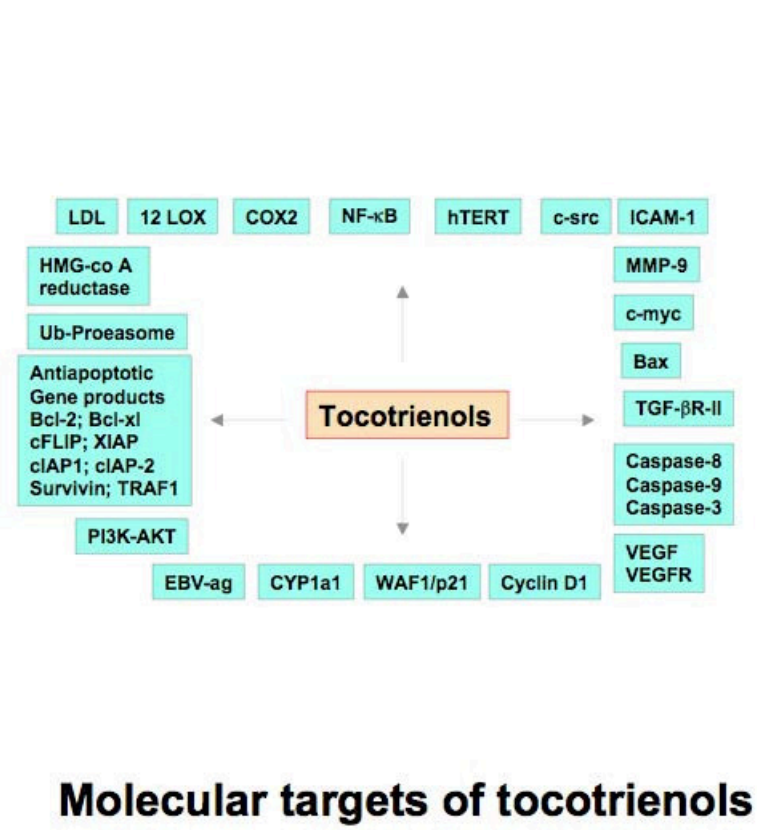
F3
LDL
12 LOX
COX2
NF-κB
hTERT
c-src
ICAM-1
HMG-co A reductase
MMP-9
c-myc
Ub-Proeasome
Bax
Antiapoptotic Gene products Bcl-2; Bcl-xl cFLIP; XIAP cIAP1; cIAP-2 Survivin; TRAF1
Tocotrienols
TGF-βR-II
Caspase-8 Caspase-9 Caspase-3
PI3K-AKT
VEGF VEGFR
EBV-ag
CYP1a1
WAF1/p21
Cyclin D1
Molecular targets of tocotrienols

Figure 3,

TABLE 1. ANTICANCER POTENTIAL OF TOCOTRIENOSL (*in vitro*)

γ and δ tocotrienols are most potent for anticancer but a for neuroprotection

Cancer	Target	Tocotrienols	Reference
Tumor cells (*in vitro*)*			Komiyama *et al*, 1989
Breast cancer cells*		α, γ, δ (180 mg/ml)	Nesaretnam *et al*, 1995
Breast cancer cells*		Synergy with tamoxifin	Guthrie *et al*, 1997
Breast cancer cells*		γ & δ	Nesaretnam *et al*, 1998
Breast cancer cells*			Nesaretnam *et al*, 2000
Breast cancer cells*			Mo and Elson, 1999
Breast cancer cells*			Yu *et al*, 1999
Breast cancer cells*		γ & δ	McIntyre *et al*, 2000b
Breast cancer cells*			McIntyre *et al*, 2000a
Breast cancer cells*	cAMP		Sylvester, 2002
Breast cancer cells*			Shun *et al*, 2004
Breast cancer cells*		γ	Shah *et al*, 2003
Breast cancer cells*	(Caspase-8, AKT, FLIP)		Shah & Sylvester, 2004
Breast cancer cells*	(AKT and NF-kB)		Shah & Sylvester, 2005
Breast cancer cells*			Takahashi & Loo, 2004
Prostate cancer cells*	(G0/G1)	TRF	Shrivastava &Gupta, 2006
Lymphoma cells*	EBV		Goh *et al*, 1994
Hepatoma cells*			Sakai *et al*, 2004
Liver cancer cells*			Har & Keong, 2005
Liver cancer cells*	CYP1A1	δ	Wada *et al*, 2005
Colon cancer cells (RKO)		TRF	Agarwal *et al*, 2004
Colon cancer cells*	hTERT, c-myc, PKC	Toco	Shay & Wright, 2006
Melanoma cells		α & δ	He *et al*, 1997
Melanoma cells		δ	Mo & Elson , 1999
Bovine aortic endothelial cells			Inokuchi *et al*, 2003
VEGF-induced HUVEC tube formation*			Mizushina *et al,* 2006
EC	VEGFR	Toco	Nakagawa *et al*, 2004
EC		Toco	Miyazawa *et al*, 2004

Tocopherol was not effective; PO is palm oil

TABLE 2. CHEMOPREVENTIVE EFFECTS OF TOCOTRIENOLS

γ and δ tocotrienols are most potent for anticancer but a for neuroprotection

Cancer	Target	Tocotrienols	Reference
Sarcoma 180, Ehrlich carcinoma*		α & γ	Komiyama *et al*, 1989
Mammary breast carcinoma (invasive)		α & γ	Komiyama *et al*, 1989
Carcinoma (invasive) DMBA-induced tumors in rats		PO	Sundram *et al*, 1989
DMBA-induced mammary tumors		Toco	Gould *et al*, 1991
DMBA-induced mammary tumors	HMG-CoA	TRF (10 mg/kg)	Iqbal *et al*, 2003 Yu *et al*, 2005
Liver cancer induced by AAF			Iqbal *et al*, 2004
Liver cancer induced by AAF		Toco	Ngah *et al*, 1991 Rahmat *et al*, 1993

Tocopherol was not effective; PO is palm oil ; 2-acetylaminofluorene (AAF)