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Commentary

Tocotrienols, the vitamin E of the 21st century: Its potential against cancer and other chronic diseases

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ABSTRACT

Initially discovered in 1938 as a “fertility factor,” vitamin E now refers to eight different isoforms that belong to two categories, four saturated analogues (α , β , γ , and δ) called tocopherols and four unsaturated analogues referred to as tocotrienols. While the tocopherols have been investigated extensively, little is known about the tocotrienols. Very limited studies suggest that both the molecular and therapeutic targets of the tocotrienols are distinct from those of the tocopherols. For instance, suppression of inflammatory transcription factor NF- κ B, which is closely linked to tumorigenesis and inhibition of HMG-CoA reductase, mammalian DNA polymerases and certain protein tyrosine kinases, is unique to the tocotrienols. This review examines in detail the molecular targets of the tocotrienols and their roles in cancer, bone resorption, diabetes, and cardiovascular and neurological diseases at both preclinical and clinical levels. As disappointment with the therapeutic value of the tocopherols grows, the potential of these novel vitamin E analogues awaits further investigation.

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1. Introduction

Preventing beriberi by eating unpolished rice, curing scurvy by eating citrus fruits, and supporting fertility by eating leafy vegetables—all of these life-sustaining properties of foods are related to factors that in 1912 came to be called vitamins (*vita* means life). In 1922, Herbert Evans and Katherine Bishop, two prominent researchers from Berkeley, first isolated fat-soluble vitamin E from green leafy vegetables and described it as a fertility factor. Vitamin E was named tocopherol in 1924 and synthesized in 1938 [for references, see [1]]. Deficiency of this vitamin is now known to cause severe degenerative diseases such as ataxia, Duchenne muscular dystrophy-like muscle degeneration, and infertility. Vitamin E is present in most edible oils to various extents, including those extracted from wheat germ oil, wheat, rice bran (0.035%), barley (0.012% or 44 mg/g oil), oats (0.03%), coconut (0.019%) and palm (0.044%; 0.78–1.08 mg/g oil) (<http://www.tocotrienol.org>).

While alpha-tocopherol was the first vitamin E analogue to be recognized, eight chemically distinct analogues are now known, consisting of alpha (α), beta (β), gamma (γ) and delta (δ)-tocopherols (TP) and alpha, beta, gamma and delta-tocotrienols (T3); all of them are referred to as vitamin E (Fig. 1). The tocopherols

are saturated forms of vitamin E, whereas the tocotrienols are unsaturated and possess an isoprenoid side chain. Some evidence suggests that human tissues can convert tocotrienols to tocopherols [2,3]. Tocopherols consist of a chromanol ring and a 15-carbon tail. The presence of three *trans* double bonds in the tail distinguishes tocopherols from tocotrienols. The isomeric forms of tocotrienol are distinguished by the number and location of methyl groups on the chromanol rings: α -tocotrienol is 5,7,8-trimethyl; β -tocotrienol is 5,8-dimethyl; γ -tocotrienol is 7,8-dimethyl and δ -tocotrienol is 8-monomethyl. While leaves and seeds of most plants contain tocopherols, tocotrienols are present in only a very small fraction of plants (Fig. 2a and b). Although some activities of tocopherols and tocotrienols are compared in this review, tocotrienols are the primary focus.

The name tocotrienol to denote a tocopherol with a true isoprenoid side chain was first suggested by Bunyan et al. [4], and the tocotrienols were described in *Nature* when isolated from the latex of the rubber plant, *Havea brasiliensis*, in 1964 [5,6]. The tocotrienols attracted no real attention until the 1980s and 1990s when their cholesterol-lowering potential [7] and anticancer effects were described [8,9]. Subsequently, rice bran, palm, and annatto (90% delta and 10% gamma) oils were described as some of the richest sources of tocotrienols by Tan and his coworkers. The tocopherols:tocotrienols ratios in rice bran, palm and annatto oils are 50:50; 25:75 and 0.1:99.9, respectively [10]. Besides tocopherols, various isomers of tocotrienols have also been detected in human milk [11].

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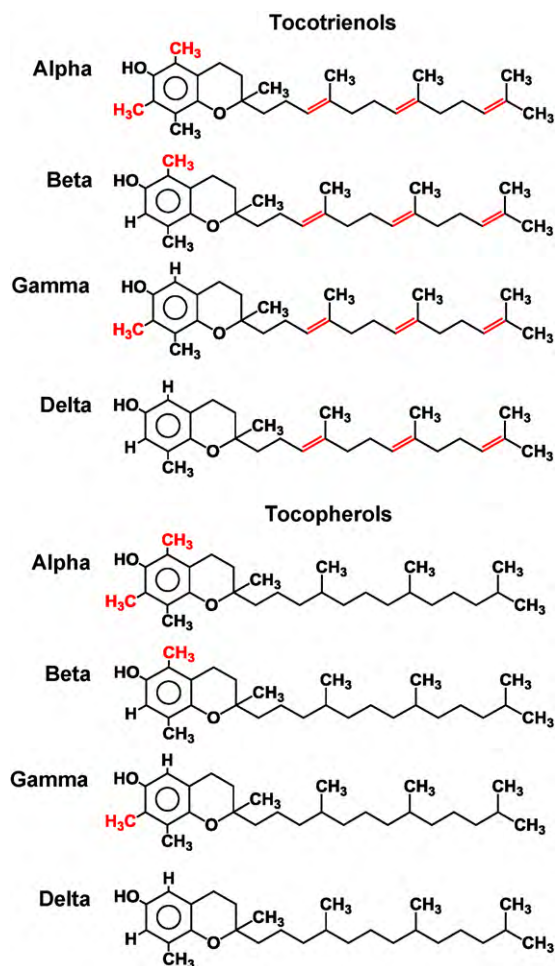


Fig. 1. Chemical structure of tocotrienols and tocopherols.

2. Molecular targets

Like tocopherols, tocotrienols exhibit antioxidant activities, and most of its effects can be linked to its antioxidant function. Molecular targets of tocotrienols can be classified as those that are modulated by binding directly [12–17] and those that are modulated indirectly. Modulation of various targets by tocotrienols may occur at the transcriptional, translational, or post-translational levels, or by direct interactions with cellular targets (Table 1). For instance, src and 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase are modulated through direct binding, whereas inflammatory transcription factors and the genes regulated by them and death receptors are modulated indirectly (Fig. 3a and b). Various studies indicate that tocotrienols exhibit antioxidant, antiproliferative, antisurvival, proapoptotic, antiangiogenic, and anti-inflammatory activities.

The antioxidant activities of this vitamin E (tocotrienols) are mediated through induction of antioxidant enzymes such as superoxide dismutase [18,19], NADPH:quinone oxidoreductase [20], and glutathione peroxidase [21], which quench free radicals such as superoxide radicals [22] (Table 1). The antiproliferative activity of tocotrienols are mediated through modulation of growth factors such as vascular endothelial growth factor (VEGF) [23], basic fibroblast growth factor (bFGF) [24] and transforming growth factor-beta (TGF- β) [25], HER2/neu [26], and interleukin-6 (IL-6) [27]. Cyclin-dependent kinases (CDK2, CDK4, CDK6) and their inhibitors, such as p21, p27 and p53 [28,29] and down-regulation of Rb phosphorylation [29–31] also mediate the

growth-suppressive effects of this agent. Moreover, inhibition of mitogen-activated protein kinases (MAPK) such as ERK [32], p38 MAPK and JNK [33] is critical to the antiproliferative effects of tocotrienols. The suppression of cyclin D1 expression induced by tocotrienols also plays an important role in the growth-inhibitory activities of this vitamin [20,29–31,34,35]. Tocotrienols impede the survival of various tumor cells by inhibiting expression of cell survival proteins such as XIAP, IAP-1, IAP-2, bcl-2, bcl-xl, c-FLIP, TRAF-1, survivin and Bfl-1/A1 [34]. Suppression of the phosphatidylinositol-3-kinase (PI3K)/AKT pathway by tocotrienols could account for its antisurvival activities [36]. Downregulation of the telomerase, c-myc, and raf-ERK signaling pathways has been linked to tocotrienol's ability to inhibit cell survival [32,37].

Various studies have revealed that tocotrienols can induce apoptosis in a wide variety of tumor cells. These effects are mediated through activation of both extrinsic and intrinsic pathways by the vitamin. The extrinsic pathways involve induction of death receptors [33] and activation of caspase-8, which leads to caspase-3 activation [38]. The activation of intrinsic pathways by tocotrienols involves mitochondrial depolarization [39] and is mediated through the upregulation of Bax [32,40,41], cleavage of Bid [40], release of cytochrome C [22,28,39,42,43], and activation of caspase-9, which in turn leads to activation of caspase-3 [28,40,44,45]. This unsaturated form of vitamin E also mediates apoptosis through DNA fragmentation [39,46] and upregulation of p53 [28] in certain cells.

The suppression of angiogenesis by tocotrienols is mediated through inhibition of VEGF expression [23,47] and VEGF receptor signaling [48–50]. Suppression of the matrix metalloproteinase (MMP)-9 gene could also contribute to the angiogenesis-suppressive activity [34,51]. Although TWIST, CXCR4, TNF, FGF, TGF- β , PDGF and IL-8 all have been linked with angiogenesis, whether any of these pathways is modulated by tocotrienols [47] is poorly understood.

Numerous lines of evidence suggest that tocotrienols exhibit potent anti-inflammatory activity. First, activation of the transcription factor NF- κ B has been closely linked with inflammation [34,52]. Second, tocotrienols have been shown to suppress the expression of TNF [34,53], IL-1 [54], IL-6 [55], IL-8 [47], inducible nitric oxide synthase [56], and cyclo-oxygenase 2 [34,52,56,57], all of which mediate inflammation. Third, tocotrienols have been shown to suppress STAT3 cell-signaling pathway, also involved in inflammation [58,59]. Hypoxia-induced factor-1 is another pathway that has been linked with inflammation and is modulated by tocotrienols [47].

Tocotrienols inhibit various protein kinases, including protein kinase C [60,61], p60 Src [61], I κ B α kinase [62], and GSK-3 β [38]. Inhibition of HMG-CoA reductase, an enzyme that is rate limiting in the pathway to cholesterol biosynthesis [63], also plays an essential role in the various activities attributed to this vitamin. There are, for instance, reports that the antitumor effects of tocotrienols are linked to its ability to inhibit HMG-CoA reductase [64,65]. Different isomeric forms of tocotrienols vary in their ability to lower cholesterol, as follows: $\delta > \gamma > \alpha > \beta$ [66]. The reduction of HMG-CoA occurs through two separate mechanisms, first the enhancement of degradation of the reductase protein and second the decrease in efficiency of translation of the reductase mRNA [66,67].

The modification by tocotrienols of various cell-signaling pathways described here has been linked to its effects against cancer, diabetes, and cardiovascular and neurological diseases.

3. In vitro studies

Numerous *in vitro* studies indicate that tocotrienols exhibit anticancer, cardioprotective, and neuroprotective effects (Table 2).

Table 1

A list of molecular targets modulated by tocotrienols in various cell types.

Targets	References	Targets	References	Targets	References
Apoptotic regulators		GSTP-1 \downarrow^4	[12]	ER- α $\downarrow^{1,2}$	[13,92]
Bax \uparrow^2	[32,40,41]	HMGCR $\downarrow^{2,4}$	[63,64,66,96]	ER- β $\uparrow^{1,2,4}$	[13,92]
Bcl-2 \downarrow^2	[20,32,34,41]	hTERT \downarrow^2	[37]	ErbB-3R \downarrow^3	[36,69]
Bcl-xL \downarrow^2	[34,85]	iNOS \downarrow^2	[56]	LDL-R \uparrow^1	[112]
Bfl-1/A1 \downarrow^2	[34]	MMP-2 $\downarrow^{1,2}$	[34,51]	PXR \uparrow^4	[215]
c-FLIP \downarrow^2	[34,38,45]	MMP-9 $\downarrow^{1,2}$	[34,51]	SXR \uparrow^4	[15]
IAP-1 \downarrow^2	[34]	NQO1 \downarrow^2	[20]	TGF- β RII \uparrow^2	[25]
IAP-2 \downarrow^2	[34]	MAO-A \uparrow^1	[177,178]	VEGFR \downarrow^2	[48–50]
Survivin \downarrow^2	[34]	PLA-2 \downarrow^3	[130]	Transcription factors	
TRAF-1 \downarrow^2	[34]	PARP \downarrow^3	[32,33,40]	C/EBP- α \downarrow^1	[216]
XIAP \downarrow^2	[34]	SOD \downarrow^2	[18,19]	CHOP $\uparrow^{1,2}$	[33,72]
Cytokines		Telomerase \downarrow^1	[37]	c-myc \downarrow^2	[32,34,37]
IFN- γ \downarrow^2	[140,207]	TIMP-1 \uparrow^2	[51]	E2F \downarrow^2	[30]
IL-12 \uparrow^2	[207]	TIMP-2 \uparrow^2	[51]	HIF-1 α \downarrow^2	[47,217]
IL-6 \downarrow^2	[55]	Growth factors		NF- κ B \downarrow^3	[34,53,56,62,122]
IL-8 $\downarrow^{1,2}$	[47]	bFGF \downarrow^2	[24]	PPAR- γ \downarrow^2	[126,218]
IL-1 \downarrow^2	[54,55,128,129]	VEGF $\downarrow^{1,2}$	[23,47]	STAT-3 \downarrow^3	[58,59]
PF-4 \downarrow^2	[167]	TGF- β \downarrow^2	[122,123]	STAT-5 \downarrow^3	[59]
TNF- α \downarrow^2	[53,193]	HER2/neu \downarrow^2	[26]	Others	
Adhesion molecules		Kinases		Akt \downarrow^3	[52,59,216]
ICAM-1 \downarrow^2	[97]	CDK-2 \downarrow^2	[29,31]	Apo B $\downarrow^{2,3}$	[3,219,220]
VCAM-1 \downarrow^2	[95,97,208,209]	CDK-4 \downarrow^2	[29–31]	Cyclin D1 \downarrow^2	[29,30,35,221]
E-selectin \downarrow^2	[95,97]	CDK-6 \downarrow^2	[27,29,31]	Cyclin D3 \downarrow^2	[27]
Enzymes		JNK \downarrow^3	[32,33,91]	Cyclin E \downarrow^2	[35]
12-LOX $\downarrow^{2,4}$	[17,98]	IKK α , β \downarrow^2	[34,62]	CYP1A1 \uparrow^1	[82]
Caspase-3 \uparrow^3	[32,39,41,122]	MAPK \uparrow^3	[33]	CYP3A4 \uparrow^1	[15,222,223]
Caspase-8 \uparrow^3	[33,38,40,45,62,76,81]	PKC-1 \downarrow^3	[36,59,62]	CYP3A5 \uparrow^1	[215]
Caspase-9 \uparrow^3	[28,40,44,45]	ERK1/2 \downarrow^3	[32,44,48]	Cyt C \uparrow^3	[28,39,42,43]
COX-2 \downarrow^2	[34,52,56,57]	GSK-3 β \downarrow^3	[38]	Id-1 \downarrow^2	[224]
DNApol \downarrow	[210]	PI3K \downarrow^3	[36,62,214]	PGE-2 \downarrow^2	[193]
eNOS \downarrow^3	[48]	PKC \downarrow^2	[37,49]	Raf-1 \downarrow^2	[32]
GGT \downarrow^2	[108,211,212]	Src $\downarrow^{2,3,4}$	[61,83,115]	Ras \downarrow^2	[193]
GST \downarrow^2	[110,212,213]	Receptors		TX-B2 \downarrow^2	[3,167]
GPx \uparrow^2	[18,137]	DR-5 \uparrow^1	[33]		
		EGFR \downarrow^3	[58]		

Modulation of various targets by tocotrienol at transcription, translation, post-translation or by direct interaction are indicated by the superscripts 1, 2, 3 or 4, respectively. 12-LOX, 12-lipoxygenase; Apo A, apolipoprotein A; bFGF, basic fibroblast growth factor; CDK, cyclin-dependent kinases; C/EBP α ; CCAAT/enhancer-binding protein- α ; CHOP, C/EBP homologous protein; COX-2, cyclo-oxygenase-2; Cyt C, cytochrome C; DR5, death receptor 5; EGFR, endothelial growth factor receptor; eNOS, endothelial nitric oxide synthase; ER- α , estrogen receptor alpha; ERK, extracellular signal-regulated kinase; FLIP, FLICE-like inhibitory protein; GGT, gamma-glutamyl transpeptidase; GPx, glutathione peroxidase; GSH, reduced glutathione; GST, glutathione S-transferase; HIF-1 α , hypoxia-inducible factor-1 α ; HMGCR, 3-hydroxy-3-methyl-glutaryl coenzyme A reductase; hTERT, human telomerase reverse transcriptase; IAP, inhibitors of apoptosis; ICAM-1, intercellular adhesion molecule-1; Id-1, inhibitor of differentiation; IFN, interferon; IKK, I κ B kinase; IL, interleukin; iNOS, inducible nitric oxide synthase; JNK, c-Jun NH(2)-terminal kinase; LDL-R, low-density lipoprotein receptor; MAO-A, monoamine oxidase A; MAPK, mitogen-activated pathway kinase; MMP, matrix metalloproteinase; NF- κ B, nuclear factor-kappa B; NQO1, NAD(P)H:quinone oxidoreductase; PARP, poly (ADP-ribose) polymerase; PDK, phosphoinositide-dependent protein kinase; PDK-1, PI3K-dependent kinase 1; PI3K, phosphoinositide 3-kinases; PF-4, platelet factor-4; PGE, prostaglandin; p-GSK3 β , phospho-glycogen synthase kinase3 beta; PKC, protein kinase C; PLA(2), phospholipase A(2); PPAR, peroxisome proliferator-activated receptors; PXR, pregnane X receptor; SOD, super oxide dismutase; SREBP, sterol regulatory element binding proteins; STAT, signal transducer and activator protein; SXR, steroid and xenobiotic receptor; TGF- β RII, tissue growth factor-beta receptor II; TIMP, tissue inhibitor of metalloproteinases; TNF, tumor necrosis factor; TRAF, TNF receptor-associated factor 1; TX-B2, thromboxane B2; VCAM-1, vascular cell adhesion molecule; VEGFR, vascular endothelial growth factor receptor; XIAP, X-linked inhibitor of apoptosis protein.

3.1. Anticancer effects

Tocotrienols have been shown to suppress proliferation and induce apoptosis in wide variety of tumor cells including those of the breast [13,25,26,29,30,33,36,42,43,45,52,59,62,68–78], colon [28,41,79], liver [40,80–82], lung [83–85], stomach [32,44,51], skin [86,87], pancreas [88], and prostate [46,89–91]. A number of mechanisms have been proposed by which tocotrienols induce apoptosis in these cancer cells, as already described. Some additional mechanisms involve induction of death receptor-5, as described recently [33]. Interaction of tocotrienols with estrogen receptors has been implicated in studies of breast cancer cells [73,92]. Various results indicate that γ - and δ -tocotrienol exhibit greater anticancer activity than α - or β -tocotrienol [27,75,82,89,93,94].

3.2. Cardioprotective effects

Tocotrienols' cardioprotective effects are mediated through their antioxidant mechanisms and their ability to suppress inflammation, and inhibit HMG-CoA reductase, a rate-limiting

enzyme in cholesterol biosynthesis [66,67,95,96], and reduce the expression of adhesion molecules and monocyte–endothelial cell adhesion [97].

3.3. Neuroprotective effects

Various reports suggest that tocotrienols are neuroprotective, as indicated by its ability to suppress glutamate-induced activation of c-Src kinase [61,98]. Tocotrienols also have activity against Parkinson disease [99].

4. Animal studies with tocotrienols

4.1. Anticancer effects

Tocotrienols exhibit activity in different models of both prevention and treatment of cancer (Table 3). Perhaps the first report about the therapeutic potential of tocotrienols for cancer in animal models was by Kato et al., who in 1985 showed that tumor-bearing rats administered with tocotrienols had an

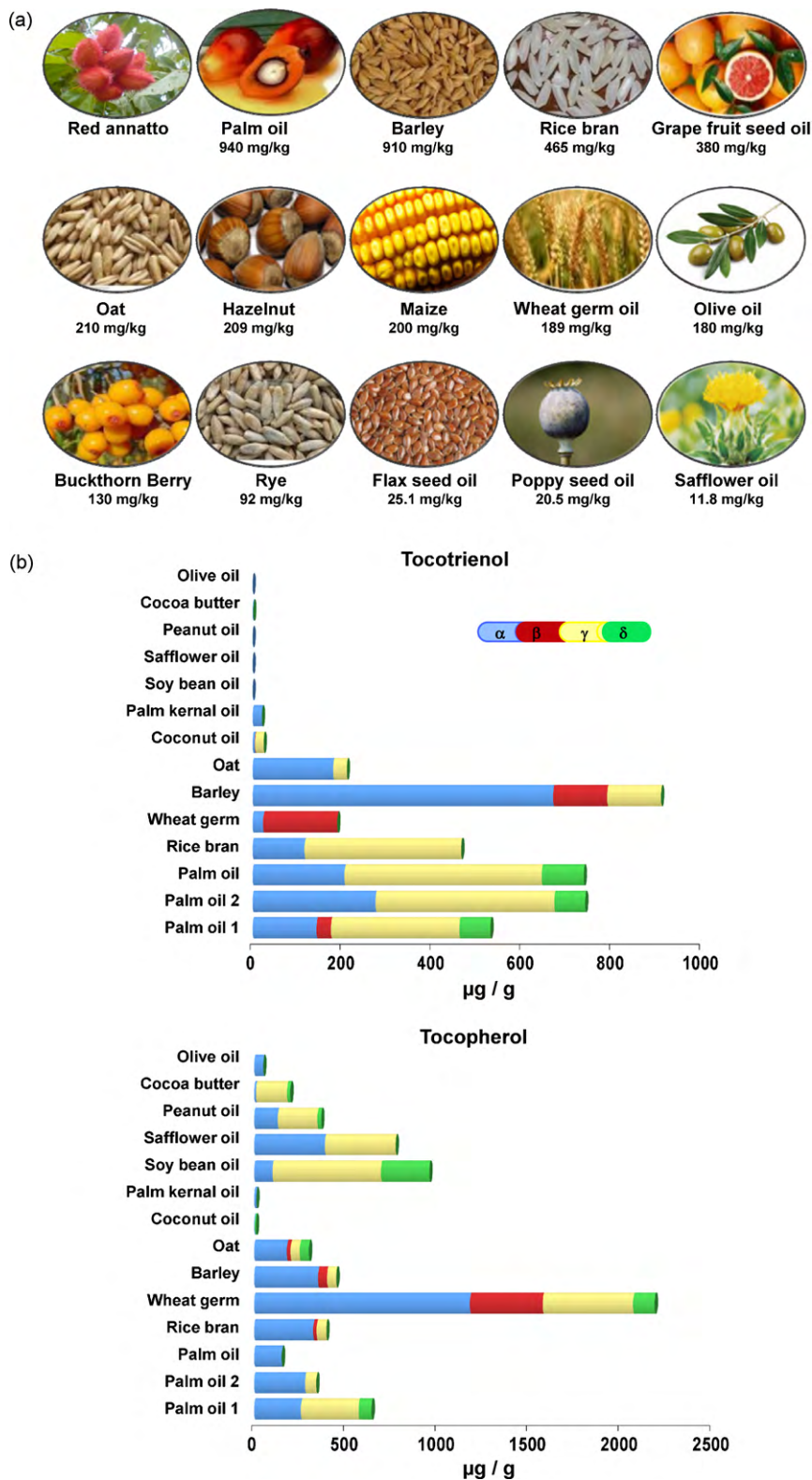


Fig. 2. (a) Natural sources of tocotrienols. For reference see red annatto [10]; palm oil [198]; rice bran oil [199]; grape seed oil, maize, wheat germ oil [200]; hazel nut [201]; olive oil [202]; buckthorn berry [203]; rye [204]; oat and barley [205]; flax seed oil, poppy seed oil, safflower oil [206]. (b) Content of tocotrienol and tocopherol isomers from various sources. For reference see <http://www.tocotrienol.org/>.

extended life span [8]. Komiyama et al. observed antitumor activity when tocotrienols were administered intraperitoneally to mice with established murine Meth A fibrosarcoma. They showed that tocotrienols were more effective than α -tocopherol, and among the tocotrienols, γ -tocotrienol was more effective than

α -tocotrienol as an antitumor agent [100]. They also showed that tocotrienols are better antioxidants than tocopherols. The growth of highly metastatic B16 melanoma in female mice was inhibited by tocotrienols, and δ -tocotrienol was more active than γ -tocotrienol in this setting [101]. In mice implanted with

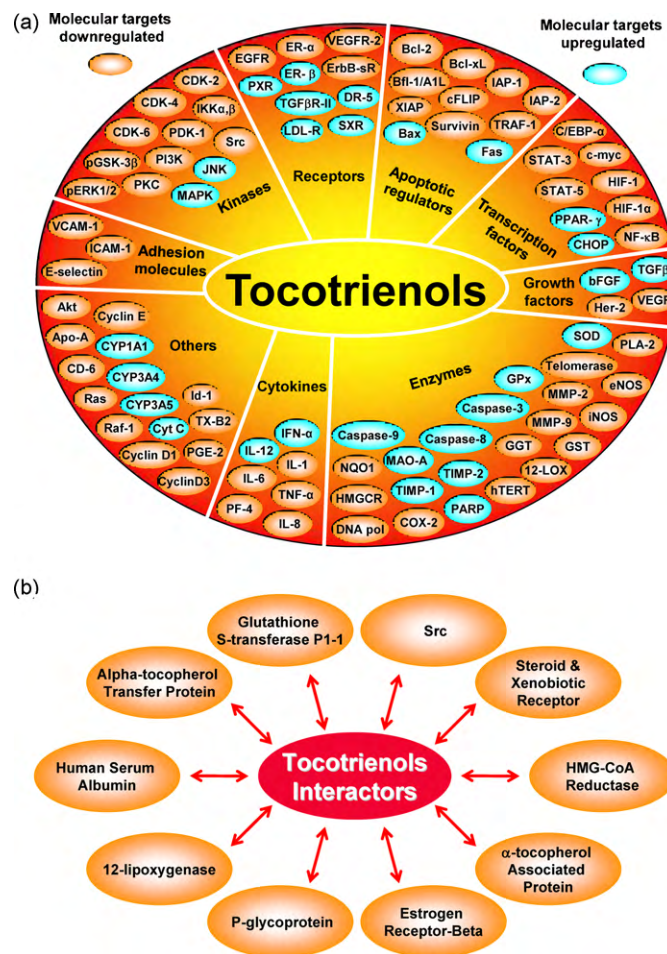


Fig. 3. (a) Molecular targets of tocotrienols. (b) Proteins that directly interact with tocotrienols.

hepatoma, both γ -tocotrienol and δ -tocotrienol delayed tumor growth, and when examined for levels of tocotrienols, the tumors contained a specific accumulation of these analogues [102].

The antitumor effects of tocotrienols appear to be mediated in part through their ability to suppress angiogenesis [23,103]. Suppression of angiogenesis is mediated through reduction in serum levels of VEGF and inhibition of the PI3K-AKT pathway. The inhibition of HMG-CoA reductase and the consequent decrease in serum cholesterol level has been linked with the tumor-suppressive action of tocotrienols [64]. Tocotrienols have also been shown to enhance the antitumor effects of other agents. In one study, δ -tocotrienol was reported to enhance the growth-suppressive effects of lovastatin in the B16 melanoma model in mice [87]. γ -Tocotrienol preferentially sensitized human prostate cancer in nude mice to radiation [104].

Besides antitumor effects against established tumors, tocotrienols have also been shown to be effective in cancer prevention models. Sundram et al. showed that palm oil, one of the richest dietary sources of tocotrienols, is effective in preventing 7,12-dimethylbenz[α]anthracene (DMBA)-induced mammary carcinogenesis in rats, but corn oil and soybean oil, which contain tocopherols but not tocotrienols, lack this activity [9]. Gould et al. reported a statistically significant increase in tumor latency in the DMBA-induced rat mammary tumor model with tocotrienols but not with tocopherols [105]. Inhibition of tumor promotion by various palm-oil tocotrienols was also reported by Goh et al. [106], in an *in vitro* assay utilizing the activation of Epstein-Barr virus (EBV) early antigen expression in EBV-genome-carrying human

lymphoblastoid cells. They showed that γ - and δ -tocotrienol derived from palm oil exhibit strong activity against tumor promotion by inhibiting EBV early antigen expression in Raji cells induced by phorbol ester. However, α - and γ -tocopherol and dimers of γ -tocotrienol or γ -tocopherol lack this activity [98]. Iqbal et al. showed that feeding tocotrienol-rich fraction (TRF; 10 mg/kg) to DMBA-administered rats suppressed mammary carcinogenesis, and this correlated with declines in serum cholesterol, low-density lipoprotein (LDL)-cholesterol, and HMG-CoA reductase protein [65]. Wada et al. examined the effect of 0.05% oral tocotrienols on spontaneous liver carcinogenesis in male mice and on glycerol-induced lung tumor promotion in male mice initiated with 4-nitroquinolone 1-oxide [82]. Incidence of liver and lung tumors was almost 80% lower in treated animals than in untreated animals.

Tocotrienols have been shown to prevent chemical-induced carcinogenesis of the liver [107] and found to suppress 2-acetylaminofluorene (AAF)-induced hepatocarcinogenesis [108]. In another study, Rahmat et al. [109] examined the effect of long-term administration of tocotrienols on hepatocarcinogenesis in rats. Liver carcinogenesis was induced by diethylnitrosamine and AAF in rats fed a diet containing 30 mg/kg tocotrienols for 9 months. Expression of biomarkers of liver carcinogenesis such as glutathione, alkaline phosphatase, and gamma-glutamyl transpeptidase was enhanced by the carcinogens but attenuated by tocotrienols, decreasing the impact of the carcinogens. A similar study by others confirmed these findings [110]. All these studies suggest that tocotrienols have potential to both prevent and treat cancer.

Table 2
In vitro studies with tocotrienols for effects against cancer, cardiovascular and neurodegenerative diseases.

Anticancer effect	
Breast cancer	
Inhibited estrogen receptor-negative and -positive cell proliferation	[73,74]
Inhibited growth of cells irrespective of estrogen receptor status	[75]
Induced cell death by DNA fragmentation	[13,70,75,225]
Suppressed preneoplastic mammary epithelial cell proliferation	[77]
Induced apoptosis through caspase pathway	[76]
Induced apoptosis through mitochondria-mediated death pathway	[43]
Induced apoptosis through TGF- β -Fas-JNK-signaling pathways	[25]
Inhibited cell proliferation and induced apoptosis in neoplastic mammary cells	[29,38,42,78]
Exhibited synergism with statin in suppressing proliferation of tumor cells	[226]
Exhibited synergism with phytochemicals in suppressing proliferation of tumor cells	[20]
Exhibited synergism with celecoxib in suppressing proliferation of tumor cells	[52]
Exhibited synergism with erlotinib/gefitinib in suppressing tumor cell proliferation	[59]
Inhibited proliferation by arresting cell-cycle progression	[29,30,72]
Inhibited tumor cell growth by suppressing HMGR activity	[71]
Induced apoptosis in tumor cells through endoplasmic reticulum stress	[72]
Inhibited proliferation through downregulation of Id1 protein	[224]
Reduced cell viability and induced apoptosis via the mitochondrial pathway	[26]
Inhibited colony formation through death receptor-5 and CHOP upregulation	[33]
Colon	
Inhibited growth and colony formation through DNA fragmentation	[28]
Induced apoptosis and inhibited cell proliferation through cell-cycle arrest	[41]
Showed synergistic inhibition of cancer cell growth	[79]
Liver	
Reduced cell viability and proliferation through DNA fragmentation	[80,81]
Exerted antiproliferative effect by inducing S phase arrest	[80–82]
Induced Bax and Bid regulated apoptosis	[40]
Lungs	
Induced apoptosis on accumulation of cells in G1 phase through mutation of ras genes	[85]
Suppressed survival and invasion capacity of the tumor cells	[83]
Enhanced cisplatin-induced cytotoxicity in mesothelioma cells	[84]
Stomach	
Induced apoptosis through downregulation of the Raf-ERK signaling pathway	[32]
Inhibited cell migration and invasion through downregulation of matrix metalloproteinase	[51]
Induced apoptosis via mitochondria-dependent apoptosis pathway	[44]
Skin	
Inhibited cell proliferation and potentiated lovastatin-mediated growth suppression	[87]
Induced apoptosis by activating procaspases and accumulating sub-G1 cell population	[86]
Pancreas	
Induced apoptosis and cycle arrest at G1 phase	[88]
Prostate	
Inhibited cell growth	[90]
Inhibited cellular proliferation and accelerated apoptotic events	[46]
Suppressed cell proliferation and invasion through multiple-signaling pathways	[91]
Activated caspase-dependent programmed cell death	[89]
Others	
Inhibited growth of human and mouse tumor cells	[100]
Inhibited tumor promotion in human lymphoblastoid cells	[106]
Inhibited both proliferation and tube formation and minimized tumor angiogenesis	[184,191]
Inhibited angiogenesis and telomerase activity	[44]
Inhibited pol lambda activity and angiogenesis	[216]
Cardiovascular diseases	
Inhibited surface cell expression and adhesion	[91]
Inhibited cholesterol biosynthesis	[60,61,82,89,90]
Neurodegenerative disorders	
Inhibited glutamate-induced death of HT4 neuronal cells	[55]
Inhibited H ₂ O ₂ -induced neuronal death and oxidative stress-mediated cell death	[217]
Attenuated homocysteic acid-induced neurotoxicity	[92]
Prevents oxidative stress stimulated cell death of cortical neurons cells	[218]
Protected methylmercury-induced neuronal cell death	[188]

CHOP, C/EBP homologous protein; ERK, extracellular signal-regulated kinase; HMGR, 3-hydroxy-3-methyl-glutaryl coenzyme A reductase; Id1, inhibitor of differentiation; JNK, c-Jun N-terminal kinase; TGF, transforming growth factor.

4.2. Cardioprotective effects

Persistent hypertension is one of the risk factors for strokes, heart attacks, and heart failure and is a leading cause of chronic renal failure. Most of the cardioprotective effects of tocotrienols are mediated through their ability to inhibit a rate-limiting enzyme in cholesterol biosynthesis and their antioxidant and anti-inflammatory activities. In one study, tocotrienols significantly depressed age-related increases in systolic blood pressure of spontaneously hypertensive rats, and the investigators concluded

that the tocotrienols' effects were more pronounced than those of α -tocopherol [111]. TRF from palm oil can reduce total cholesterol and LDL-cholesterol levels through downmodulation of hepatic HMG-CoA reductase activity [65]. Whether rice bran oil with its high content of γ -oryzanol and γ -tocotrienol has the same effect has been investigated in rats [112]. A rice bran oil diet lowered plasma triglyceride, LDL-cholesterol and hepatic triglyceride concentrations and increased hepatic cholesterol 7- α -hydroxylase, hepatic LDL receptor, and HMG-CoA reductase mRNA in rats. The γ -oryzanol and γ -tocotrienol in rice bran oil can lead to

Table 3

A list of animal studies with tocotrienols for pharmacokinetics and for effects against cancer, cardiovascular, diabetes, neurodegenerative diseases, bone metabolism and other diseases.

Pharmacokinetics	
Increased LLU-alpha concentration by oral administration in rats	[144]
Selective uptake of T3 into the rat skin	[147]
Distribution and bioavailability of α -, γ -T3 in rats elevated by sesame	[148]
Distribution and metabolism in adipose tissues and skin of rats	[148]
NOAEL of toxicity by T3 in rats	[149]
Stimulated sodium excretion <i>in vivo</i> in rats	[227]
Bioavailability (delivered by <i>ip</i> and <i>im</i> than oral) in rats	[155]
Effective distribution of T3 homologues to rat eye tissues	[152]
Preferential absorption of α -T3 than γ - and δ -T3	[146]
Postprandial levels of the natural vitamin E-T3 in human circulation	[150]
Tissue distribution and accumulation in adipose tissue	[145]
Fast intestinal uptake of γ -T3	[154]
More extensive metabolism of γ -T3 than γ -TP in rats	[143]
Bioavailability of δ -T3 is longer in pancreas with no toxicity	[141]
Anticancer effects	
Inhibited mammary carcinogenesis in female rats	[9]
Effective against sarcoma, Ehrlich and IMC carcinoma	[100]
Reduced the severity of AAF-induced hepatocarcinogenesis in rats	[108]
Attenuated DEN and AAF-induced hepatocarcinogenesis in rats	[101,103]
Reduced AAF-induced increase in enzyme activities in rats	[110]
Inhibited tumor promotion	[106]
Suppressed the growth of B16 melanoma in mice	[95]
Inhibited chemical-induced cancer in rats	[195]
Suppressed DMBA-induced mammary tumors and hypercholesterolemia	[59]
Inhibited TPA-induced skin carcinogenesis	[228]
Delayed the onset, incidence and size of human breast cancer in nude mice	[229]
Suppressed liver and lung carcinogenesis in mice	[76]
Radio sensitized human prostate tumors in nude mice	[104]
Potentiated lovastatin-induced growth suppression	[81]
Reduced UVB-induced sunburn and incidence of tumor in hairless mice	[230]
Delayed tumor growth in mice hepatoma	[102]
Suppressed tumor growth via angiogenesis	[23]
Chemosensitizer in hormone refractory prostate cancer	[231]
Anti-angiogenesis	
Suppressed neovascularization in tumor cell-implanted mice	[103]
Anti-angiogenic effect in BALB/c mice model, reduced VEGF	[23]
Cardiovascular disorders	
Depressed the age-related increase in blood pressure of SHR	[111]
Decreased levels of MDA and preserved continuity of IEL in rabbit aorta	[114]
Reduction in atherosclerotic lesion size by <i>d</i> -P ₂₅ -T3 in mice	[19,232,233]
Increased nitric oxide activity and reduced the blood pressure in rats	[19,233]
Activated NO-cGMP pathway and reduced ischemia/reperfusion myocardial injury in rats	[117]
Reduced myocardial infarct size in rats	[115]
Reduced autophagy during MI by elevating Beclin, LC3-II and mTOR signaling in rats	[119]
Diabetes mellitus	
Prevented increase in AGE in streptozotocin-induced diabetic rats	[120]
Protected against oxidative damage in diabetic KKAY mice	[124]
Reduced the antioxidant biomarker level in mice	[125]
Reduced serum creatinine level, creatinine clearance, U albumin and protein excretion in ODS rats	[234]
Modulated streptozotocin-induced inflammation in diabetic rats	[53]
Modulated diabetes-induced cognitive impairment	[122]
Lowered the blood glucose level and improved dyslipidemia in diabetic rats	[121]
Improved insulin sensitivity in mice through activation of PPARs	[126]
Neurodegenerative diseases	
Inhibited glutamate-induced pp60(c-Src) kinase activation and death of HT4 cells	[61]
Expressed T3 sensitive genes in the developing rat fetal brain	[132]
Modulated 12-lipoxygenase, a key mediator of glutamate-induced neurodegeneration	[17]
Prevented cerebral infarction induced by MCA occlusion	[133]
Protected against glutamate- and stroke-induced neurodegeneration	[98,131]
Inhibited c-Src activity leading to prevention of glutamate-induced neurodegeneration	[16]
Attenuated oxidative-nitrosative stress and inflammatory cascade in experimental model of diabetic neuropathy	[123]
Prevented intracerebroventricular STZ-induced cognitive impairment and oxidative-nitrosative stress	[127]
Ameliorated behavioral and biochemical alterations in the rat model of alcoholic neuropathy	[128]
Prevented chronic alcohol-induced cognitive dysfunction by suppression of neuroinflammation	[129]
Inhibited glutamate-induced activation of phospholipase A2	[130]
Bone metabolism	
Reduced bone resorption to a greater extent than bone formation in thyrotoxic rats	[235]
Helped in normal bone calcification in female	[138]
Reduced body fat mass and increased bone calcium content in adrenalectomized rats	[139]
Reversed nicotine-induced bone loss in rats	[54,134]
Reversed free radical-induced bone loss in rats	[55]
Exhibited antioxidant activity and prevented imbalance in bone metabolism due to free radicals in rats	[137]
Acted as an anabolic agent for bone in normal male rats	[136]
Improved normal bone structure	[134,135]

Table 3 (Continued)

Lipid metabolism	
Inhibited cholesterol esterase activity in rats	[236]
Reduced lipid peroxidation and enhanced superoxide dismutase activity in SHR	[19]
Inhibited HMGCR, increased HDL, lowered LDL and TC in pigs	[237]
Improved the lipid profile, lowered TG and increased HDL-c in rats	[238]
Enhanced cholesterol catabolism by increasing LDL-R and HMG-CoA level in rat liver	[112]
Increased fecal excretion of neutral sterol and bile acids in rats	[113]
Suppressed Akt phosphorylation in 3T3-L1 preadipocytes in rats	[216]
Others	
Enhanced proliferation and function of spleen and MLN lymphocytes	[140]
Prevented aspirin-induced gastric lesion	[142]
Blocked stress-induced changes in the gastric acidity and gastrin level in rats	[141]
Maintained renal morphology against iron induced renal dysfunction	[239]

AAF, 2-acetylaminofluorene; AGE, advanced glycosylation end-products; d-P25-T3, didesmethyl tocotrienol; DEN, diethyl nitrosamine; DMBA, 7,12-dimethylbenz[α]anthracene; HDL, high-density lipoprotein; HDL-c, HDL cholesterol; HMG-CoA, 3-hydroxy-3-methyl-glutaryl coenzyme A reductase; HMGCR, HMG-CoA reductase; IEL, internal elastic lamina; LDL, low-density lipoprotein; LDL-R, LDL receptor; LLU-alpha, 2,7,8-trimethyl-2-(beta-carboxyethyl)-6-hydroxy chroman; LP, lipid profile; MCA, middle cerebral artery; MDA, malondialdehyde; MI, myocardial infarct; MLN, mesenteric lymph node; m-TOR, mammalian target of rapamycin; NF- κ B, nuclear factor-kappa B; NOAEL, No-observed-adverse-effect level; NO-cGMP, nitric oxide-cyclic GMP; ODS, osteogenic disorder shionogi; PPAR, peroxisome proliferator-activated receptors; SHR, spontaneously hypertensive rats; STZ, streptozotocin; TC, total cholesterol; TG, triglyceride; TPA, 12-O-Tetradecanoyl-phorbol-13-acetate; VEGF, vascular endothelial growth factor.

increased neutral sterol and bile acid excretion in feces via upregulation of cholesterol synthesis and catabolism. Chou et al. observed that rice bran oil improved lipid abnormalities, reduced the atherogenic index and suppressed the hyperinsulinemic response in rats with streptozotocin/nicotinamide-induced type 2 diabetes mellitus [113].

In atherosclerosis, build-up of fatty materials such as cholesterol leads to artery wall thickening. Nafeeza et al. investigated the effect of TRF on the microscopic development of atherosclerosis and lipid peroxidation in the aortas of rabbits. After 10 weeks of treatment with TRF, cholesterol-fed rabbits had lower aortic contents of malondialdehyde, less intimal thickening and greater preservation of the internal elastic lamina than untreated rabbits [114]. Because TRF lowered lipid peroxidation, which in turn reduces intimal thickening and preserves the internal elastic lamina, they concluded that the antioxidant activities of TRF could reduce experimental atherosclerosis.

TRF and isomers of tocotrienols can improve postischemic ventricular function and reduce myocardial infarct size. They exert this cardioprotective effect through downmodulation of c-Src and upregulation of phosphorylation of Akt, thus generating a survival signal [115]. A 6-week treatment of diet supplemented with either d-P(21)-T3, d-P(25)-T3, γ -T3, or TRF showed significant effects on lipid metabolism in swine expressing hereditary hypercholesterolemia [116]. Levels of serum total cholesterol, LDL-cholesterol, apolipoprotein B, platelet factor 4, thromboxane B(2), glucose, triglycerides, and glucagon were reduced in all of the treatment groups relative to the control. The hepatic HMG-CoA reductase activity was lower, and cholesterol and fatty acid levels in various tissues were lower in all of the treatment groups.

Activation of the nitric oxide-cGMP pathway is associated with myocardial protection against ischemia; in ischemia, the function of this pathway is disturbed. Esterhuysen et al. investigated the effects of red palm oil on the myocardial nitric oxide-cGMP signaling pathway [117]. Treatment with red palm oil increased aortic output and increased levels of cGMP and polyunsaturated fatty acid in rat hearts. Their findings suggest that dietary red palm oil protects via the nitric oxide-cGMP pathway and/or changes in polyunsaturated fatty acid composition during ischemia/reperfusion. As red palm oil contains both tocopherols and tocotrienols, it is unclear which of these constituents exerted the cardioprotective effect. Newaz et al. determined the effects of γ -tocotrienol on lipid peroxidation and total antioxidant status of spontaneously hypertensive rats. Their study showed that a 3-month antioxidant trial with γ -tocotrienol reduced blood and plasma concentrations of lipid peroxides and improved total antioxidant status and

superoxide dismutase activity [19]. The investigators concluded that antioxidant supplementation with γ -tocotrienol may prevent development of increased blood pressure, reduce lipid peroxides in plasma and blood vessels and enhance total antioxidant status, including superoxide dismutase activity.

Myocardial ischemic injury results from severe impairment of coronary blood supply and produces a spectrum of clinical syndromes. Although all of the tocotrienol isomers have cardioprotective properties against myocardial ischemic injury, γ -tocotrienol was the most protective. The differential interaction of MAPK with caveolin 1/3 in conjunction with proteasome stabilization plays a unique role in tocotrienol-mediated cardioprotection, possibly by altering the availability of pro-survival and anti-survival proteins [118].

In a study of the cardioprotective properties of γ -tocotrienol in combination with resveratrol, the two agents acted synergistically, providing a greater degree of cardioprotection than either alone [119]. The basis of this effect is their ability to induce autophagy accompanied by activation of Beclin and LC3-II as well as mTOR signaling while simultaneously generating a greater amount of survival signal through activation of the Akt-Bcl-2 survival pathway.

4.3. Effects against diabetes mellitus

In diabetes the blood glucose level is persistently high because of insufficient insulin production or insulin resistance. TRF prevented increases in serum levels of advanced glycosylation end-products (AGE) in normal rats and decreased blood glucose and glycated hemoglobin levels in diabetic rats [120]. In a similar study, TRF treatment not only reduced serum glucose and glycated hemoglobin concentrations, it also reduced plasma total cholesterol, LDL-cholesterol and triglyceride levels and increased levels of high-density lipoprotein (HDL)-cholesterol, as compared to the untreated group [121]. Tocotrienols exert these effects through increasing superoxide dismutase activity and levels of vitamin C in plasma and decreasing levels of plasma and aorta malondialdehyde and 4-hydroxynonenal and oxidative DNA damage. Thus TRF lowers blood glucose level and oxidative stress markers, improves dyslipidemia, and maintains vessel wall integrity. A combination of insulin and tocotrienol treatment attenuated the diabetic condition and reversed neuropathic pain through modulation of oxidative-nitrosative stress and release of inflammatory cytokines and caspase-3 in diabetic rats [122,123]. In another study, suppression of the NF- κ B signaling pathway by tocotrienols prevented diabetes-associated cognitive deficits. Rats with streptozotocin-induced diabetes were treated with oral tocotrienols

(25 mg/kg, 50 mg/kg or 100 mg/kg body weight) for 10 weeks, which significantly prevented behavioral, biochemical and molecular changes associated with diabetes, in part through suppression of activation of the NF- κ B signaling pathway [53].

Oxidative stress is considered to be a key factor in the development of diabetes and its complications. Kanaya et al. examined the antioxidative effects of a crude lipophilic rice bran extract, Ricetriol, which contains α -tocopherol, tocotrienols, and phytosterol, in obese diabetic KKAY mice [124]. While Ricetriol did not affect hyperglycemia, body weight, or hyperlipidemia, it did significantly suppress elevation of plasma malondialdehyde and significantly increase glutathione peroxidase (GPx) mRNA expression at the 0.1% concentration; the authors suggested that Ricetriol exerts a protective effect against oxidative damage in diabetes mellitus. Yoshida et al. evaluated the antioxidant properties of natural and synthetic dietary antioxidants by using the biomarker, total hydroxyoctadecadienoic acid (tHODE) [125]. Remarkable increases in tHODE and total 8-iso-prostaglandin F (2 α) (t8-iso-PGF (2 α)) levels were observed in the plasma, erythrocytes, liver and brain of mice that were fed an α -tocopherol-stripped (E-free) diet, whereas levels of these markers were reduced in mice treated with the E-free diet supplemented with a lipophilic antioxidant (0.04% by wt) containing α -tocopherol, α -tocotrienol, and γ -tocopherol.

Fang et al. investigated the mechanism through which tocotrienols reduce blood glucose levels in patients and in preclinical animal models [126]. They proposed that tocotrienols function as peroxisome proliferator-activated receptor (PPAR) modulators. PPARs are ligand-regulated transcription factors that play essential roles in energy metabolism. Synthetic PPAR α and PPAR γ ligands have been used recently in the treatment of hyperlipidemia and diabetes. Both α - and γ -tocotrienol activated PPAR α , while δ -tocotrienol alone activated PPAR α , PPAR γ , and PPAR δ in reporter-based assays. Tocotrienols enhanced the interaction between the purified ligand-binding domain of PPAR α and the receptor-interacting motif of coactivator PPAR γ coactivator-1 α . They also found that TRF improved whole-body glucose utilization and insulin sensitivity of diabetic Db/Db mice by selectively regulating PPAR target genes [118]. All of these results indicate that tocotrienols have antidiabetic potential.

4.4. Neuroprotective effects

Numerous reports indicate that tocotrienols exhibit neuroprotective effects under a wide variety of conditions [53,122,123,127–129]. Chopra and her group noted neuroprotection by tocotrienols in an experimental model of diabetic neuropathy [123], in the rat model of alcoholic neuropathy [128], in chronic alcohol-induced cognitive dysfunction in rats [129], in intracerebroventricular streptozotocin-induced cognitive impairment and oxidative–nitrosative stress in rats [127], in diabetic nephropathy [53], and in diabetes-associated cognitive deficits [122], all through suppression of proinflammatory pathways. Sen and his group have examined extensively the prevention of glutamate-induced neurodegeneration by tocotrienols [16,17,61,98,130–132]. They found that modulation of c-Src, 12-lipoxygenase and PLA2 is involved in the neuroprotective effects of tocotrienols. Khanna et al. showed that a subattomole quantity of α -tocotrienol, but not γ -tocopherol, protected neurons from glutamate challenge. Rats given a α -tocotrienol supplement showed more protection against stroke-induced injury through downregulation of c-Src activation and 12-lipoxygenase phosphorylation at the stroke site [131]. Roy et al. reported that dietary tocotrienols are bioavailable to both mother and fetal brains and that the enrichment is greater in fetal brain tissue. They also identified a specific set of vitamin E-sensitive genes in the developing rat fetal brain using GeneChip microarray

expression profiling. *HO-3*, *LINE-1*, and *ApoB* are some of the vitamin E-sensitive genes affected by vitamin E treatment [132].

A cerebral infarction is an ischemic kind of stroke caused by a disturbance in the blood vessels supplying blood to the brain. α -Tocopherol, α -tocotrienol and γ -tocopherol significantly decreased the size of cerebral infarcts in the mice middle cerebral artery occlusion model, while γ -tocotrienol, δ -tocopherol and δ -tocotrienol showed no effect [133]. Tiwari et al. demonstrated the effectiveness of tocotrienols in attenuation of alcoholic neuropathy [128]. Treatment with α -tocopherol and tocotrienols (mixture of α -, β -, γ -tocotrienol) for 10 weeks significantly improved nociceptive threshold, paw-withdrawal threshold and superoxide dismutase levels and decreased tumor necrosis factor alpha (TNF- α) and IL-1 β levels in male Wistar rats. In another study, they investigated the effect of α -tocopherol and α -tocotrienol against intracerebroventricular streptozotocin-induced cognitive impairment and oxidative–nitrosative stress in rats. Both isoforms effectively attenuated the reductions in glutathione and catalase and reduced the malondialdehyde, nitrite and cholinesterase activity in the brains of these rats, but the effect was more potent with tocotrienols [127].

4.5. Effects on bone metabolism

Tobacco smoking has been identified as a risk factor in the development of osteoporosis, vitamin E supplements reverse nicotine-induced bone loss and stimulate bone formation [134]. Another group has shown that tocotrienols can reverse nicotine-induced bone loss in rats (Table 3) [54]. Bone histomorphometric parameters of adult male rats treated with TRF or γ -tocotrienol but not with γ -tocopherol (60 mg/kg) following nicotine treatment showed significantly higher trabecular thickness and less eroded surface than the control group. Tocotrienols are slightly superior to tocopherols in attenuating the effects of tobacco; γ -tocotrienol especially may have therapeutic potential to repair bone damage caused by chronic smoking. This vitamin is an anabolic agent for bone in normal male rats [134–136].

Other studies have shown that tocotrienols can reverse glucocorticoid-induced or free radical-induced bone loss in adrenalectomized rats [55,135,137] and improve normal bone structure [134,135,138], possibly through its antioxidant activity in bone [137]. Maniam et al. investigated the effects of vitamin E on lipid peroxidation and antioxidant enzyme levels in rat bones [137]. They found that palm-oil tocotrienols at the dose of 100 mg/kg body weight significantly reduced the level of thiobarbituric acid-reactive substance in the femur while significantly increasing glutathione peroxidase activity compared to the control group; these effects were not observed in rats treated with γ -tocopherol. Tocotrienols also showed a protective effect against free radical damage in the rat femur bones. Long-term glucocorticoid treatment is associated with severe side effects, such as obesity and osteoporosis. Ima-Nirwana et al. showed that treatment with γ -tocotrienol (60 mg/kg body weight/day) reduced body fat mass and increased fourth lumbar vertebra bone calcium content in rats, while α -tocopherol was ineffective [139]. Therefore, palm-oil-derived γ -tocotrienol has the potential to be utilized as a prophylactic agent in prevention of the skeletal side effects of long-term glucocorticoid and tobacco use.

4.6. Immunomodulatory effects

Gu et al. demonstrated the immunoregulatory effects of dietary α -tocopherol and mixture of tocotrienols on humoral- and cell-mediated immunity [140]. Their results showed that tocopherols or tocotrienols feeding enhanced expression of interferon- γ , IgA, and IgG, but not IgE, and decreased the proportion

of CD4+ T cells. Interestingly, tocotrienols decreased the expression of TNF- α . These investigators concluded that oral administration of tocopherols and tocotrienols affects the proliferation and function of spleen and mesenteric lymph node lymphocytes.

4.7. Gastroprotective effects

Azlina et al. compared the impacts of tocopherols and tocotrienols on gastric acidity, gastric tissue content of parameters such as malondialdehyde and prostaglandin E2, and serum levels of gastrin and glucagon-like peptide-1 in rats exposed to restraint stress. They found that tocotrienol-treated animals, both stressed and non-stressed, had comparable gastric acidity and gastrin levels [141]. Both tocopherols and tocotrienols had gastroprotective effects against damage by free radicals generated in stress conditions, but only tocotrienols had the ability to block stress-induced changes in gastric acidity and gastrin level. Another group showed that tocotrienols can prevent aspirin-induced gastric lesions through their ability to limit lipid peroxidation [142].

5. Pharmacokinetics of tocotrienol

Numerous studies on the pharmacokinetics, organ and tissue distribution and toxicity of tocopherols and tocotrienols have been carried out [143–155]. Yap et al. determined the pharmacokinetics and bioavailability of α -, γ -, and δ -tocotrienol given via oral, intravenous, intramuscular and intraperitoneal routes in rats. They found that oral absorption of all forms of tocotrienols was incomplete and that absorption of tocotrienols given via the intramuscular or intraperitoneal routes was negligible; they concluded that these routes of administration should be avoided [155]. They also found that α -tocotrienol had greater bioavailability than γ -tocotrienol and δ -tocotrienol. The absolute bioavail-

ability of α -tocotrienol was approximately 28%, while the bioavailability of γ - and δ -tocotrienol were around 9% [155]. Phase I cytochrome p450 3A4 enzyme and P-glycoprotein at the gastrointestinal epithelium are implicated in the oral absorption of tocotrienols. Preferential absorption of α -tocotrienol over γ -tocotrienol and δ -tocotrienol in rats is in agreement with other reports in pigs [156] and lymphatic cannulated rats [146]. These differences may be linked to the number of methyl groups in the chromanol ring, as α -tocotrienol has three, γ -tocotrienol has two, and δ -tocotrienol has one methyl group, and thus they have different lipophilicities.

In another study, following a single oral administration of δ -tocotrienol (100 mg/kg), the peak plasma concentration was $57 \pm 5 \mu\text{mol/l}$, the time required to reach peak plasma concentration was 2 h, and the plasma half-life was 3.5 h. The tocotrienols were cleared from plasma and liver within 24 h, but clearance from the pancreas was delayed [145]. δ -Tocotrienol was 10-fold more concentrated in the pancreas than in the tumor and no toxicity was shown by δ -tocotrienol (100 mg/kg) in mice. Intestinal epithelial cells absorb γ -tocotrienol faster than α -tocopherol. Tocotrienol isomers accumulated rapidly in Caco2 cells treated with micelles of vitamin E isomers consisting of bile salts, lysophospholipids, free fatty acid, and 2-monoacylglycerols and was greater than the accumulations of corresponding tocopherol isomers [154]. This finding shows that the difference in saturation of the side chains of tocopherols and tocotrienols, rather than the difference in their rings, was responsible for the rapid epithelial transport into the Caco2 cell membranes. α -Tocopherol, α -tocotrienol and γ -tocotrienol can all be retained abundantly by the skin of rats and mice, but only α -tocopherol is retained by the liver, kidney, and plasma of these animals [147]. Dietary sesame seeds can elevate absorption and concentrations of α - and γ -tocotrienol in skin and adipose tissue [145]. Kawakami et al. investigated the distribution of tocotrienols in rats and reported that

Table 4
Effects of tocotrienols in human subjects.

Biological effect	References
Pharmacokinetics	
Plasma transport and tissue concentrations of T3 in humans	[159]
α - and γ -T3 are metabolized to carboxyethyl-hydroxychroman derivatives and excreted in human urine	[161]
Pharmacokinetics and bioavailability of α -, γ - and δ -T3 varies under different food status	[160]
Lipolysis and droplet size affects T3 absorption from self-emulsifying formulations	[162]
Postprandial metabolic fate of T3-rich vitamin E differs significantly from that of α -TP	[240]
Daily supplementation of TRF did not induce immunomodulatory changes in healthy human volunteers	[241]
Neoplastic disorders	
T3 concentration of adipose tissue of human breast with cancer	[242]
T3 levels in adipose tissue of benign are higher than that in malignant breast lumps in patients in Malaysia	[243]
Higher prediagnostic serum levels is associated with lower risk of developing prostate cancer	[244]
Cardiovascular and metabolic disorders	
T3 lowers serum cholesterol in hypercholesterolemic humans	[167]
Palmivitee lowered both serum total cholesterol and LDL-cholesterol in humans	[170]
T3 induced decrease in cholesterol in hypercholesterolemic subjects	[165]
T3 attenuates collagen-induced platelet aggregation in patients with hyperlipidemia and carotid stenosis	[171]
T3 modulate cardiovascular diseases risk parameters of hypercholesterolemic humans	[166]
T3 had no effect on serum lipids, lipoproteins, or platelet function in men with mildly elevated serum lipid	[172]
α -Tocotrienyl acetate supplement decreased LDL oxidation in hypercholesterolemic humans	[158]
T3 exhibit synergistic effects with lovastatin on lipid parameters in hypercholesterolemic humans	[116]
T3 mixture does not improve cardiovascular disease risk factors in men and women with hypercholesterolemia	[173]
TRF (100 mg/day) suppressed serum cholesterol by in hypercholesterolemic humans	[3]
T3 is beneficial in prevention and treatment of type 2 diabetic patients with hyperlipidemia	[164]
T3 elevated plasma T3 levels but had no effect on lipid profile in healthy humans	[174]
T3 but not TP reduced fasting serum lipid levels in patients with mild hypercholesterolemia	[163]
T3 with citrus flavonoids decreased serum cholesterol levels in hypercholesterolemic subjects	[169]
T3 (self-emulsifying preparation) improved arterial compliance in 36 healthy male	[168]
Anti-aging effect	
T3 (160 mg \times 8 months) reduced DNA damage in older healthy adults (64)	[179]
T3 improves long-term clinical outlook and survival in patients with neurodegenerative familial dysautonomia	[178]
Skin disease	
Topical α -T3 supplementation inhibited lipid peroxidation after benzoyl peroxide treatment of human skin	[180]

T3, tocotrienols; TP, tocopherols; TRF, tocotrienol-rich fraction; LDL, low-density lipoprotein.

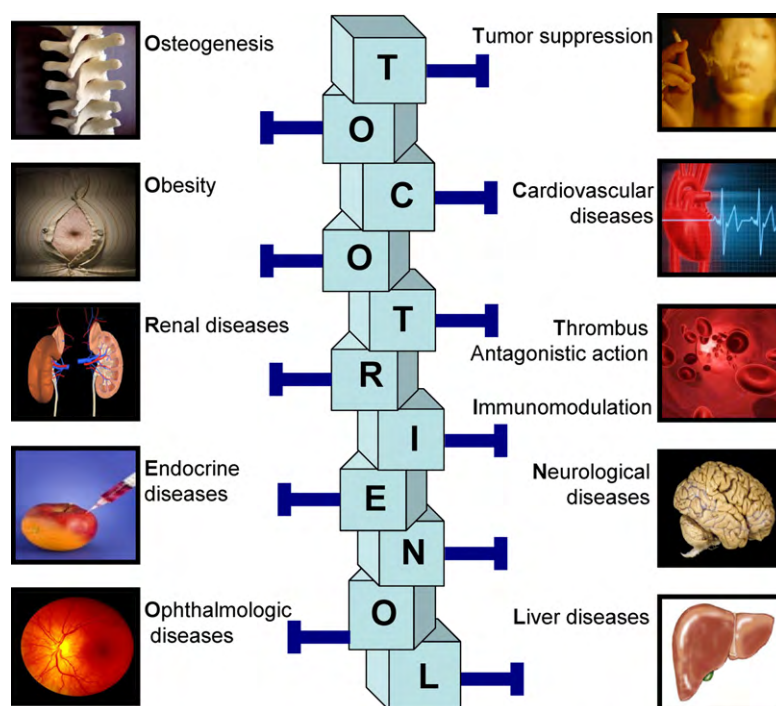


Fig. 4. Physiological functions of tocotrienols.

γ -tocotrienol was significantly distributed to the adipose tissue and that the adipose tissue concentration increased from 1.1 nmol/g to 10.2 nmol/g according to rice bran tocotrienols intake [149].

Nakamura et al. examined the 13-week oral toxicity of a tocotrienol preparation in rats and found that the no-observed-adverse-effect level of tocotrienols was 0.019% in the diet (i.e., 120 mg/kg body weight/day for male and 130 mg/kg body weight for female rats). A decrease in total cholesterol was observed in males in line with the hypocholesterolemic activity of this vitamin [157].

6. Clinical studies with tocotrienols

Numerous clinical studies have been performed to examine bioavailability and various therapeutic effects of tocotrienols in humans (Table 4 and Fig. 4).

6.1. Pharmacodynamics and pharmacokinetics

In a double-blind placebo-controlled study, the bioavailability of purified α -, γ - or δ -tocotrienol (250 mg/day for 8 weeks) in hypercholesterolemic humans was examined. At the end of the study period, plasma levels of α -tocotrienol, γ -tocotrienol and δ -tocotrienol were 0.8 μ M, 0.54 μ M and 0.09 μ M, respectively [158]. The preferential absorption of α -tocotrienol in humans noted here is in agreement with that noted in rats [146]. Hayes et al. reported that tocotrienols were transported by chylomicrons and disappeared from the plasma during chylomicron clearance [159]. Another study investigated the pharmacokinetics and bioavailability of a single oral dose (300 mg) of α -tocotrienol, γ -tocotrienol and δ -tocotrienol in healthy volunteers ($N=8$) under fed and fasting conditions. Oral bioavailability of all tocotrienol analogues was markedly increased when taken with food, with peak plasma concentrations (1.52–5.87 μ M) occurring between 3 and 5 h after ingestion. The biological half-lives of α -tocotrienol, γ -tocotrienol and δ -tocotrienol were 2.3 h, 4.4 h, and 4.3 h, respectively. The half-life of α -tocopherol is about 20 h; thus the half-lives of the tocotrienols are 4.5- to 8.7-fold shorter [160].

When the tocotrienol analogues were given at the same dose, plasma levels of α -tocotrienol were twice those of γ -tocotrienol and 10 times higher than those of δ -tocotrienol. Another study showed that α - and γ -tocotrienol are metabolized to carboxyethyl-hydroxychroman derivatives and excreted in human urine [161]. When human subjects ($n=6$) consumed 125 mg of tocotrienyl acetate daily for the first week, 500 mg daily for the second week, 125 mg daily for the third week and 500 mg daily for the fourth week, only 1–2% of α -tocotrienol and 4–6% of γ -tocotrienol metabolites was recovered in the urine. To overcome the limited oral bioavailability of tocotrienols, self-emulsifying formulations have been tested in healthy human volunteers with favorable results [162].

6.2. Effects on cardiovascular system

About 50% of persons consuming the typical Western diet will die of coronary heart disease or stroke. Hypercholesterolemia and inflammation of the coronary artery are the major risk factors for development of coronary heart disease. While dietary fat has been associated with coronary heart disease, a diet of predominantly plant foods, such as rice, oats and barley (all of which contain tocotrienols), can retard this disease. While some studies indicate that tocotrienols have cardioprotective properties in humans [2,3,158,163–171], others have failed to show the benefit [172–174].

In the first study ever performed on the effects of tocotrienols in human subjects, 22 healthy volunteers took one capsule daily containing a palm-oil-vitamin E concentrate (palmvitee) that comprised approximately 18 mg tocopherols, 42 mg tocotrienols and 240 mg palm olein for 30 days [170]. The investigators observed decreases in total cholesterol ranging from 5% to 35.9% and in LDL-cholesterol from 0.9% to 37% [170]. These cholesterol-lowering effects were attributed to tocotrienols, as tocopherols has been shown in human subjects to lack these effects [175]. Qureshi et al. performed a double-blind, crossover 8-week study comparing the effect of 200 mg palmvitee/day with that of 300 mg corn oil (which lacks tocotrienols) on the serum lipid

levels of 25 hypercholesterolemic human subjects. The serum cholesterol levels of seven subjects decreased by 31% during the 4-week period of treatment that included tocotrienols, and this effect persisted even 2 weeks after the capsules were discontinued [167]. Later, in another clinical trial, Qureshi et al. administered TRF from rice bran oil in a 12-week double-blind study in 21 hypercholesterolemic subjects. A 12% decrease in total cholesterol and 16% reduction in LDL-cholesterol were noted in subjects given TRF during the 4-week period in which the dose was 200 mg but not in the placebo group given 1.2 g corn oil. Furthermore, a 17% decrease in lipoprotein-a was noted in the treated group, which is remarkable as most cholesterol-lowering drugs do not affect lipoprotein-a [166].

The antioxidant benefit of tocotrienols has been reported in a group of patients with cerebrovascular diseases. Both tocopherols and 240 mg mixed tocotrienols were used in this trial [171]. In another clinical trial, low doses of TRF for 25 weeks were found to exhibit synergistic effects with lovastatin on various lipid parameters in hypercholesterolemic humans [2]. Further studies revealed that the effect of TRF on serum cholesterol levels was dose dependent when administered at 25 mg/day, 50 mg/day, 100 mg/day, or 200 mg/day. The maximum decrease (25%) was seen at the 100 mg/day dose [3].

In contrast to these studies, Mensink et al. showed, in a randomized, double-blind, placebo-controlled trial in 20 mildly hypercholesterolemic men who received 140 mg tocotrienols and 20 mg α -tocopherol for 4 weeks, that this regimen had no effect on serum lipid levels [172]. Whether the negative results were due to the presence of the tocopherols are not clear, but α -tocopherol has been shown to neutralize the HMG-CoA reductase-inhibitory activity of tocotrienols [63]. These results do agree, however, with those of Wahlqvist et al. [176]. In another double-blind, placebo-controlled study, the serum cholesterol-lowering efficacy of purified α -, γ - or δ -tocotrienol (250 mg/day) for 8 weeks in hypercholesterolemic humans was examined. Although at the end of the study period, plasma levels of α -tocotrienol, γ -tocotrienol and δ -tocotrienol were 0.98 μ M, 0.54 μ M and 0.09 μ M, respectively, no change in serum or LDL-cholesterol levels were observed [158]. Alpha-tocotrienol did decrease the oxidizing potential of LDL. Mustad et al. also showed a lack of effect of supplementation of tocotrienols (200 mg/day) on hypercholesterolemia [173].

Another study examined the effects of three doses of tocotrienol-rich vitamin E (TRE) on plasma tocotrienol isomer concentrations, arterial compliance, plasma total antioxidant status, aortic systolic blood pressure, and serum total cholesterol and LDL-cholesterol levels in healthy men. This randomized, blinded endpoint, placebo-controlled clinical trial with a parallel design involved 36 male subjects who took either an oral placebo or TRE at doses of 80 mg, 160 mg, or 320 mg daily for 2 months. Baseline tocotrienol isomer concentrations were low and in some subjects, not detectable. At the end of the study period, all TRE-treated groups showed significant increases in α -, δ - and γ -tocotrienol concentrations from baseline relative to the placebo group. There was a linear dose and blood level relationship for all the isomers. There was no significant difference between groups, however, in pulse wave velocity, arterial compliance, plasma total antioxidant status, aortic systolic blood pressure, or serum levels of total cholesterol or LDL-cholesterol from baseline to end of treatment. Groups receiving 160 mg or 320 mg of TRE showed significant reductions in their aortic systolic blood pressure, and the group receiving 320 mg showed a significant 9.2% improvement in total antioxidant status [174].

The progression of atherosclerosis is more rapid in individuals with type 2 diabetes than in the general population, and 80% of those with type 2 diabetes will die of an atherosclerotic event. Since in these patients hyperglycemia per se confers increased

risk for cardiovascular disease, the presence of even a borderline-high-risk LDL-cholesterol level signals the need for aggressive LDL-lowering therapy. Thus Baliarsingh et al. investigated the therapeutic impacts of tocotrienols on serum and lipoprotein lipid levels in patients with type 2 diabetes in a randomized, double-blind, placebo-controlled design involving 19 subjects with type 2 diabetes and hyperlipidemia. After 60 days of TRF treatment, subjects showed average declines of 23%, 30%, and 42% in serum total lipids, total cholesterol, and LDL-cholesterol, respectively. Tocotrienols mediated a reduction of LDL-cholesterol level from an average of 179 mg/ml to 104 mg/ml. No hypoglycemic effect was observed in these patients because their glucose and glycated hemoglobin levels at baseline were close to normal values [164]. These findings suggest that daily intake of dietary TRF by individuals with type 2 diabetes will be useful in the prevention and treatment of hyperlipidemia and atherogenesis.

6.3. Other uses

Familial dysautonomia, a genetic neurodegenerative disorder affecting primarily individuals of Ashkenazi Jewish descent, is caused by mutations in the *IKBKAP* gene, which encodes the IkappaB kinase complex-associated protein (IKAP). The more common or major mutation causes aberrant splicing, resulting in a truncated form of IKAP. Tissues from individuals homozygous for the major mutation contain both mutant and wild-type IKAP [177] transcripts. The apparent leaky nature of this mutation prompted a search for agents capable of elevating the level of expression of the wild-type IKAP transcript. It has been shown that tocotrienols can increase the transcription of *IKAP* mRNA in familial dysautonomia-derived cells, with corresponding increases in the correctly spliced transcript and normal protein. Because ingestion of tocotrienols elevates IKAP and MAO-A in familial dysautonomia patients, Rubin et al. examined their impact on the frequency of hypertensive crises and cardiac function in individuals with this disorder. After 3–4 months of tocotrienol ingestion, approximately 80% of patients reported a significant ($\geq 50\%$) decrease in the number of crises. In a smaller group of patients, a postexercise increase in heart rate and a decrease in the QT interval were observed [178]. On the basis of these findings, the authors hypothesized that tocotrienol therapy improves the long-term clinical outlook and survival of individuals with familial dysautonomia.

The free radical theory of aging suggests that free radicals are the leading cause of deteriorating physiologic function during senescence. Free radicals attack cellular structures or molecules such as DNA, resulting in various modifications to the DNA. Accumulation of unrepaired DNA contributes to a variety of disorders associated with the aging process. Chin and his coworkers performed a randomized, double-blinded, placebo-controlled study to evaluate the effect of Tri E tocotrienol on DNA damage. Sixty-four subjects aged 37–78 years completed the study. A daily dose of 160 mg of Tri E tocotrienol was given for 6 months. Blood samples were analyzed for DNA damage using the comet assay, frequency of sister chromatid exchange, and chromosome 4 aberrations. Results showed that this treatment significantly reduced DNA damage as measured by comet assay after 3 months and that DNA damage remained low at 6 months. The frequency of sister chromatid exchange was also reduced after 6 months of supplementation, most markedly in the subjects older than 50 years, while urinary levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG) were significantly reduced. A strong positive correlation was observed between sister chromatid exchange with age, whereas weak positive correlations were observed in DNA damage and 8-OHdG, which were reduced with supplementation [179]. However, no translocation or stable insertion was observed in chromosome 4. Thus Tri E tocotrienol

Table 5

Tocotrienols are more potent than tocopherols.

	References
In vitro studies	
T3 is more potent than TP in reducing gamma-glutamyl transpeptidase and glutathione S-transferase	[212]
T3 is more potent than TP in inducing apoptosis of tumor cells	[94]
T3s are more potent than TP in inhibiting growth and inducing apoptosis of mouse mammary epithelial cells	[70]
T3s preferentially accumulate than TP in mouse mammary epithelial cells	[70]
T3s are more effective than TP in preventing glutamate-induced neuronal cell death	[61]
T3s, but not TP, inhibited both the proliferation and tube formation of bovine aortic endothelial cells	[188]
T3s are more readily transferred and incorporated into the membranes than TP	[183]
T3 had greater peroxy radical scavenging activity than TP in liposomal membrane	[182]
T3, not TP inhibited human endothelial cell proliferation and suppressed tumor-induced angiogenesis	[189,195]
T3, not TP reduced VEGF-stimulated tube formation in HUVEC	[49]
T3 protects astrocytes better than TP from H ₂ O ₂ -induced-cell loss and apoptosis	[191]
T3 is more effective than TP in protecting against glutamate-induced cell death in HT4 neuron cell	[61]
T3s are more potent than TP in protecting cerebellar granule cells against methyl mercury toxicity	[192]
Accumulation and secretion rate of T3 isomers in Caco2 cells is faster than TP isomers; oral administration caused faster appearance and disappearance of T3 than TP	[154]
T3 is more effective than TP in suppressing LPS-induced IL-6, PGE2 production from macrophages	[193]
In vivo studies	
T3 were more effective in inhibiting the growth of sarcoma 180, Ehrlich carcinoma, and IMC carcinoma than TP	[100]
T3 showed significant increase in DMBA-induced tumor latency than TP	[105]
T3 showed 40–60 times higher antioxidant activity against induced lipid peroxidation and 6.5 times better protection of cytochrome P-450 against oxidative damage than TP	[181]
Reduction of linoleic acid desaturation was more clear with T3 than with TP	[111]
No T3 in plasma but platelet concentration of δ-T3 doubled; TP was found in LDL and HDL in human; T3 deposited in adipose tissue while TP was detected in all tissue except adipose in hamster	[159]
Lymphatic transport and recovery of T3 was twice higher than that of TP in thoracic duct-cannulated rats	[146]
T3 feeding (0.2% in diet) gave higher CD4+/CD8+ ratio than TP in mesenteric lymph node lymphocytes	[140]
T3 exerted stronger antioxidant activity than TP <i>in vivo</i>	[140]
T3 (60 mg/kg body weight/day) was more effective than TP in reducing body fat mass and preventing steroid-induced osteoporosis	[139]
Concentration of T3 increased markedly in eye tissue than TP	[152]
T3 but not α-TP reduced the serum levels of IL-1 and IL-6 in rats	[55]
T3 (60 mg/kg body weight) was better than TP in protecting bone resorption caused by free-radicals	[55]
T3 has the ability to block the stress-induced changes in the gastric acidity and gastrin level than TP	[141]
T3 are detected in postprandial (fasted) human plasma earlier than TP but at significantly lower level than TP	[240]
T3 is a better antioxidant than TP in a deep fat frying system	[198]
Total cholesterol and LDL-C levels declined in T3 group but not in those on TP	[163]
T3 is superior than TP in suppressing nicotine-induced loss of calcium from bone	[54]
T3 but not TP reduced the levels of lipid peroxidation and increased GPO activity in the femur of rats	[137]
T3, but not TP can maintain the noradrenalin level and prevent gastric lesions in rats exposed to stress	[245]
T3 is more extensively than TP metabolized to sulfated CEHC form	[143]
T3 was superior than TP, in reversing nicotine-induced bone loss in rats	[134]
T3 has better effects than TP on static and dynamic bone histomorphometric parameters	[135]
T3 is better than TP as an anabolic agent for bone in normal male rats	[136]

CEHC, 2-(beta-carboxyethyl)-6-hydroxychromon; DMBA, 7,12-dimethylbenz(α)anthracene; GPO, glutathione peroxidase; HDL, high-density lipoprotein; HUVEC-human umbilical vein endothelial cells; IL, interleukins; LDL, low-density lipoprotein; LPS, lipopolysaccharide; PGE2, prostaglandin-2; T3, tocotrienols; TP, tocopherols; VEGF-vascular endothelial growth factor.

supplementation may be beneficial by reducing free radical damage as indicated by reductions in DNA damage, sister chromatid exchange frequency and urinary 8-OHdG level. Topical application of α-tocotrienol has been shown to prevent benzyl peroxide-induced lipid peroxidation of human skin [180].

7. Tocotrienols vs. tocopherols

Tocotrienols differ from tocopherols in that the former contain three double bonds in their isoprenoid side chain while the latter do not; this may account for the differences in their efficacy and potency *in vitro* and *in vivo* (Table 5) [61,133,181–183]. While over 30,000 papers have been published on tocopherols, fewer than 600 exist on tocotrienols, most published within the last 5 years. Tocopherols are present mainly in corn, wheat and soybeans, whereas tocotrienols occur mainly in barley, oats, palm, and rice bran. Although tocopherols and tocotrienols are structurally very similar and both are metabolized through similar mechanisms involving initial ω-hydroxylation followed by five cycles of β-oxidation [184], tocotrienols have been found to exhibit superior antioxidant activity [96,181,185]. McIntyre et al. showed that tocotrienols were several-fold more effective than tocopherols in inhibiting the proliferation of mouse mammary tumor epithelial

cells and in inducing apoptosis [70]. Almost millimolar doses of tocopherols were required for antiproliferative effects [186]. The authors showed that these differences could be linked to preferential accumulation of tocotrienols as compared to tocopherols. These differences may also be due to α-tocopherol transfer protein, which binds to α-tocopherol with higher affinity than to tocotrienols [187]. When their respective effects on proliferation of bovine endothelial cells, a marker of angiogenesis, were measured, only tocotrienols (not tocopherols) inhibited this proliferation [188]. Another study showed that oral administration of tocotrienols but not tocopherols blocked tumor-induced angiogenesis. These investigators showed that tocotrienols down-regulated VEGF receptor expression in HUVEC cells and blocked VEGF signaling [189].

Suarna et al. reported that when rats or humans were treated with tocotrienols and tocopherols, tocotrienols provided oxidative protection but tocopherols did not [190]. α-Tocopherol has been reported to attenuate the inhibitory effects of tocotrienols on HMG-CoA activity [63]. Tocotrienols have been shown to be converted to tocopherols *in vivo* [2]. High concentrations of γ-tocotrienol but not α-tocopherol were cytotoxic to astrocytes. This difference was attributed to the greater prooxidant activity of tocotrienols at high concentrations. At low concentrations,

Table 6
Comparative effects of various tocotrienol isomers.

Activity	References
γ -T3 is 30 \times more active than α -T3 or δ -T3 in inhibiting cholesterol biosynthesis in HepG2 cells	[67,96]
γ -T3 is more active than α -T3, and δ -T3 in oxidation of lipids and protein in brain mitochondria	[246]
α -T3 exhibits faster lymphatic transport and higher absorption in rats than γ T3 and δ -T3	[146]
γ -T3 is more active than α -T3, and δ -T3 in oxidation of lipids and protein in liver microsomes	[93]
γ -T3 and δ -T3 but not α -T3 inhibit growth of both ER+ and ER– breast cancer cells	[75]
δ -T3 are more potent than other T3s in promoting apoptosis of breast cancer cells	[94]
α -T3 was more active than γ -T3 or δ -T3 in preventing LDL oxidation in hypercholesterolemic humans	[158]
γ -T3 is more active than α -T3 or δ -T3 in lowering total cholesterol in high fat diet fed hamsters	[247]
γ -T3 was more active than α -T3 or δ -T3 in inducing PXR-mediated gene expression	[215]
α -T3 but not γ -T3 or δ -T3 can prevent cerebral infarction in mice	[133]
α -T3 is more potent than other T3 as antioxidant and as a prooxidant	[183]
α -T3, but not γ -T3 or δ -T3 exhibit neuroprotective action in rat striatal neuron cells	[248]
δ -T3 is more active than $\beta > \gamma > \alpha$ -T3 in inhibiting proliferation and tube formation of bovine aortic endothelial cells	[189]
δ -T3 is more potent than other isomers in inhibiting VEGF-stimulated tube formation by HUVEC	[49]
δ -T3 is more active than α -T3, β -T3 or γ -T3 in suppression of adhesion of monocytes to endothelial cells via VCAM-1	[95]
	[208]
δ -T3 is more active than other T3 in suppression of tumors <i>in vitro</i> and <i>in vivo</i>	[82]
γ -T3 is better than α -T3 as an anti-oxidant	[198]
γ -T3 was more cardioprotective than α -T3 or δ -T3 but δ -T3 was most active in stabilizing proteasomes	[115,118]
δ -T3 is more active than α -T3 or δ -T3 in inhibiting DNA poly λ and angiogenesis	[210]
δ -T3 is more active than γ -T3 and α -T3 as an antioxidant in rat liver microsomal membranes and cells	[249]
δ -T3 is more active than δ -T3 in stimulating ubiquitination and degradation of HMG-CoA reductase	[250]
δ -T3 was more active than other isomers in induces cell death in AR– and AR+ prostate cancer cell lines	[89]
γ -T3 is more potent than α -T3 or δ -T3 in inhibiting proliferation and inducing apoptosis of HeLa cells	[27]
γ -T3 is better than δ -T3 in promoting bone formation in male rats	[135]

AR, androgen receptor; ER, estrogen receptor; LDL, low-density lipoprotein; HUVEC, human umbilical vein endothelial cells; PXR, pregnane X receptor; T3, tocotrienols; VCAM-1, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

however, tocotrienols were found to be antioxidant and to protect cells from hydrogen peroxide-induced killing [191]. This is consistent with studies showing that tocotrienols are more effective than tocopherols in protecting against glutamate-induced cell death in HT4 neuron cell culture [61]. Whether these differences were due to the differential rates of uptake of tocotrienols and tocopherols by the neuronal cells is controversial [191]. Tocotrienols were many times as potent as tocopherols in protecting cerebellar granule cells against methyl mercury toxicity, an effect that was linked to the difference in the antioxidant potency of the two forms of the vitamin [192]. *In vitro* studies showed that tocotrienols have greater anti-inflammatory activity than tocopherols as measured by lipopolysaccharide-induced production of IL-6 and prostaglandin E2 [193]. Mishima et al. showed that α -tocotrienol and γ -tocotrienol were more effective than α -tocopherol in preventing cerebral infarction *in vivo* in mice [133].

Any number of mechanisms could account for the difference in potency of tocotrienols and tocopherols. First, because of structural differences, tocotrienols may be more uniformly distributed in the lipid bilayer. Second, the chromanol ring of tocotrienols may interact more efficiently with the lipid bilayer than that of tocopherols. Third, tocotrienols may have a higher recycling efficiency [194]. Fourth, cellular uptake of tocotrienols is 70 times higher than that of tocopherols [151]. All of these factors may contribute to tocotrienol's greater efficacy. It has also been shown that tocotrienol isomers are accumulated and secreted at greater rates in Caco2 cells than tocopherol isomers. When administered orally to mice, tocotrienols appeared faster in the plasma but at lower levels than tocopherols [154].

Alpha-tocotrienol mediates some of its effect by inhibiting HMG-CoA reductase activity [66], while α -tocopherol induces HMG-CoA reductase activity [63].

8. Tocotrienol isoforms

The isoforms of tocotrienols, which differ in their number of methyl groups, also differ in their biological activities (Table 6).

While various studies have indicated that α -tocotrienol is highly neuroprotective [61,131], δ - and γ -tocotrienol have been shown to exhibit the greatest anticancer effects. *In vitro* studies suggest that there may be as much as a 30-fold difference in the ability of α , γ , and δ isomers of tocotrienol to inhibit cholesterol biosynthesis [67]. The antioxidant capacity of these three isomers is α -tocotrienol > γ -tocotrienol > δ -tocotrienol [185]. The antioxidant activity of α -tocotrienol is similar to that of α -tocopherol [190]. McIntyre et al. showed that various tocotrienols differ in their potency in inhibiting the proliferation of mouse mammary tumor epithelial cells and in inducing apoptosis [70]. They identified the relative potencies of these three isomers as δ -tocotrienol > γ -tocotrienol > α -tocotrienol. These observations agree with that of Inkouchi et al., who showed that the relative potencies for the suppression of proliferation of bovine and human endothelial cells and tube formation were δ -tocotrienol > β -tocotrienol > γ -tocotrienol = α -tocotrienol [188,189,195]. All these reports point to differences in the mechanisms of action of the tocotrienol isomers.

9. Conclusion

While a lot is known about tocopherols, very little is known about tocotrienols. There is some evidence, however, that tocotrienols may be superior in its biological properties, and that its anti-inflammatory and antioxidant activities could prevent cancer, diabetes, and cardiovascular and neurodegenerative diseases (Fig. 4). Tocotrienols were discovered a half-century ago, but most of their biology has been revealed only in the last decade. More clinical and preclinical studies are needed to fully realize their potential. Disappointment with tocopherols, as indicated by two recent very large randomized controlled clinical trials for prevention of prostate cancer [196], is growing as it fails to meet expectations. These trials showed that there was a statistically nonsignificant increased risks of prostate cancer in vitamin E (α -tocopherol acetate) group. Similar negative results were previously reported with vitamin E when its effect was examined on cancer cardiovascular events [197]. Are tocotrienols, the vitamin E that we should be investigating in the 21st century?

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