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Palm Oil Tocotrienols in Cancer Chemoprevention and Treatment

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Abstract

Cancer remains a worrying cause of fatality worldwide despite the advancement in medicine. Among the dietary phytonutrients, tocotrienols have been extensively studied for their bioactivity against cancer. Palm oil is a rich source of tocotrienols. The most common formulation of tocotrienols is the tocotrienol-rich fraction of palm oil (TRF). The anticancer activities of tocotrienols were once presumed due to their antioxidant and free radical scavenging properties. However, recent evidence suggested that tocotrienols are capable of demonstrating cancer-fighting properties through their influence in various signalling pathways. The selectivity of tocotrienols in killing cancer cells without affecting normal cells is indicative of their potential role in cancer treatment and prevention. Tocotrienols had proven to be particularly effective in the chemoprevention and treatment of breast, colorectal, pancreatic, prostate and liver cancers in many *in vitro* and *in vivo* animal experiments. However, the efficacy of tocotrienols in the management of human cancers are still questionable due to their poor bioavailability and lack of well-designed clinical trials. Nevertheless, due to their superb safety profiles, palm oil tocotrienols are still considered ideal candidates for future large scale clinical trials to prove their efficacy to treat or prevent cancers in humans.

Keywords: Palm oil, vitamin E, tocotrienols, TRF, chemoprevention, antioxidant

1. Introduction

Vitamin E is a fat-soluble antioxidant that comprises two major classes, the tocopherols and the tocotrienols. Structurally, tocotrienols are similar to tocopherols in which both isomers of vitamin E consist of chromanol core ring and polyprenyl side chain. However, the difference lies in the fact that the polyprenyl side chain of tocotrienols has three unsaturated bonds at 3', 7' and 11' positions, which are connected to carbon number 2 of the chiral centre [1] (**Figure 1**). Similar to tocopherols, tocotrienols also have four different isomers, which is determined by the number and position of the methyl groups on the chromanol ring. They are α -tocotrienol, β -tocotrienol, γ -tocotrienol and δ -tocotrienol [2] (**Figure 2**). Tocotrienol discovery was first annotated in 1961 and was described in greater detail in 1964, in which it was identified from the latex of the rubber plant, *Hevea brasiliensis*, in 1964 [3]. Tocotrienols first received critical attention in the early 1980s when it was first reported that they were able to lower cholesterol levels *in vitro* (hepatocytes of chicken and mouse) as well as *in vivo* (animal

Figure 1.
The chemical structure of tocopherols and tocotrienols.

Figure 2.
Chemical structures of the four isoforms of tocotrienols.

experimentation using chicken and mouse). In the early 1990s, the anti-cancer properties of tocotrienols were also reported [3].

The concentrations of tocotrienols in various plants have been well-characterized and described. Palm oil, rice bran, wheat germ oil, coconut oil and annatto seeds have all been ascertained to contain tocotrienols in varying concentrations [4, 5]. Palm oil contains 0.66% α -tocotrienol, 0.019% β -tocotrienol, 0.71% γ -tocotrienol, 0.31% δ -tocotrienol. Rice bran contains 0.43% α -tocotrienol,

0.08% β -tocotrienol, 0.63% γ -tocotrienol, 0.04% δ -tocotrienol. Wheat germ oil 1.94% α -tocotrienol and 0.05% δ -tocotrienol, whereas in coconut oil there is 0.2% α -tocotrienol, 0.04% γ -tocotrienol, 0.76% δ -tocotrienol [6, 7]. In annatto seeds, most of the tocotrienol is δ -tocotrienol with a content ranging from 140 to 147 mg/100 g of dry seed [8]. Tocotrienols are the predominant vitamin E found in palm oil, rice bran and annatto seeds [9]. Out of all the various sources of tocotrienols, palm oil is the most sustainable, most easily available, and one of the richest sources of tocotrienols, i.e., the vitamin E isomer most extensively used in Asian countries as a health supplement. The various vitamin E components found in palm oil include α -tocopherol, α -tocotrienol, γ -tocotrienol, and δ -tocotrienol. The tocotrienol-rich fraction of palm oil (TRF) consists of 23.54% α -tocotrienol, 43.16% γ -tocotrienol, 9.83% δ -tocotrienol, and 23.5% α -tocopherol and is extracted from palm oil post-esterification and following distillation, crystallization, and chromatography processes [6, 7].

As a potent antioxidant, tocotrienols exert a variety of beneficial biological and health effects. Tocotrienols have been shown to have cardioprotective and anti-ageing effects [10]. Studies have also suggested that tocotrienols prevent atherosclerosis and improved blood vessel function in diabetics [10]. In an animal experimental model, the deleterious effects of the strong oxidant ferric nitrilotriacetate on bones were prevented by the administration of tocotrienols [11]. Previous studies had shown that tocotrienols prevented hepatotoxicity due to exposure to harmful chemicals and prevented alterations in the acidity of stomach content due to the increase in gastrin secretion [12, 13]. Tocotrienol, in combination with ascorbic acid, had been shown to increase the levels of neutrophils and lymphocytes, thus strengthening the immunity of the body [14]. In patients with rheumatoid arthritis, tocotrienols administration was associated with a reduction in joint inflammation [15].

Tocotrienols are thought to treat and prevent cancer by suppressing the secretion of angiogenic factors from carcinogenic cells, and by acting as adjuvant drugs to improve the efficacy of existing anticarcinogenic drugs due to their immunomodulating properties [16]. Delta-tocotrienol has specifically been suggested to be a viable alternative treatment for brain and lung malignancies [17]. There have been suggestions that the tocotrienols, either alone or in combination with other bioactive compounds, is beneficial for the prevention and treatment of cancer patients [18, 19]. This review will therefore focus on the role of tocotrienols in cancer chemoprevention and cancer therapeutic management. Many studies have associated the antioxidant properties of vitamin E with the alleviation of carcinogenesis [20–22]. Therefore, this review will also discuss the antioxidative properties of vitamin E (which includes the tocotrienols) in the treatment of cancers. The antioxidant activity associated with vitamin E (tocopherols and tocotrienols) are thought to be the most effective free radical scavengers, which could prevent the generation of reactive oxygen species (ROS) molecules. It has been suggested that tocopherols and tocotrienols prevented living cells from becoming malignant by quashing the attack initiated by free radicals [23, 24]. In addition to their antioxidant properties, the anticancer effects of tocotrienols had also been shown to be related to their interaction with different intracellular signalling pathways. Therefore, this review will also elaborate upon the various pathways affected by tocotrienols in different types of cancer.

2. Antioxidants and free radicals

Antioxidants can exist in either water-soluble or water-insoluble forms. Vitamin C, the prototypical representative of water-soluble antioxidant, can

be found in cellular fluids. Vitamin E, which comprise the tocopherols and tocotrienols, is the typical water-insoluble antioxidant and can mostly be found in cellular membranes [1, 2]. Antioxidants can further be classified as enzymatic or non-enzymatic entities. Interaction between antioxidants and free radicals will result in the inactivation of free radicals damaging effects on our bodies. The human body defence mechanism against the actions of free radicals would usually involve the enzymatic actions of antioxidants which would result in the reduction of lipid peroxidation levels [25].

Free radicals are molecules with one or more unpaired electrons. Free radicals cause damage when they react with other molecules to find electrons to pair with their unpaired electrons. The other molecules then lost their electrons, causing them to become free radicals themselves, thus creating a chemical chain reaction of free radical production [26]. Oxidative and chemical stress in the body due to pollutants, xenobiotics and certain foods can expedite the formation of free radicals [22, 27, 28]. The free radical chain reaction may cause damage to cellular homeostasis due to its potential in causing alterations in the lipid, protein and DNA structure [27]. The damaged molecules may initiate mutation and growth of tumours. Several studies throughout the last few decades have suggested that oxidative stress plays a role in the development of many conditions, including cancer, cardiovascular disease, neurodegenerative disorders and inflammatory diseases such as arthritis [29].

The mitochondria is the chief target of free radical damage due to its preponderance to produce reactive oxygen species (ROS). The metabolic processes occurring within the mitochondria e.g., the electron transport chain may cause leakage of electrons. These electrons may in turn react with water to form ROS such as the superoxide radical, or via an indirect route the hydroxyl radical. These radicals then damage the mitochondria's DNA and proteins, and these damaged components in turn are more liable to produce ROS by-products. Thus a positive feedback loop of oxidative stress is established that, over time, can lead to the deterioration of cells and later organs and the entire body [30].

The most highly reactive free radical species are the hydroxyl radical (OH), hydrogen peroxide (H_2O_2), superoxide anion radical (O_2^-), and peroxynitrite radical ($ONOO^-$) [31–33]. The hydroxyl (OH) radical is the most active oxygen species amongst the others, whereby it could potentially cause serious biological perturbations and peroxidation of lipid-based cellular membranes. Superoxide radical (O_2^-) inflicts severe damage after interaction with various biological cellular components [34]. H_2O_2 toxicity is due to the oxidation of proteins, membrane lipids and DNA by the peroxide ions [35]. Peroxynitrite radical is an oxidant and nitrating agent. Because of its oxidizing properties, peroxynitrite inflicts damage to various cellular components e.g. DNA and proteins. Peroxynitrite formation in the body has been attributed to the reaction of the superoxide free radicals with the nitric oxide free radicals [36, 37].

Lipid peroxidation is the oxidative damage caused by free radicals when they attack the polyunsaturated fatty acids (PUFAs) of the cell membranes. Lipid peroxides or lipid oxidation products are the results of this oxidation process. These fatty acid radicals are unstable molecules that react immediately with molecular oxygen, thus creating a peroxy-fatty acid radical. This radical is also an unstable species and reacts towards other free fatty acids to produce more lipid peroxides, or cyclic peroxides if they reacted with each other. This cycle can linger on continuously as the new fatty acid radical reacts in the same way. Reactive aldehydes such as malondialdehyde (MDA) and 4-hydroxynonenal (HNE) would be the end products of lipid peroxidation, which are potentially mutagenic and carcinogenic. For example, MDA reacts with DNA to create DNA adducts [38–40].

When a free radical reacts with an inert molecule, a new radical molecule is formed, which is why the process is called a “chain reaction mechanism”. The free radical reaction terminates when two radicals react and produce a non-radical species. Certain molecules within the cells can accelerate the termination of lipid peroxidation by neutralizing free radicals, thus protecting the cellular membrane from being damaged. Such molecules are known as antioxidants, of which the vitamin E tocotrienols are important examples [41].

3. Vitamin E as antioxidants and free radical scavengers

The number of methyl groups on the chroman ring influence the antioxidative effects of the various isomers of vitamin E. Delta-tocopherol and alpha-tocopherol each have one and three methyl groups respectively. The alpha isomers of vitamin E are thought to have the highest antioxidant activity, followed by the beta, gamma and delta isomers. It is generally believed that the antioxidative of tocopherol is greater than tocotrienol. However, more recent studies have indicated that tocotrienol has higher antioxidant properties [42, 43].

As a free radical scavenger, vitamin E reacts with ROS indirectly in vitro. As tocopherol has been extensively studied compared to tocotrienol, its pathway during reaction with ROS is well-documented. This reaction will eventually lead to the formation of α -tocopheroxyl radical (α -Toc $\bullet$) [44]. The antioxidative reaction goes on and on, until the final product i.e., lipid peroxide is formed. α -tocopherol is able to deliver hydrogen ion to peroxy radical (LOO $\bullet$) during lipid hydroperoxide formation (LOOH). The α -tocopherol radical formed (α -Toc $\bullet$) will undergo a series of reactions with the peroxy radical (LOO $\bullet$) to eventually produce inert adducts (Figure 3) [45, 46].

Figure 3. Summary of whole antioxidative reaction of vitamin E. The figure was modified from Ref. [46]. The reactions involving tocotrienols are thought to be similar to that of tocopherols. Abbreviations: α -Toc $\bullet$, α -tocopheroxyl radical; α -TocH, α -tocopherol; L $\bullet$, lipid radical; L, low density lipoprotein; LH, unsaturated fatty acid; LO $\bullet$, alkoxy radical; LOO $\bullet$, lipid peroxy radical; LOOH, lipid hydroperoxide.

Vitamin E is also known to react with other radicals as well. The reaction of vitamin E with alkoxy radical produces α -tocopherol radical (α -Toc $\bullet$). A previous report had also stated that the reaction between two α -tocopherol radical (α -Toc $\bullet$) will produce inert non-radical dimers [47]. In terms of inhibition of lipid peroxidation, the alpha isomer of vitamin E has the highest potency, followed by the beta and gamma isomers which are equipotent, and the least potent is the delta isomer [46].

In in vivo situations, a variety of hydrophilic and hydrophobic antioxidant components exists and reacts with various moieties. It has been shown that the hydrophilic antioxidant ascorbic acid is able to reduce α -tocopherol radical (α -Toc $\bullet$) back to α -tocopherol (α -TocH) [48].

The reactions involving tocotrienols are thought to be similar to that of tocopherols. In fact, a previous study had found that consumption of tocotrienol-rich rice bran oil decreased levels of plasma phospholipid hydroperoxide (PLOOH) in rats [49]. It must be remembered however that the supramolecular structures derived from various derivatives are too complex to be simulated by in vitro models to be compared with in vivo conditions [46].

4. Antioxidant effects of tocotrienols

Similar to tocopherol, tocotrienol displays antioxidative effects by acting as a scavenger towards the chain-propagating peroxy radical [50]. Alpha-tocotrienol is more potent as an antioxidant than alpha-tocopherol with regards to the scavenging of peroxy radicals in liposomes [51]. Alpha-tocotrienol is disseminated more evenly in the phospholipid bilayer of the plasma membrane than alpha-tocopherol. Alpha-tocotrienol also collides with radicals in a more efficient manner, thus giving further credential to alpha-tocotrienol as a better antioxidant than alpha-tocopherol [50]. In the phospholipid bilayer of the plasma membrane, the distribution of alpha-tocotrienol is more evenly spread. The collision between free radical species and alpha-tocotrienol was also found to be more efficient. These two reasons contribute to the assumption that alpha-tocotrienol possess a better antioxidative effect compared to alpha-tocopherol [50].

Another study also concluded that alpha-tocotrienol is more potent than alpha-tocopherol, whereby tocotrienols were able to inhibit the free radical activation within monocytes [52]. In this experiment, the generation of free radicals was achieved by injecting rodents with a toxic chemical (ferric nitrilotriacetate) intraperitoneally, in which the rodents were supplemented with alpha-tocotrienol and alpha-tocopherol concurrently throughout the study. It was discovered that alpha-tocotrienol could inhibit free radical activation at a lower dose compared to alpha-tocopherol [52].

It had been suggested that many health benefits of tocotrienols have been linked to their antioxidative activity. A previous study had indicated that tocotrienols were able to decrease the oxidative stress level in subjects with hyperlipidaemia and carotid stenosis [53]. Tocotrienols have been shown to exert antiatherogenic effects through oxidative and non-oxidative pathways [54]. The reduction in DNA damage is brought about by the free radical scavenging activity of tocotrienols. Tocotrienol supplementation might provide benefit to healthy older adults by protecting their DNA from damage [55]. The reduction in DNA damage is postulated to prevent the onset of cancer [3].

5. Anticancer effects of tocotrienols

The results of various studies in cell lines and animals indicated that the damage incurred by free radicals could be prevented by antioxidants. However, the

conclusions derived from observational studies in humans are mixed, due to the diverse difference in human genetics, general health and metabolic capability of our bodies [21]. Many diseases (including cancer) are strongly related to oxidative stress conditions [10]. Oxidative stress has always been associated with the process of carcinogenesis and the adverse effects of cancer management i.e., radiotherapy and chemotherapy [56]. Therefore, it was once postulated that similar to the tocopherols, the major actions of tocotrienols in preventing cancer is through their antioxidant and free radical scavenging activities [45].

Several important signalling pathways are activated by the presence of oxidative stress in the cell. These pathways could facilitate tumour development through deregulation of cellular proliferation, angiogenesis, and metastasis [56]. It was noted, however, that consumption of a diet rich in antioxidants e.g., vitamin E and vitamin C, has been beneficial in preventing cancer [57–60]. A study on the pattern of human food consumption had inferred that the intake of foods rich in antioxidants is correlated with decreased breast cancer incidence within the population [61].

A lot of research has been published since the 1980s on the anticarcinogenic effects of tocotrienols. This has led to an accumulation of numerous works of literature on the anticancer activity of tocotrienols, especially on breast cancer. Apart from breast malignancy, other cancers in which tocotrienols intervention had been postulated to be beneficial are liver, prostate, pancreatic, cervical, colorectal, and skin cancers. From the year 2000 onwards, it had become very clear that the anticancer mechanisms of tocotrienols goes way beyond their antioxidant and free radical scavenging properties. Apart from inhibiting the growth of cancer, tocotrienols are able to initiate apoptosis in cancerous cells. The anticancer effects of tocotrienols are manifested through the inhibition of angiogenesis and tumour cell progression [2, 62]. An isomer of tocotrienols i.e., delta-tocotrienol, was found to inhibit the expansion of cancerous cells and initiated the process of apoptosis significantly in an in vitro study using human colon cancer cell lines [63]. Using animal models, delta-tocotrienol was shown to reduce the incidence of colon cancer and initiated apoptosis in rats [63]. Delta-tocotrienol was able to halt the rate of proliferation of cancerous pancreatic cells without affecting normal pancreatic cells [63]. The growth of colorectal cancer cells was found to be prevented by administering tocotrienols supplementation to mice [63]. Studies using cancerous stem cells indicated that melanoma can be treated and prevented with delta-tocotrienol [64].

6. Mechanism of action of tocotrienols in cancer prevention and treatment

Tocotrienols possess several mechanisms which are deemed to be anticarcinogenic i.e., including anti-inflammatory, anti-proliferative, anti-survival, anti-angiogenic properties. These properties are mediated through the regulation of several signalling pathways which influence the process of carcinogenesis [24].

Tocotrienols affect anti-inflammatory activities by repressing COX-2, hypoxia-inducible factor-1 (HIF-1), inducible nitric oxide synthase (iNOS), prostaglandin E2 (PGE2), and interleukin (IL)-1, IL-6, and IL-8. There are convincing suggestions that the anticarcinogenic activity of tocotrienols is mediated mainly by the repression of two main transcription factors, NF- κ B and STAT3 [24].

Tocotrienols were found to suppress the tumour necrosis factor-alpha (TNF- α)-induced NF- κ B activation, resulting in the downregulation of its associated gene products which are responsible for the survival of cells, which includes inhibitors of apoptosis proteins (IAP)-1, -2, B-cell lymphoma 2 (Bcl-2), B-cell lymphoma-extra

large (Bcl-xL), cellular FLICE-like inhibitory protein (cFLIP), X-linked inhibitor of apoptosis (XIAP), survivin etc. [65]. The regulators of STAT3 e.g., Src kinase, Janus kinase (JAK) 1 and JAK2 are all inhibited by tocotrienols, which eventually resulted in the downregulation of STAT3. Tocotrienols suppress the growth of cancer cells by means of downregulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase [24], cyclin-dependent kinases (CDK)-2, -4, -6, c-Jun, c-Myc, mitogen-activated protein kinases (MAPK), phosphoinositide 3-kinase (PI3K)/Akt, Wnt/ β -catenin, amongst others [65]. Tocotrienols have also been reported to facilitate the arrest of cellular growth and apoptosis through activation of CDK inhibitors (p21, p27, p53), caspase-3, -8, 9, Bcl-2-associated X (Bax) and enhancing cleavage of Bid, Apaf-1, Fas, etc. [54, 66]. Furthermore, tocotrienols were found to inhibit angiogenesis in cancer through downregulation of angiopoietin-1 fibroblast growth factor (FGF), metalloproteinase-9 (MMP-9), TNF- α , and vascular endothelial growth factor (VEGF) [16, 24, 63].

7. Tocotrienols as chemopreventive and chemotherapeutic agents for various cancers

The anticarcinogenic potential of tocotrienols was first acknowledged in 1985, in which the α -tocotrienol isomer had been shown to lengthen the age of rats afflicted with tumour [3]. Subsequently, numerous studies have been performed to highlight the postulated anti-cancer properties of tocotrienols in breast, colorectal, liver, lung, pancreas, prostate and stomach carcinomas. The following paragraphs cover the details of various studies performed using tocotrienols concerning cancer chemoprevention and management (**Table 1**).

7.1 Tocotrienols in breast cancer

Tocotrienols were found to possess anti-proliferative and pro-apoptotic activities in breast cancer cells. Tocotrienols had particularly been shown to reduce the levels of cyclin D1 and Cyclin-Dependent Kinases (CDK) 2, 4 and 6 and to enhance the expression of CDK inhibitors [24]. Tocotrienols are also implicated in the suppression of the PI3K/Akt/mTOR and the Ras/Raf/MEK/ERK signalling pathways and to decrease c-Myc levels [70]. Tocotrienols were able to induce intrinsic apoptosis in breast cancer cells, accompanied by cytochrome *c* release, mitochondrial membrane depolarization, caspase activation, DNA fragmentation and poly(ADP-ribose) polymerase cleavage [72, 77]. In breast cancer cells, tocotrienols were also able to trigger the extrinsic apoptotic pathway by activation of caspase-8 [78].

Tocotrienols were also shown to exert potent anticarcinogenic effects in mammary carcinomas through reduction of proliferation by means of downregulation of the HMG-CoA reductase activity and inhibition of cholesterol synthesis, and also through the induction of oxidative stress-related mitochondrial apoptosis [68, 73].

The Human Epidermal Growth Factor Receptor 2 (HER-2) is a receptor tyrosine-protein kinase that induces breast cell proliferation. It is encoded by the *erbB-2* oncogene. Overexpression of this oncogene is found in 30% of all breast tumours, thus representing an important biomarker and target for breast cancer management [118]. A previous study had shown that HER-2 receptors and tocotrienols specifically accumulate in breast cancer cell lipid raft microdomains. Furthermore, it had been discovered that tocotrienols markedly transform the composition of the lipid rafts, with subsequent disruption of their integrity, and the consequent inactivation of the associated HER-2 receptors and the downstream signalling pathways [67].

Types of Cancer	In vitro/ In vivo	Cell line Model	Mechanism of action	Reference
Breast Cancer	In vitro ^c	MDA-MB-231; T-47D; MCF-10A	↓Wnt/β- catenin	[65]
	In vitro ^c	SKBR3; BT474	↓HER2	[67]
	In vitro	MCF-7; T47D; MDA-MB-23	↓HMGR	[68]
	In vitro ^c	MCF-7 and MDA-MB-231	↑ER stress	[69]
	In vitro	+SA; MCF-7	↓c-Myc	[70]
	In vitro ^c	+SA; MCF-7; MDAMB-231	↓Akt/mTOR	[63]
	In vivo ^h	+SA mammary tumor growth in syngeneic mice	↓Akt/mTOR	[71]
	In vitro	MDA-MB-231; MCF-7	↓NF-κB	[72]
	In vitro	—	↓PI3K/Akt	[63]
	In vitro ^d	SKBR3	↓p38; ↓ERK1/2	[73]
	In vitro ^{d,e}	4 T1	↓IL-8; ↓VEGF	[63]
	In vitro ^c	MCF-7;MDA-MB 231	↑ER stress	[63]
	In vitro ^c	MCF-7; MDA-MB-435	↑JNK/CHOP/DR5	[63]
	In vitro ^c	MCF-7	↑NQO2	[24]
	In vitro ^e	MCF-7	↑ER-β	[74]
	In vitro ^c	+SA	↓G1-S progression	[24]
	In vitro ^{a,c,d}	MDA-MB-231; MCF-7	↑NRF2; ↓KEAP1	[24]
	In vitro	MDA-MB-231; MCF-7	↑JNK; ↑p38 MAPK; ↑DR5	[63]
	In vitro ^{d,e}	4 T1	↑IL-24; ↓VEGF; ↓IL-8	[63]
	In vivo	BALB/c mice inoculated with 4T1 ⁱ	↑ IL-24	[63]
	In vitro	MDA-MB-231	↑ER-β	[75]
	In vitro	+SA	↑ER stress	[63]
	In vivo ^e	BALB/c mice inoculated with 4T14T1 ⁱ	↓VEGF	[63]
	In vitro ^c	MCF-7	↓NF-κB	[65]
	In vitro ^c	+SA	↓PI3K/PDK-1/ Akt	[63]
	In vivo	Athymic mice inoculated with MCF-7 ^j	↓c-Myc	[76]
	In vitro ^c	MDA-MB-231	↑Mitochondrial disruption	[77]
	In vitro	+SA	↑Caspase-8	[78]
	In vivo ^e	Sprague–Dawley rats administered with DMBA ^k	↓HMG-CoA	[79]
Colorectal Cancer	In vivo ^c	Athymic mice inoculated with HCT 116 ^j	↓NF-κB	[80]
	In vivo ^e	Balb/c nude mice inoculated with SW620 human colon cancer cell ^j	↓Wnt	[65]

Types of Cancer	In vitro/ In vivo	Cell line Model	Mechanism of action	Reference
	In vitro ^d	DLD-1	↑Caspases; ↓pAkt	[63]
	In vivo ^f	Athymic nude mice inoculated with DLD-1 ^j	↑p21; ↑p27; ↑Caspase-3,-9; ↓pAkt	[63]
	In vitro ^c	SW620	↓Wnt	[65]
	In vitro	SW620	↓Wnt	[65]
	In vitro ^c	HT-29	↓β-catenin/Tcf	[81]
	In vitro ^c	HT-29	↑Bax/ Bcl-2 ratio	[82]
	In vitro ^d	DLD-1	↓HIF-1α	[16]
	In vitro ^d	DLD-1	↓PI3K/PDK/Akt	[83]
	In vivo ^d	Athymic Balb/c nude mice inoculated with DLD-1 ^j	↓PI3K/PDK/Akt	[83]
	In vitro	DLD-1	↓Telomerase activity	[84]
Gastric Cancer	In vitro ^e	RKO	↑p53	[85]
	In vitro	SGC-7901	↓MMP-2; ↓MMP-9	[86]
	In vitro	SGC-7901	↓β-catenin	[87]
	In vitro ^c	SGC-7901	↑Caspase-3,-9	[88]
	In vitro	SGC-7901	↓MAPK	[89]
Lung Cancer	In vitro ^b	A549	↓Caspase-8	[90]
	In vitro	A549; U87MG	↑Caspase-8	[17]
	In vitro ^d	A549; H1650	↓Notch-1	[91]
	In vitro	A549	↓Akt; ↓HIF-2α	[92]
	In vitro ^c	H1299	↓NF-κB	[65]
	In vitro ^g	A549	↓Ras & RhoA prenylation	[93]
Pancreatic Cancer	In vitro ^d	L3.6pl; MIA PaCa-2	↓VEGF; ↓MMP-9	[63]
	In vivo ^d	L3.6pl orthotopic mice ^m	↓MMP-9	[63]
	In vitro ^d	MIA PaCa-2	↑Bax	[94]
	In vivo	LSL-Kras(G12D/+); Pdx-1-Cre ^q mice	↓MEK/ERK; ↓Akt; ↓NF-κB	[95]
	In vitro	Panc-1; MIA PaCa-2; BxPC-3	↓ErbB2	[65]
	In vitro ^c	BxPC-3; MIA PaCa-2; Panc-1	↓NF-κB	[96]
	In vivo	MIA PaCa-2 orthotopic mice ^m	↓NF-κB	[96]
	In vitro ^c	MIA PaCa-2; PC3	↓STAT3	[65]
	In vivo ^c	MIA PaCa-2 orthotopic mice ^m	↓STAT3	[65]
	In vitro	PANC-1; MIA PaCa-2; BxPC-3	↓HMGR	[97]
Prostate Cancer	In vitro	PC3	↓Fyn/HIF-1α	[98]
	In vitro	PC-3; LNCaP	↑DHS; ↑DHC	[99]
	In vivo	LNCaP mice xenograft ^l	↑DHS; ↑DHC	[99]
	In vitro	CHO-7; SRD-15	↓SREBP-2	[100]

Types of Cancer	In vitro/ In vivo	Cell line Model	Mechanism of action	Reference
Liver Cancer	In vitro	PC-3;CRL-1435;LNCaP;CRL-1740	↓TGFβ2	[101]
	In vitro	PC-3; DU145	↓ CD133/CD44	[102]
	In vitro ^d	PCa	↓NF-κB; ↓EGFR	[103]
	In vitro ^e	LNCaP; DU145; PC-3	G0/G1 cell cycle arrest	[104]
	In vitro ^c	HepG2	↑Peroxisdoxidin-4	[105]
	In vivo	HCCLM3_Luc2 ^m	↓Akt/ mTOR	[106]
	In vitro ^c	HepG2;C3A; SNU-38; PLC/PRF5	↓STAT3	[107]
	In vitro	HepG2	↓TG;↓VLDL secretion	[108]
	In vitro	MH134	↑ PARP fragmentation	[109]
	In vivo	MH134 ⁿ	↑ PARP fragmentation	[109]
	In vitro	Hep3B	↑Caspase-8, -9	[110]
	In vitro ^d	HepG2	↑S phase arrest	[111]
	In vivo	4NQO ^o	↑S phase arrest	[111]
	In vivo	DEN & AAF ^p	↓GSH-Px;↓GST; ↓GSSG-Rx	[112]
	In vivo	AAF ^p	↓GGT; ↓UDP-GT	[12]
	In vitro ^d	BLM; A375	↑ER-stress	[113]
Skin cancer	In vivo ^d	A375 xenograft ^l	↑ER-stress	[113]
	In vitro	B16	↑ERK	[114]
	In vitro	B16F10	↑Syntaxin7; ↑Vps16; ↑Vps3; ↑Vps41	[115]
	In vitro ^d	A2058; A375	↑Caspase-3; ↓CDK-4	[116]
	In vitro	C32; G361	↓NF-κB; ↑JNK	[117]

Abbreviations: ↑- Upregulation; ↓- Downregulation; AAF - 2-acetylaminofluorene; Bax - BCL2-Associated X; Bcl-2 - B- cell lymphoma 2; CDK - cyclin-dependent kinase; DEN - Diethylnitrosamine; DHC - Dihydroceramide; DHS - Dihydrosphingosine; DMBA - 7,12 Dimethylbenz(a)anthracene; DR - death-receptor; EGFR - epidermal growth factor receptor; ER - Endoplasmic reticulum; ER-β -Estrogen receptor beta; ErbB- erb-b2 receptor tyrosine kinase; ERK - extracellular signal-regulated kinase; GGT-gamma-glutamyltranspeptidase; GSSG-Rx-glutathione reductase; GSH-Px-glutathione peroxidase; GST- glutathione S-transferase; HER2 - Human epidermal growth factor receptor 2; HIF-Hypoxia- inducible factor; HMGR - HMG-CoA reductase; IL - Interleukin; JNK - Jun amino-terminal kinases; KEAP - Kelch Like ECH Associated Protein; MAPK - Mitogen-activated protein kinases; MMP - Matrix metalloproteinases; mTOR - mechanistic target of rapamycin; NF-κB - nuclear factor kappa-light-chain-enhancer of activated B cells; NQO2-NAD(P)H dehydrogenase quinone 2; pAkt - phosphorylated Akt; PARP - Poly (ADP-ribose) polymerase; PDK - 3-phosphoinositide dependent protein kinase; PI3K-Phosphatidylinositol-4,5-bisphosphate 3-kinase; Ras - rat sarcoma virus; pRb- phosphorylated retinoblastoma protein; SREBP-2 -sterol-regulatory-element-binding protein isoform 2; STAT3 - Signal transducer and activator of transcription 3; TGF-β - Transforming growth factor beta; TG - triglyceride; UDP-glucuronyltransferase; VEGF-Vascular endothelial growth factor; VPS - Vacuolar protein sorting-associated protein.

^aAlpha-tocotrienol.
^bbeta-tocotrienol.
^cgamma-tocotrienol.
^ddelta-tocotrienol.
^eTocotrienol-rich fraction (TRF).
^fRice bran tocotrienol.
^g6-O-carboxypropyl-alpha-tocotrienol.
^hOxazine derivatives of gamma- & delta-tocotrienol.
ⁱBALB/c mice.
^jathymic nude mice.

^kSprague–Dawley rats.
^lxenografts mice.
^mOrthotopic mice.
ⁿC3H/HeN mice.
^oddY mice.
^pRattus norvegicus.
^qMutant mice.

Table 1.
The Summary of Tocotrienols Mechanism of Action Against Different Cancers.

Almost 70% of human breast cancers are oestrogen-dependent and oestrogen receptor-positive. Tocotrienols have been postulated to facilitate the nuclear translocation of the anti-proliferative Oestrogen Receptor (ER) β and to decrease the tumorigenic ER α expression in breast cancer cells [74]. Additionally, a previous study had suggested that the delta isomers of the tocotrienols were able to induce cytotoxic effects in breast cancer cells independently of their ER status [68].

In ER β positive breast cancer cells, tocotrienols potentially activated the ER β signalling pathway and increased the expression of the estrogen-responsive genes such as MIC-1. This will subsequently trigger the caspase-dependent apoptosis pathway [75]. Past research has also shown that tocotrienols induce apoptosis in breast cancer cells by increasing endoplasmic reticulum (ER) stress and autophagy [69, 119]. Moreover, tocotrienols also induced apoptosis *in vitro* by inhibiting NF- κ B, PI3K/Akt/mTOR, and subsequently downregulate FLIP, increase Bax/Bcl-2 ratio and PARP cleavage [63, 72].

Another finding revealed that the apoptotic property of gamma-tocotrienols in breast cancer cells is mediated by *de novo* ceramide synthesis-dependent activation of JNK/CHOP/DR5 signalling. The anti-angiogenic effect of delta-tocotrienol against breast cancer was also mediated by its ability to reduce the synthesis of pro-angiogenic markers such as IL-8 and VEGF [63]. Apart from these findings from cellular experiments, a number of studies performed in animals have also confirmed the anti-cancer activities of tocotrienols against breast cancer. For example, it has been strongly suggested that tocotrienols increased tumour latency and reduced the tumour incidence and number in 7,12 dimethylbenz(a)anthracene-induced breast cell carcinomas in rats [120]. A recent study had suggested that gamma-tocotrienol could potentially acts as proteasomes inhibitor which was able to conquer the deficiencies in growth-inhibitory or pro-apoptotic molecules in breast cancer cells. The inhibition of proteasome proteins was postulated to induce apoptosis in breast cancer cells [121].

Apart from the various tocotrienol isoforms, other formulations of tocotrienols have also been shown to be effective in the treatment and prevention of breast cancer. This is exemplified by tocotrienol oxazine derivatives, which is effective in suppressing breast carcinoma progression by inactivating the pAkt, NF- κ B, COX-2, cyclin D1, CDK-2, -4, -6 pathways, and also by amplifying the levels of cell-cycle arrest proteins (p21 and p27) [71].

A relatively new formulation of tocotrienols i.e., the annatto tocotrienols (comprising 90% delta-tocotrienol and 10% gamma-tocotrienol), which is derived from the annatto fruit, has been found to suppress the progression of breast carcinoma by accelerating the process of apoptosis and senescent-like growth arrest in HER-2/neu transgenic mice [122].

The tocotrienol rich fraction derived from palm oil (TRF) has also been shown to be effective in experimental breast cancer management. Treatment of MCF7-injected athymic mice with tocotrienol-rich fraction (TRF) resulted in significant downregulation of c-Myc and CD59 glycoprotein precursor gene involved in the immune system, which positively contributed towards its anticarcinogenic effects [76]. Another tocotrienol product derived from palm oil i.e., tocomin, which

consists of a mixture of naturally occurring tocotrienols and tocopherols, induced apoptosis in breast cancer cells [119].

A small-scale clinical trial was conducted in female patients with early breast cancer in order to investigate the efficacy of tocotrienols administration as a potential adjuvant with tamoxifen [123]. These patients were diagnosed with either stage I or II oestrogen receptor-positive breast cancer, and were divided into two groups. The treatment group was administered 400 mg/day tocotrienol-rich fraction (TRF) derived from palm oil, in addition to conventional tamoxifen chemotherapy. The control group was administered a placebo, together with tamoxifen. The result of the experiment indicated that the 5-year breast cancer-specific survival was 98.3% in the treatment group and 95% in the control group, while the 5-year disease-free survival was 86.7% and 83.3%, respectively. The mortality risk was 60% lower in the TRF group versus controls, however, it was not statistically significant. This was probably due to the small sample size of the experiment. Accordingly, these studies comprehensively summarize the possible benefits of tocotrienols (in particular the TRF) in the prevention and management of breast cancer.

7.2 Tocotrienols in colorectal cancer

The potential advantages of tocotrienols in the treatment of colorectal cancer have been investigated for the past several years. It was recently established that the delta isomer of tocotrienol could potentially suppress the progression of colon cancer cells by downregulating Wnt-1, β -catenin, c-jun, and cyclin D1 signals [124]. Correspondingly, the gamma isomer of tocotrienol was able to hinder the expansion of HT-29 colon carcinoma cells through the suppression of Bcl-2 and increment of Bax and caspase-3 signals [82]. The delta isomer of tocotrienol was proclaimed to decrease telomerase activity by inhibiting PKC activity in colorectal adenocarcinoma cells, which subsequently causes the downregulation of c-Myc and human telomerase reverse transcriptase (hTERT) expression, thus indicating tocotrienols' anticarcinogenic potential [82, 84].

Furthermore, the gamma isomer of tocotrienol also significantly induced apoptosis *in vitro* and *in vivo* by downregulating NF- κ B and its regulated gene products [80, 82]. Additionally, previous experiments have also claimed that tocotrienols suppressed colon carcinoma growth and initiated apoptosis by inactivating pAkt, upregulating CDK inhibitors (p21, p27), caspase-3, and -9, and deregulating β -catenin/Tcf (T-cell factor) signalling [66, 81].

Remarkably, the tocotrienol-rich fraction (TRF) derived from palm oil also initiated apoptosis in colon carcinoma cells through the activation of p53 and alteration of Bax/Bcl2 ratio [85]. Furthermore, an *in vivo* study has established that TRF reduced the growth of human colon cancer mice xenografts via the inhibition of Wnt pathway [125]. In addition, past research has also demonstrated that the delta isomer of tocotrienol prevented the hypoxia-induced VEGF and IL-8 overexpression and decreased the HIF-1 α expression, which subsequently inhibited the angiogenesis process in colon cancer cells [83, 126]. In summary, these studies strongly validated tocotrienols as promising nutraceuticals for the management of colon carcinoma.

7.3 Tocotrienols in gastric cancer

The gamma isomer of tocotrienol was first discovered to induce intrinsic apoptosis in human gastric cancer cells through the repression of the MAPK signalling [88, 89]. The gamma isomer of tocotrienol was also found to exhibit potent anti-metastatic and anti-angiogenic activity in gastric carcinoma. Specifically, it inhibited cell migration and invasion potential, by lowering the expression of the matrix

metalloproteinases MMP-2 and MMP-9 and by raising the levels of Tissue Inhibitor of Metalloproteinase-1 (TIMP-1) and TIMP-2 [86]. The gamma-tocotrienol also significantly prevented the over-expression of hypoxia-mediated HIF-1 α and VEGF synthesis by alteration of the ERK signalling pathway [127]. Furthermore, gamma-tocotrienol significantly reduced the expression of VEGFR-2 in HUVEC cells grown in a conditioned medium of gastric adenocarcinoma cells [87]. Recently, a study had shown that the gamma-tocotrienol significantly inhibited human gastric cancer SGC-7901 and MGC-803 cellular growth in vitro as well as in xenografted mice through its effect on the NF- κ B activity [128]. Additionally, gamma-tocotrienol was noted to intensify the anticarcinogenic activity of capecitabine in human gastric carcinoma cell lines, as well as in nude mice xenografted with human gastric carcinoma cells [129].

7.4 Tocotrienols in lung cancer

In pulmonary carcinomas, the various tocotrienol isoforms may potentially be acknowledged as the new interventional alternatives for the successful management of the disease. In order to substantiate this claim, a previous study had suggested that all of the tocotrienol isoforms convincingly induced apoptosis in lung carcinoma cells through the activation of caspase-8 and mitochondrial cytochrome c release [17, 90]. Anticarcinogenic activity towards pulmonary carcinomas exerted by delta-tocotrienol was also achieved by raising the levels of microRNA, miR-34a, which subsequently suppressed the levels of Notch-1 and its downstream targets i.e., Bcl-2, cyclin D1, and survivin [91]. 6-O-carboxypropyl-alpha-tocotrienol, which is an analogue of alpha-tocotrienol, has been found to exhibit more potent anticarcinogenic activity in A549 lung carcinomatous cells [92, 93]. In addition, past research had suggested that tocotrienols inhibited lung carcinoma cells adaptation of hypoxic conditions by inhibiting Src-induced Akt activation, as well as through reducing HIF-2a levels [92]. Tocotrienols had also been claimed to induce apoptosis in human pulmonary adenocarcinoma that contained Ras mutation [93]. Additionally, a recent study showed that delta-tocotrienol inhibited glutamine uptake in non-small-cell lung cancer (NSCLC) cell lines A549 and H1229, which subsequently triggered the inhibition of cellular proliferation and induction of apoptosis via downregulation of the mTOR pathway [130].

7.5 Tocotrienols in pancreatic cancer

The gamma-tocotrienol isomer halted pancreatic cancer progression, both in cellular and animal studies, through inhibition of NF- κ B innate activation and consequently, inhibition of the gene products under NF surveillance e.g. as c-Myc, CXCR-4, cyclin D1, MMP-9 and VEGF, amongst others [96]. Besides, delta-tocotrienol exhibited its chemopreventive activity by inhibiting the growth of pancreatic intraepithelial neoplasm (PIN) in K-ras transgenic mouse model via suppression of the K-ras downstream gene products such as MEK/ERK, PI3K/Akt and NF- κ B, and intensified Bax and caspase-3 activities [95].

Both cellular and animal work has ascertained that delta-tocotrienol initiated the G1 cell cycle arrest through increasing the nuclear accretion of p27 (Kip1). The tocotrienols also suppressed pancreatic carcinoma growth through the inhibition of ErbB2 and mevalonate signalling, as well as initiation of the caspase-dependent apoptotic pathway [79, 97, 131]. Delta-tocotrienol was found to trigger EGR-1 signalling, thus increased the expression of Bax and eventually turned-on the apoptotic process [94]. In a small-scale phase 1 clinical trial involving patients with pancreatic ductal neoplasia, gamma-tocotrienol administration was shown to be

safe and effective in increasing the cleaved caspase-3 level in the cells of the cancerous tissue, which indicated apoptosis of the cancer cells [132]. In addition, it was recently discovered that delta-tocotrienol significantly suppressed the pancreatic ductal adenocarcinoma (PDAC) and PDAC stem-like cells metastatic process in vivo [133].

7.6 Tocotrienols in prostate cancer

Studies performed on human prostate carcinoma cells had shown that gamma-tocotrienol stimulated the process of apoptosis and autophagy in these cells. Gamma-tocotrienol supplementation in LNCaP-xenograft mouse significantly reduced tumour progression in these animals [99].

Additional studies further discovered that gamma-tocotrienol stimulated apoptosis of prostate carcinoma cells by causing under-expression of TGF β 2, NF- κ B, EGFR, Fyn/HIF-1 α and Id genes, concurrent with the stimulation of the JNK signalling pathway [98, 101, 103]. Fascinatingly, gamma-tocotrienol carried out its anti-invasive effect by inhibiting mesenchymal markers and significantly improving the expression of E-cadherin and β -catenin [103]. It has also been published that gamma-tocotrienol increasingly attenuated the expression of prostate cancer stem cells (CSC) markers CD133/CD44, which are thought to be the main cause of remission in androgen-independent prostate cancer [102]. Moreover, tocotrienols were found to degrade the sterol regulatory element-binding protein-2 (SREBP-2) in prostate cancer cells, thereby reducing their viability through reduced cholesterol level [100].

Correspondingly, TRF also illustrated its chemopreventive and therapeutic activities against prostate cancer by inducing cell cycle arrest and apoptosis studies involving cell lines [104]. Furthermore, daily supplementation of TRF to transgenic adenocarcinoma mouse prostate mouse model (TRAMP) significantly suppressed tumour formation and high-grade neoplastic lesions due to the overexpression of pro-apoptotic proteins Bcl-2 antagonist of cell death (BAD), caspase-3 and CDK inhibitors (p21 and p27) [134].

7.7 Tocotrienols in liver cancer

Previous studies have substantiated the anticarcinogenic effects of tocotrienols against hepatocellular carcinoma (HCC) through its effect on a number of important signalling pathways [42, 107, 109–111]. The potency of tocotrienol isoforms against HCC cells were regarded as delta-tocotrienol > beta-tocotrienol > alpha-tocotrienol > gamma-tocotrienol [111, 120]. Gamma-tocotrienol was thought to suppress the proliferation of HCC cells by overexpression of peroxiredoxin-4 (Prx4) [105]. Moreover, in HCC, gamma-tocotrienol intervention resulted in increased expression of Bax, caspase-8 and caspase-9; raising Bid fragmentation; suppressing STAT3 and its associated proteins such as Bcl-2, Bcl-xL, survivin, cyclin D1, Mcl-1, and VEGF. All these aforementioned mechanisms gave rise to the anti-proliferative and apoptotic effects in HCC. [107, 110].

Interestingly, palm oil tocotrienols (palmvitee) supplementation surprisingly diminished the progression of hepatocarcinogenesis initiated by chemical carcinogens such as diethylnitrosamine (DEN)/2-acetylaminofluorene (AAF) in rats [12, 112].

Specific tocotrienol isomers such as gamma and delta-tocotrienols also substantially decreased the progression of HCC in mouse xenograft and orthoptic models through the nullification of the Akt/mTOR signaling pathway [106, 109]. It was pertinent to note that both the gamma and delta-tocotrienols were sequestered only in tumour sites and not in normal tissues, which implied

that these tocotrienol isomers act specifically on the tumours [109]. In HCC, gamma-tocotrienols displayed lipid-lowering function, which might facilitate its anticarcinogenic activity [108, 135]. The mechanism in which tocotrienols exert its lipid-lowering ability includes the regulation of various lipogenic enzymes e.g., fatty acid synthase (FAS), sterol regulatory element-binding transcription factor 1 (SREBF1), stearoyl CoA desaturase 1 (SCD1) and carnitine palmitoyl transferase 1A (CPT-1A) [135].

In addition, the tocotrienols were also able to inhibit the upstream regulators of lipid homeostasis genes e.g., diacylglycerol O-acyltransferase 2 (DGAT2), apolipoprotein B (ApoB)-100, SREBP1/2 and HMGCR. These reactions will cause a reduction of TGs, cholesterol and very low-density lipoprotein (VLDL) secretion in HepG2 HCC cells [108]. Accordingly, these studies conjointly exposed the potential of tocotrienols in the prevention and treatment of HCC.

7.8 Tocotrienols in skin cancer

One of the earliest application of tocotrienols is in the protection of skin against ultraviolet rays damage. In recent years, the beneficial effects of tocotrienols against skin cancer had been acknowledged. For example, delta-tocotrienol and its peroxy dimer were discovered to be able to prevent the expansion of melanoma cells [136]. The delta isomer of tocotrienols was demonstrated to trigger G1 cell cycle arrest in A2058 and A375 human melanoma cells. This was achieved through suppression of CDK-4 and activation of caspase-3 pathway [116]. Additional studies had demonstrated that gamma-tocotrienol initiated apoptosis in melanoma cells due to inhibition of NF- κ B, EGFR, Id family proteins and JNK signalling pathway [117]. The anticarcinogenic effect of δ -T3 has also been deduced by its capability to induce apoptosis via ER stress in melanoma conditions, either in cellular and animal model research [64, 113].

An animal study had found that intravenous administration of alpha-tocotrienol encapsulated within transferrin-bearing vesicles resulted in exhaustive tumour eradication in 60% of B16-F10 melanoma tumour and lengthened the durability of the mice [137]. The gamma-tocotrienol treatment prevented cell invasion in human melanoma through blockade of mesenchymal markers and reclamation of E-cadherin and γ -catenin [117]. In addition, delta-tocotrienols prevented the synthesis of melanin in B16 melanoma cells through stimulation of ERK signalling pathway, which resulted in the under-expression of melanogenesis-related proteins e.g., microphthalmia-associated transcription factor (MITF), tyrosinase and tyrosinase-related proteins, TYRP-1 and TYRP-2 [138].

Interestingly, it was also discovered that tocomin (a tocotrienol preparation derived from palm oil) facilitated the degradation of melanosomes in melanoma cells by upregulating endosome docking/fusion proteins including syntaxin7, vacuolar protein sorting-associated protein Vps16, Vps33, and Vps41 [114]. Mutually, these studies had indicated the undeniable potential of tocotrienols for the management of skin cancer.

7.9 Other cancers

Besides the types of cancers mentioned above, tocotrienols were also postulated to be able to prevent and treat other forms of carcinomas. Previous research has indicated that the gamma isomer of tocotrienols was able to initiate apoptosis in neuroblastoma SH-SY5Y cells through several postulated mechanisms [115]. Another previous research had concluded that gamma-tocotrienol negated the effect of NF- κ B in squamous cell carcinoma of the tongue, which resulted in

apoptosis [139]. It was also postulated that delta-tocotrienol triggered apoptosis by means of repression of STAT3 signalling in human bladder cancer [140]. Additionally, it has been concluded that alpha- and gamma-tocotrienol triggered apoptosis in HeLa cervical cancer cells through induction of Bax and IL-6 gene expression, promoting cytochrome c release, and suppression of Bcl-2, cyclin D3, CDK6, and p16 gene expression machinery [141, 142]. Likewise, gamma- and delta-tocotrienol also initiated apoptosis in cervical cancer by stimulating ER stress [143]. In multiple myeloma, gamma-tocotrienol suppressed NF- κ B and STAT3 signalling and their associated proteins such as Bcl-2 and cyclin D1, thus indicating its postulated role as a potential alternative therapy for multiple myeloma sufferers [139, 144]. A recent result from a small-scale phase II clinical trial involving patients with ovarian cancers showed that the combination of tocotrienol and bevacizumab increased the rate of disease control, progression free survival and overall survival significantly [145].

8. Conclusion

The tocotrienols have been acknowledged in preclinical studies as a unique, safe and effective natural compound that could be described as a multi-target anticarcinogenic agent. Many studies had confirmed the superiority of tocotrienols in terms of health benefits compared to their chemical siblings i.e., the tocopherols. Studies after studies had arduously confirmed the ability of tocotrienols to regulate various crucial signalling pathways related to the development and growth of cancer (**Table 1**). This makes tocotrienols prime candidates to be used as a mono-chemotherapeutic anticarcinogenic agent, as well as in combination therapy with other well-known chemotherapeutic agents, with regards to cancer management. No doubt, several studies in humans have confirmed the safety and efficacy aspects of tocotrienols. However, the purported superiority of tocotrienols as potent therapeutics is severely hampered by their insolubility and low bioavailability. In order to address these issues, tocotrienols have been formulated in the form of nanoemulsions, liposomes, micelles complexes, as well as lipid conjugates with established chemotherapeutic drugs in order to elevate their bioavailability and efficacy. Nevertheless, a further appraisal is still needed for these formulations with regards to their actual efficacy. Consequently, more studies are still needed to find suitably effective tocotrienols delivery systems and to further improve the bioavailability and efficacy of tocotrienols. The limited amount of tocotrienols found in nature, and the prohibitive financial means needed for their extraction, led to the implication that tocotrienols are quite expensive to produce. Therefore, more studies are on the cards to find cheaper extraction procedures that produces a high yield of tocotrienols-rich fraction, as well as individual tocotrienols isomers depending on the situation. Furthermore, a considerable amount of research is still needed to elucidate which isomers are effective against which types of carcinomas. It is quite surprising that no major clinical trial has been attempted to explore the potential of tocotrienol in cancer. Therefore, large-scale clinical trials and high-profile translational studies are indeed crucial to establish once and for all the efficacy of tocotrienols or their isomers in the treatment of various types of cancers.

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Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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