Chapter

Tocotrienol: An Underrated Isomer of Vitamin E in Health and Diseases

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Abstract

Vitamin E was first discovered as a fertility factor in 1922 in the laboratory of Herbert McLean Evans, a scientist and anatomist. Following this discovery, it was extensively researched and found to possess a potent antioxidant property. It soon dawned that the family of vitamin E has eight members: four tocopherols, namely α-, β-, δ- and γ-tocopherol; and four tocotrienols in the form of α-, β-, δ- and γ-tocotrienols. This chapter discusses this rather unknown and underrated isomer of vitamin E with unsurpassed health benefits: tocotrienols. Until recently, tocotrienols rarely figured in vitamin E research in spite of their relative superiority to tocopherol coupled with their abundant presence in palm oil. In fact, since palm oil contains about 70% of all tocotrienol homologues, it would be no exaggeration to call it nature's best kept secret, if not the most promising natural substance in influencing health and disease. While highlighting the wonders of tocotrienols as a safe and efficacious product, this chapter offers a panoramic view of recent research into tocotrienols that demonstrates their undeniable benefits in conferring protection against cancer as well as a whole litany of ailments including cardiovascular, metabolic, autoimmune, bone and neurological diseases. Admittedly, many of these researches were conducted in the laboratory, with some preclinical trials translated into clinical trials. Nonetheless, it is hoped that more randomised clinical trials will be carried out on a global scale in the near future. From the vessels in the heart to the neurons in the brain, tocotrienols have the extraordinary potential to be the future of vitamin E research.

Keywords: vitamin E, tocotrienols, health benefits

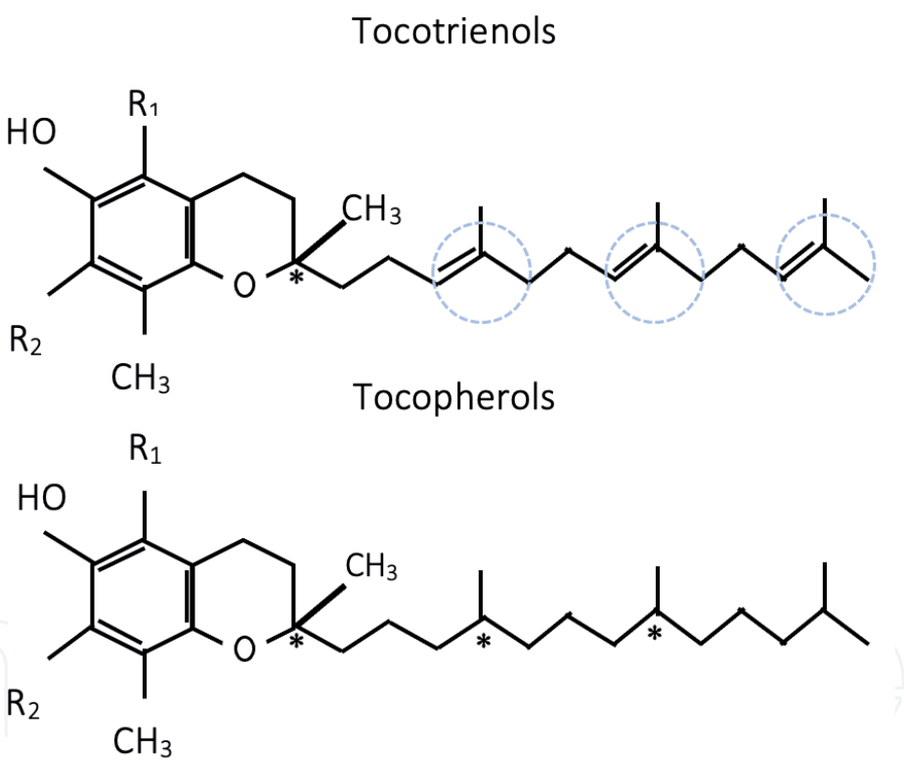
1. Introduction

Vitamin E, an important nutrient in the human diet that is readily available in lipid-rich plant products, is well known for its antioxidant properties with multiple health benefits. Historically, drug discovery researches have focused on natural products that abound in biological compounds with pharmacologic properties [1]. The discovery of vitamin E began in 1922 when Herbert Evans and Katherine Bishop [2] isolated an uncharacterised fat-soluble compound (which they termed 'substance X') from green leafy vegetables that they imagined might play a role in fertility. When the compound was finally identified in 1924, it was named tocopherol — derived from the Greek word tokos meaning childbirth and pheros which means to

bring forth [3]. Vitamin E was rediscovered as 'factor 2 antioxidant' in 1965 [4]. Not surprisingly, as the major isoform of Vitamin E ever identified, α-tocopherol was thrust into the limelight while its sisters were ignored. Tocopherol is regarded as the most biologically active and potent antioxidant currently in existence. However, recent studies have shown that tocotrienols may have superior anti-oxidant [5], anti-inflammatory [6], anti-cholesterolaemic, [7–11] anti-cancer [12, 13], anti-diabetic [14–16], anti-atherogenic [17, 18], blood pressure lowering, [19, 20] and neuroprotective effects [21–23]. Unfortunately, despite the recent interest in tocotrienols, it comprises only 3% of all vitamin E research papers listed in PubMed [24].

2. Biochemical properties of vitamin E isoforms

Generally, vitamin E is classified into tocopherols and tocotrienols, and there are eight isoforms altogether: α-, β-, γ-, and δ-tocopherol, and α-, β-, γ-, and δ-tocotrienol. Structurally, they are very similar and possess a chromanol head formed by phenolic and heterocyclic rings, and a phenyl tail [25]. Designation as α-, β-, γ- or δ-tocopherol or tocotrienols is dependent on the methyl substitutions on



Isomer	R_1	R_2
α	CH_3	CH_3
β	CH_3	H
γ	H	CH_3
σ	H	H

Figure 1.
The different structures between tocopherols and tocotrienols.

the phenolic ring [26]. The main difference between the two groups is that tocopherols have a long-saturated carbon side-chain with chiral centres, whereas tocotrienols possess three unsaturated bonds in the carbon side-chain with one chiral centre [27]. This unique property somehow increases the efficiency of tocotrienols in its metabolic function; it allows a better penetration of saturated fatty layers by tocotrienols as compared to tocopherols. **Figure 1** above illustrates the difference between the structures of tocopherols and tocotrienols [28].

3. Sources of vitamin E

Vitamin E occurs naturally in vegetables, plants and plant oils. With regard to tocopherols, α-tocopherol is generally found in green leafy plants while γ-tocopherol occurs in the non-green parts of the plants, notably seeds and fruits [29]. Based on the United States Department of Agriculture nutrient database, α-tocopherol is commonly found in almonds, avocados, hazelnuts, peanuts and sunflower seeds; β-tocopherol in oregano and poppy seeds; γ-tocopherol in pecans, pistachios, sesame seeds and walnuts; and δ-tocopherol in edamame and raspberries. Both α-tocopherol and γ-tocopherol are present in food oils such as corn, peanut and soybean oil. Conversely, tocotrienols are rarely found in food sources or vegetable oils, with rice bran and palm oil being the only known exceptions. This explains the scarcity of scientific literature on tocotrienols compared to tocopherols as a form of vitamin E that is widely accepted by the public. In fact, most people are unaware that up to 70% of vitamin E from crude palm oil consists of tocotrienols [30, 31]. Studies have proven that the extraction of crude palm oil (scientifically known as *Elaeis guineensis*) can yield up to 800 mg/kg of tocotrienols in the form of α-tocotrienol and γ-tocotrienol [32]. Moreover, cereal grains such as barley, oat, rice, rye and wheat contain a higher concentration of tocotrienols than tocopherol in a ratio of 79:21, 77:23, 67:55, 51:49 and 55:45 respectively [24]. However, in food supplements, tocotrienols are often prepared in soft-gel capsules. Even at a dose of 1000 mg daily, this is equivalent to a daily intake of 16.7 mg of tocotrienol/kg/day for a 60-kg person, or about seven times below the level where no adverse effects were observed in rats [33]. Hence, the usual dosage for any experimental use in humans has always been 400 mg daily in two divided doses which is a safe dosage with no observable adverse effects on any study patients to date.

4. Bioavailability and pharmacokinetics of vitamin E

Compelling evidence from recent research prove that tocotrienols are detected at appreciable levels in the plasma after supplementation, whether this was done on a short-term or long-term basis [34]. While both compounds are basically bioavailable, tocotrienol has a shorter plasma half-life [33]. One study showed that the half-life of α-, γ- and δ-tocotrienols in human plasma was estimated to be 2.3, 4.4 and 4.3 hours respectively [35]. However, the half-life of α-tocopherol and γ-tocopherol was 57 and 13 hours respectively [36]. Given that tocotrienols are essentially oil-based compounds, and that emulsions are known to increase the absorption of oil-based compounds based on the new system of self-emulsifying drug delivery system [37], new products such as Tocovid Suprabio™ were developed following this technique. This new product led to a threefold increase in the peak plasma concentration of α-tocotrienol in humans compared to a previous study [38]. It has also been shown that the bioavailability of tocotrienols is dependent on several

factors, food status being one of them. The mean apparent volume of tocotrienol distribution values is lower in the fed state, which means that the absorption is much better than in the fasting state [35]. Undoubtedly, tocotrienols have a very different pharmacokinetics from tocopherols which remain longer in the bloodstream. However, the biodistribution of tocotrienols pointed to the accumulation of the compound in the vital organs [34]. Therefore, tocotrienols would score high in terms of therapeutic efficacy since this requires not only bioavailability but also presence in the target organs.

5. Vitamin E as an anti-oxidant

One of the most well-known effects of vitamin E is its anti-oxidant capability in inhibiting the peroxidation of lipids after its incorporation into the cellular membranes [39]. It is well documented that tocotrienol scavenges the chain propagating the peroxyl radicals [39]. Indeed, α-tocotrienol has a much stronger anti-oxidant effect than α-tocopherol. This superiority is due to a more even distribution of α-tocotrienol in the plasma membrane as a result of a more efficient collision of α-tocotrienol with the radicals. Compared to tocopherols, tocotrienols also have a higher recycling efficiency thanks to their chromanoxyl radicals [39]. These anti-oxidant properties of tocotrienol have a lasting impact on health in general. For instance, patients with hyperlipidaemia and carotid stenosis have been shown to demonstrate a significant reduction in thiobarbituric-acid-reactive substances that were related to platelet peroxidation. It is also proven that tocotrienols have the ability to scavenge free radicals that cause DNA damage, hence providing protection especially to the older age group [40].

6. Preventing cardiovascular diseases

One of the most feared ailments is cardiovascular disease, and with 17.9 million deaths every year, the World Health Organization (WHO) considers it the main cause of death globally [41]. WHO estimated that out of five mortalities from cardiovascular diseases, four were caused by heart attacks and strokes, with almost a third of these deaths occurring in people less than 70 years of age [41]. Among the modifiable risk factors of atherosclerosis that cause heart attacks are hyperlipidaemia, hypertension, diabetes mellitus and thrombosis. Given its ability as a lipid-lowering, blood pressure-lowering, anti-diabetic and anti-thrombogenic agent, the effects of vitamin E – especially tocotrienol – deserve a thorough investigation.

6.1 Prevention of atherosclerosis

Atherosclerosis is considered the most important event that leads to heart attack and stroke as a result of abnormal deposits of lipids, cholesterol and plaque build-up. Animal studies have been conducted in rabbits to look at the microscopic development of atherosclerosis and lipid peroxidation. After ten weeks of treatment with tocotrienol-rich fraction (TRF) which normally consists of 80% tocotrienol and 20% tocopherol, the researchers [42] found that the cholesterol-fed rabbits had a lower content of malondialdehyde (MDA) or modified low density lipoprotein – a diagnostic biochemical marker for atherosclerosis. The rabbits also had less intimal thickening, while their internal elastic lamina was better preserved compared to those fed on a normal diet. Another study [43] showed that atherosclerosis is prevented through the modulation of the peroxisome proliferator-activated receptors (PPAR) when TRF is administered. A different study [44] found that, after

being given TRF, subjects undergoing chronic haemodialysis showed improvement in their high-density lipoprotein (HDL), triglycerides and total plasma cholesterol as compared to placebo. All these studies prove that TRF intake essentially improves the lipid profiles, thereby preventing atherosclerosis.

6.2 Protection against reperfusion injury

Another important issue is related to myocardial ischaemia reperfusion injury. This happens when blood flow is restored to an infarcted myocardium either via percutaneous transluminal coronary angioplasty or bypass surgery. Restoring the blood flow, a process known as reperfusion, could also cause injury to the heart muscles and is therefore termed as myocardial ischaemia reperfusion injury. Reperfusion injury could account for almost 50% of the final size of myocardial infarction [45]. Almost all isoforms of tocotrienol have been shown to have cardioprotective effect. Nonetheless, γ-tocotrienol is demonstrably the most potent in myocardial ischaemic injury model. This particular study [46] shows that the interaction between mitogen-activated protein kinase (MAPK) with caveolin and proteasome plays an important role in the cardioprotective effect of tocotrienol that is achieved by altering the availability of pro-survival and anti-survival proteins.

6.3 Reduction of thromboembolic events

The discussion on this topic would be incomplete without any mention of thromboembolic events. In one animal study on dogs [47], an injection of intravenous tocotrienols and tocopherols was administered; it was noted that the cyclic flow that measures the acute platelet-mediated thrombus formation and collagen-induced platelet aggregation was significantly reduced in those receiving tocotrienol compared to those injected with tocopherol.

All these data suggest that tocotrienols provide better cardioprotective effect than tocopherols insofar as myocardial infarction, stroke or thrombosis is concerned.

7. Lipid-lowering effect

Studies on the hypercholesterolaemic properties of tocotrienols have gained traction after it was shown that the addition of tocotrienols significantly lowered the cholesterol level [48]. This effect was mediated by the inhibition of HMG-CoA reductase by post-transcriptional suppression of the enzyme itself by tocotrienols [49]. Indeed, γ-tocotrienol has been observed to have a dramatic 30-fold activity in inhibiting HMG-CoA reductase [50]. A later study further indicated that the American Heart Association Step 1 diet and TRF25 (25–200 mg/day) from rice bran could reduce the total cholesterol, LDL, triglycerides, and also apolipoprotein B in hypercholesterolaemic patients [51]. Another study demonstrated that when 30 mg tocotrienols are mixed with 270 mg flavonoids, the total serum cholesterol level, LDL, triglycerides and apolipoprotein B are also reduced in hypercholesterolaemic patients [52]. Furthermore, hypercholesterolaemic patients with non-alcoholic fatty liver disease who were treated with mixed-tocotrienols showed a higher percentage of normal liver echogenic response [53]. A study on atherogenesis using human monocyte-macrophages showed that α-tocotrienol, like the new compound FeAOX-6 which combines both the anti-oxidant structural features of tocopherols and carotenoids, reduced the cholesterol accumulation in the cells, with α-tocotrienol having a more potent effect [54].

8. Anti-diabetic effect

Diabetes mellitus – which has risen dramatically in all countries irrespective of their income levels – is a chronic metabolic disease characterised by elevated blood sugar level that could affect the eyes, kidneys and nerves in the long run. While Type II diabetes develops when the body becomes resistant to insulin, Type I diabetes arises when the pancreas produces less or no insulin at all. According to current WHO estimates, approximately 422 million people worldwide suffer from diabetes [55]. Indeed, about 1.6 million deaths are attributed to diabetes on a yearly basis [55]. Alarmingly, these dismal numbers have been growing steadily in the last few decades.

Studies on the antidiabetic effects of vitamin E were conducted as early as the 1990s to determine any possible association between vitamin E and diabetic risks [56–58] as well as the correlation between the dietary intake of vitamin E and insulin action [59, 60]. In a 2004 study with a very long follow-up, it was demonstrated that the intake of vitamin E reduces the risk of Type II diabetes onset [61]. It was also found that TRF reduces the total cholesterol level, low-density lipoprotein (LDL) and total plasma lipid in diabetic patients [62]. Patients who were given canola oil enriched with tocotrienol also showed a significant reduction in their urine microalbumin and the serum C-reactive protein (CRP) known for its protective effect on the kidney and against nitrosative stress [63]. In an animal model, it was observed that both TRF and α-tocopherol improved the vascular endothelial function in streptozotocin-induced diabetic rats through their sparing effect on endothelium derived nitric oxide bioavailability [64]. Another study determining the effects of TRF on erythrocyte membranes and leukocyte deoxyribonucleic acid (DNA) damage in streptozotocin-induced diabetic rats revealed that daily supplementation of tocotrienol for four weeks could inhibit lipid peroxidation while increasing the level of antioxidant markers [65]. In an animal study on the cognitive function and neuroinflammatory cascade in streptozotocin-induced diabetes, it was shown that the administration of tocotrienol significantly prevented behavioural, biochemical and molecular changes associated with diabetes. This points to the potential benefit of tocotrienol in preventing diabetic encephalopathy [66].

8.1 Preventing diabetic nephropathy

Diabetic nephropathy is a common complication of both Type I and Type II diabetes. Diabetic nephropathy (also called clinical nephropathy, proteinuria or microalbuminuria) is defined by the presence of protein of >0.5 g/24 h in the urine [67] and it increases the risk of death. In an animal study [68] designed to investigate the impact of tocotrienol in streptozotocin-induced diabetes in terms of renal function and reno-inflammatory cascade, it was found that tocotrienol has a more profound effect than tocopherol in preventing biochemical and molecular changes associated with diabetes [68]. It was concluded from the study [68] that tocotrienol modulates the release of pro-fibrolytic cytokines, apoptosis, the ongoing inflammation, and the associated oxidative stress, which confers a renoprotective effect on the kidneys. Another study [69] was designed to determine whether TRF from palm oil (PO) or rice bran oil (RBO) could improve the renal function of rats as a result of their hypoglycaemic and anti-oxidant effect. The results analysed the fasting blood glucose, glycosylated haemoglobin, renal function biological markers, and oxidative stress in the serum and urine of the rats. It was revealed that both palm-oil TRF (PO-TRF) and rice bran oil TRF (RBO-TRF) significantly improved renal function and glycaemic status, although PO-TRF conferred a better efficacy than RBO-TRF [68]. Hence, it was concluded that PO-TRF was more effective as a neuroprotective

and hypoglycaemic agent compared to RBO-TRF [69]. Another study [70] revealed that TRF ameliorated lipid induced nephropathy in type-II diabetes by modulating the TGF-β – besides leveraging on its hypoglycaemic, hypolipidaemic and antioxidant properties – in order to prevent the increased expression of collagen type IV and fibrinogen. A recent prospective, randomized double-blind study [71] that was conducted to assess the effect of tocotrienol-rich vitamin E on diabetic nephropathy found that it attenuates the progression of diabetic nephropathy. It was also observed that a 12-week supplementation with tocotrienol-rich vitamin E led to a statistically significant improvement in renal function despite having no effect on glycaemia [71].

8.2 Preventing diabetic retinopathy

One of the most common complications of diabetes mellitus is diabetic retinopathy which could lead to blindness in severe cases [72]. It is estimated that the prevalence of diabetic retinopathy worldwide is about 35%, with approximately 10% of the world population afflicted with a vision-threatening disease [73, 74]. A strong correlation has been established between chronic hyperglycaemia and poor diabetic control with diabetic retinopathy [75]. Indeed, with the incidence of diabetes mellitus rising worldwide [76], a concomitant increase in diabetic retinopathy is to be expected [77]. A characteristic feature of diabetic retinopathy is retinal microvascular changes accompanied by an earlier neurodegeneration [78]. Oxidative stress, which induces hyperglycaemia, is considered as one of the main factors responsible for microvascular complication in diabetes mellitus [79]. Hyperglycaemia triggers cellular events resulting in inflammatory cytokines reactions that in turn accelerate microvascular changes [80]. Another important event is angiogenesis, an over-expression of vascular endothelial growth factor (VEGF) associated with neurodegeneration and diabetes-induced oxidative stress [81]. As mentioned earlier, antioxidants confer their benefit in oxidative stress-induced diseases, including diabetic retinopathy [82, 83], by scavenging free radicals through the hydrogen atom situated at the chromanol ring [84]. Indeed, a recent study [85] on streptozotocin-induced diabetic retinopathy in rats alluded to the beneficial effect of tocotrienol in preventing retinal neurodegenerative changes; it was shown that TRF prevented diabetic-induced changes in retinal layer thickness, retinal cell count, retinal cell apoptosis and retinal expression of VEGF.

8.3 Preventing diabetic neuropathy

One of the complications faced by almost 26% to 53% of diabetic patients worldwide is diabetic peripheral neuropathy [86, 87] that significantly impairs their quality of life [86]. The total cost of diabetic care [88] is around 4.2-fold higher among diabetic patients with neuropathic pain [89]. The mainstay treatment for managing diabetic neuropathy surely lies in glycaemic control and pain management [88]. To that end, various pharmacological agents [90, 91] have been used, but they are all limited either by their adverse effects or by having no effect at all on the pathway of the neuropathic pain [92]. It is believed that oxidative stress plays a role in the pathogenesis of peripheral neuropathy [93]. One animal study with diabetic rats has shown that neuropathic pain is reversed by tocotrienols via the modulation of oxidative-nitrosative stress, caspase-3, and inflammatory cytokine release [94]. Another prospective study [95] on human subjects was aimed at evaluating the protective effect of mixed tocotrienol on the white matter lesion (WML) that reflects neurodegenerative changes; it was shown that subjects who received 200 mg of mixed tocotrienols twice daily for two years have attenuated progression of WMLs compared to placebo [95]. However, a recent study by the investigators of the

Vitamin E in Neuroprotective Study (VENUS) [96] found that the supplementation of oral mixed tocotrienols of 400 mg daily on diabetic patients with neuropathic pain did not show any remarkable improvement in alleviating the neuropathic symptoms. Nonetheless, the researchers qualified their statement by saying that their observation on the lancinating pain among the subsets of patients studied would require further exploration. More optimistically, a more recent randomized-controlled study [97] on the effects of tocotrienol on diabetic neuropathy showed that supplementation of tocotrienol-rich vitamin E of 200 mg twice daily led to a higher serum nerve growth factor (NGF) and improved the nerve conduction velocity for all nerves tested after eight weeks of supplementation. The researchers concluded that TRF could be a disease-modifying agent that targets the NGF in improving nerve conduction velocity [97].

9. Preventing neurological diseases

Neurodegenerative diseases have been widely believed to be caused by oxidative damage due to reactive oxygen species [98]. Indeed, the increased levels of oxidative stress have been associated with numerous pathophysiological conditions together with derangements in mitochondrial complex I activity [99, 100]. Since vitamin E is a potent anti-oxidative agent, it is hypothesised that the neuroprotective effects of vitamin E is mediated via its anti-oxidative property [101]. A growing body of evidence supports the view that tocotrienol is a potent neuroprotective agent against Alzheimer's disease [102]. However, as it stands today, the pathogenesis of Alzheimer's disease remains unclear with a few different hypotheses [103]. Nonetheless, the ability of tocotrienol in reducing oxidative stress and promoting cellular repair contributes to its positive and beneficial effect in protecting the neurons. Admittedly, no clinical trials are available to support the hypothesis that tocotrienol could prevent Alzheimer's disease, with available data based on only four human epidemiological studies [104–107]. With more studies in the future, this research gap could certainly be narrowed. **Figure 2** below summarizes the possible pathways for the neuroprotective actions of tocotrienol.

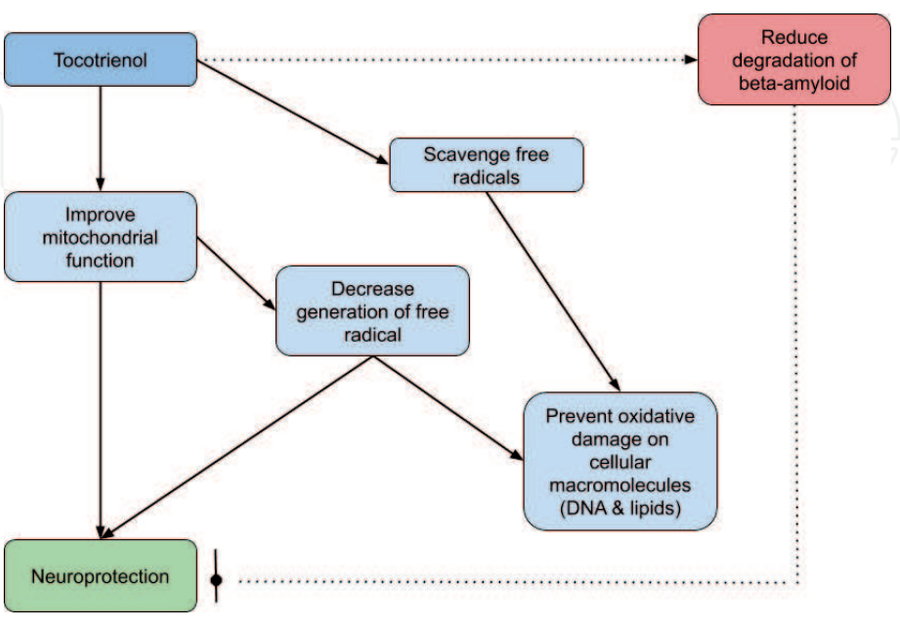


Figure 2.
A summary of the current in vitro evidence of neuroprotective actions of tocotrienol. Legend: Solid line represents beneficial effects of tocotrienol on neurons. Dotted line represents potential adverse effects of tocotrienol on neurons.

10. Preventing bone diseases

Osteoporosis, a metabolic bone disease requiring extensive healthcare, is common in both men and women, though women suffer fragility fracture from osteoporosis at a ratio of 6:1 to men [108]. Osteoporosis is caused by an imbalance in bone remodelling, where the rate of bone resorption is faster than bone formation [109]. While it is known that menopause in women leads to oestrogen deficiency, in men, however, it is due to late-onset testosterone deficiency [110, 111]. The existing therapies for osteoporosis include bisphosphonates, teriparatide and strontium ranelate, all of which increase bone mineral density [112]. Recent studies have tried to explore the use of natural products to cure osteoporosis. With its inherent antioxidative and anti-inflammatory properties that are implicated in the pathogenesis of osteoporosis, tocotrienol is an agent of choice for such studies [113, 114]. Oxidative stress is known to damage osteoblasts by affecting both its differentiation and survival [115]. Oxidative stress also affects the signalling of osteoclasts and promotes the differentiation process [116]. Similarly, proinflammatory cytokines such as tumour necrosis factor (TNF), interleukin 1 (IL-1), and interleukin-6 (IL-6) promote osteoclasts differentiation [117]. The expression of proinflammatory cytokines is also suppressed by tocotrienol [118]. Hence, it is reasonable to assume that by reducing both oxidative stress and inflammation, the process of osteoporosis could be mitigated, if not prevented, by tocotrienol. A study on bone histomorphometry [119] that describes the bone volume and trabecular number, thickness and separation showed that palm tocotrienol preserved the trabecular bone structure, volume, and trabecular separation in rats with ovarian deficiency from ovariectomy. It was also demonstrated in another study [120] that in the bone loss model of rats, palm tocotrienol decreased the eroded surface and increased the osteoblast number, osteoid surface and osteoid volume in the supplemented study animal as compared to the other arm of the study. In another experiment on ovariectomised rats [121], the group that was treated with palm vitamin E showed significantly higher bone mineral density at the femur and vertebrae compared to the untreated group. The bone calcium level at the femur and vertebra of orchidectomised and ovariectomised was also found to be restored with palm vitamin E supplementation [122, 123]. Nonetheless, while tocotrienol has been proven to improve bone density and microarchitecture, and enhance bone biomechanical strength, the study [124] done was not convincing enough to show any statistical difference. The effects of tocotrienol on the bone are summarised below in **Figure 3** [125].

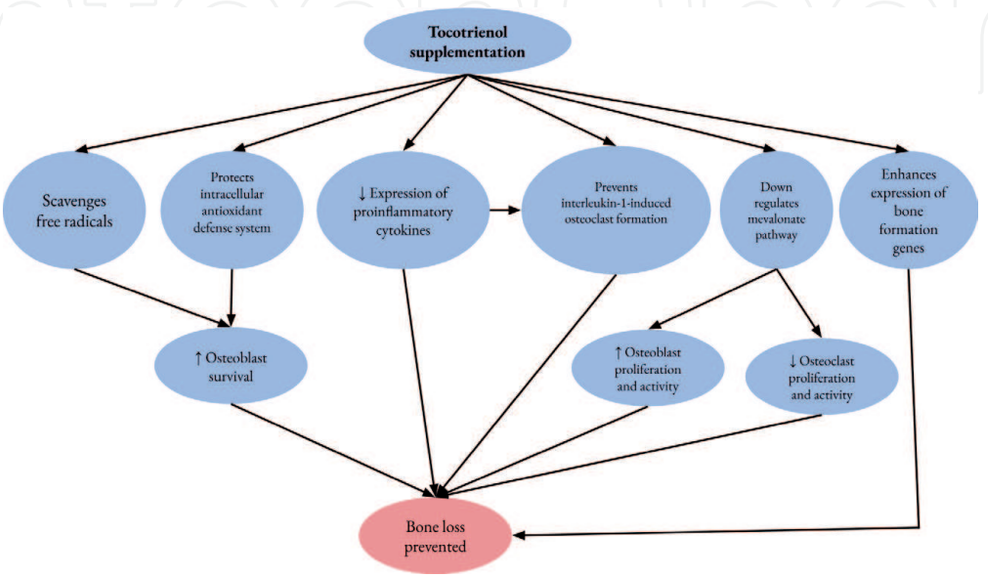


Figure 3.
The effects of tocotrienol on bone histomorphometry, bone mineral and bone calcium content.

Let us now look at the mechanism of actions of tocotrienol in the prevention of osteoporosis. Studies have revealed that oxidative stress plays a major role in the development of osteoporosis [126, 127]. Any increase in the oxidative stress process would lead to a decrease in differentiation of osteoclasts [128] as well as the bone resorption activity [129], which would subsequently impair the musculoskeletal system. Some in vivo studies [124, 130] which supplemented the study rats with tocotrienol showed a reduction in oxidative stress and anti-oxidant enzyme activities such as malondialdehyde. Additionally, an in vitro study [131] showed that γ-tocotrienol homologue decreased the oxidative damage on primary osteoblast culture. Tocotrienol exerts its effect by preserving the antioxidant enzyme activities in bone cells affected with oxidative stress [132]. Another effect is via the mevalonate pathway which is known to regulate osteoblastogenesis and osteoclastogenesis [133]. Tocotrienol suppresses the mevalonate pathway via the hydroxy-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, an enzyme that is also involved in cholesterol synthesis [134]. Another study [135] further revealed that tocotrienol, in combination with statins, enhances bone static histomorphometry and remodeling markers in the ovariectomised rats although it could not be confirmed whether this was via the mevalonate pathway alone or if it involved some other pathways as well. The anti-inflammatory effect of tocotrienol in preventing proinflammatory cytokines such as IL-1 and IL-6 has also been shown to preserve bone health in rats [120, 136, 137]. It is worth noting that the differentiation and activity of osteoclasts and osteoblast are governed by some genes [138] and that supplementation of palm vitamin E has been shown to significantly enhance the gene expression [139]. Another study [140] demonstrated that tocotrienol could enhance the gene expression related to bone formation and osteoblast activity. All the above-mentioned studies confirmed that tocotrienol possesses some promising bone-protective effect: it increases the osteoblast number, mineral deposition and bone formation; and it reduces the osteoclast number, thereby preventing the bone resorption, erosion, and degeneration of bone mineral density and microarchitecture. The summary of the whole mechanism is illustrated in **Figure 4** below.

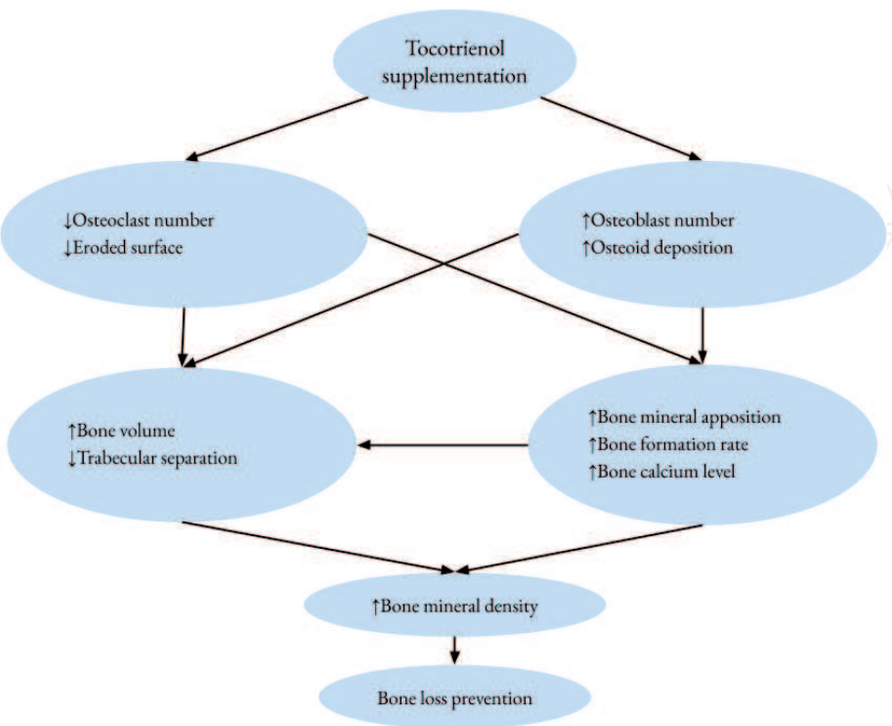


Figure 4.
The bone protective mechanism of Tocotrienol.

11. Preventing autoimmune diseases

One of the most common autoimmune diseases is rheumatoid arthritis. With a prevalence of about 0.5 to 1.0% worldwide [141], it is presented as a typical systemic autoimmune disease of unknown aetiology that affects many joints [142]. The joint inflammation is characterised by some marked changes in the cartilage from the effects of proinflammatory mediators such as cytokines and C-reactive protein [143]. These include destruction of cartilage [144], leukocytes infiltration [145], and bone erosion [146]. The proinflammatory cytokines such as tumour necrosis factor-α (TNF-α), Interleukin-1α (IL-1α) and IL-1β [147] play a role in modulating inflammatory responses in the affected joints [148]. These cytokines have been shown to be involved in the pathogenesis of rheumatoid arthritis in animal studies. Since such studies closely mimic human disease [149], the development of biological agents that have the potential to modulate the cytokine mediators could yield an effective prevention against rheumatoid arthritis [150]. It has been demonstrated in an animal study [151] that palm γ-tocotrienol exerts an effect against both oxidative stress and joint pathology. In another study [152], it was discovered that palm δ-tocotrienol somehow reduced inflammation in arthritic rats. This should not be surprising given that palm tocotrienol has been shown to downregulate proinflammatory cytokines such as TNF-α, IL-1α, IL-β, IL-6 and IL-8 [153]. In another recent study [154] on the temporomandibular joint (TMJ) of a rat model, it was observed that in the group fed with TRF, the bone mineral density was notably increased. The researchers concluded that the concomitant decrease of plasma level of inflammatory cytokines with the increased bone density is sufficient evidence that TRF could be used in the management of TMJ rheumatoid arthritis.

It is also pertinent to look at another common ailment: bronchiole asthma. This chronic respiratory problem with a female preponderance afflicts more than 339 million people worldwide, according to a WHO estimate [155]. An increase in antinuclear antibodies and autoantibodies against bronchial epithelial antigens or endothelial antigens suggest that asthma is an autoimmune disease [156]. As the first experiment to demonstrate the effectiveness of tocotrienol in preventing asthma, a study [157] on rats showed that γ-tocotrienol possesses better free radical-neutralizing activity in vitro; reduces the eosinophil and neutrophil counts in vivo; and promotes lung-endogenous antioxidant activity. Another study investigated the effect of tocotrienol on airway remodelling [158], undoubtedly one of the characteristic features of asthma. It was shown that several inflammatory mediators were involved in airway remodelling [159, 160] and the most important among them is transforming growth factor beta1 TGF-β1 [161, 162]. The researchers convincingly proved the effect of γ-tocotrienol on the TGF-β1 induced differentiation of human airway smooth muscle and the extracellular deposition and the down-signaling of the airway smooth muscle cells activated by TGF-β1 [158]. This study suggested that γ-tocotrienol could play a therapeutic role in regulating airway remodelling in asthmatic patients.

12. Gastroprotective effect

Non-steroidal anti-inflammatory drugs (NSAIDs) are probably the most frequently used therapeutic agents in the world [163] for the treatment of pain, arthritis and trauma, besides many other indications. Achieving more than 73 million prescriptions per year [164], NSAIDs have been notoriously associated with gastrointestinal bleeding [165]. In an earlier study on a rat model of three different study groups [166], it was found that both TRF and tocopherol were equally

effective in preventing aspirin-induced gastric ulcer. In another recent study [167] on a rat model comparing control to a group fed with omeprazole and another group with tocotrienol, it was discovered that while both groups were effective against gastric ulcer, the tocotrienol group displayed various modes in its protective effect – via the nitric oxide (NO) pathway and superoxide dismutase (SOD) activity – and in reducing TNF-α activity.

13. Radioprotective effect

With the increasing adoption of radiation in both clinical and non-clinical applications [168], human exposure to radiation is set for an exponential increase. Radiation toxicity is manifested in oxidative stress and DNA damage [169], inflammatory changes [170] and cell apoptosis [171]. Studies were carried out to examine the potential benefits of naturally occurring products such as vitamin E, a potent anti-oxidant with the capacity to neutralize free radicals from radiation exposure by donating H atoms [172]. It was shown that exposure to ionizing radiation yields reactive oxygen species (ROS) and nitrogen species (RNS), hydroxyl radical, superoxide, peroxynitrite and hydrogen peroxide. These reactive species of ROS and RNS with radiation-induced radicals damage proteins, DNA and lipids, besides activating intracellular signalling pathways that release cytochrome C from the mitochondria, eventually leading to cell apoptosis [173–175]. Thanks to its potent anti-oxidant properties, tocotrienol has been a subject of several studies and has been reported to be radioprotective [176–178]. Studies on a rat model [176, 179] have showed the protective effect of γ-tocotrienol against radiation-induced DNA damage through the activation of haematopoietic progenitors, red and white blood cells including platelets, and also through the inhibition of 3-hydroxy-3-methylglutaryl-CoA Reductase (HMG-CoA Reductase) – a protein-coding gene-mediated nitrosative stress [180]. It is also proven that γ-tocotrienol increases serum IL-6 and granulocyte colony stimulating factor (G-CSF), both of which induce haematopoiesis and are protective against radiation-induced neutropenia and thrombocytopenia in mice [181].

14. Anti-cancer effect

Cancer (also known as malignant tumours or neoplasms) is the second leading cause of mortality globally according to WHO [182], with an estimated 9.6 million deaths in 2018. The cancer burden keeps on growing inexorably, exerting its pressure emotionally and financially on individuals and families, not to mention the community and health system. While chemotherapy has been the mainstay of treatment, it is limited by a few factors such as tumour immune evasion [183, 184], drug toxicity and resistance, and inappropriate cancer metabolism [185], all of which lead to possible metastases and recurrence. Hence the search for a more effective and potent anti-cancer agent. Buoyed by the earlier success in extracting anti-cancer agents from plants, the search has been on for a natural product. Tocotrienol became the choice of study due to its multitargeted actions in destroying cancer cells, promoting cancer cells apoptosis and inhibiting angiogenesis and metastases [186–188]. It is certainly beyond the scope of this writing to discuss all the research conducted on the effects of tocotrienol on cancer. Notable among the most recent research papers on this subject are "Tocotrienols and Cancer: From the State of Art to Promising Novel Patents" [189] and "Tocotrienols Modulate a Life or

Death Decision in Cancers" [190]. For our purpose, it suffices to understand how tocotrienol exerts its anti-cancer effect. The mechanism of action is illustrated in **Figure 5**. Indeed, the effect of tocotrienol in suppressing the growth of different form of malignancies, including that of the uterine, ovary, prostate, liver, gastric, breast and brain, is well documented [191, 192]. **Figure 5** below depicts the possible mechanism of actions of tocotrienols in exerting its anti-cancer effect [193].

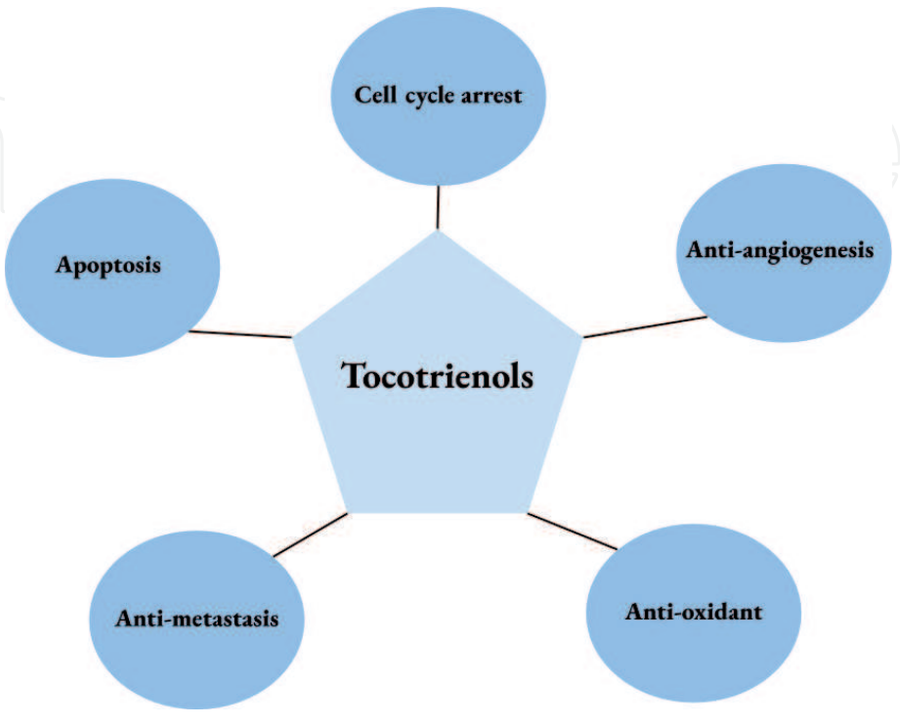


Figure 5.
Anti-cancer mechanism of actions of tocotrienol.

14.1 Apoptosis

As an innate defence mechanism against cancer, apoptosis is considered critical [194, 195]. Natural molecules have the potential to exert their apoptosis-inducing quality [196–199] and tocotrienols are one of those compounds that could exert the anti-neoplastic activity via this apoptosis mechanism [200]. One study [201] demonstrated that γ-tocotrienol caused substantial apoptosis in tumour cells by down-regulating several oncogenic gene products' expression. It also displayed chemosensitisation and anti-invasive properties against prostate cells [202], and induced apoptosis in gastric cancer cells [203]. In another study [204], both α-tocopherol and γ-tocotrienol showed anti-proliferative activities and apoptosis on both the cervical carcinoma and hepatoma cell lines. Tocotrienols were also found to induce apoptosis in breast cancer cell lines [205] and effected both apoptosis and antiangiogenic activity of murine mammary cancer cells in mice [206]. A different study revealed that δ-tocotrienol is more efficacious than both α- and γ-tocotrienol in exerting its apoptosis effect on both human lung adenocarcinoma and glioblastoma [207]. In a study [208] on human bladder cancer cells, δ-tocotrienol was observed to have effectively induced apoptosis and chemosensitization, in addition to arresting the growth of human bladder cells. A study conducted on human chronic myeloid leukaemia cells [209] found that γ-tocotrienol was an effective inducer of apoptosis in the myeloid leukaemia cells. TRF mixture is also found to prevent cell proliferation, migration, and tumour cell invasiveness by inducing apoptosis in non-small cell lung cancer

cells (NSCLC) [210]. Furthermore, γ-tocotrienol exerted its anti-proliferative effect and induced apoptosis in human cervical cancer cells [211].

14.2 Cell cycle arrest

Cell cycle has its checkpoints from one phase to another, and any aberrant activation may lead to the proliferation of tumour cells. Hence, it is imperative to target these checkpoints in cancer therapy [212]. The cell cycle and its checkpoints are illustrated in **Figure 6** below [213].

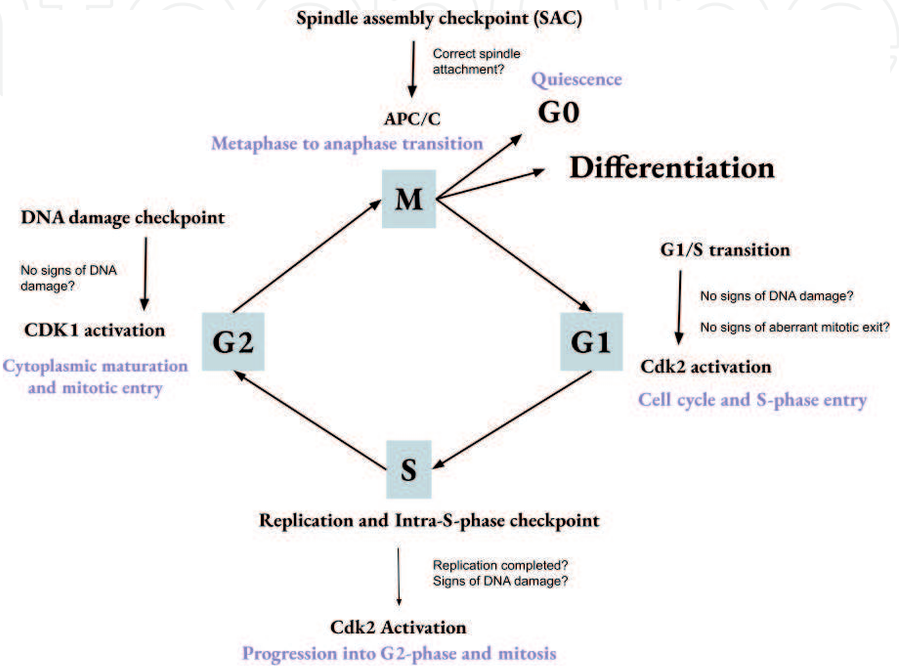


Figure 6.
The cell cycle and its checkpoints. There are four phases in the cell cycle – G1 phase, S-phase, G2-phase, and M-phase. The checkpoints control the progression of the cell cycle which is unidirectional in nature.

It is worthy of note that γ-tocotrienol had an effect on the G2/M arrest and apoptosis of breast cancer cells, with the potential to reverse multi-drug resistance [214]. Another study on brain cancer cells [215] documented the anti-proliferative effect of γ-tocotrienol in combination with another agent, jerantinine (an indole alkaloid obtained from leaves extract) which led to G0/G1 cell cycle arrest. The combination effect of γ-tocopherol and δ-tocotrienol was also cited in successfully arresting the G1 phase and G2/M phase in the cell cycle of prostate cancer cells [216], besides inhibiting prostate cancer cell growth. A synergistic effect was observed between δ-tocotrienol and geranylgeraniol (a compound synthesised endogenously in the human body via mevalonate pathway) in arresting G1 phase activity in prostate carcinoma cells [217]. With the addition of γ-tocotrienol, the cell cycle at G0/G1 phase was also arrested while the S phase was reduced in cervical cancer HeLa cells [211]. In short, tocotrienols, whether alone or in combination with other agents, are capable of exerting their inhibitory effects through the checkpoints in the cell cycle. This promising evidence supports their future development as therapeutic agents in modulating the checkpoints of the cell cycle.

14.3 Anti-angiogenesis

Angiogenesis, defined as the formation of new blood vessels, is an important process for tumour growth and metastases [218] triggered by chemical signals from tumour

cells. Researchers have identified more than a dozen angiogenic activators, including vascular endothelial growth factor (VEGF) which is a powerful angiogenic factor in neoplasms as well as normal tissue [219]. Therefore, targeting these angiogenic factors seemed to be the most rational intervention to combat tumour growth [220, 221]. Several trials [222–224] have shown the effectiveness of tocotrienol in inhibiting angiogenesis in various cancers, with the process illustrated in **Figure 7** below [225].

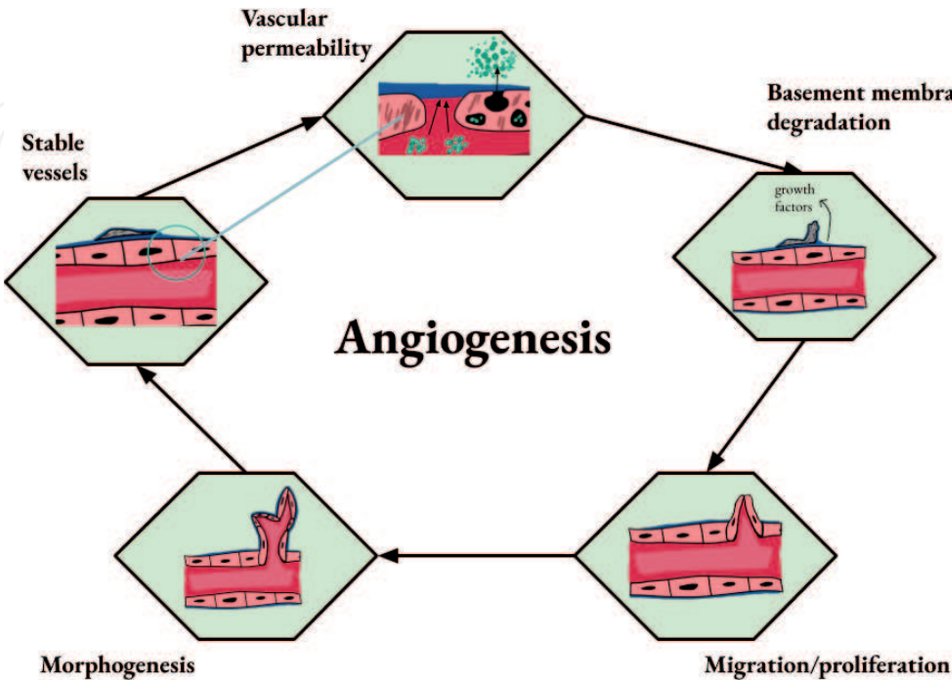


Figure 7.
The angiogenic cascade. (A) During the process of angiogenesis, stable vessels undergo (B) a vascular permeability increase which allows extravasation of plasma proteins. (C) Degradation of the ECM by matrix metalloproteases (MMPs) relieves pericyte-endothelial cells (EC) contacts and liberates extracellular matrix (ECM)-sequestered growth factors. (D) ECs then proliferate and migrate to their final destination and (E) assemble as lumen-bearing cords.

A study has shown that both δ- and γ-tocotrienol inhibit angiogenesis and proliferation in human hepatocellular carcinoma cells [226]. In another study, it was demonstrated that δ-tocotrienol inhibited tumour angiogenesis via VEGF and MMP-9 in pancreatic cancer cells; it also decreased the expression of cell surface markers in cancer stem cells [227]. Another study revealed that δ-tocotrienol exhibited potential against both melanoma and its associated stem cells [228, 229], while displaying suppressive action on prostate cancer stem-like cells [230]. Recent findings also indicated that tocotrienols displayed antiangiogenic protein expression of VEGF in colorectal cancer [231], malignant mesothelioma [232], breast cancer [233], ovarian carcinoma [234], and head and neck squamous cell carcinoma [235]. All these studies provide ample evidence of the role of tocotrienol in arresting tumour growth by inhibiting angiogenesis.

14.4 Anti-metastasis

The morbidity and mortality from cancer are mainly caused by cancer metastases; in fact, almost 90% mortality is thought to be due to metastases [236]. Cancer metastasis starts at the primary tumour with the detachment of metastatic cells which then travel to different parts of the body either through the bloodstream or lymphatic drainage, and thereafter settle and start growing at the distal site [237]. To put it simply, the process of metastasis involves four essential steps: detachment, migration, invasion and adhesion. This is illustrated in **Figure 8** below [238].

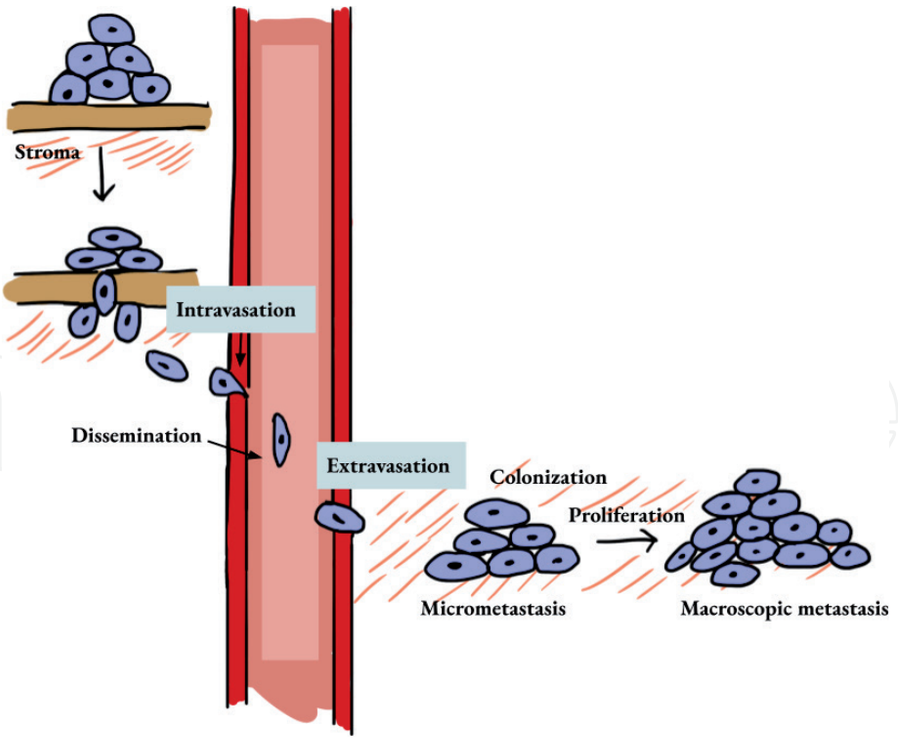


Figure 8.
A schematic representation of the four stages of metastatic dissemination of cancer cells from the primary tumour into the blood circulation, involving detachment, migration, invasion and adhesion.

Cancer survival rate has improved significantly over the years from early diagnosis and inhibition of cancer growth. Nevertheless, the mainstay of cancer treatment for metastasis remains chemotherapy or radiotherapy. Tocotrienols have gained prominence in the last several years due to their anti-proliferative, anti-angiogenic, anti-migratory and anti-metastatic properties as exhibited in vivo and in vitro data [239]. Indeed, for metastasis to occur, cancer cells need to detach and migrate to a distant target organ, a process followed by adhesion and local invasion [240]. The ability of tocotrienol in halting cell migration has been demonstrated in several studies [224, 241–243]. In one study on human umbilical vein endothelial cells (HUVEC), treatment with δ-tocotrienol suppressed VEGF-induced migration by 50% [224]. Another study proved a dose-dependent inhibition of non-small cell lung cancer (NCSLC) cells migration [241], while a different one demonstrated the ability of γ-tocotrienol in inhibiting in-vitro human gastric cells migration [242]. In another study on VEGF-stimulated HUVEC migration essay, it was found that γ-tocotrienol suppressed the migratory potential of the HUVEC cells [243]. After the cancer cells migration, the subsequent event in the process of metastases is cell adhesion and invasion; this is preventable by suppressing the tumour cell invasion after adhesion [242]. An in vitro study has shown that after being treated with δ-tocotrienol, a pancreatic cancer mouse model no longer displayed any signs of invasive cancer [244]. A previous study has also showcased the ability of γ-tocotrienol in halting the invasion of the prostatic cancer cells in the control group [202], thereby suppressing the main process in the perpetuation of metastasis.

14.5 Anti-oxidant

Oxidative stress refers to an imbalance of free radicals or reactive oxygen species (ROS) and antioxidants in the body [245]. This imbalance has been linked to a litany of chronic conditions including neurodegenerative disease, cardiovascular disease, diabetes mellitus, and many other pathologies such as cancer [246]. A variety of

deleterious modifications of macromolecular components such as DNA, lipids and proteins were due to this chronic oxidative stress [247]. There is also a possibility that ROS mediates an indirect attack on DNA, resulting in secondary reactive intermediates that would couple with the DNA bases to form DNA adducts [248]. This formation is central to what is known as carcinogenesis [249]. Oxidative lesions have been implicated in the aetiology of cancer due to the oxidative DNA damage [250–254]. It is now clear how carcinogenesis is perpetuated by this oxidative stress process, as illustrated in **Figure 9** below [255].

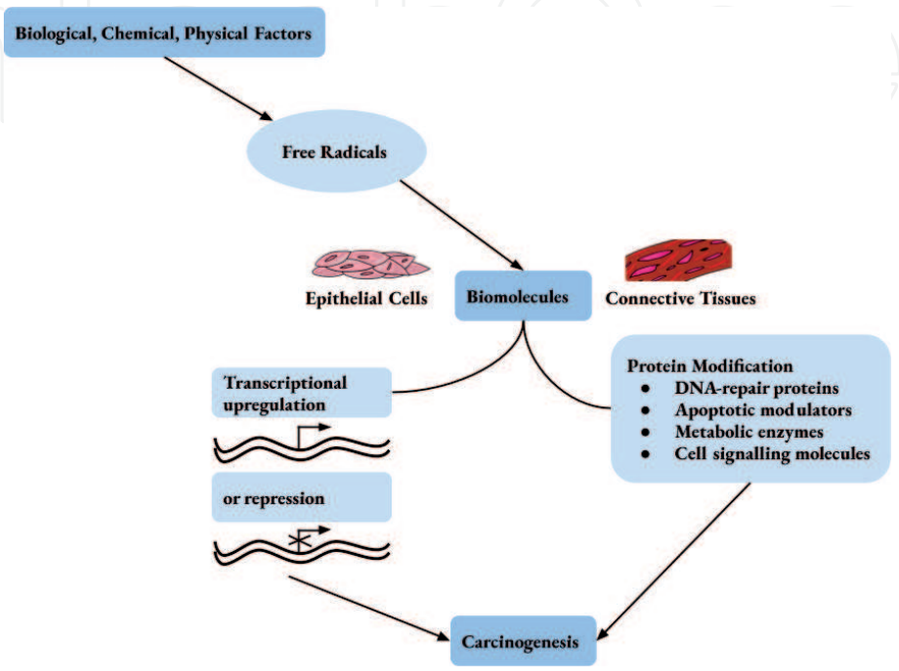


Figure 9.
Oxidative stress mediating cancer development. Biological, chemical and physical factors mediated free radicals (ROS) which damage the biomolecules that initiate the neoplastic cells through the up-regulation of transcriptional factors and inactivation of tumour suppressor genes. They also alter the functions of DNA repair proteins, apoptotic modulators, metabolic enzymes and signalling pathways that induce the neoplastic condition.

Evidence from clinical and laboratory studies have showed that the elevated level of ROS contributed to both cancer initiation and cancer progression. Consequently, the most rational, if not preventive, approach is to use antioxidants for combating ROS [256]. Although the results regarding the use of dietary antioxidants were promising, research on this topic is still inconclusive and controversial [257]. Moreover, while studies have indicated that anti-oxidant supplementation resulted in an increase in survival rates and tumour response, with fewer toxicities than controls, a systematic review previously done on this topic showed no evidence of interference by antioxidants on chemotherapy mechanisms that conclusively proves that anti-oxidants (such as vitamin E) improve tumour response rate or the patients' survival [258]. Despite promising results on improving the side effects from chemotherapy or radiotherapy treatment of cancer, further research into anti-oxidants [259], especially vitamin E in general and tocotrienol in particular, is highly warranted.

15. Discussion

Long ignored despite being close yet superior to its related isomer tocopherol, tocotrienol is increasingly becoming a subject of interest in vitamin E research

among the scientific community. One of the main reasons why it was understudied could be due to its abundant presence in palm oil, itself a much maligned product that had to bear the full brunt of a damaging smear campaign for decades. In fact, palm oil contains about 70% of all tocotrienol homologues namely α-, β-, δ- and γ-tocotrienols. Consequently, it would be no exaggeration to say that palm oil is nature's best kept secret, if not the most promising natural substance in influencing health and disease.

Growing interest in tocotrienols has led to research exploring the molecular basis of their action in health. This chapter has highlighted the recent advances in this rapidly developing field of study. Indeed, recent studies have shown that tocotrienols may have superior chemopreventive or chemotherapeutic effects when used either alone or in combination with tocopherols. Indeed, tocotrienols are well adapted for their biochemical function. Thanks to their organic structure featuring a long-saturated carbon side-chain, they are able to penetrate more efficiently in the lipid membrane and in the intermembrane of tissues containing saturated fatty layers. This ability contributes immensely to their therapeutic efficacy.

Without doubt, the beneficial health effects of tocotrienols are partly related to their anti-oxidant activity. Though both tocotrienol and tocopherol have the ability to scavenge the free radicals directly by donating the phenolic hydrogen of their chromanol ring, tocotrienol is considered a better anti-oxidant due to its generally uniform distribution in the membrane bilayer coupled with a stronger disordering of its membrane lipid structure. Vitamin E, in particular tocotrienol, was shown to play a vital role in maintaining the integrity of the central nervous system through its anti-oxidant property. Indeed, as an organ with very high metabolic needs in terms of oxygen consumption, the brain is extremely susceptible to any forms of oxidative stress. However, current evidence is largely focused on Alzheimer's disease – an age-related inflammatory neurodegenerative disease characterised by the presence of pathognomonic amyloid plaques and neurofibrillary tangles. It is postulated that the main mechanism of action of tocotrienol in attenuating the neurodegenerative changes is via its anti-oxidant action, either by inhibiting the production of ROS or by reducing the lipid peroxidation by-products. Admittedly, a gap still persists in this area insofar as other neurodegenerative conditions (such as Parkinson's disease) are concerned. Notwithstanding the fact that some recent studies have reported contradicting outcomes on the relationship between tocotrienol and Parkinson's disease, it is hoped that future studies will shed more light in this area.

Given the potential of tocotrienol in preventing auto-immune diseases, especially through its anti-inflammatory properties, the evidence available warrants further investigation into its molecular action. That would enable the development of drug targets to combat inflammatory diseases. Nevertheless, the therapeutic potential of tocotrienol as an anti-inflammatory agent cannot be denied. On the one hand, δ-tocotrienol somehow lessened joint inflammation in arthritic rats by reducing the level of proinflammatory cytokines. On the other hand, in a human study, γ-tocotrienol improved airway remodelling that characterises bronchiole asthma which is essentially an inflammatory disorder. Another rat model also showed that tocotrienol is effective against gastric ulcer. The gastroprotective effect of tocotrienol was mainly modulated through a reduction in inflammatory response, besides its anti-oxidative properties. Though this protective effect was witnessed in various animal models of gastric ulcer, clinical studies on the use of tocotrienol in patients with peptic ulcer disease or even gastritis are yet to be conducted.

As one of its health benefits, tocotrienol – through its ability to improve the lipid profiles – has been shown to confer a cardioprotective effect, at least with respect to atherosclerosis, myocardial infarction and thrombosis. There is sufficient evidence

to prove that tocotrienol, especially in the form of γ-tocotrienol, is anti-cholesterolaemic; this is achieved by inhibiting the mevalonate pathway responsible for the synthesis of cholesterol and other isoprenoids. Overall, the potential of tocotrienol as a potential hypocholesterolaemic agent is evidenced by in-vitro, in-vivo and human clinical trials. Thus, tocotrienol supplementation is highly recommended for patients suffering from hypercholesterolaemia.

In fact, human studies on the effects of tocotrienol on cardiovascular disease have been limited to its anti-hypercholesterolaemic property. The only exception is an ongoing clinical study at the National Heart Institute of Kuala Lumpur, Malaysia. Conducted by this author, it investigates the ability of tocotrienol in preventing atrial fibrillation in post-coronary artery bypass grafting surgery. Indeed, while tocotrienol has been shown to be protective against cardiovascular disease in animal models, its direct effects on humans are inconsistent. Our current evidence serves as a basis for further clinical trials aimed at validating the positive effects of tocotrienol especially among patients susceptible to cardiovascular complications.

The potency of α-tocotrienol as an anti-atherogenic agent, besides being a bulwark against cerebrovascular disease, is well documented. Several animal models have demonstrated that tocotrienol protects against ischaemic stroke by attenuating brain lesion volume. A similar scenario was observed during clinical trials where it was shown to attenuate the progression of brain white matter lesion. Consequently, it could be safely concluded that tocotrienol protects against cerebrovascular disorders.

Tocotrinol-rich vitamin E (TRF) has been observed to ameliorate diabetes in animal studies through its superior antioxidant, anti-hyperglycaemic and anti-inflammatory properties. A recent clinical trial also showed that TRF significantly reduced serum creatinine level, and therefore has the potential to be used as a supplement in the treatment of diabetic nephropathy. Moreover, the anti-diabetic properties of tocotrienol in preventing nephropathy, retinopathy and neuropathy have been proven in several other studies.

Studies conducted on animal models have demonstrated that tocotrienol can mitigate, if not prevent, osteoporosis in rats by reducing oxidative stress and inflammation. Indeed, tocotrienol has been proposed to counter osteoporosis which leads to fragility fracture, a leading cause of morbidity and mortality worldwide. It is postulated that tocotrienol mediated bone protection via its anti-oxidant, anti-inflammatory, mevalonate suppression and gene-modulating properties. Despite strong evidence in animal models showing improved bone structure and strength after tocotrienol supplementation, limited human clinical trials on the effects of tocotrienol on bone health has been a serious impediment to its clinical use.

The role of γ-tocotrienol in protecting against radiation toxicity has been a subject of numerous animal studies, and the results are very promising. With the widespread use of ionising radiation in various non-clinical applications such as construction, sterilization of food products and engineering, exposure to radiation – whether intentional or unintentional – is very high. Studies have shown that γ-tocotrienol has a protective effect against radiation injury by increasing haematopoietic progenitors, neutrophils, platelets, white blood cells and reticulocytes. It has also been demonstrated that γ-tocotrienol protects against vascular injury by inhibiting HMG-CoA reductase. Since tocotrienols accumulate in the small intestine and colon at a higher level than tocopherols, they could protect the gastrointestinal tract from injury.

Last, but certainly not least, with cancer being one of the leading causes of death worldwide, the role of tocotrienol as an anti-cancer agent cannot be underestimated. Tocotrienol has been shown to modulate intracellular signalling pathways; it induces apoptosis and cell cycle arrest, and inhibits angiogenesis, cell proliferation

and metastases. Compared to its isoform tocopherol, tocotrienol displayed superior activities in anti-cancer studies. Indeed, in a structural-activity relationship study, the chromanol ring and phytyl carbon tail played a major role in inducing cancer cell apoptosis. However, despite the abundance of cell and animal studies investigating the role of tocotrienol, evidence regarding its preventive effects on cancer remain inconclusive, with most trials still at the preliminary stage. Nonetheless, our improved understanding of the mechanism of actions of tocotrienol in the suppression of cancer cell growth by inhibiting proliferation, migration, and invasion should not be discounted; it will inform more targeted research into cancer therapy in the future.

16. Conclusion and future direction

This chapter has highlighted the wonders of tocotrienols which, thanks to their efficacy and safety profile, are attracting increased attention. Examining the latest research into tocotrienols, it has demonstrated the undeniable benefits of tocotrienols in conferring protection against cancer as well as a whole litany of diseases including cardiovascular, metabolic, autoimmune, bone and neurological diseases. Admittedly, many of the researches were conducted in the laboratory, with some preclinical trials translated into clinical trials. Nonetheless, it is hoped that more randomised clinical trials will be carried out on a global scale in the near future. From the vessels in the heart to neurons in the brain, tocotrienols have the extraordinary potential to be the future of vitamin E research.

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