Chapter

Neuroprotective Potentials of Natural Vitamin E for Cerebral Small Vessel Disease

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Abstract

Cerebral small vessel disease (CSVD) refers to a spectrum of clinical and neuroimaging findings resulting from pathological processes of various etiologies affecting cerebral arterioles, perforating arteries, capillaries, and venules. It is the commonest neurological problem that results in significant disability, but awareness of it remains poor. It affects over half of people over 65 years old and inflicts up to third of acute strokes, over 40% of dementia, and a significant decline in physical ability in otherwise asymptomatic, aging individuals. Moreover, the unifying theory for the pathomechanism of the disease remains elusive and hence the apparent ineffective therapeutic approaches. Given the growing literature for natural vitamin E (tocopherols and tocotrienols) as a potent antioxidant, this chapter attempts to consolidate the contemporary evidence to shed plausible insights on the neuroprotective potentials of natural vitamin E in addressing the heterogenous CSVD spectrum, in health and in disease.

Keywords: cerebral small vessel diseases, vitamin E, antioxidants, dementia, aging

1. Introduction

The recognition of vitamin E for its nutritive value was first linked to reproductive health in laboratory rats, then coined as factor X [1]. While alpha-tocopherol was the first vitamin E isomer to be recognized, there are now eight chemically distinct isomers known, consisting of alpha (α), beta (β), gamma (γ), and delta (δ)-isoforms of tocopherols and tocotrienols [2]. Current recommendations for adequate intake values are established based on α-tocopherol alone, whereas other forms of vitamin E need to meet other criteria [3]. Nature affords tocopherols in abundance, particularly in plants such as peanuts, sunflower seeds, and sesame seeds. The major dietary source of tocopherol is largely from corn and soybean oil consumption [4]. In contrast, the less ubiquitous tocotrienols are found in certain cereals and vegetables such as palm oil and annatto. A non-food source of tocotrienols is also recognized, namely, the latex of the rubber plant [2].

The well-established bioactivity of vitamin E is its antioxidant property by means of lipid peroxidation of cellular membranes [2]. As such, this property lends vitamin E the roles in promoting vascular health in arterial compliance studies and endothelial dysfunction biomarker. Pertinent to this, vitamin E

involvement is the vascular endothelium, which lines the intraluminal surface of blood vessels and is involved in the regulation of vascular tone, platelet activity, thrombosis, and the overriding pathogenesis of atherosclerosis [5, 6]. Vitamin E engages with the production of nitric oxide (NO) that relaxes the vascular smooth muscle while limiting free radicals to maintain arterial compliance [7]. More recently, vitamin E has been linked with anti-atherogenic effects that decrease low-density lipoprotein (LDL) oxidation and downstream inhibition of protein kinase C (PKC), adhesion molecules, monocyte transmigration, and vascular smooth muscle cell proliferation [8].

Therefore, the foregoing facts on vascular health and vitamin E profiles offer interrelated perspectives for a largely unexplored neurological condition termed cerebral small vessel diseases (CSVD). CSVD variable manifestations inflict small blood vessels or microcirculation at the subcortical and deeper parts of the brain. It has been widely reported to cause cerebral ischemic stroke or lacunar stroke that accounts for nearly a third of all stroke subtypes worldwide [9–12]. The pathological consequences of small vessel disease on the brain parenchyma rather than the underlying diseases of the vessels is frequently viewed as the basis of CSVD [13]. Notably, CSVD lesions can be silent, and the affected individual may not have any apparent clinical symptoms. This silent (subclinical) lesion, with higher numbers (single or multiple), poses as a risk for vascular cognitive impairment, dementia, Alzheimer's disease, and full-blown stroke [14, 15].

Furthermore, aging and chronic hypertension are known to accelerate CSVD, as the two conditions (physiological and pathological, respectively) may result in less efficient ability to self-regulate cerebral blood flow (cBF) from the concurrent varying systemic blood pressure levels and increased arterial stiffness which increases the speed and flow pulsatility in cerebral arterioles [16]. These hemodynamic changes are postulated to cause variable degrees of endothelial damage in the blood-brain barrier (BBB) and alter its permeability through an increase of the shear stress [17]. Hence, the BBB breakdown is an important etiopathogenesis feature of CSVD [17–19].

In addition, there is an elevated production of reactive oxygen species (ROS) in CSVD that ultimately leads to endothelium dysfunctions [20, 21]. This is mainly due to the cumulative reactions and processes (i.e., high blood pressure, very low density of lipoproteins, diabetes mellitus, homocysteinemia, and smoking) that trigger and escalate the inflammatory responses and oxidative stress [20, 21]. This, in turn, heightens the release of adhesion molecules and recruits leukocytes, causing higher leukocyte-endothelial cell (EC) adhesion and reduced cBF. Accordingly, nicotinamide adenine dinucleotide phosphate (NADPH) oxidases intensify the oxidative stress (a major source of ROS in vessel wall) and the consequent destructive impact on EC-dependent NO signaling [22, 23].

Collectively, this chapter focuses on highlighting the contemporary evidence on vitamin E, especially α-tocopherol and α-tocotrienol, their neuroprotective potential in relation to the heterogenous spectrum of CSVD manifestations, in promoting health as we age, and in mitigating disease.

2. Natural sources of vitamin E

2.1 Forms and structure

Vitamin E was first discovered in 1922 by Herbert Evans and Katherine Bishop at the University of California in Berkeley when they studied nutritive dependencies in reproduction [1]. They observed that rats fed with a purified diet of casein 18%,

cornstarch 54%, lard 15%, butterfat 9%, and salts 4% and adequate vitamin A (as cod liver oil), vitamin B (as yeast), and vitamin C (as orange juice) did not reproduce. They observed in females defective placental function, whereas the ovaries, ovulation, and implantation were unimpaired; and in males, there was a complete atrophy of the seminiferous epithelium [24, 25]. The addition of lettuce to the diet prevented embryo resorption during rodent gestation, and healthy pups were born again, thus, leading to the discovery of an anti-sterility factor, then termed as factor X. Wheat germ oil was later found to be a rich source of factor X. It was not until some 10 years later that Evans successfully isolated the components of vitamin E family and named them tocopherols (Greek: *toc* (child), *phero* (to bring forth), and *–ol* because it behaves chemically like an alcohol) [25, 26].

Meanwhile, tocotrienol was named by Bunyan and colleagues, when they identified the unsaturated derivatives of tocols, isolated from the latex of the rubber plant (*Hevea brasiliensis*) [27]. The structure of tocotrienols was further described by Pennock and colleagues, who found that palm oil was a rich source of this "new tocopherol" [28]. Palm oil derived from *Elaeis guineensis* (African oil palm) now represents the richest source of the lesser characterized vitamin E, α-tocotrienol.

α-Tocopherol is currently the only form of vitamin E recognized to meet human requirements, and recommended adequate intake values are established based on α-tocopherol alone. Other forms of vitamin E must fulfill the following to be recognized as vitamin E: (1) converted to α-tocopherol in humans and (2) recognized by the α-tocopherol transfer protein. Plasma α-tocopherol concentrations in humans range from 11 to 37 μmol/L, whereas γ-tocopherol concentrations are roughly 2–5 μmol/L, and tocotrienol concentrations are less than 1 μmol/L in non-supplemented humans [3].

Tocopherols are widely found in nature, predominantly in plant seeds such as peanuts, sunflower seeds, almonds, walnuts, and sesame seeds. The major dietary source of tocopherol comes from the widespread use of corn and soybean oil [4]. Tocotrienols, which are less ubiquitous, are found in certain cereals and vegetables such as palm oil, rice bran oil, and annatto. Lower levels of tocotrienols can be found in grapefruit seed oil, oats, hazelnuts, maize, olive oil, buckthorn berry, rye, flaxseed oil, poppy seed oil, and sunflower oil [3]. A non-food source of tocotrienols is the latex of the rubber plant. While it has been shown that the different vitamin E forms are interconvertible by plants, there has been no convincing evidence that the same is true for animals [29].

While alpha-tocopherol was the first vitamin E isomer to be recognized, there are now eight chemically distinct isomers known, consisting of alpha (α), beta (β), gamma (γ), and delta (δ)-isoforms of tocopherols and tocotrienols [2], as shown in **Figure 1**. The molecular structure of vitamin E is based on a chromanol ring with a side chain at the C2 position. While the lipophilic tail of tocopherols is completely saturated, tocotrienols have three double bonds, at the 3′, 7′, and 11′ positions. Plants synthesize eight different forms of vitamin E, tocopherols and tocotrienols, which include α, β, γ, and δ forms that differ in the number of methyl groups on the chromanol ring [29]. The slight difference in structure between isoforms translates into striking variations in activity. Compared with tocopherols, tocotrienols are more efficiently incorporated into membranes and cultured cells [30], thus giving rise to more potent antioxidant activities.

2.2 Mechanism and regulation of metabolism

Upon oral administration, vitamin E, a lipid-soluble vitamin, requires biliary and pancreatic secretions in order to form micelles for the subsequent uptake by intestinal epithelial cells [3]. Therefore, the absorption of vitamin E is enhanced if

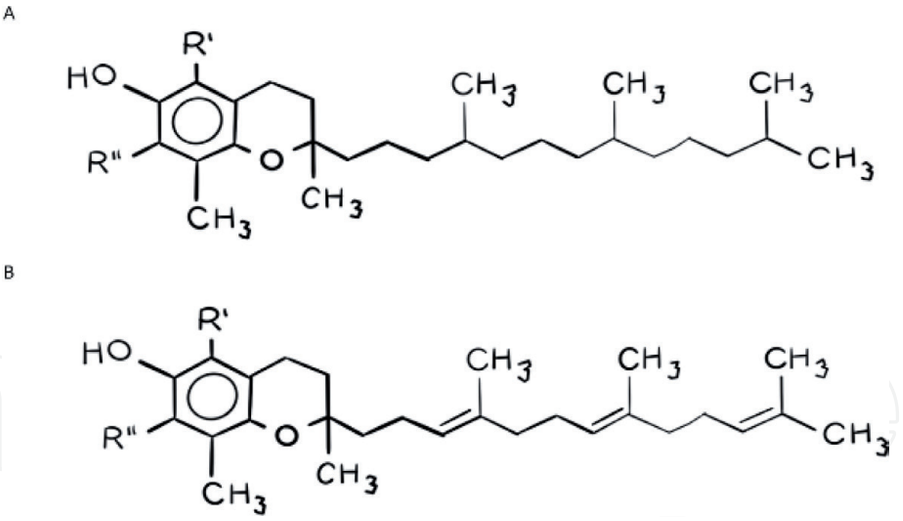

Figure 1.
Chemical structures of (A) tocopherol and (B) tocotrienol. Note the three double bonds in the tocotrienol side chain. Note: Isoforms—α (R′ = CH_3, R″ = CH_3); β (R′ = CH_3, R″ = H); γ (R′ = H, R″ = CH_3); δ (R′ = H, R″ = H).

taken with food which contributes fat, thereby triggering the secretion of enzymes that facilitate the formation of micelles required for absorption. Despite many years since its discovery, there is still a lack of understanding of the mechanism of absorption, liver trafficking, and disposition of vitamin E isoforms [31].

The general understanding of vitamin E absorption and trafficking is that orally administered vitamin E undergoes intestinal luminal processing, where it accumulates in lipid droplets, which then coalesce with nascent chylomicrons [32]. The vitamin E isoforms are not discriminated during the intestinal absorption or incorporation into chylomicrons. Chylomicrons then transport vitamin E from the intestine through circulation to the liver, which metabolizes or resecretes vitamin E back into the plasma for trafficking to tissues via enriched lipoproteins.

After the liver takes up chylomicron remnants, vitamin E isoforms with greater affinity to α-tocopherol transport protein (αTTP) are preferentially bound for transport to tissues, thereby avoiding catabolism. αTTP expressed in the liver is required to facilitate vitamin E transport from the liver to other tissues and organs. The discrimination of vitamin E isoforms occurs in the liver as a result of differing affinity of isoforms to αTTP. αTTP has the ability to bind to both α-tocotrienol and α-tocopherol, but αTTP binds to α-tocotrienol with approximately 10 fold lower affinity than that for α-tocopherol [33]. All lipoproteins are involved in the trafficking of α-tocopherol to the tissues, although very low-density lipoprotein apparently leaves the liver preferentially enriched in α-tocopherol compared with LDL or high-density lipoprotein (HDL) [29]. Discrimination between dietary forms of vitamin E is dependent upon the hepatic αTTP to maintain circulating α-tocopherol [34]. α-tocopherol is also most retained in tissues due to preferential binding by αTT, facilitating secretion into plasma [2] and trafficking to tissues, whereas large portions of other forms of vitamin E are catabolized through general xenobiotic processes [4].

Interestingly, a study using αTTP knockout mice showed that orally administered α-tocotrienol was absorbed and delivered to vital organs, despite being deficient of αTTP [35]. In organs such as adipose tissue, skin, skeletal muscle, and the heart, α-tocotrienol levels were many folds higher than α-tocopherol in supplemented αTTP knockout mice. Oral supplementation of the female mice with α-tocotrienol also restored fertility, suggesting that it can be successfully delivered to the relevant tissues and that α-tocotrienol supported reproductive function under

conditions of α-tocopherol deficiency. These findings suggest TTP-independent mechanisms for the tissue delivery of oral α-tocotrienol. While αTTP may contribute to tocotrienol trafficking, αTTP does not represent a major or sole mechanism of α-tocotrienol transport in the body [35].

Vitamin E is metabolized by ω-hydroxylation by cytochrome P450 (CYP), followed by β-oxidation and conjugation to generate carboxychromanols and conjugated counterparts [2, 29]. The tail of vitamin E isoforms is ω-hydroxylated by CYP 4F2 and subjected to several rounds of β-oxidation, which ultimately results in the formation of carboxyethyl hydroxy chromanol (CEHC) (**Figure 2**). Thus, the tail-shortened, water-soluble metabolite, CEHC, is synthesized and excreted in the urine [36]. Conjugation such as sulfation and glucuronidation of the phenolic on the chromanol may also take place in parallel with β-oxidation when there is a high intake of vitamin E forms [4]. Although α-tocopherol largely escapes catabolism and ends up in the blood circulation, α-CEHC is synthesized endogenously when the quantity of hepatic α-tocopherol exceeds the capacity of αTTP to facilitate α-tocopherol secretion from the liver into the circulation [31].

Traber and colleagues established that urinary α-CEHC might be useful to noninvasively assess α-tocopherol adequacy, especially in populations with metabolic syndrome-associated hepatic dysfunction that likely impairs α-tocopherol trafficking. Their finding also suggests that people with metabolic syndrome may have a higher requirement for vitamin E due to poorer trafficking leading to lower apparent α-tocopherol bioavailability. However, it is still unknown whether urinary α-CEHC excretion reflects α-tocopherol intake from a single meal or whether its changes reflect long-term vitamin E status [31].

Recently, Traber and colleagues, which lead as one of the most prolific research groups in vitamin E tocopherol, suggested novel approaches to assess α-tocopherol absorption and trafficking in order to establish human vitamin E requirements [32]. Their study observed that the absorption of α-tocopherol is not necessarily limited by the absence of fat or fasting and that the absorption is highly dependent on chylomicron assembly processes. The transport of α-tocopherol across the intestines may be prolonged during fasting and

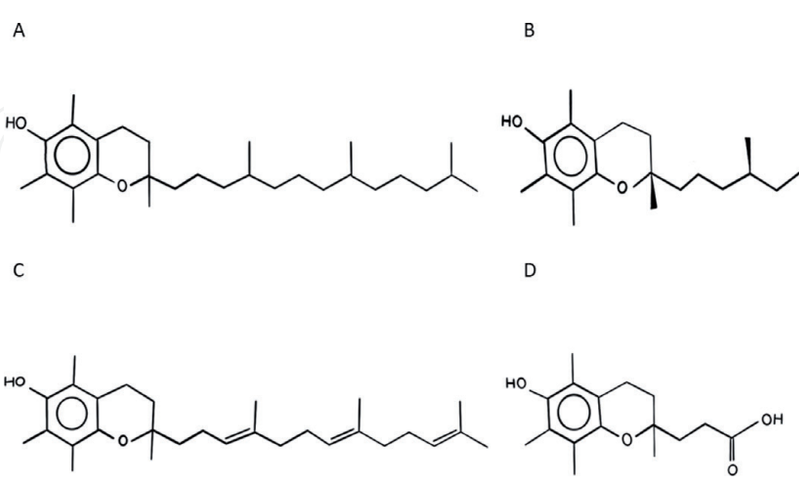

Figure 2.
Tocol structures. The chromanol head group is identical in the alpha-forms of synthetic (A) all-racemic α-tocopherol [2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl) chroman-6-ol], (B) natural (RRR) α-tocopherols [(R)-2,5,7,8-tetramethyl-2-((4R,8R)-4,8,12-trimethyltridecyl) chroman-6-ol], (C) α-tocotrienol [2,5,7,8-tetramethyl-2-((3E,7E)-4,8,12-trimethyltrideca-3,7,11-trien-1-yl) chroman-6-ol], and (D) the metabolite of all three isoforms, α-carboxyethyl hydroxychromanol (CEHC) [3-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl) propanoic acid]. CEHC results from the ω-hydroxylation, followed by β-oxidation of the side chain (as well as conjugation with glucuronide, sulfate, or other compounds), yielding a water-soluble molecule that is largely excreted in urine [34].

potentiated by eating. However, the authors recognized the conclusion derived from the study has several limitations, including small sample size, lack of randomization or blinding, and compliance issues, leading to an imbalance with attendant potential for baseline and residual confounding. Nevertheless, if proven in a larger trial, this observation changes the conventional thinking that vitamin E needs to be taken with or immediately after meal to enhance absorption and also reflects that there is still much to learn on the absorption and transport of vitamin E in humans.

2.3 Antioxidant activities

The most established bioactivity of vitamin E is its antioxidant property, primarily against lipid peroxidation in biological membranes [2]. By quenching the lipid radicals, vitamin E, as chain-breaking antioxidant, terminates the chain reaction of the oxidation of polyunsaturated fatty acids (PUFAs) [3]. This function is critical to ensure the integrity of cellular membranes and systems which rely on the abundance of PUFAs, such as the nervous system. Hence, neurological symptoms such as progressive ataxia and hyporeflexia are manifestations of vitamin E deficiency as a result of malabsorption.

Tocopherols and tocotrienols are potent antioxidants that scavenge lipid peroxyl radicals by donating hydrogen from the phenolic group on the chromanol ring [4]. A synergistic antioxidant system made up of vitamin C and other hydrogen donors such as thiol antioxidants, namely, glutathione and lipoic acid, reacts with the resulting tocotrienoxyl or tocopheroxyl radicals to regenerate vitamin E [37], returning it to its reduced state for further use (**Figure 3**). There is very little evidence in vivo for more advanced vitamin E oxidation products [34].

Packer and colleagues noted that the substituents on the chromanol nucleus and properties of side chain (saturated vs. unsaturated) were critical to the effectiveness of the different vitamin E homologs [37]. Preferential distribution of α-tocopherol to the tissues in vivo may have contributed to its greater impact compared with other homologs, but the structural differences between α-tocopherol and α-tocotrienol have given rise to differences in reactivity observed in in vitro and in vivo studies.

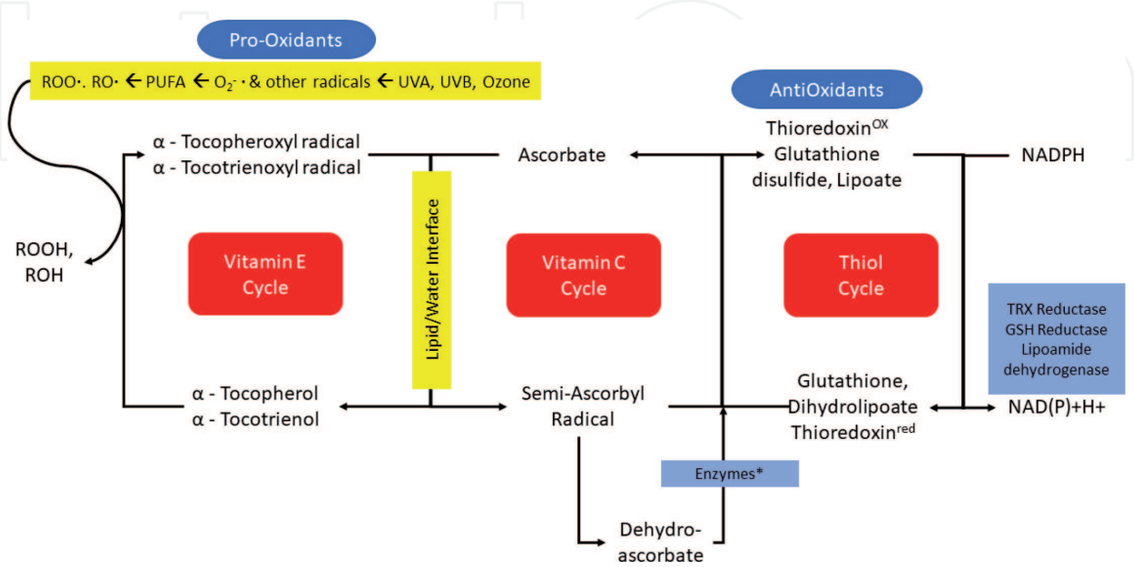

Figure 3.
*The antioxidant network showing the interaction among vitamin E, vitamin C, and thiol redox cycles [37]. Notes: *thiol transferase (glutaredoxin), protein disulfide isomerase, glutathione (GSH)-dependent dehydroascorbate reductase, thioredoxin (TRX) reductase.*

Tocotrienols were suggested to be more effective scavengers of peroxyl radicals due to more even distribution in the phospholipid bilayer, more effective interaction with lipid peroxyl radicals [4], stronger disordering of membrane lipids, and greater recycling of chromanoxyl radical due to closer location to the membrane surface [37]. The chromanoxyl radical of α-tocotrienol was found to be recycled in membranes and lipoproteins more quickly than the corresponding α-tocopheroxyl radical [38].

The antioxidant activity of vitamin E is critical to a healthy nervous system, as evident from the consequences of neurological function under deficient condition. The vitamin E protection of PUFAs leads to neuroprotective effects under pathologic and high oxidative stress conditions. Due to the early discovery of α-tocopherol as an essential vitamer and its ubiquitous nature, most research in vitamin E, concerning the mechanisms of action and physiological implications of deficiency, has centered on tocopherols. Tocotrienols, without having any apparent consequence of deficiency and being not inherently detectable in non-supplemented humans or animals, were not the focus of vitamin E-related research until much later. Since the discovery of rich sources of tocotrienols and subsequent availability as an active ingredient, there is growing evidence that tocotrienols have superior potency in terms of antioxidant activity and modulation of impaired biochemical pathways resulting in physiologically beneficial effects.

Arachidonic acid (AA), one of the most abundant PUFAs of the central nervous system, is highly susceptible to oxidative metabolism under pathologic conditions. [39]. A number of neurodegenerative conditions in the human brain are associated with disturbed PUFA metabolism of AA, including acute ischemic stroke [40]. Cleaved from the membrane phospholipid bilayer by cytosolic phospholipase A_2 ($cPLA_2$), AA is metabolized by both enzymatic and nonenzymatic pathways into neurotoxic metabolites. Palm oil-derived α-tocotrienol at nanomolar concentrations has been shown to attenuate both enzymatic and nonenzymatic mediators of AA metabolism and neurodegeneration [39] (**Figure 4**).

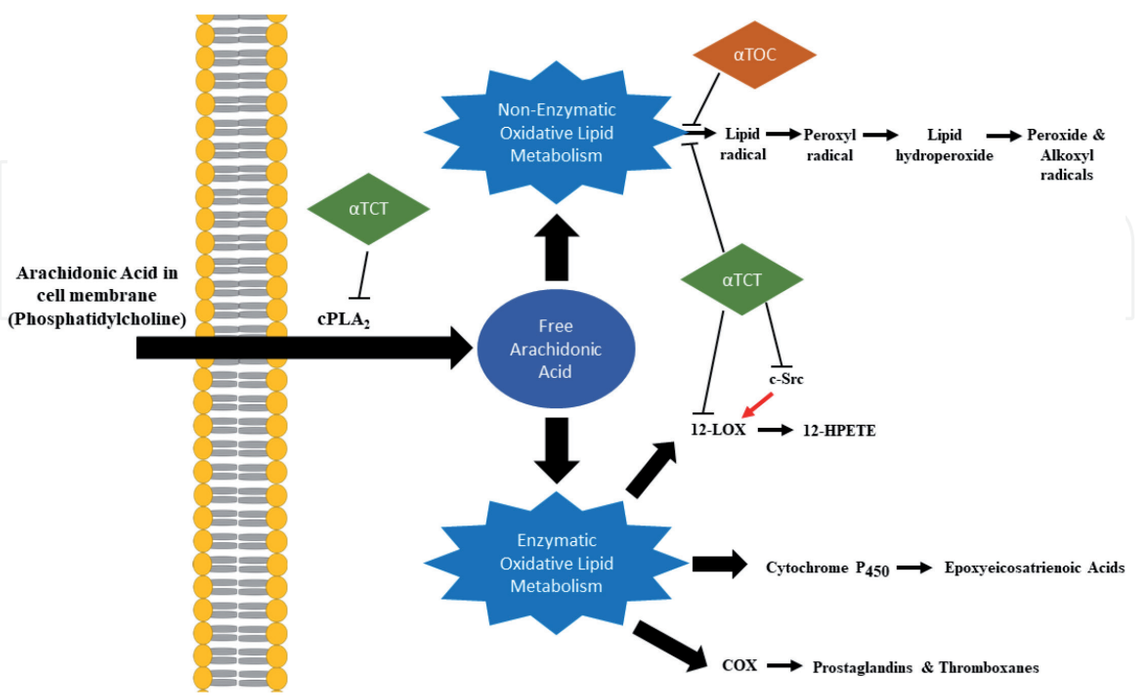

Figure 4.
The arachidonic acid (AA) cascade and potential target sites for α-tocopherols (αTOC) and α-tocotrienols (αTCT) [39]. $cPLA_2$, cytosolic phospholipase A2; 12-LOX, 12-lipoxygenase; c-Src, proto-oncogene tyrosine-protein kinase or simply c-Src (cellular sarcoma); 12-HPETE, 12-hydroperoxyeicosatetraenoic acid; COX, cyclooxygenase.

2.4 Benefits in vascular health

Vitamin E has also been associated with improved vascular health in studies measuring arterial compliance and endothelial dysfunction as biomarkers. Vascular endothelium, which lines the blood luminal surface of vessels, is involved in the regulation of vascular tone, platelet activity, and thrombosis and intimately involved in the pathogenesis of atherosclerosis [5, 6]. The endothelium is an integral part of the vasculature and is involved in promoting an atheroprotective environment via the complementary actions of endothelial cell-derived vasoactive factors [41]. Vasomotor tone is modulated through the release of endothelium-derived relaxing factors (EDRFs) such as NO [6]. Impaired vascular homeostasis can lead to endothelial dysfunction, which contributes to atherosclerosis [41]. Intact endothelium is also needed for normal arterial compliance, a predictor of cardiovascular events. Arterial compliance, which can be assessed by pulse wave velocity (PWV) and augmentation index (AI), can be improved in healthy subjects even with dietary interventions [7].

In a randomized controlled trial, subjects with the following risk factors, hypercholesterolemia (13 subjects), smokers (14 subjects), or both (15 subjects), were supplemented with placebo or vitamin E for 4 months. The authors hypothesized that long-term supplementation with vitamin E would improve endothelium-dependent relaxation in hypercholesterolemic patients and/or chronic smoking, two risk factors that have been associated with increased radical formation, impaired endothelial vasodilator function, and increased plasma levels of autoantibodies against oxidized LDL [6]. The study found the most severe endothelial vasodilator dysfunction in patients with both risk factors present. Vitamin E significantly improved endothelium-dependent relaxation in forearm resistance vessels of hypercholesterolemic smokers. There was a significant relationship between improvement in acetylcholine-induced vasodilation and the change in autoantibody titer against oxidized LDL ($r = -0.59$; $p = 0.002$) [6].

Moreover, in a randomized controlled trial, 36 healthy male volunteers were supplemented with placebo or tocotrienol-rich vitamin (50, 100, 200 mg/day) with self-emulsifying formula for 2 months [7]. Arterial compliance was assessed using carotid-femoral PWV and AI, at baseline and after 2 months of supplementation. Subjects treated with tocotrienols at doses of 100 and 200 mg/day showed significant improvement in arterial compliance with PWV reductions of 0.77 m/s ($p = 0.007$) and 0.65 m/s ($p = 0.002$), respectively. The placebo group did not show a reduction in PWV and AI compared with baseline. The treatment had no effect on blood pressure, serum total cholesterol, and LDL-C [7], which are potential confounding factors to the observed improvement in arterial compliance. The improvement in vascular function can be achieved through mechanisms involving enhanced NO production by the endothelium and inhibition of free radicals that inactivate EDRF. Vitamin E can potentially increase the production of NO, which relaxes the vascular smooth muscle cells, while also neutralizing free radicals which preserve the action of EDRF to maintain arterial compliance [7].

In addition to promoting vascular health, vitamin E is also postulated to exert anti-atherogenic effects via its ability to decrease LDL oxidation, quench free radicals, inhibit protein kinase C (PKC), inhibit expression of adhesion molecules and monocyte transmigration, and impair vascular smooth muscle cell proliferation [8].

3. Cerebral small vessel disease

The general ischemia implicated in CSVD of small blood vessels (i.e., arterial tree occlusion in particular) involving the subcortical and deeper parts of the brain

has been widely reported to cause cerebral ischemic stroke or lacunar stroke and accounts for nearly 30% of all stroke subtypes worldwide [9–12].

3.1 Characteristic and classification

The complexity and overlapping pathophysiological mechanism of the disease make the interpretation of CSVD debatable. However, it is a widely accepted view that pathological consequences of small vessel disease (SVD) on the brain parenchyma rather than the underlying diseases of the vessels serve as the basis of CSVD [13]. Hence, the injury in the brain parenchyma that is linked with leptomeningeal and intracerebral vessel pathology that vascularizes with poor collaterals in the deep white matter and subcortical gray matter is the main diagnostic landmark of CSVD. Moreover, CSVD is generally due to several vasculo-pathological processes that affect and cause occlusion to the small perforating cerebral arterioles, capillaries, and venules (of sizes 50–400 mm), which are small arteries (chiefly of middle cerebral artery tributaries) that penetrate and supply the brain subcortical region, resulting in various lesions in the brain [42–46].

Several manifestations of CSVD can be seen through clinical, radiological (i.e., neuroimaging such as CT or MRI), or pathological phenomena with various etiologies [46–49]. Recent advancement in neuroimaging techniques had enabled the imaging-based (such as MRI) identification and characterization of multiple manifestation of CSVD including white matter hyperintensities (WMHs) of presumed vascular origin or leukoaraiosis, lacunes of presumed vascular origin (i.e., small subcortical infarcts and silent brain infarcts, SBI), perivascular spaces, microinfarcts, and cerebral microbleeds (CMBs) [46, 50, 51]. Alarmingly, the aforementioned lesions can be silent, and the affected individual may not have any clinical symptoms. More importantly, this silent lesion with higher number of single or multiple, is associated with higher risk of mild cognitive impairment, dementia, Alzheimer's disease, and full-blown stroke [14, 15].

There are several etiopathogenic classifications of CSVD. However, the most prevalent forms of CSVD are amyloidal CSVD (sporadic and hereditary cerebral amyloid angiopathy [CAA]) and non-amyloidal CSVD (arteriolosclerosis, age-related, vascular risk-factor-related SVD, i.e., microatheroma, lipohyalinosis, fibrinoid necrosis, and segmental arterial disorganization) [42, 52, 53]. Other less common forms of CSVD include inherited or genetic CSVD that is recognizably different from CAA (i.e., Fabry's disease and cerebral autosomal dominant arteriopathy with subcortical ischemic strokes and leukoencephalopathy [CADASIL]), inflammatory and immunologically mediated CSVD (i.e., rheumatoid vasculitis, lupus erythematosus, and CNS vasculitis secondary to infection), venous collagenosis, and other CSVD (i.e., non-amyloid microvessel degeneration in AD and postradiation angiopathy) [42, 52, 53].

3.2 Neuroepidemiology and health burden

Different manifestations of CSVD based on neuroimaging findings result in different and overlapping health burden and epidemiology [54]. Increasing age has been reported to elevate the finding of WMHs, lacunes, perivascular spaces, and CMBs in healthy populations [54–56]. However, increased vascular risk factors are consistent with the prevalence of CMBs but not in other imaging findings [56, 57]. Race, ethnicity, and gender with adjusted age also explain the variability of these imaging findings, whereby some findings had reported that higher WMH grade and volume were found in ethnic or racial minorities than non-Hispanic white [58] and WMHs were much higher in women than men, although no definite mechanism

was reported for this gender difference [59]. In addition, previous study had reported stroke-free elderly Hispanic and/or Latino had SBI (16%), especially in subcortical region (82.9%) [60] and perivascular spaces (48%) [61].

In other ethnic groups, previous study had reported that the prevalence of WMHs in South Asians and Europeans is similar, although South Asian elderly individuals with known vascular risk are more likely to be associated with higher WMHs [62]. Meanwhile, data in three Asian countries (Singapore, Hong Kong, and Korea) have shown that elderly Asians with higher SVD burden are associated with cognitive decline [63]. This was further supported by the Taizhou Imaging Study, whereby the authors found increased incidental findings of WMHs (10.68%), lacunes (26.69%), CMBs (18.51%), and perivascular spaces (27.76%) in elderly Chinese with vascular risk [64]. However in the Japanese population, most are having moderate to mild dilated perivascular spaces, especially in the centrum semiovale and basal ganglia [65]. Thus, it is apparent that more data are required to understand the role of racial and/or ethnic contributions for the presence of different CSVD manifestations.

The effects of several manifestations of CSVD on cognition seem to be invariably influenced by the location of the lesion(s). The damaged and reduced white matter integrity in the frontal lobe and its dysfunction are associated with reduced transmission of information to other parts of the brain in the presence of WMHs [54], lacunes (deep nuclear [78.2%], posterior fossa [10.1%]) [66], and perivascular spaces [65, 67]. In contrast, temporal lobe lesion is more associated with the findings of lobar and deep CMBs [68, 69]. Several studies have reported that an increase in WMHs is associated with worse general and specific domain of cognitive performance, especially in executive function, processing speed, and episodic memory [70–73]. Intriguingly, an increase in WMHs with reduced cognitive performance is similar to the individual with amyloid load, mild parkinsonism, and functional impairments [70].

Furthermore, reduced cognitive ability has been reported in elderly and non-demented people with the presence of lacunes of presumed vascular origin [54, 72, 74]. Memory declines have also been associated with thalamic infarcts, whereas decreased psychomotor speed is associated with non-thalamic infarcts [75]. In contrast, the presence of a lesion in the perivascular spaces reduces the individual processing speed [76] and, in others, reported no effect on the cognitive performance [67]. Meanwhile, a decrease in global cognitive performance and domain specific has been linked with the location of CMBs [77].

3.3 Pathomechanism

Despite the growing insights from histopathological, epidemiological, and physiological studies in the past two decades, the underlying pathomechanism of CSVD remains contentious [46, 53]. In general, it is recognized that advanced age and the presence of chronic hypertension may reduce the ability to self-regulate cBF in response to various systemic blood pressure levels and increased arterial stiffness, hence the increased speed and flow pulsatility in cerebral arterioles [16]. These hemodynamic changes are postulated to inflict a certain degree of endothelial damage in the BBB and alter its permeability through an increase of the shear stress [17]. Hence, the BBB breakdown is an important etiopathogenesis feature of CSVD [17–19].

Another key factor thought to contribute to the pathogenesis of CSVD is endothelial dysfunction, with elevated biomarkers as the surrogates [78, 79]. The endothelial dysfunction involvement is also associated with metabolic syndrome [80, 81] and hence a strong link with CSVD. Furthermore, this dysfunction is also implicated for a higher risk of aging-related disease [82, 83]. In addition to the endothelium,

cross-talk among cellular components of the BBB, such as pericytes, astrocytes, and oligodendrocyte precursor cells (OPCs), may be involved in the microvascular damage as precursors for the onset and progression of CSVD [84, 85]. In relation to this, reduced white matter integrity due to changes in oligodendrocytes has been shown in CSVD, whereby the EC-OPC signaling became compromised and altered the ECs' ability to secrete the releasing factor crucial for the growth and survival of OPCs to eventually cause oligodendrocytes prone to damage [86]. Therefore, the interaction of multiple BBB components may play a crucial role in the discovery and development of new prevention steps and therapies for CSVD.

In parallel, an increased activity of matrix metalloproteinase-2 (MPP2) from endothelial cell membrane (ECM) also caused tight junctions (TJs) to dissemble. TJ damage eventually leads to basement membrane degradation and endothelial damage and, hence, endothelial dysfunction. This results in BBB damage, making it vulnerable to the infiltration of neutrophils, monocytes, and blood components into the ECM [53]. Activated neutrophils induce the activation of ROS, proteolytic enzymes, and cytokines, thus causing higher leukocyte-EC adhesion and reduced cBF (**Figure 5**). Meanwhile, activated monocytes will be induced by cytokine and neopterin to cause inflammation in the ECs. Cumulatively, the increased shear and oxidative stress from the system also lead to the activation of blood components and increased production of microparticles, reduced tissue factor pathway inhibitor, and increased fibrinogen accumulation that result in lumen narrowing and consequent cBF reduction [53].

Understandably, the role of hypoperfusion or reduced cBF in endothelial dysfunction for CSVD has been hypothesized [87]. Generally, the regulation of cBF is mediated by NO signaling; thus, NO serves as a marker for endothelial dysfunction [88]. Since endothelial dysfunction is associated with increased BBB permeability, this would worsen brain parenchyma and white matter lesions given the reduced integrity of ECs [89]. In addition, the increased expression of the mutated NOTCH3 gene (a genetic determinant of CADASIL) in pericytes was found to contribute to CSVD pathogenesis due to abnormal cross-talk between ECs and pericytes [87]. Therefore, one can posit that increased BBB permeability, reduced cBF, and impaired cerebral autoregulation serve as three main interrelated underlying pathogenesis precursors to the development and progression of CSVD, notwithstanding the role of other potential and novel factors.

3.4 Role of reactive oxygen species

Multiple studies have reported that the early detection of cognitive and motor decline in neurodegenerative disease has been linked with protein, lipids, sugar, and nucleic acid oxidation [90, 91]. Therefore, it can be postulated that changes or damage to the cerebral vasculature, BBB, and cBF is due to localized oxidative stress, hence initiating the neurodegenerative changes in the brain tissue.

Generally, overproduction of oxidants by NADPH oxidases and malfunction or reduced activities of antioxidant enzymes may result in oxidative stress [52]. The imbalance between antioxidants and prooxidants in aging and age-related neurological disease is regarded to be mainly due to ROS [92] which is a large group of oxygen radicals (i.e., superoxide anion radical, hydroxyl radical, peroxyl radical, and alkoxyl radical) and non-radicals (i.e., hydrogen peroxide, organic hydroperoxide, singlet molecular oxygen, electronically excited carbonyls, and ozone) [52, 64]. NADPH oxidase- and superoxide dismutase-mediated enzymatic conversion of molecular oxygen to superoxide initiates the production of ROS; however, the production of ROS can also be mediated by spontaneous transformation of non-radical hydrogen peroxide [93].

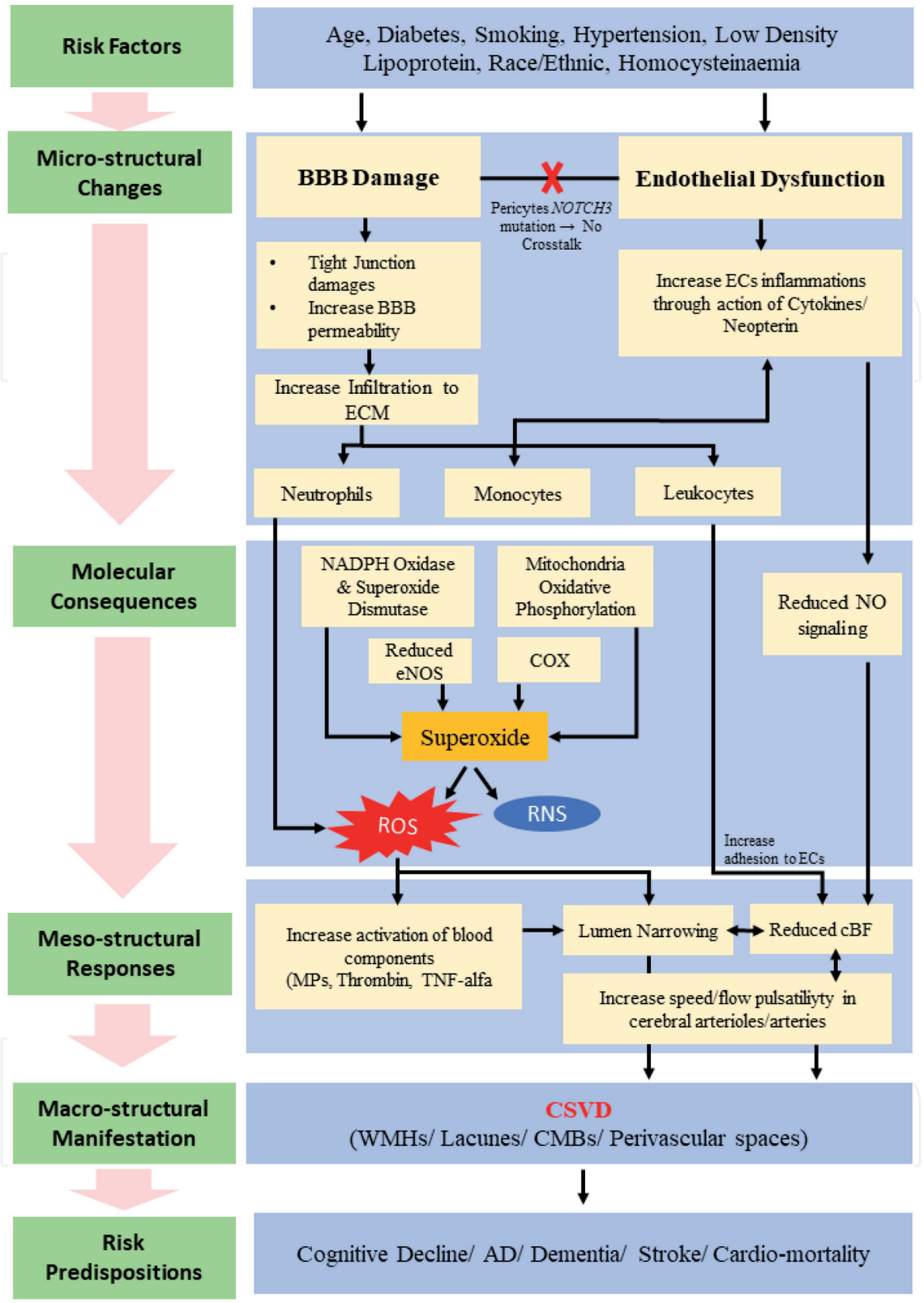

Figure 5.
General pathomechanism and role of ROS in CSVD. ECs, endothelial cells; BBB, blood–brain barrier; ECM, extracellular matrix; cBF, cerebral blood flow; NO, nitric oxide; eNOS, endothelial nitric oxide synthase; ROS, reactive oxygen species; RNS, reactive nitrogen species; COX, cyclooxygenase; NADPH, nicotinamide adenine dinucleotide phosphate; MPs, microparticles; TNF-alpha, tumor necrosis factor-alpha; WMHs, white matter hyperintensities; CMBs, cerebral microbleeds; AD, Alzheimer's disease.

There are multiple oxidative markers used to correlate with neurodegenerative disease including CSVD, for example, thioredoxins (positively correlate with severity of acute ischemic stroke and infarct volume) [94], thioredoxin reductase

(reduced thioredoxin reductase attenuates the capacity of endothelium-dependent vasodilatory) [95], and peroxiredoxins (higher during stroke onset and traumatic brain injury) [96]. Moreover, reduced plasma levels of uric acid and vitamins E, A, and C have been used as antioxidant biomarkers for Alzheimer's disease and also Parkinson's disease [97–100]. Similarly, coenzyme Q10 (i.e., ubiquinone Q10) is another antioxidant that has been shown to provide potential protective effects for a spectrum of CSVD and cerebral metabolic syndrome [82].

In CSVD, the elevated production of ROS is mainly due to reactions and process (i.e., high blood pressure, very low density of lipoproteins, diabetes, and homocysteinemia and smoking) that lead to inflammatory mechanism and oxidative stress hence causing endothelium dysfunction [20, 21]. Induction of oxidative stress further enhanced the releasing of adhesion molecules and recruiting of leukocytes causing higher leukocyte-EC adhesion and reduced cBF (**Figure 5**). NADPH oxidases induce oxidative stress (major source of ROS in vessel wall), and its destructive impact on EC-dependent NO signaling has been widely studied [22, 23]. The NADPH oxidases can be stimulated by mechanical forces and vasoactive agonists (i.e., thrombin, platelet-derived growth factor, and tumor necrosis factor-alpha) hence enhancing the production of ROS through superoxide anion radical synthesis [101–103].

Another two key enzymes that facilitate the production of ROS include cyclooxygenase (COX) and enzymatic cascade in mitochondria (i.e., oxidative phosphorylation). COX is an important enzyme that produces superoxide in cerebral blood vessels through prostaglandin H2 synthesis mediated by AA [104, 105]. Superoxide can also be synthesized after endothelial nitric oxide synthase dysfunction that halts the NO production. This eventually reduces the bioavailability of NO and, in turn, facilitates the production of reactive nitrogen species (RNS) to cause reduced anti-inflammatory, reduced vasodilating, increased platelet aggregation, disinhibition of leukocyte adhesion, and reduced antiproliferative effects of NO [52, 106]. Hence, biomarkers of oxidative stress can be used to study the redox imbalance in individuals with WMHs while it draws a plausible therapeutic avenue with targeted dietary supplements to reduced ROS and RNS that would be neuroprotective against CSVD onset and/or manifestations [107].

4. Prospects of vitamin E for CSVD neuroprotection

As remarked in the previous sections, increasing body of evidence indicated that oxidative stress might play a pivotal role in the largely elusive pathomechanism of CSVD and other neurodegenerative disease, including cognitive impairment. Moreover, targeting oxidative stress, as a therapeutic approach of vascular-related disease, has been an area of continuing interest given its significance on the aging world population and the rising trend of noncommunicable disease burden, typically cardio-cerebrovascular disorders which include CSVD. However, informative and converging data on vitamin E and its neuroprotective potential for CSVD are scarce.

Central to this proposition of vitamin E potential in CSVD is the involvement of ROS in the physiological role for normal regulation of cerebral vascular event. Hence, a balance between mitigating oxidative stress and normal physiological role should be considered in this ROS-centric approach for natural vitamin E in CSVD neuroprotective potentials. Nonetheless, the idea of attaining or sustaining certain levels of antioxidants to mitigate vascular oxidative stress remains a contentious issue. For instance, antioxidants such as vitamin E have been proven beneficial for vascular function in small clinical and experimental trials [108],

whereby vitamin E supplementation had been shown to reduce the onset of WMHs in small clinical trials [109]. Moreover, natural vitamin E also had been shown favorable to lessen cognitive impairments in CSVD animal models

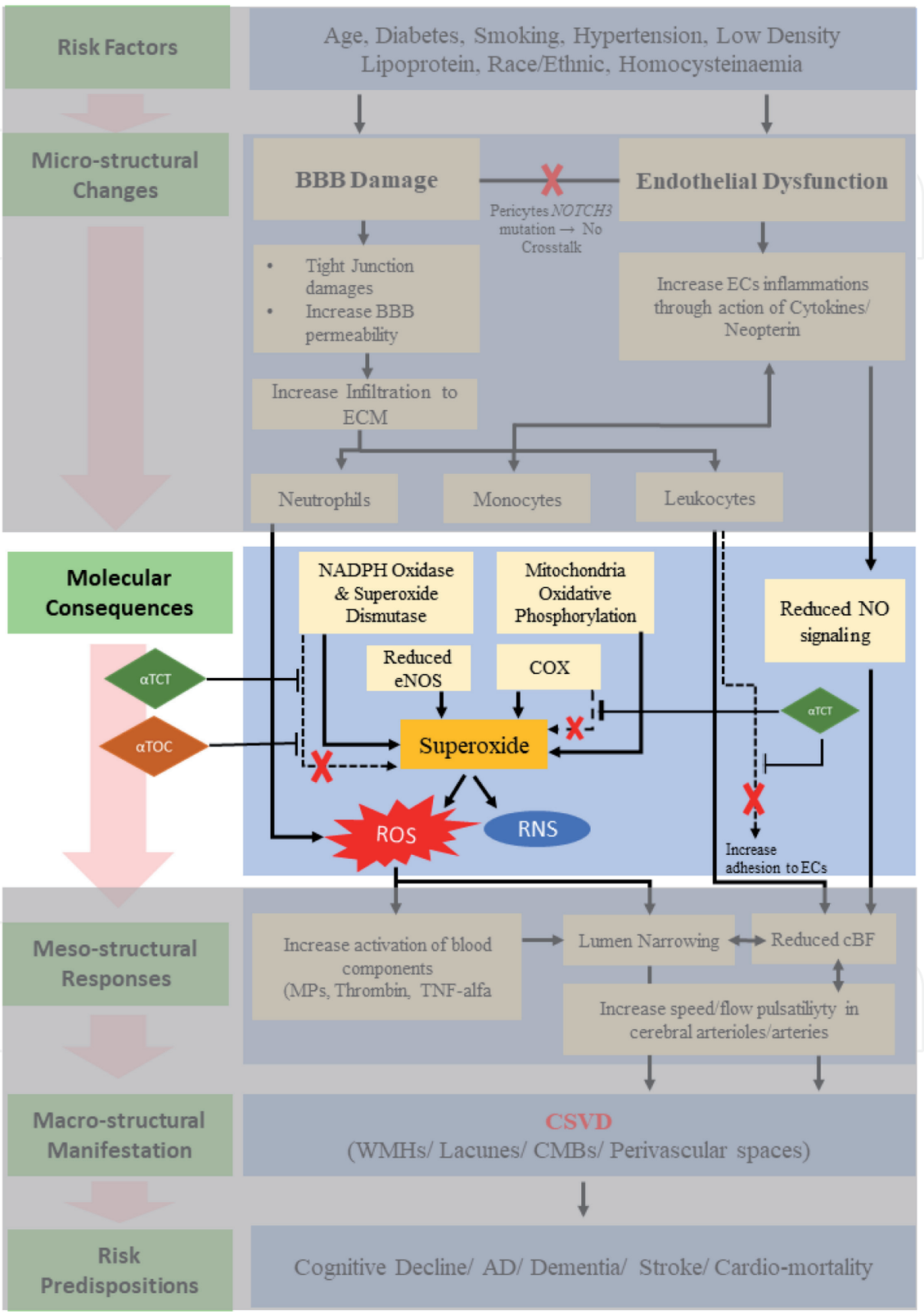

Figure 6.
Putative neuroprotective potentials of natural vitamin E in targeting ROS in CSVD manifestations. αTCT, α-tocotrienols; αTOC, α-tocopherols; ECs, endothelial cells; BBB, blood–brain barrier; ECM, extracellular matrix; cBF, cerebral blood flow; NO, nitric oxide; eNOS, endothelial nitric oxide synthase; ROS, reactive oxygen species; RNS, reactive nitrogen species; COX, cyclooxygenase; NADPH, nicotinamide adenine dinucleotide phosphate; MPs, microparticles; TNF-alpha, tumor necrosis factor-alpha; WMHs, white matter hyperintensities; CMBs, cerebral microbleeds; AD, Alzheimer's disease.

[110, 111]. Notwithstanding, a larger-scale clinical trial had shown less convincing beneficial outcomes on stroke and vascular disease prevention with antioxidant (i.e., vitamin E) supplementation [112].

Moreover, utilizing other antioxidants such as coenzyme Q10 has been reported to have potential neuroprotective effects in treating oxidative stress-induced metabolic syndrome with CSVD-related deterioration with reduced plasma level of coenzyme Q10 in experimental animal model with metabolic syndrome [82]. Nonetheless, recent studies on oxidative stress-induced diet reported weak or no apparent association in modifying the cardiovascular risk in an animal model (normotensive wild-type mice, C57BL/6 J), at least in its impact on systemic blood pressure [113].

The inconsistency in the reports of the potential neuroprotective effects of antioxidant (natural vitamin E) in cerebrovascular disease is partly due to the apparent lack of optimization in terms of concentrations/doses of the vitamin E used. This is despite the supportive data on supra(optimal)-physiological concentration of vitamin E (especially α-tocotrienol) that can interrupt the superoxide and NO reaction [108] to reduce the activation of ROS and endpoint BBB disintegration in CSVD. Hence, we are tempted to posit that appropriate nutritive consumptions of vitamin E could prove advantageous to attenuate BBB damages that underlie CSVD heterogenous manifestations, i.e., by halting the leukocyte-EC adhesion that can further degrade the BBB damages with WMHs. Biomarkers of oxidative stress can serve to monitor the redox imbalance in individuals with WMHs while exploring the putative therapeutic avenue with targeted dietary supplements as neuroprotective potentials against CSVD onset and/or disease manifestations. As such, the vitamin E neuroprotective merits could prevent a comprising reduction of cBF in cerebral ischemia in numerous CSVD manifestations, be it silent or symptomatic, from the ROS-centric targeting (**Figure 6**).

5. Challenge and future direction

Although data on therapeutic regimes had shown promising increased plasma levels of antioxidants, whether this translates to increased levels in the vasculature remains unknown. Even if sufficient levels of antioxidants were achieved in vascular cells, the antioxidants might in fact exert prooxidant effects as a result of their conversion to radical species following their reactions with superoxide [114, 115]. Either way, a single approach of conventional antioxidant supplementation would be suboptimal in combating oxidative stress in CSVD [108].

Corroboratively, with multiple studies having successfully linked the potential therapeutic and neuroprotective potentials of vitamin E in vascular health domains, a multicenter and adequately powered clinical trial is much needed for CSVD. Such data would further strengthen the nutritive value of vitamin E for CSVD neuroprotective supplements. In addition, opportunities exist to examine the connectivity of white matter tracts to exhibit vitamin E role in protection of small vessel collateral circulation as well as an increased expression of proarteriogenic (new blood vessel formation) genes in future research.

6. Conclusion

CSVD, as the commonest neurological condition as we age, could benefit from the potency of vitamin E antioxidant neuroprotective potentials through oxidative stress and BBB integrity modulation. This chapter converges contemporary

evidence to shed plausible insights on the neuroprotective potentials of natural vitamin E in addressing the heterogenous CSVD spectrum, in health and disease.

Acknowledgements

Authors thank MIGHT Newton-Ungku Omar Fund, grant number Universiti Sains Malaysia (USM) 304.PPSP.6150151.N118. The authors would like to thank Enago (www.enago.com) for the English language review.

Conflict of interest

The authors acknowledge that there is no conflict of interests in this work.

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