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Key Words: tocotrienol; Alzheimer's; mevalonate; HMG CoA reductase; prenylation; inflammation

Abbreviations:

A β : amyloid β protein; **AD**: Alzheimer's disease; **ApoE**: apolipoprotein E; **APP**: amyloid precursor protein; **BACE1**: β -secretase; **CI**: confidence interval; **CN**: cognitively normal; **FPP**: farnesyl pyrophosphate; **FTI**: farnesyl transferase inhibitor; **GGPP**: geranylgeranyl pyrophosphate; **GGTI**: geranylgeranyl transferase inhibitor; **GRAS**: Generally Recognized As Safe; **HMG CoA**: 3-hydroxy-3-methylglutaryl coenzyme A; **LDLR**: low-density lipoprotein receptor; **LLA**: lipid-lowering agent; **LPS**: lipopolysaccharide; **MCI**: mild cognitive impairment; **NF κ B**: nuclear factor kappa B; **NLRP3**: NOD-like receptor family pyrin domain-containing 3; **OR**: odds ratio; **PS**: presenilin; **ROS**: reactive oxygen species; **SREBP**: sterol regulatory element binding protein; **TPA**: 12-O-tetradecanoyl phorbol-13-acetate; **TRAIL**: tumor necrosis factor-related apoptosis-inducing ligand; **TREM2**: triggering receptor expressed on myeloid cells 2; **WML**: white matter lesion.

Abstract

Currently there is no cure for Alzheimer's disease (AD); clinical trials are underway to reduce amyloid generation and deposition, a neuropathological hallmark in brains of AD patients. While genetic factors and neuroinflammation contribute significantly to AD pathogenesis, whether increased cholesterol level is a causative factor or a result of AD is equivocal. Prenylation of proteins regulating neuronal functions requires mevalonate-derived farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP). The observation that the levels of FPP and GGPP, but not that of cholesterol, are elevated in AD patients is consistent with the finding that statins, competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, reduce FPP and GGPP levels and amyloid β protein production in preclinical studies. Retrospective studies show inverse correlations between incidence of AD and the intake and serum levels of the HMG CoA reductase-suppressive tocotrienols; tocopherols show mixed results. Tocotrienols, but not tocopherols, block the processing and nuclear localization of sterol regulatory element binding protein-2, the transcriptional factor for HMG CoA reductase and FPP synthase, and enhance the degradation of HMG CoA reductase. Consequently, tocotrienols deplete the pool of FPP and GGPP and potentially blunt prenylation-dependent AD pathogenesis. The anti-inflammatory activity of tocotrienols further contributes to their protection against AD. The mevalonate- and inflammation- suppressive activities of tocotrienols may represent those of an estimated 23,000 mevalonate-derived plant secondary metabolites called isoprenoids, many of which are neuroprotective. Tocotrienol-containing plant foods and tocotrienol derivatives and formulations with enhanced bioavailability may offer a novel approach in AD prevention and treatment.

1. Introduction

The socioeconomic burden of Alzheimer's disease (AD) coupled with lack of a clear understanding of its molecular mechanism and effective treatments call for more in-depth investigations of this debilitating disease with novel approaches. Here we first summarize the risk factors including genetic variation, heredity, age and neuroinflammation, and follow up with the fundamentals of AD pathogenesis. The ambiguous link between AD and cholesterol levels in plasma, serum and brain tissues stands in contrast with a notable observation that intermediates of the mevalonate pathway by which cholesterol is synthesized are elevated in AD patients; these intermediates support prenylation of proteins regulating neuronal function. The preclinical studies of statins that inhibit the biosynthesis of these mevalonate-derived intermediates, albeit with equivocal clinical outcomes, lend support to the preventive and therapeutic potentials of mevalonate-suppressive tocotrienols, vitamin E molecules with structures and biological activities distinct from those of the more commonly studied tocopherols. Emerging literature also reveals a variety of neuroprotective activity of tocotrienols. We delineate potential mechanisms of tocotrienols based on their impact on the mevalonate pathway that, when coupled with their anti-inflammatory activity, renders them – and potentially the broad class of dietary phytonutrients they represent – promising candidates in protection against AD.

2. Risk Factors for AD

Risk factors associated with AD have been identified through their functional and physical interaction with neuropathological proteins of AD, amyloid β protein ($A\beta$) and Tau. Age and greater inflammation are well-established risk factors, and multiple genes have been found to facilitate the disease onset and progression.

a. Genetic variation

Genetic and neuropathologic evidence suggests that AD is caused in part by the overproduction and lack of clearance of A β [1, 2], accompanied by enhanced neuroinflammation [3]. Detrimental mutations in genes encoding presenilin 1 and 2 (PS1 and PS2) and amyloid precursor protein (APP) alter APP processing mediated by β -secretase (BACE1) and γ -secretase (a.k.a. PS1/2) [4-6], leading to an increased ratio of A β ₄₂/A β ₄₀ and to early onset familial AD. A beneficial mutation in APP reduces A β production and protects against the onset of sporadic AD [7].

Genetic analysis of risk factors reveals that one or two aberrant copies of the apolipoprotein E (ApoE) ϵ 4 alleles are a major risk factor for late-onset sporadic AD. The risk factor gene ApoE has three major isoforms, ApoE ϵ 2, ϵ 3, and ϵ 4. ApoE ϵ 3 is found in the majority of the healthy population; ApoE ϵ 2 allele is found to be protective from incidence of AD, and ApoE ϵ 4 allele is the strongest known risk factor for AD. The major receptor for all forms of ApoE is the low-density lipoprotein receptor (LDLR) that regulates amyloid plaque deposition, and overexpression of the LDLR enhances blood-brain barrier-mediated ApoE ϵ 2, ϵ 3, and ϵ 4 clearance, thus leading to reduced A β accumulation [8]. Brains of sporadic AD patients carrying the ApoE ϵ 4 allele were found to have an increased density of A β deposits and a limited capability to clear A β [3]. The AddNeuroMed Project, a multicenter European longitudinal study, examined the biomarkers for AD; assessment of 168 AD patients, 166 subjects with mild cognitive impairment (MCI), and 187 cognitively normal (CN) people found that the percentages of subjects carrying any ApoE ϵ 4 allele were 52%, 41% and 29%, respectively, in these three groups, suggesting a potential correlation between neurodegeneration and ApoE ϵ 4 [9].

b. Heredity

The majority of AD cases are sporadic in nature, and a small percentage of AD patients are familial cases. Currently, only three genes, PS1, PS2 and APP, are known to cause AD. Autosomal dominant mutations in PS1, PS2 and APP lead to early onset, familial AD, and mutant PS1 accounts for the majority of these inherited cases. Interestingly, PS1/PS2 are the enzyme called γ -secretase that cleaves the precursor to generate $A\beta$, and APP is the precursor of $A\beta$ [4-6]. Therefore, mutations in either enzyme or precursor of $A\beta$ initiate onset of disease in all familial cases.

c. Age and inflammation

Epidemiological studies reveal that aging is the single most significant risk factor contributing to AD. Among elderly at 65 years old and above, 5% of them have sporadic or familial AD. This number dramatically increases to 50% in elderly over 85 years old. Many factors associated with aging directly or indirectly contribute to the pathogenesis of AD. As imbalanced $A\beta$ homeostasis is an upstream event of neuroinflammation and neurodegeneration, enhanced microgliosis and astrocytosis are directly associated with neuronal loss. Previous studies have shown that some microglia cells originate from the bone marrow. These cells can migrate towards $A\beta$ plaques, mainly because of attraction by $A\beta_{42}$. These microglia cells are able to eliminate $A\beta$ by phagocytosis, which provides a novel therapeutic opportunity for bone marrow stem cells to remove $A\beta$ deposit in brains of AD patients [10]. Genetic mutations found in several genes lead to changes to immune molecules and reduce $A\beta$ uptake. Mutations in the microglial receptor TREM2 (triggering receptor expressed on myeloid cells 2) triple a person's

risk for AD [11, 12]. CD33 is another gene linked to AD and functions to suppress A β uptake and clearance. AD risk variants reduce expression of CD33 [13, 14]. Systemic analysis of hundreds of AD brains reveals changes in networks related to immunologic molecules and microglial cells, including microglial protein TYROBP that binds TREM2 and may regulate CD33 [15].

Physiological alteration provides manifestation of risk factors associated with AD pathogenesis. Many responses characteristic of AD are in part triggered by A β . Interleukin-1 β is implicated in AD and inflammatory disorders. When microglia cells engulf extracellular aggregates such as A β , they trigger inflammasomes (such as NOD-like receptor family pyrin domain-containing 3 (NLRP3)), activate caspases and promote IL-1 β release [16]. This pathway was validated in AD transgenic mice where NLRP3 was shown to contribute to AD-like pathology in mouse brains [17]. Recent studies have shown that A β can bind to scavenger receptors expressed on microglia such as CD36 – a central regulator of immune responses that drives inflammatory diseases [18] – enter microglia and activate inflammation. Another scavenger receptor Scara1 function similarly to CD36 and clears extracellular A β [19].

3. AD Pathology

a. Plaques and tangles

Neuritic plaques and neurofibrillary tangles (NFT) are two characteristic hallmarks in brains of AD patients. Neuritic plaques are composed of heterogeneous A β peptides. Biochemical/immunohistochemical findings have revealed neurotoxic properties of different A β isoforms in brain. Compared to shorter A β peptides like A β 40 and A β 38, the 42-residue A β 42 enhances aggregation propensity [20], leading to accelerated formation of small (low-n) A β

oligomers (oA β) [21]. It has been documented that the oligomeric form of A β seems to be the most toxic species of A β as well as the precursor to the fibrillary A β found in senile plaques [1, 21-24].

The second hallmark of AD is NFT. Hyperphosphorylated Tau is the main component of NFT. Phosphorylated Tau appears early in neurons from subjects suffering MCI and accumulates in neurofibrillary neurons as AD progresses. They localize to the dystrophic neurites, a change correlating with synaptic and cognitive deficits. Phosphorylated Tau gradually loses normal function to promote microtubule assembly and becomes highly stable and prone to aggregation.

b. Role of cholesterol and mevalonate pathway in causing plaques and tangles

Preclinical studies suggest the cholesterol-AD connection, though evidence for whether elevated cholesterol level is a causative factor or a casualty of AD is equivocal. A hypercholesterolemic diet increased the A β load in a transgenic mouse model [25]. Dietary cholesterol induced a two-fold increase in A β concentration in rabbit hippocampal cortices [26], and accumulation of A β can be reversed by removing cholesterol from diet [27]. Early studies using partially purified γ -secretase complex were carried out to understand the effect of cholesterol on its activity. When different levels of cholesterol were presented in membrane vesicles composed of a known content of phospholipids such as phosphatidylethanolamine and phosphatidylcholine, efficacy of γ -secretase cleavage of its substrate to generate A β 40 and A β 42 was either dramatically increased or decreased depending on the composition of phospholipids. However, there is no direct relationship between the amount of cholesterol and the level of phospholipids such as phosphatidylethanolamine and phosphatidylcholine. Statins, competitive inhibitors of the rate-limiting enzyme in cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl

coenzyme A (HMG CoA) reductase, directly decrease cholesterol levels and reduce processing of APP and generation of A β in cell-based studies. When farnesyl pyrophosphate (FPP), geranylgeranyl pyrophosphate (GGPP), cholesterol and A β 40 were quantified in cells treated with different inhibitors, reduction of A β 40 was found in the presence of lovastatin and an oxidosqualene cyclase inhibitor that block cholesterol synthesis [28]. In transgenic mice modeling AD, simvastatin improves hippocampus-dependent spatial memory and rescue memory deficits. Furthermore, simvastatin potentiates the N-methyl-D-aspartate receptor-mediated synaptic transmission [29]. Additional evidence suggested that modulation of neuronal activity by APP is mediated by decrease in cholesterol biosynthesis and hydroxylation [30].

Retrospective and prospective studies in humans do not always produce consistent outcomes [31]. A number of retrospective studies found a lower prevalence of AD in subjects taking statins compared to those not taking statins. A nested case-control study derived from the UK-based General Practice Research Database examined 284 cases with dementia and 1080 controls; individuals of 50 years and older who were prescribed statins had a significantly lower adjusted relative risk of dementia including AD with an odds ratio (OR) of 0.29 and 95% confidence interval (CI) of 0.13-0.63 ($P = 0.002$) [32]. A cross-sectional analysis showed that patients taking statins had a 60-73% ($P < 0.001$) lower AD prevalence than the total patient population and those taking other medications for hypertension or cardiovascular diseases [33]. An observational study followed 342 AD patients (108 normolipidemic, 105 untreated dyslipidemic, and 129 dyslipidemic treated with lipid-lowering agents (LLAs) including 47% with statins) with the mean age of 73.5 years for 34.8 months; patients treated with LLAs had a slower decline on the mini-mental state examination score ($P = 0.0102$) than patients with untreated dyslipidemia or normolipidemia. Treatment with LLAs was positively associated with

the probability of lower cognitive decline (OR = 0.45, $P = 0.002$) [34]. However, the hypothesis that cholesterol is involved in the development of AD is plagued by inconsistent plasma, serum or brain cholesterol levels in AD patients, the lack of efficacy of statins in prospective studies, and potential non-A β protein targets affected by cholesterol modulation [31].

c. Potential for prevention and treatment of AD by blocking the mevalonate pathway

Cholesterol is synthesized via the mevalonate pathway consisting of multiple enzymes that include, among others, HMG CoA reductase and FPP synthase (Figure 1) [35]. In addition to the bulk end product cholesterol, the mevalonate pathway also produces many non-sterol intermediates such as FPP. FPP can also be directed for the synthesis of GGPP by GGPP synthase. FPP and GGPP serve as the lipid substrates for protein prenylation, an essential step in the membrane anchoring and biological activities of a number of membrane proteins including the nuclear lamins and small G proteins such as Ras, Rho, Rac and Rab [36]. Prenylation of proteins facilitates protein-protein interaction and the prenylation status of small G proteins determines their membrane association and subcellular locations [37], which regulates many cellular functions including synaptic plasticity.

Previous studies have demonstrated that FPP and GGPP levels in AD patients are elevated by 36% and 56%, respectively, as compared to age-matched controls without a significant change in cholesterol levels or HMG CoA reductase expression [31, 38]. These findings suggest that mevalonate-derived non-sterol factors might play a role in AD pathogenesis. The observation that patients treated with LLAs had lower cognitive decline than those with normolipidemia also supports a potential role of non-sterol factors [34].

Elevation of FPP and GGPP was caused by an increased expression of FPP and GGPP synthases, which provide additional FPP and GGPP for protein prenylation of small G proteins. Statins reduce levels of FPP and GGPP as a consequence of inhibition of HMG CoA reductase. GGPP stimulates γ -secretase and increases the production of A β [39], an effect reversed by statin-induced blockage of protein prenylation [40]. Conversely, in cell culture lovastatin induced neurite outgrowth, an effect reversed by geranylgeraniol [41]; geranylgeraniol might be phosphorylated and converted to GGPP to support prenylation and suppress neurite outgrowth. Increased prenylation of small GTPase Rho1, the fly orthologue of vertebrate RhoA, induced neurodegeneration in *Drosophila* [42]. In AD transgenic mice, simvastatin-mediated depletion of FPP and inhibition of farnesylation promote enhancement of hippocampal long-term potentiation [43].

The potential role of prenylation in AD pathophysiology has led to studies exploring whether farnesyl transferase inhibitors (FTIs), geranylgeranyl transferase inhibitors, and bisphosphonates (inhibitors of FPP synthase) may have impact on AD [44]. In a transgenic mouse model overexpressing mutant APP and PS1 genes, deleting one copy of farnesyltransferase reduced A β deposition and neuroinflammation; behavioral tests reveal a rescue of spatial learning and memory function [45].

4. Tocotrienol, Mevalonate Pathway, and AD

Literature suggests that plant-based foods have neuroprotection effects. A prospective cohort study of 3,718 human subjects aged 65 years and older based on food frequency questionnaire assessed cognitive functions at baseline and 3-year and 6-year follow-ups. The rates of cognitive decline among persons in the fourth and fifth quintiles of vegetable intake were

slower by 0.019 ($P = 0.01$) and 0.018 ($P = 0.02$) standardized units per year compared with that among persons in the lowest quintile; the overall mean change per year was a decline of 0.04 standardized units [46]. Strawberry, spinach and blueberry extracts protect against age-related neuronal decline. Extracts of these fruits and vegetable fed to 19-month-old Fischer 344 rats for 8 weeks reversed age-related deficits in several neuronal and behavioral parameters. Blueberry particularly improves motor function that relies on balance and coordination [47]. These fruits and vegetables contain a large number of isoprenoids [48], secondary metabolites of the plant mevalonate pathway [49]. The estimated 23,000 [50] isoprenoids include pure and mixed isoprenoids; the former consist of multiples of the five-carbon mevalonate-derived isoprene unit and include mono-, sesqui-, di-, tri- and poly- terpenoids depending on the number of the isoprene units in the isoprenoid structure, and the latter are partially built with isoprenes in their structures. A number of isoprenoids, including the monoterpenes 1,8-cineole and geraniol, the sesquiterpene valerenic acid, the diterpene ginkgolide A, and the triterpene ginsenoside Rg1, have been found to possess neurological effects via actions such as inhibition of cholinesterase and modulation of γ -aminobutyric acid [51]. In cultured rat cortical neurons, the tetraterpene lycopene protects against $A\beta$ -induced neurotoxicity [52].

The isoprenoids bear striking resemblance with the statins in suppressing HMG CoA reductase activity, albeit via mechanisms distinct from the competitive inhibition of statins. In eukaryotic cells HMG CoA reductase is subject to a multivalent regulation at the transcriptional and posttranscriptional levels. Cholesterol and its oxygenated products elicit a negative feedback inhibition on the transcription of the enzymes in the pathway, including HMG CoA reductase and FPP synthase, via the transcriptional factor sterol regulatory element binding protein 2 (SREBP-2); membrane cholesterol prevents the cleavage and nuclear localization of SREBP-2.

A non-sterol isoprenoid, currently identified as the diterpene geranylgeraniol or a geranylgeraniol-derived product, at the presence of sterols, enhances a proteasome-mediated degradation HMG CoA reductase [53]. Several monoterpenes including *d*-limonene, perillyl alcohol and geraniol and the sesquiterpenes *trans*, *trans*-farnesol [49, 54, 55] and β -ionone [56] – in addition to the diterpene geranylgeraniol [57] – have been shown to suppress HMG CoA reductase activity (Figure 1).

The most potent reductase suppressors identified to date among the isoprenoids are the tocotrienols, vitamin E molecules with a farnesyl side chain. The vitamin E family is comprised of α -, β -, γ - and δ - tocopherols and their tocotrienol counterparts, a total of eight molecules (Figure 2). Tocotrienols block the processing and maturation of SREBP-2 and enhances the degradation of HMG CoA reductase [58, 59]. The tocotrienols differ from tocopherols, the widely studied and publicized vitamin E family members, in structures, biological activities and health impacts. The parallel effect of statins and tocotrienols on HMG CoA reductase activity is mirrored in their shared biological activities including hypocholesterolemic [60], anti-cancer [61], anti-inflammatory [62] and bone-protective effects [63]. In contrast, the tocopherols with a saturated phytyl tail do not impact the degradation of HMG CoA reductase [58] or affect the maturation of SREBP-2 at physiological concentrations [64]. In many studies tocopherols lack the biological activities of tocotrienols [65-68] or even attenuate the tocotrienol effects [69, 70].

Lower incidences of both AD and MCI were found in populations carrying higher levels of tocotrienol and tocopherol. In an 8-year follow-up to the Cardiovascular Risk Factors, Aging, and Dementia study, the subjects in the middle tertile of the γ -tocopherol/cholesterol ratio had a lower risk of cognitive impairment – the multi-adjusted OR with 95% CI was 0.27 (0.10-0.78) – than those in the lowest tertile. The highest tertile of the serum total tocopherol was not

associated with a lower incidence of cognitive impairment (OR of 1.10 with 95% CI of 0.44-2.70). As a comparison, the highest tertile of the serum total tocotrienol had an OR of 0.84 with 95% CI of 0.35-2.04. Furthermore, the highest tertile of the serum γ -tocotrienol, a tocotrienol with a potent HMG CoA reductase-suppressive activity [58, 59], had an OR of 0.50 with 95% CI of 0.20-1.26. The highest tertile of the serum α -tocotrienol – with its much weaker HMG CoA reductase-suppressive activity [58, 59] – had an OR of 1.18 with 95% CI of 0.49-2.86 [71]. In the aforementioned AddNeuroMed Project, the mean plasma levels of individual vitamin E molecules, total tocopherols, total tocotrienols, and total vitamin E in AD subjects were lower than those in the CN subjects; MCI and AD patients were 92% (OR of 0.08 with 95% CI of 0.02-0.26) and 94% (OR of 0.06 with 95% CI of 0.02-0.21) less likely to be in the highest tertile of total plasma tocotrienols than the lowest tertile [9]. In MRI scans, levels of vitamin E provide acceptable sensitivity and specificity to differentiate AD and MCI from control subjects, and predict conversion of MCI subjects to clinical AD after 1 year [72]. Additional studies suggest that tocotrienols rather than tocopherols may provide protection. The incidence of AD was inversely associated with combination of different forms of vitamin E rather than a single isoform of α -tocopherol in a 6-year follow-up study of 232 subjects aged 80+ years; multi-adjusted hazard ratios for developing AD and 95% CI for total tocopherols, total tocotrienols, and total vitamin E were 0.55 (0.32-0.94), 0.46 (0.23-0.92), and 0.55 (0.32-0.94), respectively, when comparing persons in the highest and lowest tertiles [73]. Comparison of human subjects taking different isoforms of vitamin E indicates that mixtures of tocopherols and tocotrienols rather than α -tocopherol alone exhibit protection against AD. A 4-year follow-up in the Chicago Health and Aging Project (1993-2003) assessed 1041 persons with 162 AD cases; the adjusted relative risks of incident AD per 5 mg/d increase in intake of α -tocopherol and α -tocopherol

equivalents with 95% CI were 0.66 (0.43-1.03) and 0.56 (0.32-0.98), respectively [74]. In studies showing the inverse correlation between tocotrienol and cognitive decline, the age of subjects ranged from early [71] and mid 70s [9, 72, 74] to mid 80s [73]. There is no apparent association between the impact of tocotrienol and the age of subjects based on reported ORs in a limited number of studies, though the single study with the oldest subjects seemed to show the lowest OR value with tocotrienol [73]. In a separate study with a younger population in which 121 subjects aged ≥ 35 years with cardiovascular risk factors and white matter lesions (WMLs) were given 200 mg mixed tocotrienol twice a day, the mean WML volume was found to be significantly lower in the group supplemented with tocotrienol as compared to the placebo group ($P = 0.019$) at the end of 2-year study [75]. Studies of supplementing AD patients with vitamin E containing tocopherols as the primary components result in variable outcomes and no clear beneficial effect for AD patients [76, 77].

Epidemiological evidence for the inverse correlation between tocotrienol and AD incidence is consistent with preclinical studies showing neuroprotective activity of tocotrienols. α -Tocotrienol was more effective than α -tocopherol in preventing cognitive deficits in rats induced by intracerebroventricular streptozotocin insult. Behavioral tests using Morris water maze clearly reveal a rescue of memory dysfunction by tocotrienol, which effectively reduced malondialdehyde and nitrite, and attenuated the decreases in glutathione and catalase [78, 79]. Supplementation with tocotrienol-rich-fractions reduced anxiety, improved spatial learning and memory, reduced DNA damage and level of malondialdehyde, and increased antioxidant activity in aged rats [80]. Tocotrienols attenuated neurite degeneration induced by 2,2'-azobis (2-methylpropionamide) dihydrochloride [81] and may also suppress elevated oxidative stress and mitochondrial injury. Additionally, tocotrienols maintain cell survival against neuro injury

caused by glutamate, the main excitatory neurotransmitter that becomes excitotoxic under disease conditions [82, 83].

It is unknown whether the correlation between tocotrienol intake and AD risk is attributable to tocotrienol-mediated HMG CoA reductase suppression and consequent decrease in FPP and GGPP, though the latter would be consistent with tocotrienol-mediated blockage of SREBP-2 maturation. Lending support to the reductase hypothesis is the finding that, in addition to statins and aforementioned isoprenoids, the reductase-suppressive resveratrol [84], a polyphenol found in grape skin and red wine – among other food sources – triggers autophagy and lysosomal degradation of A β in APP-HEK293 cells and reduces cerebral A β levels and deposition in the cortices in mice [85]. The aforementioned statin-mediated reduction of FPP and GGPP observed in preclinical studies has not manifested in human studies, a plausible cause for equivocality of statins in human trials.

5. Tocotrienols and Inflammation

The anti-inflammatory activity of tocotrienols may have contributed to their potential protection against AD. In human breast cancer cells [86, 87], colon carcinoma cells [88], malignant melanoma cells [89], pancreatic cancer cells [90], gastric cancer cells [91], metastatic oral cancer cells [92], adipocytes [93, 94], and macrophages [95-98], tocotrienols inhibit the DNA-binding activity of nuclear factor kappa B (NF κ B), a major mediator in chronic inflammation, and suppress tumor necrosis factor α - and lipopolysaccharide (LPS)-induced NF κ B expression. Moreover, the in vitro NF κ B-suppressive activity of tocotrienols manifested in gastric cancer [91] and pancreatic cancer [99] in nude mice and in the cerebral cortices and hippocampi of ethanol-fed rats [100]. Recent reviews [101-103] have summarized the anti-

inflammatory activity of tocotrienols.

The finding that tocotrienol-mediated ablation of NF κ B activity was reversed by supplemental mevalonate [104], the product of HMG CoA reductase, suggests that reductase suppression mediates the anti-inflammatory activity of tocotrienols and may unify that of diverse isoprenoids. The monoterpenes limonene and trihydroxy ketone E-4-(1,2,4-trihydroxy-2,6,6,-trimethylcyclohexyl)-but-3-en-2-one inhibited NF κ B activation in human HL60 clone 15 leukemia cells [105] and PC-3 prostate cancer cells [106], respectively. α -Pinene and geraniol, two monoterpenes found in *Salvia lavandulaefolia* (Spanish sage) essential oil, inhibited the production of thromboxane B₂ and leukotriene B₄, respectively, in rat leucocytes [107]. The monoterpenes hookerins A and B isolated from the herb *Pterocephalus hookeri* inhibited NF κ B expression in a reporter luciferase assay in human embryonic kidney HEK293 cells [108]. Perillyl alcohol, an oxidative product of limonene, suppressed NF κ B in B-lymphoma [109], while geraniol suppressed 12-O-tetradecanoyl phorbol-13-acetate (TPA)-induced inflammatory responses and up-regulation of NF κ B and cyclooxygenase-2 in mice [110, 111]. The monoterpenes isopropoxy-carvacrol [112], 4'-geranyloxyferulic acid [113] and (-)-myrtenol [114] also showed anti-inflammatory activity in mice. A sesquiterpene β -ionone inhibited TNF-related apoptosis-inducing ligand (TRAIL)-induced NF κ B activation in human HepB3 and HepG2 hepatocellular carcinoma cells [115], and farnesol attenuated the 1,2-dimethylhydrazine-induced infiltration of the inflammatory cells in mucosal and submucosal layers of the colon of Wistar rats [116]. Over 100 sesquiterpene lactones blocked NF κ B activity [117, 118], while parthenolide inhibited the inflammasome [118]. Diterpene coronarin D suppressed NF κ B activation in human KBM-5 chronic myeloid leukemia and A293 embryonic kidney carcinoma cells [119]. Another diterpene carnosol reduced LPS-stimulated nitric oxide production and

NF κ B in RAW 264.7 cells [120], reduced pro-inflammatory leukotrienes in human polymorphonuclear leukocytes [121], and inhibited cyclooxygenase-2 in 184B5/HER human mammary epithelial cells [122]. Garcinol, a mixed polyisoprenoid, inhibited the activation of NF κ B in human BxPC-3 and Panc-1 pancreatic cancer cells [123] and squamous cell carcinoma of the head and neck [124]. Additionally, a triterpene lupeol suppressed TPA-induced activation of NF κ B in CD-1 mice [125]. The HMG CoA reductase suppressive tetraterpene lycopene [126-128] suppresses the production of tumor necrosis factor- α and activation of NF κ B, CD14 and Toll-like receptor 4 in LPS-activated primary human umbilical vein endothelial cells [129] and abrogates A β -mediated neuroinflammatory cascade and learning and memory deficits [130] while ameliorating fructose-induced neuroinflammation and cognitive impairment [131] in experimental models of AD.

Coincidentally, accumulating evidence supports the anti-inflammatory and NF κ B suppressive activity of statins [132-135]. Reminiscent of the findings with tocotrienols [104], mevalonate attenuated the simvastatin effect on NF κ B [136]. Whether mevalonate deprivation and anti-inflammation mediate the potential roles of statins and tocotrienols in AD and the neuromodulatory activity of isoprenoids warrants further studies.

6. Current Therapeutics and Potential of Tocotrienols as Preventive/Therapeutic Agents

Since neuropathological hallmarks in the brains of AD patients include A β -containing neuritic plaques and Tau-containing neurofibrillary tangles, therapeutic efforts have been devoted to agents that may effectively reduce the pathology. A number of amyloid-based therapeutics have been developed and tested in clinical trials. Although several high-profile phase III clinical trials failed in the past several years, recent findings in maintaining cognitive

function by Biogen's immunotherapy provide strong evidence to support the validity of amyloid-based therapies.

In clinical trials, the antibody Aducanumab (BIIB37) performs best among many immunotherapies, such as AAB-003 by Janssen/Pfizer, ACI-24 by AC Immune, Affitope AD02 by AFFiRiS AG, BAN2401 by Eisai, LY3002813 by Eli Lilly, MED1814 by AstraZeneca, and SAR228810 by Sanofi. Uniquely, Aducanumab recognize amino acid 3-6 of aggregated A β but not monomeric A β . For the clinical trial of Aducanumab, enrolled subjects underwent amyloid PET tracer florbetapir to confirm diagnosis of early AD. The results from the phase I study revealed that amyloid deposit levels dropped in all treatment groups after 6 months and even more after one year, while the control group receiving the placebo showed a slight increase in amyloid deposit. These results clearly show the target engagement and demonstrate a reduction of amyloid deposit by Aducanumab. Aducanumab is the only agent in clinical trials that demonstrates a clinical benefit to cognitive function, such as MMSE and CDR-SB tests. A lower-point drop was found in the group receiving the antibody, compared to a greater-point drop in the placebo group. The overall positive responses from the phase I trial prompted a direct entry of Aducanumab into phase III trials [137].

A second class of promising amyloid-based therapies is the β -secretase inhibitors, including AZD3293 by AstraZeneca, BI 1181181 by Boehringer Ingelheim, E2609 by Biogen, JNJ-54861911 by Janssen, and MK-8931 by Merck (phase III). These compounds are highly potent and reduce A β in animals and humans; success in any one of these compounds in clinical trials would further support the validity of amyloid-based therapies for AD.

Despite the multiple therapeutics tested in the past decade to reduce the pathological burden and to maintain cognitive function, the molecular mechanism of AD pathogenesis is still

not completely clear. Toxicities – such as those associated with some recent γ -secretase inhibitors – and lack of efficacy preclude a cure for AD to date.

Extensive *in vitro*, *in vivo* and human studies have demonstrated the safety of tocotrienols derived from oils of palm, rice bran and annatto seed [138]. Palm- (GRN 000307) and annatto- (GRN 000471) derived tocotrienols have obtained FDA-approved Generally Recognized As Safe (GRAS) status. At non-toxic levels, tocotrienols and tocotrienol-containing formulations were found to possess triglyceride- [139, 140] and cholesterol- [140] lowering, anti-inflammatory [140] and neuroprotective [141, 142] effects in humans. The safety profile of tocotrienols, coupled with their impacts on the mevalonate pathway and inflammation – mechanisms delineated in sections 4 and 5 of this review – renders tocotrienols promising agents for AD prevention or therapy.

7. Summary and Future Directions

The potential of tocotrienols in AD prevention or treatment is likely dependent on their impact on the mevalonate pathway, SREBP-2 processing, cholesterol biosynthesis, inflammation, and neuroprotection. Strawberry, spinach and blueberry extracts protect against age-related neuronal decline with mixed effect on antioxidant status; reactive oxygen species (ROS), but not glutathione, were reduced. The differential effects of tocotrienols and tocopherols in protection against AD and the finding that FTIs reduce ROS production and increase the viability of mouse neuronal cortical cells [143] suggest that antioxidant activity may be secondary to prenylation inhibition.

In conclusion, the potential effects of tocotrienols on the mevalonate pathway intermediates FPP and GGPP and inflammation, coupled with the safety profile of tocotrienols -

distinctive from those of the experimental drugs - render these vitamin E molecules promising candidates for AD prevention and/or treatment. The broad plant-food-based sources for tocotrienols, including avocados, bananas, berries, cabbage, cherries, coconut, corn, Kiwi, green pea, onions, peaches, pears, plums [144-146], grape [147, 148], peanuts [149], hazelnut [150], cashew [151], horse chestnuts, litchi [152, 153], cereals, wheat [154], olive fruit [155], annatto [156], and specialty oils from palm, rice bran, barley, and oat [157, 158] suggest that protection against AD mediated by tocotrienols and potentially the mevalonate-suppressive isoprenoids may be nutritionally relevant. Preclinical and clinical studies need to determine the efficacy and mechanism of action of tocotrienol. Once targets for tocotrienols are identified, tocotrienol derivatives [159] and novel formulations such as self-emulsifying drug delivery systems [160, 161], nanoemulsion [162], and nanoparticles [163] with enhanced bioavailability, accurate target delivery and engagement, and higher potency could be developed. Combinations of tocotrienols with other pharmaceutical and non-pharmaceutical approaches, each with different, but preferably complementary, mechanisms of action for greater efficacy and yet less adverse effects, may further add to the potential of this class of agents as AD preventives and therapeutics.

Figure 1. The mevalonate pathway consisting of steps catalyzed by enzymes including 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase and FPP and GGPP synthases provides farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP) for the prenylation of proteins regulating neuro functions. FPP also leads to the biosynthesis of sterols that elicit feedback inhibition of HMG CoA reductase expression via its transcriptional factor, sterol regulatory element binding protein-2 (SREBP-2). Statins and isoprenoids including tocotrienols suppress HMG CoA reductase; the former via competitive inhibition and the latter, transcriptional downregulation and acceleration of protein degradation. Statins and tocotrienols may have preventive and therapeutic values for Alzheimer's disease through depletion of FPP and GGPP. Farnesyl- and geranylgeranyl- transferase inhibitors (FTIs & GGTIs) and bisphosphonates may also be neuroprotective by inhibiting prenyl transferases and FPP synthase, respectively. Furthermore, tocotrienols may suppress NF κ B-mediated neuroinflammation as a consequent to FPP and GGPP ablation. The dotted arrow indicates a postulated connection.

Figure 2. The structures of tocopherols and tocotrienols. Tocopherols and tocotrienols share a common chromanol ring where the number and position of the methyl group determine the vitamin E isomers (α , β , γ and δ) within each category, but differ in their side chains. The unsaturated farnesyl moiety of tocotrienol is associated with biological activities of tocotrienols distinct from those of tocopherols.

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ACCEPTED MANUSCRIPT

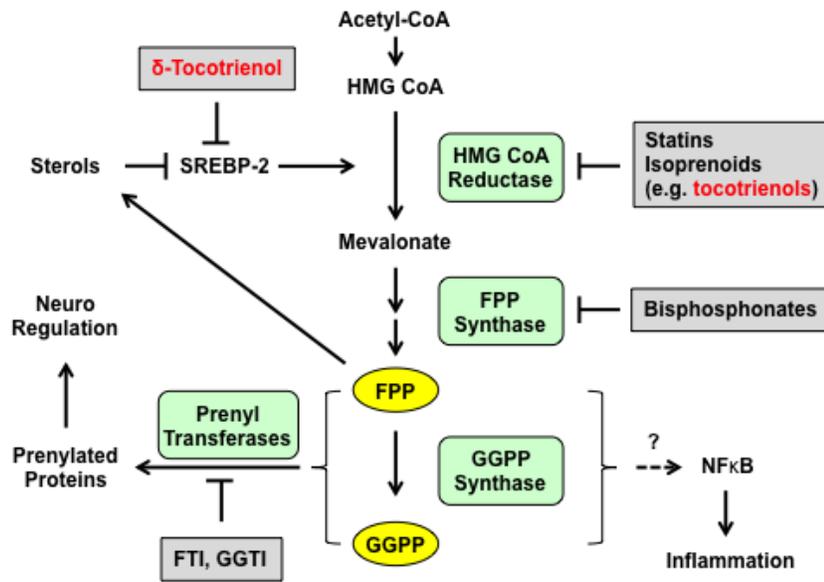


Fig. 1

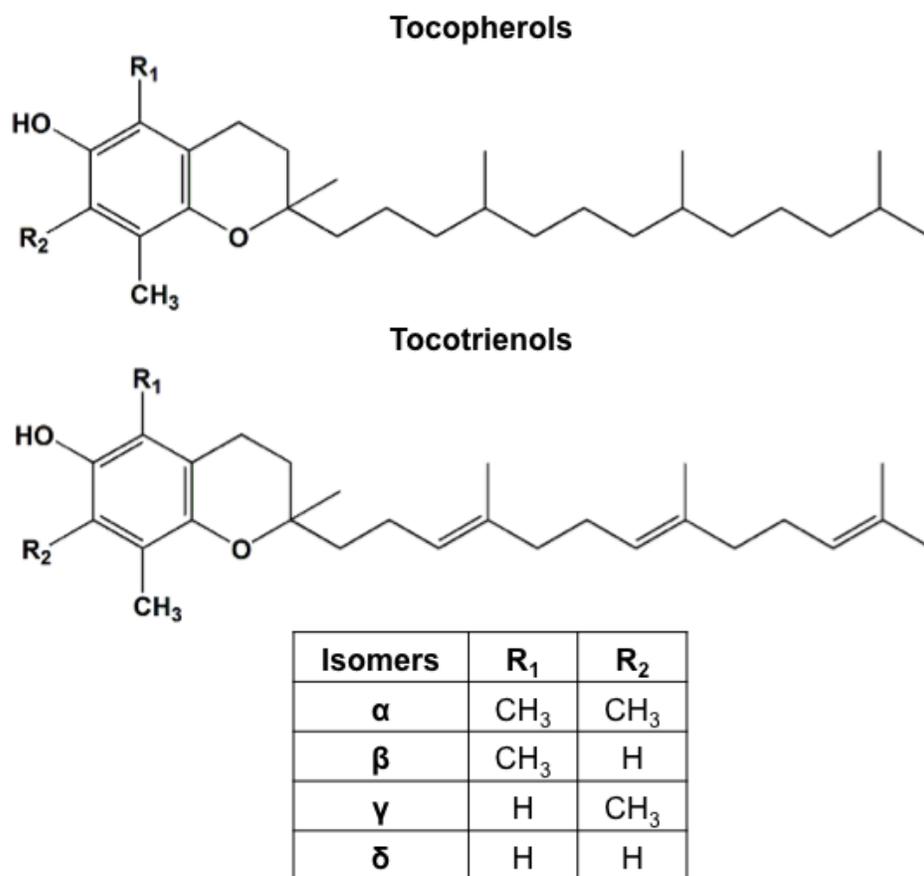


Fig. 2