BioFactors

Review Article

Vitamin E in aging, dementia, and Alzheimer's disease

*Yash B. Joshi and Domenico Praticò**

Department of Pharmacology, Temple University, School of Medicine, Philadelphia, PA, USA

Abstract.

Since its discovery, vitamin E has been extensively researched by a large number of investigators in an attempt to fully understand its role in a variety of pathophysiological contexts. The vast majority of published work has focused on vitamin E's antioxidant properties, which is why it is well known as a lipophilic antioxidant that protects membranes from being oxidatively damaged by free radicals. However, several lines of investigation have recently revealed that vitamin E has biological roles unrelated to its antioxidant properties. Among these roles, vitamin E has been described as: a regulator of signal transduction, gene expression, and redox sensor. In parallel with the discovery of novels cellular functions of vitamin E, the introduction of the free radical theory of brain aging has propelled a renewed interest in this vitamin. Most of the resulting work has been based on the postulate that, by preventing and/or minimizing the oxidative stress-dependent brain damage, vitamin E could be used as therapeutic approach. In this article, we will consider the existing literature regarding the biological properties of vitamin E and the potential therapeutic and/or preventative roles that this natural dietary factor plays in brain aging, cognition, and Alzheimer's dementia.

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E-mail: praticod@temple.edu

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1. Introduction

Almost a century has passed since Evans and Bishop [1] first described a "substance X," today known as vitamin E, as a critical factor for post-fertilization placental development in rats. Later work would implicate the rancid fat present in the experimental diet responsible for the pathologies observed in animals, which could be ameliorated by the addition of greens or wheat germ oil concentrates containing vitamin E to rodent diet [2–4].

Since its discovery, vitamin E has been extensively researched by a large number of investigators in an attempt to fully understand its role in a variety of pathophysiological contexts.

The vast majority of published work has focused on vitamin E's antioxidant properties, which is why it is well known as a lipophilic antioxidant that protects membranes from being oxidatively damaged by free radicals [5]. However, several lines of investigation have recently revealed that vitamin E has biological roles unrelated to its antioxidant properties. Among these roles, vitamin E has been described as: a regulator of signal transduction and gene expression, redox sensor, and modulator of specific cell functions via interaction with certain membrane domains. On the basis of this emerging work, it is clear that vitamin E is a complex molecule with varied and pleiotropic effects [6–10].

In parallel with the discovery of novels cellular functions of vitamin E, the introduction of the free radical theory of brain aging has propelled a renewed interest in this vitamin. The theory posits that reactive oxygen species are responsible for age-related oxidative damage to the brain, and that accumulation of oxidative damage to neuronal components with age may underlie the molecular basis of pathological brain aging and subsequent neurodegenerative processes [11]. As result, by preventing and/or minimizing the oxidative stress-dependent brain damage, it has been postulated that vitamin E could be used an important therapeutic strategy.

In this review, we will consider the existing literature regarding the biological properties of vitamin E and the potential therapeutic and/or preventative roles that this natural dietary factor plays in brain aging, cognition, and Alzheimer's dementia.

2. Biochemistry and pharmacokinetics

Vitamin E belongs to a group of eight structurally related lipophilic chromanol congeners. Vitamin E found in natural

*Address for correspondence: Domenico Praticò, MD, Department of Pharmacology, MRB 706A, 3420 North Broad street, Philadelphia, PA 19140, USA. Tel.: +215-707-9380; Fax: +215-707-7068.; E-mail: praticod@temple.edu.
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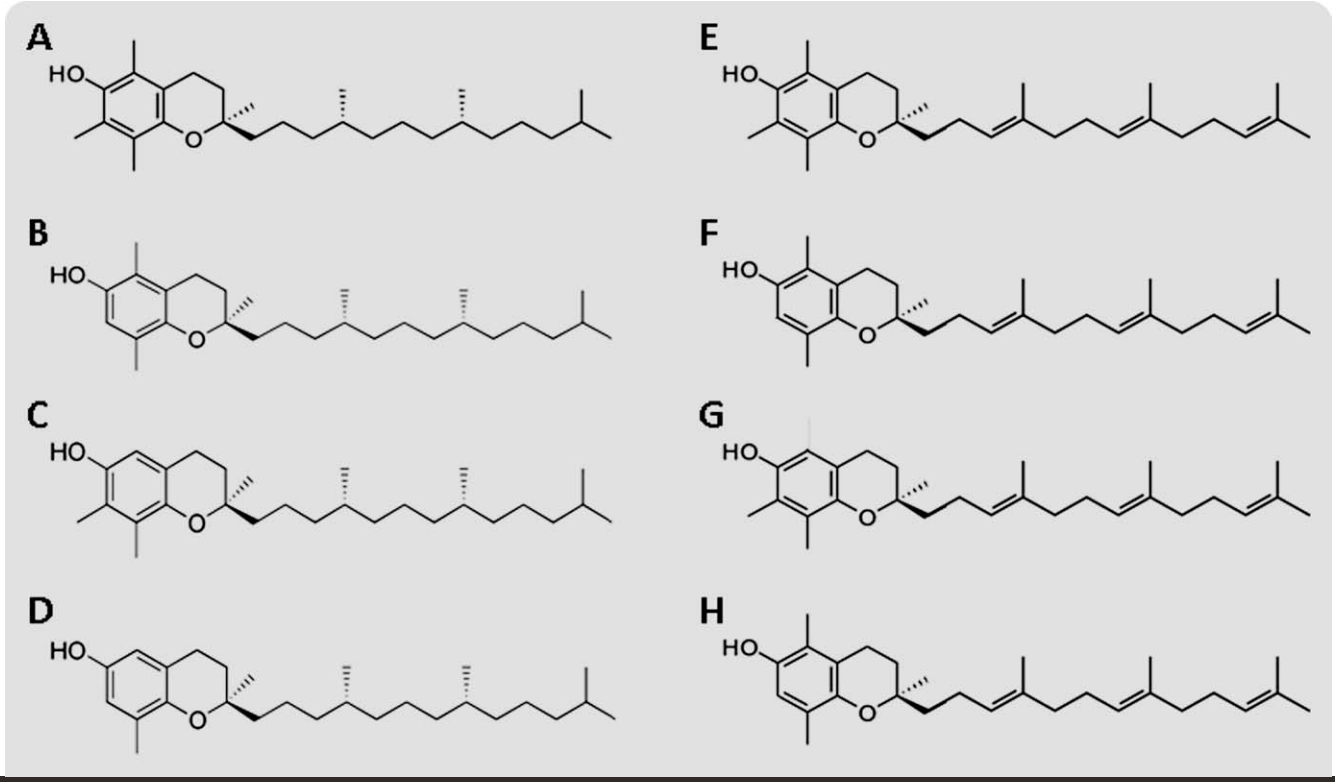

Fig. 1. Molecular structure of vitamin E congeners. α-tocopherol (A), β-tocopherol (B), γ-tocopherol (C), δ-tocopherol (D), α-tocotrienol (E), β-tocotrienol (F), γ-tocotrienol (G), and δ-tocopherol (H). α-tocopherol is the most abundant and well-studied vitamin E molecule.

food includes both four tocopherols and four tocotrienols all of which have saturated and three double bonds in their phytyl tails, respectively. The tocopherols and tocotrienols are further subdivided into α-, β-, γ-, and δ- based on the hydroxyl and methyl substitution in their phenolic rings (Fig. 1).

The most studied congener of vitamin E molecule is α-tocopherol, and both terms will be used interchangeably in the current article. Alpha-tocopherol is the most abundant congener found in nature, has the most potent biological activity and corrects human vitamin E deficiency symptoms [12,13]. When produced synthetically, it is composed of eight stereoisomers with the RRR-α-tocopherol as the most biologically active form [14]. The most abundant sources of vitamin E are vegetable oils, which typically contain all four tocopherol congeners (α-, β-, γ-, δ) in varying proportions. Other important sources are nuts and seeds such as sunflower seeds.

Because all forms of vitamin E are lipid soluble they are easily absorbed from the intestinal lumen after dietary intake via micelles created by biliary and pancreatic secretions [15–17]. Vitamin E is then incorporated into chylomicrons and secreted into the circulation where, transported by various lipoproteins, it travels to the liver. Plasma α-tocopherol concentrations in humans range from 11 to 37 μmol/L, whereas γ-tocopherol are between 2 and 5 μmol/L. The liver plays a central role in regulating α-tocopherol levels by directly acting on the distribution, metabolism, and excretion of this vitamin [18]. The major hepatic regulatory mechanism is the α-tocopherol transfer protein, α-TTP, which has been identified in a variety of mammals, including humans [19]. This protein facilitates secretion of α-tocopherol from the liver into the bloodstream, by acquiring it from endosomes and then delivering it to the plasma membrane where it is released and promptly associates with the different nascent lipoproteins [20].

Plasma concentration of vitamin E depends completely on the absorption, tissue delivery, and excretion rate. The estimated α-tocopherol half-life in plasma of healthy individuals is ∼ 48 to 60 H, which is much longer than the half-life of γ-tocopherol (i.e., 15 H). These kinetic data underscore an interesting concept that while α-tocopherol levels are maintained, the other forms of vitamin E are removed much more rapidly. Vitamin E metabolites are shorter and carboxylated forms [carboxyethyl-hydroxychromans, (CEHC)] of the original molecule, resulting from an initial ω-oxidation by the cytochrome P450s, with a subsequent β-oxidation and glucuronide conjugation, are excreted in the urine or bile [21].

3. Physiological functions

All forms of vitamin E meet the chemical definition of an antioxidant moiety: "chain-breaking free radical scavenger." Indeed consistent data have shown that all isoforms act as potent antioxidants in conventional *in vitro* paradigms. The free hydroxyl group on the aromatic ring (see Fig. 1) is thought to be responsible for this property, and a relatively

stable form of the original vitamin E is formed when a hydrogen from this group is donated to a free radical [22]. Yet, definitive proof that vitamin E possesses antioxidant properties has been hampered for a long time because of a lack of sensitive and specific analytical techniques to measure this biologic event *in vivo*. Currently available markers of oxidative damage, including carbonyls, 8-Oxo-2'-deoxyguanosine (8-oxodG), malondialdehyde (MDA), pentane exhalation, lipid hydroperoxide, glutathione (GSH), and Glutathione peroxidase 1 (GPx1), F2-isoprostanes. All of them do not appear capable to confirm or deny *in vivo* vitamin E antioxidant activity as their levels under various experimental and clinical conditions, or modulation after vitamin E supplementation, are not always consistent.

Apart from antioxidant properties, more recent studies have clearly demonstrated that vitamin E also possesses important non-antioxidant cellular and molecular functions. One of the first roles of α-tocopherol in cell signaling was the report that it inhibits smooth muscle cell proliferation, decrease protein kinase C activity, and controls expression of the α-tropomyosin gene [23]. These functions are not related to its antioxidant activity, since β-tocopherol, which has a similar antioxidant activity, does not have any of these cellular functions. Other enzymes which have been reported to be inhibited by vitamin E are: 5-lipoxygenase (5LOX), phospholipases A2, and cyclo-oxygenase 2 (COX2). In addition, α-tocopherol seems to be able to activate other enzymatic moieties: protein phosphatase 2 A (PP2A), diacylglycerol kinase (DAG kinase), 3-hydroxy-3 methyl-glutaryl-Coenzyme A reductase (HMG-CoA reductase). For a more detailed list of those non-antioxidant activities, we recommend a recent review article by Brigelius-Flohe [24].Some non-antioxidant properties of vitamin E could play a key role in neuroprotection. Thus, it has been recently shown that α-tocotrienol, at nanomolar concentrations, protects mouse hippocampal and cortical neurons from cell death by modulating neurodegenerative signaling cascades. Furthermore, it has been shown that α-tocotrienol modulates 12-lipoxygenase and phospholipase A2 activities, which are implicated in glutamate-induced neuronal cell death [25,26]. Finally, some vitamin E forms (α- and γ-tocopherol, tocotrienols) also exhibit potent anti-inflammatory properties [27,28].

4. Vitamin E and dementia

4.1. Aging, cognitive function, and dementia

Current epidemiologic evidence indicates that neuropsychiatric aging-associated diseases such as dementia and Alzheimer's disease (AD) will dramatically increase in the next century due to the expansion of the aged population worldwide. It is therefore clear to general practitioners, geriatricians, neurologists, and other health care professionals that in the near future, several diagnostic, therapeutic, and socioeconomic challenges will have to be addressed. Currently, 18 million people suffer from dementia in Europe, Africa, Asia, and Latin America, while at least 5 million people are thought to have some form of dementia in the United States. Current estimates of AD prevalence are thought to be greater than 10% in North America and by 2050 there will be over 13 million AD cases in the United States alone [29–32].

Dementia is one of the most common diseases in the elderly, with crude prevalence rates between 5.9% and 9.4% for subjects aged over 65 worldwide [33]. The lowest age- and gender-specific prevalence of all-causes dementia reported in the literature is 61.1% among women aged 100 or greater [34–36]. Dementia drastically affects daily life and everyday personal activities, and the costs of care for patients with dementia are therefore immense [37].

Prevention appears to be particularly prominent among anti-dementia strategies as there are no efficacious pharmacologic treatments for dementia [38]. Further, both primary and secondary prevention can be carried out within a multidimensional scheme with the highest chances of success if adopted in the early adulthood. However, the US Preventive Services Task Force suggests there is insufficient evidence to support instituting a universal dementia screening preventative/therapeutic programme [39]. Syndromes of cognitive impairment in non-demented older adults have been the focus of studies aiming to identify subjects at high risk to develop dementia. Mild cognitive impairment (MCI), characterized by isolated memory deficits in non-demented persons with subjective memory problems, normal general cognitive functioning, and intact activities of daily living, is thought to affect 10–17% of the elderly population [40]. The effort of identifying MCI subjects is very important because it has the main aim of allowing the earliest symptomatic stages of dementia to be better recognized and treated.

In the attempt of preventing the development of dementia, there are several risk factors to be taken into account, some of which are non-modifiable and include age, gender, and genetic influence. Of several modifiable risk factors, cardiovascular and lifestyle interactions have received recent interest. Among vascular risk factors, considerable evidence from randomized controlled trials and longitudinal cohort studies has established the relationship between hypertension, hyperlipidemia, and dementia. Both systolic hypertension above 160 mmHg and serum cholesterol above 6.5 mmol/L (240 mg/dL) are known to be associated with an increased relative risk of 1.5 and 2.1, respectively, to develop AD [41]. However, rigorous randomized controlled trials, cohort, and case-control studies have found that intervention strategies aimed at treating vascular disease or associated comorbidities do not modify dementia risk. Thus, statin therapy, acetylsalicylic acid regimens and carotid artery stenosis reopening, or treatment of type 2 diabetes mellitus, hyperlipidemia, and hyperhomocysteinemia should not be recommended as primary prevention strategies with the single specific purpose of reducing the risk of dementia.

Modulation of lifestyle factors against dementia onset and progression has been the focus of recent research efforts. Among these factors, it is evident that diet plays a crucial role in the prevention of age-related clinical conditions including dementia, and bioactive compounds, such as the antioxidants contained in fruits and vegetables, are important determinants of the protective dietary effects. This

Table 1
Epidemiologic studies examining the diet and cognition in the elderly

Authors	Study design	Subjects	Findings
Morris et al. [49]	Prospective	3,718 participants	High vegetable consumption associated with slower rate of cognitive decline in elderly participants
Scarmeas et al. [50]	Nested case-control	2,226 participants	Higher adherence to Mediterranean diet associated with reduced risk of AD
Scarmeas et al. [51]	Prospective	1,984 participants	Higher adherence to Mediterranean diet associated with reduced risk of AD in elderly participants
Barberger-Gateau et al. [52]	Cohort	8,085 participants	Frequent consumption of fruits, vegetables, fish and omega-3 rich oils was with reduced risk of AD in elderly participants
Scarmeas et al. 2007 [53]	Prospective	192 participants	Higher adherence to Mediterranean diet associated with decreased mortality in AD patients

AD, Alzheimer's disease.

evidence has been based mainly upon the consistent observation and the strong epidemiologic data showing that poor diet and physical inactivity lead to chronic disease such as AD that are among the leading causes of death for Americans [42].

4.2. Antioxidant vitamins, cognition, and dementia

Oxidative stress, which is caused by an imbalance between oxidants and antioxidants leads to loss of function of the resulting oxidized biomolecules, is a well-documented pathogenic mediator in neurodegenerative disorders, particularly dementia and AD [43]. Oxidatively damaged proteins, lipids, and DNA have been found in brains of AD patients as well as in their peripheral tissues [44]. While it remains an open question what initiates and propagates oxidative stress in AD, multiple antioxidant strategies have been tried in recent decades to assess potential beneficial effects against AD development and/or progression.

Fruits and vegetables are perhaps the best source of antioxidant micronutrients due to their low saturated fat content and because multiple protective components contained in these foods allow synergistically improved bioavailability over single vitamins. A large body of epidemiological evidence from natural nutrition studies have revealed that decreased food intakes, eating behaviour disturbances, and loss of body weight are particularly significant problems among patients with AD. Malnutrition has also been shown to be associated with a more rapid decline in AD patients [45]. The effects of dietary counseling on fruit and vegetable intake as well as the effect of improved fruit and vegetable intake on the levels of circulating antioxidants, biomarkers of oxidative stress, and cognitive performance in healthy subjects are positive and beneficial [46–48]. In patients with age-associated neurocognitive disease such as AD, who have increased circulating levels of biomarkers of oxidative stress, a targeted nutritional intervention aimed at increasing plasma antioxidant levels and at decreasing the ongoing condition of oxidative stress might prove beneficial if implemented in conjunction with standard therapeutic options (see Table 1).

In a prospective study by Shatenstein et al., 36 community-dwelling patients in early stages of AD and 58 age-matched cognitively intact community-based controls were followed over an 18-month period to document the natural evolution of dietary and nutrition status among elderly community-dwelling adults with AD [48]. Nutrient intakes from diet and supplements were higher in control subjects, with significant differences in energy, calcium, iron, zinc, vitamin K, vitamin A, and dietary fiber as well as n-3 and n-6 fatty acids. Suboptimal diet occurred early in the onset of the disease and the authors suggested that AD patients would benefit from systematic dietary assessment and intervention to prevent further deterioration in food consumption and malnutrition.

High vegetable consumption was associated with a slower rate of cognitive decline over 6 years after adjusting for age, gender, race, education, cardiovascular-related conditions, and risk factors in a prospective cohort study of over 3,700 older participants of the Chicago Health and Age Project [49]. In this study, the consumption of green leafy vegetables, rich in antioxidant micronutrients, showed the strongest inverse linear association with the rate of cognitive decline. The specific protection shown by vegetables and particularly by the green leafy ones appears to be in disagreement with the concept that fruit and vegetable consumption might be beneficial in the frame of a generally healthy lifestyle, as health-conscious individuals tend to consume relatively high levels of both fruits and vegetables.

Healthy diet in general and the Mediterranean regimen in particular have been recently shown to affect risk for and mortality from AD [50–54]. The existing evidence does not support the recommendation of specific supplements, foods, or diets for the prevention of AD. However, a review of 34 studies in the areas of dietary restriction, antioxidants and Mediterranean diet provides evidence that nutritional interventions against dementia and AD have significant potential of influencing disease development [55].

4.3. Vitamin E and AD: clinical evidence

Recently, an association between a higher quintile of adherence to a Mediterranean diet and lower inadequacy for vitamin E has been suggested [56]. Vitamin E, known to reach therapeutic levels in brains of AD patients, decreases lipid peroxidation susceptibility by 60% in AD patients as compared to controls [57]. Post-mortem analysis of cerebrospinal fluid also reveals that α-tocopherol levels positively correlate with perceptual speed and AD pathology in patients [58]. Most of the studies on vitamin E have focused on α-tocopherol levels, both in its absolute levels and as the ratio of the serum tocopherol concentration to the sum of the serum concentrations of cholesterol and triglycerides, however, the contribution of γ-tocopherol as a source of antioxidant activity needs to be considered further. The richest sources of vitamin E in many diets are vegetable oils such as soybean oil and corn oil which interestingly contain more γ-tocopherol than α-tocopherol, but the biological activity of γ-tocopherol is only 15% of that of all-rac-α-tocopheryl acetate. No commercial preparations contain γ-tocopherol, despite animal studies showing that giving α-tocopherol to rats increases the γ-tocopherol forebrain content, and evidence that a combination of tocopherol forms ingested with food rather than α-tocopherol alone have been suggested to be important in the vitamin E protective association with AD [59,60].

Based upon the hypothesis that if vitamin E enhances neuronal survival, there should be a positive relation between serum concentrations and cognitive function. To this end, vitamin E plasma levels have been measured in several recent human studies, and its deficiency has been consistently found in patients with AD and MCI. Five causal criteria have been established to evaluate the strength of evidence linking the availability of a micronutrient to cognitive or behavioural function which include: a plausible biological rationale, a consistent association, cause and effect specificity, a dose-response relationship, and the ability of experimentally manipulate the effect [61]. These criteria have been already used for docosahexaenoic acid, choline, and vitamin D [62–64]. As far as vitamin E is concerned, it appears that the criteria most convincingly satisfied are the biological rationale and the associations between vitamin E intake/levels found [65–73].

On the basis of the biological rationale, a seminal multicenter clinical trial by Sano et al. showed that AD patients randomly assigned to receive α-tocopherol (2000 IU/d) had a slow functional decline, though this was also found to be true for the patients assigned to receive selegiline or selegiline plus vitamin E, with no effect of any treatment on cognitive tests. Further trials of vitamin E supplementation have demonstrated no major benefit against cognitive impairment or the progression to AD in MCI subjects [74–76]. There are several potential reasons for this discrepancy. One key point is the largely unexplored relationship between intake of fruits and vegetables, antioxidant micronutrient status and cognitive performance in healthy subjects. There are, however, some hints of biological interactions between these components after evaluation of independent measurements in healthy subjects, and it is also likely that when the clinical symptoms of AD appear, a large proportion of neuronal cells might already be destroyed. Therefore the intervention with vitamin E, especially when a single form is used instead of a network, could come too late.

In randomized controlled trials high doses of α-tocopherol have usually been used, while a balanced intake of different vitamin E congeners can be more effective in terms of neuroprotection. Indeed, epidemiological evidence suggests that the protective effect of vitamin E against AD can be due to the contribution of its different forms, while intake of high doses of α-tocopherol can decrease the bioavailability of the other congeners potentially increasing mortality risk [77–79]. More information is needed to clarify biological effects and interactions of all vitamin E tocopherols and tocotrienols in humans, in order to better refine their potential therapeutic effects in preventing cognitive decline and dementia in older adults.

4.4. Vitamin E and AD: *in vitro* evidence

AD pathology is characterized by the presence of extracellular plaques composed of amyloid beta and intracellular neurofibrillary tangles composed of hyperphosphorylated aggregates of the microtubule-associated tau protein. While both pathologies contribute to the cognitive decline in AD, it is widely believed that amyloid beta plays a central role in AD pathogenesis given that patients with familial, early-onset AD have genetic mutations in the amyloid beta precursor protein or the protein complexes that process it to yield amyloid beta [80]. The molecular mechanism whereby vitamin E exerts potential protective effects in AD remains elusive, however, given what is known about AD pathogenesis and vitamin E biology several molecular pathways may be involved.

Amyloid beta peptides have been shown to oxidize proteins through specific amino acid residues which is thought to be one of the reasons why there is an elevated oxidative stress burden in AD brains [81]. Application of vitamin E in rat neuronal cultures prevents amyloid beta-associated reactive oxygen species from forming and decreases oxidative stress markers [82]. In addition, vitamin E protects against oxidation-mediated reduction in neurotransmission-associated proteins such as synaptobrevin and synaptotagmin [83]. This line of *in vitro* experimentation supports the protective anti-oxidant functions of vitamin E in the AD context.

Vitamin E and related tocopherols and tocotrienols inhibit several AD-relevant enzymes which include NADPH oxidase, 5LOX, and COX2, all of which have been implicated in neuroinflammation, oxidative damage and the development of AD pathology [84–86]. Moreover, vitamin E activates PP2A, a phosphatase which plays a significant role in tau homeostasis and has been shown to be downregulated in human AD brains [87]. Thus, vitamin E may exert therapeutic effects by acting on a network of enzymatic and non-enzymatic pathways to decrease production of pathologic AD proteins.

Other functions of vitamin E, such as its role in modulating gene expression or action upon lipid rafts and other cell membrane domains in the AD context are not known,

and further work must be carried out to investigate how vitamin E may, if at all, influence AD also through those mechanisms. Given emerging evidence regarding the non-antioxidant bioactive properties of other tocopherols and tocotrienols, it is possible that the activity of vitamin E congeners, especially γ-tocopherol, can explain the schism between natural epidemiological observations and clinical trials (for a review on this literature, we recommend [88]). Examining the non-antioxidant roles of vitamin E and the contribution of related congeners would provide fruitful areas of future investigation.

5. Conclusions and future directions

It has been almost 90 years since the discovery of vitamin E, but its functional roles still require much more investigation. Isolation and identification of the various types of tocopherols and tocotrienols have been an enormous help to the field in establishing biological effects, and the evidence accumulated so far supports a primary role as antioxidant, but new roles have also emerged: modulator of specific signaling pathways and genes involved in metabolic, inflammatory events. In general, vitamin E levels are under tight control, with mainly α-tocopherol retained and delivered to different tissues.

Most of the human observational epidemiological studies are in general consistent with the hypothesis that there is an inverse correlation between vitamin E levels and intake, cognitive function, and ultimately the risk to develop dementia and AD. Experiments with vitamin E *in vitro* also support the role of this molecule in mitigating the effects of AD pathology. In sharp contrast, randomized clinical trials with vitamin E apparently do not fully support this evidence. Considering these novel aspects of vitamin E biochemistry including the biological properties of related congeners, it should not be surprising that many of the clinical studies, both epidemiological and interventional, which did not take into consideration those aspects, are inconclusive.

More research aimed at defining the uses and the dosage of different tocopherols and tocotrienols in prospective interventional studies is warranted before a final conclusion can be reached.

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