



The emerging relationship between vitamin K and neurodegenerative diseases: a review of current evidence

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Received: 4 May 2022 / Accepted: 6 September 2022 / Published online: 3 November 2022
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Abstract

Neurodegenerative disease refers to a group of disorders that predominantly damage the neurons in the brain. Despite significant progress in the knowledge of neurodegenerative diseases, there is currently no disease-modifying drug available. Vitamin K was first established for its involvement in blood clotting, but there is now compelling evidence indicating its role in the neurological system. In particular, the results of recent studies on the effects of vitamin K2 on preventing apoptosis, oxidative stress, and microglial activation in neuron cells through its role in electron transport are very promising against Alzheimer's disease. In addition to its protective effect on cognitive functions, its inhibitory effects on inflammation and α -synuclein fibrillization in Parkinson's disease, which has been revealed in recent years, are remarkable. Although there are many studies on the mechanism and possible treatment methods of neurodegenerative diseases, especially Parkinson's and Alzheimer's disease, studies on the relationship between vitamin K and neurodegenerative diseases are very limited, yet have promising findings. Vitamin K has also been proposed for therapeutic use in multiple sclerosis patients to lower the intensity or to slow down the progression of the disease. Accordingly, the aim of this study is to review the current evidence for the use of vitamin K supplementation in neurodegenerative diseases, in particular Alzheimer's disease, Parkinson's disease, and multiple sclerosis.

Keywords Neurodegenerative disease · Alzheimer's disease · Parkinson's disease · Vitamin K

Introduction

Neurodegenerative diseases are protein aggregation abnormalities with neurodegeneration, referring to a group of disorders predominantly damaging the neurons in the brain. The most frequent neurodegenerative disorders are Alzheimer's disease (AD) and Parkinson's disease (PD). Multiple sclerosis, Huntington's disease, frontotemporal dementia, amyotrophic lateral sclerosis, and spinocerebellar ataxias are among the other neurodegenerative disorders [1–3].

Oxidative injury, autophagy dysfunction, inflammation, protein aggregation, genetic and epigenetic characteristics,

mitochondrial dysfunction, apoptosis, diminished growth factor functions, and synaptic plasticity loss are all implicated in neurodegenerative diseases causing loss of function and eventually death of neurons in the brain and peripheral nervous system [4].

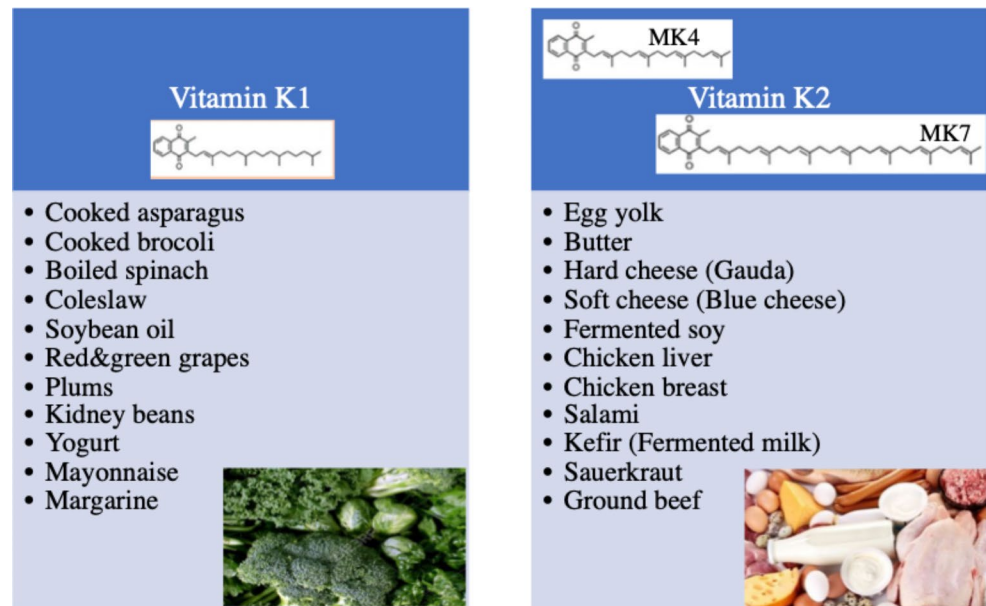
Neuron cells have high oxygen consumption; high concentration of polyunsaturated lipids, which are prone to oxidation, and a limited antioxidant defense system leading to the deleterious effects of oxidative stress on biomolecules. Biomolecules including lipids, proteins, DNA/RNA, etc. are very sensitive to free radicals and are all negatively impacted by oxidative stress in the neuronal cells [5, 6]. Different ROS like $\text{OH}\cdot$ and ONOO can functionally modify the heterocyclic lipid and protein bases. The heterocyclic DNA/RNA bases are more susceptible to oxidative stress, in particular, guanine is more vulnerable to the assault of ROS, leading to the generation of 8-hydroxyguanine and 8-hydroxy-2-deoxyguanosine. Increased ROS attack susceptibility leads to the generation of 8-hydroxyguanine, and amounts of these modified bases are seen in PD brains, indicating that OH radicals 8-hydroxy-2-deoxyguanosine are

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Fig. 1 Sources of Vitamin K1 and K2 in food. Vitamin K1 (phylloquinone) is mainly found in green leafy vegetables whereas Vitamin K2 (menaquinones-MK) is found in animal proteins and fermented foods



involved. As oxidative species, elevated amounts of these changed bases are seen in PD. Additionally, protein carbonylation and nitration are mostly seen in brains. Accordingly, oxidative stress is suggested to increase the risk of neurodegenerative diseases by leading to abnormal protein folding and function [5, 6].

Despite breakthroughs in our understanding of the neurobiology of neurodegenerative disorders, no disease-modifying treatments have been approved. Therapies may alleviate several physical and mental signs and symptoms of neurodegenerative disorders however, there are presently no known cures to decrease the development of the disease [2]. It is important to fully understand the causes and processes of these diseases characterized by protein aggregation and neurodegeneration, to provide effective disease-modifying treatments [4, 7, 8].

Vitamin K was first established for its involvement in blood clotting, but today compelling proof shows that it also plays a role in the neurological system. Vitamin K is involved in the formation of sphingolipids. Accordingly, sphingolipid metabolism changes have been linked to

cognitive impairment as a result of aging and neurodegenerative disorders like AD. Furthermore, increasing evidence shows the impact of Vitamin K on psychomotor activity and cognition, and the distinct antioxidant and anti-inflammatory properties of K vitamers menaquinone-4 (MK-4) are worth mentioning [9, 10]. Although there are many studies on the mechanism and possible treatment methods of neurodegenerative diseases, especially PD and AD disease, studies on the link between vitamin K and neurodegenerative diseases belong to the last decade [9–13].

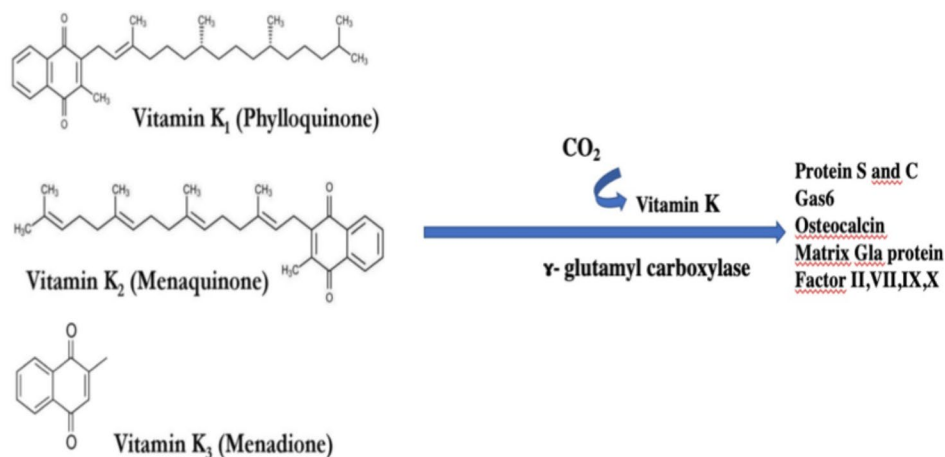
The aim of this study is to evaluate the potential for vitamin K administration in neurodegenerative diseases,

in particular AD, PD, and multiple sclerosis (MS). Accordingly, the integrated review format was applied to this article [14]. When combining and integrating the studies in literature where basic research is restricted, this technique appears to be more acceptable, while attempting to offer a meaningful literature summary to health experts. The available biomedical research was evaluated using MEDLINE/PubMed, conference proceedings, and books. The terms examined were Vitamin K (K1 and K2) and its involvement in neurodegenerative diseases including AD, PD, multiple sclerosis, Huntington's disease, frontotemporal dementia, amyotrophic lateral sclerosis, and spinocerebellar ataxias. However, since the studies focused on AD, PD, and MS the relationship between vitamin K and these degenerative diseases is mentioned in the following sections. For this purpose first, the structure and functions of vitamin K will be explained, then its effects on AD, PD, and MS, and the mechanisms of these effects will be reviewed.

Structure and function of vitamin K

Vitamin K refers to a class of fat-soluble vitamins and, occurs in two forms, K1 and K2. The primary form is Vitamin K1 (phylloquinone) is mainly present in green leafy vegetables, bound to the chloroplast membrane. Vitamin K2 (menaquinones-MK) is a group of bacterial-derived vitamins present in animal proteins and fermented foods [15]. Menadione, often known as vitamin K3, is a synthetic version of vitamin K that can be found in supplements and the intestines transform vitamin K3 into vitamin K2 [16]. Sources of Vitamin K1 and K2 in food are given in Fig. 1.

Fig. 2 Role of Vitamin K as a cofactor for the conversion of glutamate residues via the endoplasmic reticulum resident vitamin K-dependent gamma-glutamyl carboxylase to gamma carboxyglutamic acid (Gla) in vitamin K-dependent proteins



Although Vitamin K1 is present only in one form, the MK family has multiple isoforms. In both human and rat brains, short chain menaquinone-4 (MK-4) is the most abundant vitamer and has been shown to defend against oxidative stress and the activation of the inflammatory reaction [17]. Furthermore, MK-4 depletion has been linked to poor cognitive function in rat models [18]. MK-7, MK-8, and MK-9 are long chain menaquinones that are present in fermented foods including cheese, curd, and sauerkraut [19].

They are regarded as necessary cofactors in the activation of numerous proteins that function in the homeostasis of coagulation and calcium in humans. Vitamin “K” is derived from the K in the Germanic word “Koagulation”, which refers to the capacity to coagulate blood or inhibit bleeding. Over the last several years, a lot has been discovered about vitamin K2 and its function in osteoporosis and vascular calcification associated with osteoarthritis, as well as cancer and cognition [20].

Vitamin K1 and K2 are well recognized for their cofactor role in blood coagulation for the endoplasmic reticulum enzyme, γ -glutamyl carboxylase. This post-translational modification of glutamic acid residues of blood coagulation factors to gamma-carboxyglutamic acid (Gla), produces Gla-containing proteins. Blood coagulation factors including factor II (prothrombin), VII, IX, X, protein C, and protein S are well-known examples of Gla-containing proteins, which are synthesized in the liver [21]. The carboxylation reactions of two vitamin K-dependent proteins, Gas-6 and protein S, whose activity helps to appropriate brain homeostasis, are also facilitated by vitamin K [4, 22] (Fig. 2). Furthermore, vitamin K functions as a cofactor in the creation of sphingolipids, a key component of the membrane of neurons in the brain [23]. The function of these elements in brain metabolism has been emphasized in several studies using in vitro and murine models [24–26]. In several cases, a link to neurodegenerative disorders was discovered, which might be investigated further in human investigations [18, 27].

Bone proteins containing Gla are osteocalcin, matrix Gla, and the pit protein S, and are generated by osteoblasts. The involvement of Vitamin K is essential for glutamate carboxylation to Gla. Matrix Gla protein (MGP) and vitamin K are related because inactive MGP needs vitamin K to carboxylate it to become active. Since MGP is a peripheral protein, the vitamin that may most readily carboxylate MGP is Vitamin K2, which is the most common form of vitamin K in the non-hepatic tissue [28].

Therefore unlike vitamin K1, vitamin K2 can activate different extrahepatic Vitamin K- dependent proteins including MGP, osteocalcin, and Gas6. Vitamin K1 does not appear to have a substantial impact on vascular calcification, as revealed in multiple studies, but Vitamin K2 is being investigated for its function in the regulation of calcification [29, 30]. This may be partially explained by the fact that LDL molecules targeting extra-hepatic organs contain more Vitamin K2 than Vitamin K1 and that this makes it more effective in carboxylating peripheral VKDPs [31]. This might explain why Vitamin K2 has stronger anti-calcification properties than Vitamin K1 [32].

Vitamin K2 deficiency is related to vascular calcification and osteoporosis. Vitamin K-dependent protein-MGP when activated, prevents the calcification of the vascular and soft tissues [33]. Carboxylated osteocalcin (OC) increases after vitamin K2 administration, and uncarboxylated OC is associated with the frequency of clinical fractures [34]. Even 15 mg vitamin K2 (MK-4) supplementation three times a day, is quite safe and does not cause hypercoagulation [35]. Vitamin K has a critical role in sphingolipid metabolism and Gas-6 and Protein S are the nervous system proteins that are vitamin K-dependent.

In addition to its protective action in neuronal membranes, vitamin K may also play an independent protective function in the myelin membranes, against oxidative stress. In primary cultures of immature fetal cortical neurons as well as the oligodendrocyte precursors, it has recently been

shown that MK-4 and, to a smaller extent, phylloquinone, inhibit oxidative damage, which was characterized as free radical buildup and cell death [36]. This is a significant finding since it suggests that oxidative stress is the primary driver of age-related impairments in motor and cognitive function. Because the addition of warfarin or 2-chloro-vitamin K1 as a

γ -carboxylase inhibitor did not reduce the protective effect of vitamin K, it appeared to be independent of the -carboxylation of vitamin K-dependent proteins [37].

Vitamin K and neurodegenerative diseases: possible mechanisms

Vitamin K–dependent protein Gas6

Gas6 (75 kDa) a secreted protein discovered in 1993, is encoded by the growth arrest–specific gene. It contains recognition sites for γ -carboxylation by the vitamin K-dependent carboxylase [19]. It was implicated in chemotaxis, mitogenesis, cell proliferation, and myelination in the neurological system. All of these effects have been connected to the protein's capacity to attach to the Tyro3, Axl, and Mer (TAM) receptors and cause phosphorylation of the receptors [19]. The binding of Gas6 to the receptor tyrosine kinases TAM family, causes their activation, a process that is reliant on Gla units. The post-translational modification of Gas6 on its glutamic acid residues forming Gla, is mediated by the γ -glutamyl carboxylase enzyme requiring vitamin K [29]. Gas-6 is vital for the nervous system's proliferation and survival. In neural and glial cells, it also has anti-apoptotic, mitogenic, and myelinating properties [8, 18].

Axl is necessary for the proliferation of a variety of cells as well as the continuation of gonadotropin-releasing hormone-expressing neurons, regulating their migration from the olfactory bulb through the hypothalamus. Tyro3's exact involvement in cell survival is unknown, however, it has been linked to Axl-like actions [38]. Mer prevents oxidative stress-induced apoptosis in primary macrophages [39].

The dissemination of Gas6 in the CNS of rats was shown before. In rat embryos during the first development stages, Gas6 is expressed primarily in non-neuronal tissues. Purkinje neurons express Gas6 at high levels, also adult rats express Gas6 in cerebral cortex, hippocampus as well as midbrain, and cerebellum. At embryonic day 14, Gas6 is also found in motor neurons. The dorsal root ganglia neurons and ventral horn neurons in the spinal cord have also been shown to express Gas6 [40]. The expression of Gas6 in adults was also studied as a function of age. Age-dependent decrease of Gas6 has been reported in the synaptosomes of rats' striatum, hippocampus, and the frontal cortex. The

frontal cortex showed the most extreme reduction in expression, and levels decreased in 24-month-old rats, compared with the 6-month-old rats, while the striatum and the hippocampus also showed a 55% reduction in expression [41].

Gas-6 reduces the proinflammatory response by down-regulating interleukin-1b expression which triggered nitric oxide-synthase, according to studies employing microglial cells from mice [42]. Microglial cell recruitment to neuronal regions of damage was decreased in two recent mouse models utilizing Mer and Axl knock-out animals, which also affected phagocytic activity through cytoskeleton alterations [43, 44]. Moreover, by inhibiting low-voltage Ca^{2+} influx channels, Gas-6 has been demonstrated to reduce β -amyloid-activated apoptosis, which is a characteristic feature of AD [45]. On the other hand, it was discovered recently that Gas-6 inhibits Tyro3, preventing the accumulation of β -amyloid [46].

Consequently, Gas6 has been regarded as the main modulator of cell survival and proliferation, as well as the myelination process, based on studies acquired over the last 15 years [41–46].

The number of studies examining the relationship between vitamin K and Gas6 is very limited.

Extrahepatic Gla protein carboxylation and vitamin K-dependent coagulation were both improved but not totally normalized by intravenous vitamin K1 at a high dosage of 10 mg after 24 h, according to a recent report [47].

In a prospective screening study, the effects of intravenously administered vitamin K1 were investigated on the plasma levels of Gas6 and its soluble Axl receptor, in intensive care patients. A small yet significant increase in Gas6 levels was reported and a dramatic increase in soluble Axl receptor was detected in only one patient. Studying the restoration of Gas6 carboxylation deficiencies was suggested to be necessary to confirm a real vitamin K impact [48].

Vitamin K–dependent protein protein S

Protein S as the cofactor of protein C has long been recognized for its anticoagulant properties, but new research has found that in addition to enhancing post-ischemic cerebral blood flow, it may also regulate inflammation, angiogenesis, and cancer [49]. Protein S, like Gas6, is found in the brain, although in a considerably smaller amount [50].

The locus coeruleus, choroid plexus, and astrocytes, have been shown to express the protein in the nervous system. mRNA of Protein S is found in rabbit brains, in the pyramidal neurons of the cortex and hippocampus, and also in the dentate gyrus, in granule neurons. mRNA of Protein S was also shown to be expressed in glioblastoma and neuroblastoma cell lines and has been demonstrated to be increased in nerve damage [50, 51].

Protein S has a similar amino acid structure with Gas-6, and hence fulfills some of its functions as a TAM receptor ligand [10]. A link between Tyro3/Akt signaling pathway suppression and hypoxia-induced death of hippocampus neurons has been shown, suggesting that protein S may have a protective role in cerebral infarction [52]. Protein S, in particular, protects cells from the N-methyl-D-aspartate-induced toxicity and apoptosis through the Tyro3/Akt pathway [40]. When applied to stroke animal models in high concentrations, this discovery may imply adjuvant function of protein S to tissue plasminogen-activator to minimize cerebral post-ischemic damage, without raising bleeding risk [10]. Protein S also appears to maintain the structure of the blood-brain barrier, acting as a protective barrier against persistent ischemia damage and blood-brain barrier-related diseases [53].

Although the research is limited, the evidence so far indicates that protein S may exert antithrombotic properties and signaling-mediated neuroprotective effects to defend the brain and nervous system. Serious thrombotic and necrotic phenotypes seen in animals missing protein S in their brains is consistent with antithrombotic properties and neuroprotective effects of protein S [54].

In previous studies, the effects of vitamin K on protein S were examined. As has been demonstrated for hepatocytes [55], vitamin K had no direct impact on the secretion or activity of protein-S in the MG 63 cells, but it might counteract the effects of warfarin [56]. The results are shown with endothelial cells [57] and also with a megakaryoblastic cell line [58], which show that Vitamin K promotes protein-S secretion and activity, are in contrast.

Role of vitamin K in sphingolipid metabolism

Vitamin K is known to increase the synthesis of sphingolipids, which are one of the primary families of eukaryotic lipids and an important component of brain cell membranes [59]. They are important regulators of cell proliferation, differentiation, and survival [10, 60]. They are now recognized to have a role in essential cellular activities such as senescence, and cell-cell interactions, in addition to their structural role. Some sphingolipids in the brain, are strongly linked to MK-4 [51]. Ceramides, sphingomyelin, cerebroside, sulfatides, and gangliosides are the most common sphingolipids found in neuronal cell membranes [60].

The effects of vitamin K on the synthesis of sphingolipids have been investigated. The sphingolipids ceramide phosphorylethanolamine and ceramide phosphorylglycerol are present in the rumen strains of *Porphyromonas levii*, formerly known as *Bacteroides melaninogenicus*. Vitamin K is necessary for the growth of this particular bacterial species, and phylloquinone or menadione can provide this need. The

bacteria only grow slowly in a media devoid of vitamin K, but DNA/RNA or protein synthesis continues to occur [61]. It was also demonstrated using tagged phosphorus that the vitamin K-free diet is connected with a decreased production of sphingolipids. Critical proof that vitamin K may play a particular function in sphingolipid metabolism was provided when vitamin K was added to the medium and caused an acceleration of sphingolipid production before there was a rise in overall growth [37]. These investigations into *P. levii*'s sphingolipid metabolism were then expanded to include mammalian models, notably the mouse and rat. When vitamin K antagonists were administered to mice, their brain serine palmitoyltransferase activity, a key enzyme in sphingolipid synthesis, dropped by 19%. This activity was then recovered after a 3-day supplementation of vitamin K (phylloquinone) [62].

Sphingolipids play a central role in myelination, and myelin stability maintenance. Changes in sphingolipid metabolism have a significant impact on plasma membrane organization and alterations in the composition of myelin sphingolipids may play a key role in the phenotypic of illnesses defined by demyelinalization such as Multiple sclerosis [23]. Ceramide has sphingosine, a long-chain sphingoid base, with a fatty acid linked with an amide bond at the C2 position, serving as the foundation for more complicated sphingolipids [63]. Attaching multiple head groups to the C1 location of ceramide produces more complicated sphingolipids. The structural variety and combinations within the long-chain sphingoid base, fatty acids, and the head group variants are responsible for the large number of sphingolipids species [64, 65].

The research group of Meir Lev is the first to prove the findings on vitamin K's function in sphingolipid metabolism. Vitamin K was demonstrated to work as a growth factor for *Bacteroides melaninogenicus* rumen strain, in an early study published in Nature in 1958 [51, 61]. This bacterial growth requirement for vitamin K was then discovered to be connected to homeostasis of cell membrane [61].

Sphingolipid metabolism have been shown to play a key role in a variety of cellular activities and signaling cascades, including neuroinflammation, and is increasingly being linked to the pathogenesis of CNS defects [66, 67]. Because of microglial activation and amyloid precursor protein (APP) buildup, these polar lipids have been linked to neuro-inflammatory and neurodegenerative conditions [66].

The reactive appearance and altered function of the glial compartment are described as neuro-inflammation, which is a neuropathological phase in AD [67]. Even though apparent inflammatory glial response is thought to be caused by neuronal loss or malfunction, it is thought that microglia and astrocyte activation contributes to the course of AD. Microglia, the CNS's innate immune cells, are the most

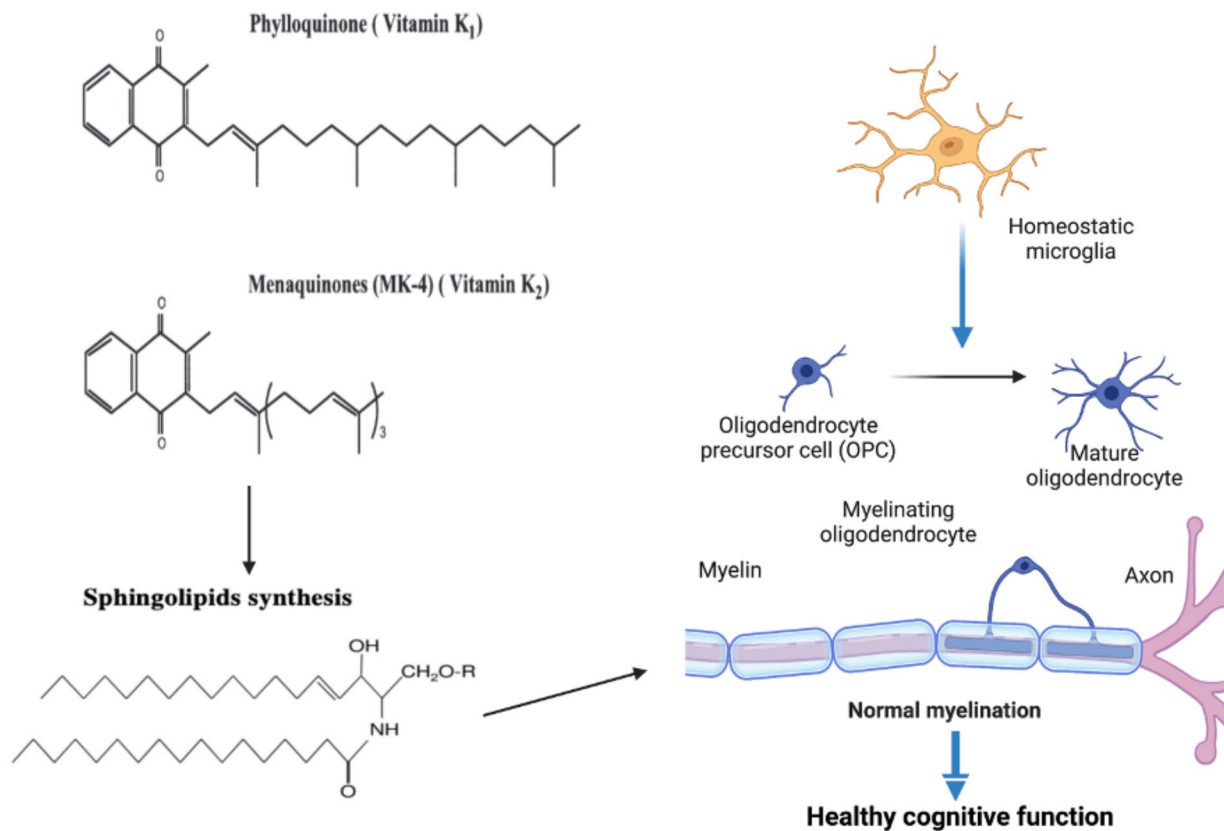


Fig. 3 The role of Vitamin K in the synthesis of sphingolipids and cognitive function. Sphingolipids are found in high amounts in the membranes of brain cells and Vitamin K is needed for their synthesis.

As important components of the oligodendrocyte membrane, sphingolipids play a central role in myelination, and maintenance of myelin stability and healthy cognitive function. Created with BioRender.com.

important cellular participants in neuroinflammatory processes. On the other hand, microglia has a multifaceted role that includes an anti-inflammatory effect in which they ingest toxic proteins and apoptotic cells, as well as a (chronic) pro-inflammatory phenotype that fosters neurotoxicity by producing and secreting excessive amounts of inflammatory regulators [68, 69].

The major signaling molecules of the sphingolipids system to initiate a pro/anti-inflammatory activity are ceramide and sphingosine-1-phosphate [69]. For instance, in the dopaminergic neurons, mitochondrial sphingosine-1-phosphate has been shown to promote mitochondrial function in a mouse PD model [70].

Accordingly, sphingolipids are related with a number of diseases, including AD, where inflammation is a result of microglial activation driven by β -amyloid plaques [71]. As important components of the oligodendrocyte membrane, sphingolipids govern myelination in the CNS (Fig. 3). Antibodies against myelinic sphingolipids have been reported in the serum and cerebrospinal fluid samples of individuals with multiple sclerosis, as well as ceramide buildup in lesions [10, 71].

Recent studies that demonstrate the regulation of brain sphingolipids by nutritional vitamin K expand Lev's work and highlight the potentially much further influence of vitamin K in brain function, given the critical role of these lipids in cell signaling activities [68–71].

Vitamin K and neurodegenerative diseases

Vitamin K and Alzheimer's disease

The incidence of Alzheimer's disease (AD), the most common type of dementia, has increased dramatically in recent years and, AD continues to be a primary cause of persistent impairment and mortality. 50 million dementia patients have been reported globally in 2018 [64]. The mental, physiological, and economic burden of Alzheimer's disease affects not just people and families, but community as a whole, because there is no treatment or slowing of the disease's course [72]. A number of hereditary and non-genetic variables including the alleles of the apolipoprotein E (APOE) gene have also been linked to its etiology [73].

Extracellular accumulation of the neurotoxic β -amyloid (amyloid beta (β) peptides) and neurofibrillary tangles (tau proteins) in the brain are the two hallmarks of AD. Accordingly, senile plaques which are extracellular amyloid deposits that accumulate, are frequently linked to AD as a physiological characteristic of the disease, which are extracellular amyloid deposits that accumulate. Hyperphosphorylated tau proteins are the most important constituents of neurofibrillary tangles. Phosphorylated tau accumulates in neurons during AD. Before reaching a steady state that is susceptible to aggregation, phosphorylated tau gradually loses its usual function and binds to microtubules [74]. Apolipoprotein E (APOE), presenilin 1 (PSEN1), presenilin 2 (PSEN2), and the amyloid precursor protein (APP) are related to AD. Early-onset AD, which accounts for 5% of all cases, is caused by mutations in the genes for APP, PSEN1, and PSEN2. Although APOE mutations do not directly cause late-onset illness, they significantly raise the prevalence of the condition in adults over 65 [6, 75].

Vitamin K has important effects on the neurological system and as a result of our research in databases, we determined that Alzheimer's disease is associated with vitamin K2 more than vitamin K1. Although both vitamin K1 and K2 have been shown to have positive effects on brain health, unlike VK1, VK2 can activate a range of extrahepatic vitamin K-dependent proteins having different complex activities. One of the best studied is Gas6, which has a wide distribution in the nervous system where it regulates neuroinflammation [72, 76].

In European diets, vitamin K2 accounts for only 10% of dietary vitamin K [72]. Almost all MKs are produced by bacteria, and the majority of them may be found in fermented foods including natto, sauerkraut, pickled vegetables, and certain cheeses. MK-4 is the sole Vitamin K2 isoform formed by conversion from Vitamin K1 rather than bacterial production, and it may be found in meat, fish, and egg yolk [72].

Booth et al. (2022) measured the concentrations of vitamin K and related metabolites in human brains, as well as their relationships to pre-mortem tests of cognitive function and post-mortem neuropathologic results in 325 participants, in order to assess the hypothesis that higher vitamin K levels are connected to specific changes that reduce the risk of dementia and cognitive decline. Additionally, relationships between plasma vitamin K levels of ante-mortem blood sampling and post-mortem neuropathologic results were examined. MK4, the main vitamin K metabolite in the brain, was found in higher quantities in the post-mortem brain and was linked to improved cognitive ability before death. Improved cognitive function and a decrease in the rate of cognitive decline were also linked to increased plasma vitamin K1 concentrations. Increased

neuronal MK4 concentrations were also linked to lower levels of neurofibrillary tangle density, high Braak stage, and the presence of Lewy bodies, according to further analysis of neuropathologically defined outcomes. These results add to the expanding research showing a protective relationship between dietary consumption of vitamin K and aging-related cognitive deterioration [77].

Drugs used in the prevention and treatment of thromboembolic disorders in older persons are known as vitamin K antagonists. Brangier et al., validated the cross-sectional association between the use of vitamin K antagonists and reported decreased cognitive performance during 24 months of follow-up in geriatric patients using vitamin K antagonists [78].

Soutif-Veillon et al., [79] aimed to explore the relationship between dietary vitamin K consumption and older individuals' subjective memory complaints, namely their existence and severity. It was found that in older persons not taking vitamin K antagonists, higher dietary vitamin K consumption was linked to fewer and milder subjective memory complaints.

A lifelong low intake of vitamin K was linked to a loss in spatial learning capacity in 20-month-old rats. This association was made with greater levels of ceramides in the hippocampus and decreased levels of gangliosides [18].

Vitamin K2 reduced neuronal death caused by β -amyloid, in PC12 cells originating from a rat pheochromocytoma. The cells that had been pretreated with Vitamin K2 showed significantly reduced apoptosis when exposed to either hydrogen peroxide (H_2O_2) or β -amyloid. Pretreatment with Vitamin K2 also lowered the number of apoptotic signaling proteins, lowered the Bax/Bcl-2 ratio, decreased reactive oxygen species (ROS), and raised glutathione, a potent antioxidant. The particular class of serine/threonine kinases known as mitogen-activated protein kinases (MAPKs) regulates cellular development, death, and responses to external stimuli including cellular stress. p38 MAPKs are the effector enzymes in the MAPK pathway. Mammalian cells' phosphorylated p38 MAPKs react to external stressors and thus stimulate apoptosis [80]. According to studies, the p38 MAPK signaling pathway in AD is activated when H_2O_2 levels rise (Fig. 4) [80–82].

By reducing the phosphorylation of p38 MAPK, vitamin K2 lowered phospho-p38 MAPK to p38 MAPK ratio and prevented cell death whereas $A\beta$ and H_2O_2 stimulated phospho-p38 MAPK. Therefore, vitamin K2 was suggested to prevent apoptosis through activating the p38 MAP kinase pathway [82]. Damage to mitochondria, reduction in the mitochondrial membrane potential, and increased ROS generation cause a caspase-mediated apoptotic pathway, which is the primary cause of AD pathogenesis [83]. Accordingly, vitamin K may inhibit apoptosis by inhibiting the phosphorylation of p38 MAPK in relation to its antioxidant effect.

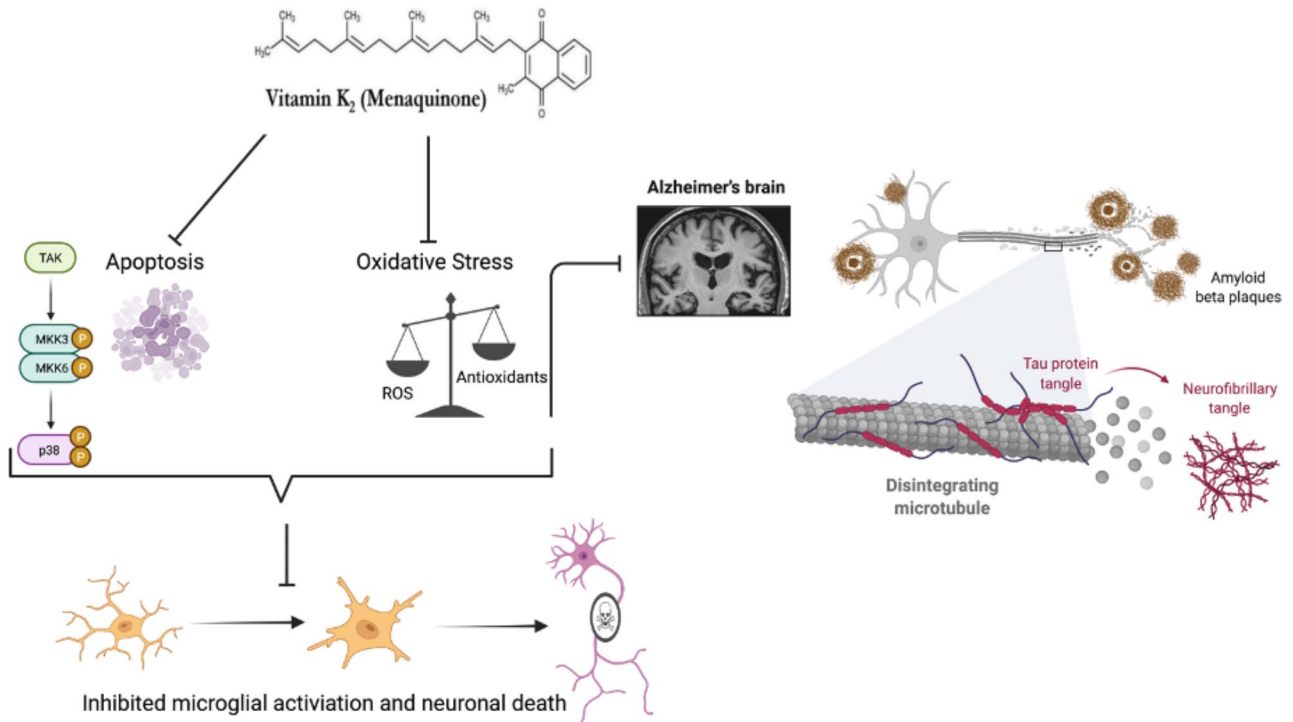


Fig. 4 Potential mechanisms of the beneficial effects of Vitamin K2 in Alzheimer's disease (AD) include inhibition of apoptotic signaling proteins and oxidative stress through decreased reactive oxygen species activation of potent antioxidants. The inhibition of the p38 MAP

kinase pathway was discovered as a mechanism for Vitamin K2's putative protective involvement in Alzheimer's disease. Inhibition of glial activation prevents neurodegeneration in AD. Created with BioRender.com.

Table 1 Studies evaluating the effect of Vitamin K on Parkinson's Disease

References	Purpose and Study Population	Analysis Method	Results
Vos et al. 2012 (103)	In pink1 mutated Drosophila (Heix mutants) electron carrier function of Vitamin K2 was evaluated.	Time-dependent ATP production were evaluated in mitochondria isolated from Drosophila.	Vitamin K2, acted as a mitochondrial electron transporter that supported ATP synthesis, and was able to reverse mitochondrial dysfunction.
Prasuhn et al., 2021 (104)	Potential effects of MK-7 were evaluated in MitoPD patients having heterozygous mutations in Parkin and PINK1, sporadic PD patients, and healthy individuals.	31P-Magnetic resonance spectroscopy imaging measurements were conducted in pre- and post-medication intake.	Pilot data revealed increased ATP levels in two homozygous PINK1 mutation carriers treated with MK-7.
Yu et al., 2020 (105)	Serum VK2 levels of PD patients were compared with those of the control group and PD patients	Enzyme-linked immunosorbent assay was used to detect VK2 in plasma	VK2 was reported to be related with the onset and progression of PD, and suggested to be used as a biomarker for PD diagnosis and prognosis.
Yu et al., 2016 (106)	Molecular mechanisms of the effects of MK4 on rotenone-induced microglial activation were investigated in vitro.	TNF- α and IL-1 β levels in BV2 cells were measured by ELISA kits. Mitochondrial membrane potential, ROS production, and cell viability were evaluated.	MK-4 inhibited microglial activation, neuronal cell death and lowered ROS generation and suppressed NF-B activation.
da Silva et al., 2013 (108)	Effect of vitamin K on α -syn aggregation were investigated and compared with other anti-fibrillogenic molecules.	BL21(DE3)pLysS E. Coli transfected with pT7-7-wt plasmid containing human α -syn.	Vitamins K interacted with the N-terminus α -syn and regulated pro-fibrillization of α -syn and fibril-destabilizing protein fibrillization.

Studies on the mechanisms of the antioxidant effect of vitamin K continue. Primary cortical neurons exposed to nanomolar doses of vitamin K are protected against oxidative cell death brought on by GSH deficiency. Moreover, the

antioxidant effect of vitamin K in this model was unrelated to its recognized biological function in carboxylation [36].

A very recent investigation found comparable results in a C6 cell line of rat astroglia that had been transfected to express A β . Increased Vitamin K2 concentrations resulted in cells

surviving longer as a result to prevention against β -amyloid-induced neuronal cell death [84]. The inclusion of warfarin, which blocks vitamin K-dependent carboxylation, reversed this action. Vitamin K2 also decreased the amount of ROS in a dose-dependent manner and inhibited the activation of caspase-3, an enzyme that initiates β -amyloid-induced apoptosis. Moreover, the researchers discovered that Gas6 protects Vitamin K2 against A cytotoxicity, which supports findings from an earlier investigation reporting dramatically reduced β -amyloid-induced chromatin condensation and DNA fragmentation by Gas6 [60, 64]. Based on these studies mentioned above we suggest that there is compelling evidence for the antiapoptotic and antioxidant capabilities of Vitamin K2.

Neuroinflammation and persistent glial hyperactivation have been linked to neurodegeneration and the etiology of AD [72, 73]. Although, the clearance of $A\beta$ by astrocytes and microglia can protect neurons, prolonged persistent activation might hasten or even induce neurodegeneration. Activated microglia sets off an inflammatory cascade that results in the release of an overabundance of proinflammatory mediators. Through a number of processes, including loss of synapse, neuron death, and neurotoxic astrocytes activation, the disturbance of microglial homeostasis lead to a chronic neuroinflammation state and eventually leads to neurodegeneration [85, 86].

When the mouse microglia-derived MG6 cells were exposed to LPS, MK-4 reduced microglial inflammation, NF- κ B signaling, the generation of major inflammatory cytokines (TNF- α , IL-1 β , and IL-6), as well as cytokine overexpression [87]. In rat astrocytes, MK-7 was reported to counteract the increase of proinflammatory cytokines generated by glial activation [88]. MK-7 also inhibited the generation of reactive oxygen species (ROS) in hypoxic astrocytes, supporting the antioxidant actions of VK2 [88, 89].

Mitochondrial dysfunction has been demonstrated in AD, and the link between mitochondrial dysfunction leading to neuroinflammation, and neurodegeneration in AD, as well as PD, and multiple sclerosis has been reported [72, 89]. Vitamin K2 lowered brain β -amyloid levels, enhanced ATP generation, repaired mitochondrial dysfunction, enhanced climbing ability, and extended longevity in arctic mutant $A\beta$ 42 drosophila [90]. Vitamin K2 also increased the expression of genes involved in autophagy and considering that stimulating autophagy has been proven to minimize $A\beta$ neurotoxicity and enhance cognition, it is noteworthy that Vitamin K2's ability to minimize β -amyloid neurotoxicity and restore mitochondrial dysfunction makes it a promising novel treatment for AD.

The connection between vitamin K insufficiency and cognitive deterioration is still up for discussion today [10]. There is a clear link between declining cognitive and behavioral abilities and low vitamin K consumption or serum concentration in

a group of people 65 and older. In specific, Presse et al. [91] presented the findings of a cross-sectional investigation on 320 old people from the NuAge study who were aged 70 to 85 and free of cognitive decline in 2013. The findings highlighted the significance of vitamin K in memory consolidation by demonstrating that recruited people with greater blood phyloquinone significantly improved verbal episodic memory whereas no link was identified with non-verbal episodic memory, speed of processing, or executive skills [91].

Higher vitamin K consumption is linked to slower cognitive decline in older individuals' community-based research. Moreover, better cognitive performance is related to greater levels of circulating vitamin K, which suggests that vitamin K may have a role in the pathophysiology causing cognitive decline [92–94].

Vitamin K2 was shown to enhance ATP levels and reduce cognitive decline in mice expressing β -amyloid or phosphorylated tau proteins in anesthetics exposed mice. Effects of two isoflurane and desflurane as different anesthetics on transgenic mice and wild-type mice were examined. Isoflurane exposed transgenic mice developed mutant forms of the APP gene, which is linked to familial Alzheimer's disease and demonstrated cognitive delay and they had fewer synapses and lower levels of ATP generated in their hypothalamus, both of which were alleviated by Vitamin K2 therapy [72, 95]. Vitamin K2 has also been shown to reduce sevoflurane induced tau phosphorylation and cognitive impairments newborn mice [96]. As these studies evaluated distinct indicators for AD in mice, and both showed that Vitamin K2 has neuroprotective benefits implies that Vitamin K2 might be useful in the treatment of AD.

In addition to all these studies that directly correlate AD with vitamin K, we think that the effect of vitamin K on atherosclerosis-related vascular health, which is an important feature of AD, should also be emphasized. There is strong evidence that vascular health is intimately connected to AD. Atherosclerosis of the brain, small vessel disease, cerebral amyloid angiopathy, and blood-brain barrier failure have all been linked to AD [97]. According to the results of population-based cohort and cross-sectional studies Vitamin K2, rather than Vitamin K1, has been shown to function in arterial health [98, 99]. Based on the link between vascular health and AD, Vitamin K2 might be suggested to be useful in preventing the disease.

Vitamin K and Parkinson's Disease

PD has a complex molecular structure, with numerous cellular constituents and metabolic procedures related in the disease's genesis and progression [100]. Mitochondrial dysfunction is a widely proposed pathophysiological pathway in sporadic PD that leads to neurodegeneration.

Under specific brain pathological conditions, mitochondrial respiratory chain structure may have an influence on energy efficiency, mROS, and neuronal survival [101].

PD patients' brains contain high amounts of iron, enhanced dopamine oxidation, and decreased endogenous antioxidants (glutathione and coenzyme Q10). Dopamine's oxidative metabolism generates peroxides that combine with ferrous iron to make extremely lethal hydroxyl radicals. Increased oxidative stress is associated with the degeneration of dopaminergic neurons in PD patients. Moreover, genetic variations are one of the risk factors causing PD. DNA variants in SNCA, PARK2, PINK1, DJ-1 (PARK7) and LRRK2 are related to familial PD [6].

Despite the rarity of monogenic PD, homozygous or compound-heterozygous PARK2 and PINK1 mutations have been linked to mitochondrial dysfunction and subsequent bioenergetic deficiencies. However, it is preferable to focus on specific pathways for genes and pathophysiological markers of the afflicted person when developing tailored therapy choices for PD patients [102].

In bacteria Vitamin K2 is found as a membrane-bound electron carrier. Using a pink1 mutated model (Heix mutants), vitamin K2 has been reported to be vital and sufficient for the transfer of electrons in *Drosophila* mitochondria, resulting rescued mitochondrial defects. Like ubiquinone, Vitamin K2 has been reported to be able to transfer the electrons, leading to an effective ATP production in *Drosophila* mitochondria. In pink1 and parkin mutant adult flies, vitamin K2 was even beneficial in treating systemic locomotion deficits. Vitamin K2 did not directly impact mitochondrial reconfiguration, but it did contribute to the proton motif force that aids ATP generation, comparable to ubiquinone, by enhancing ETC efficiency. Accordingly Vitamin K2 has been suggested to be a potentially viable treatment for mitochondrial dysfunction, particularly in PD patients with Pink1 or Parkin deficiency [103].

Clinical research investigating the neuroprotective effects of increasing mitochondrial bioenergetics in vivo, may help to develop individualized treatment of PD patients. In a recent project, the investigation of the potential effects of MK-7 (long-chain menaquinone 7, MK-7) in mitoPD patients having heterozygous mutations in Parkin and PINK1, sporadic PD patients, and healthy individuals has been proposed. The researchers suggested that MK-7 might act as a mitochondrial enhancer and facilitate the transport of electrons within the ETC. Their pilot data reported increased ATP levels of two homozygous PINK1 mutation carriers treated with MK-7, through 31P-Magnetic resonance spectroscopy imaging measurements pre- and post-medication intake [104]. In another clinical study, serum VK2 levels of PD patients were compared with those of the control group and PD patients had considerably lower

serum VK2 levels. Accordingly, VK2 was suggested to be related with the onset and progression of PD, and to be used as a biomarker for PD diagnosis and prognosis. Long-term low level of VK2 was proposed to be a factor contributing to the PD process by increasing the coagulation signal [105].

Growing research reports that vitamin K2 is associated with inflammatory regulation. In rotenone treated BV2 cells, a mouse microglial cell line MK-4 inhibited microglial activation by restoring mitochondrial membrane potential, lowering ROS generation and suppressing NF- κ B activation. MK-4 also inhibited neuronal cell death induced by microglial activation [106].

As a presynaptic neuronal protein, α -synuclein has been associated to PD both genetically and neuropathologically. α -Synuclein may play a role in the pathogenesis of PD in a variety of ways, however it is widely assumed that abnormal soluble oligomeric conformations of α -synuclein, known as protofibrils have toxic effects that cause neuronal death by affecting a variety of intracellular pathways, such as synaptic function [107]. In a study that approaches the relationship between PD and Vitamin K from a different perspective, the effects of vitamin K, on α -synuclein were investigated and compared to other anti-fibrillogenic compounds including quinones, polyphenols, and lipophilic vitamins. In substoichiometric doses, vitamin K slowed α -synuclein fibrillization, and it was suggested that, 1,4-naphthoquinone can control α -synuclein fibrillization, which may act as a possible framework for developing novel monoamine oxidase inhibitors [108].

Taken together, these findings summarized in Table 1 demonstrate that Vitamin K may enhance ETC efficiency and ATP production, may present anti-inflammatory and anti-fibrillogenic properties and has the potential to treat inflammatory illnesses. However, further data and thorough analyzes are needed before confirming a causal link between Vitamin K2 and the development of PD.

Vitamin K and multiple sclerosis

Multiple sclerosis (MS) is a neurodegenerative disease illness that affects the CNS and is caused by an autoimmune process. MS damages the CNS's myelinated axons, destroying myelin and axons to variable degrees [109]. As a chronic demyelinating disorder, MS affects young and middle-aged individuals and is one of the most frequent debilitating neurological disease [110]. It is more common in women than in males, and it is more prevalent in the northern hemisphere. The primary pathophysiology of the disease is thought to involve a variety of immunological cells [111]. Environmental factors, or the interaction of environmental parameters and susceptible genes, are considered to play a key part in the disease's genesis. A number of variables that can

influence the emergence and spread of MS, and VK2's anti-autoimmune activity may have a preventive action [112].

Vitamin K1 and K2 prevent the activation of 12-lipoxygenase and the generation of ROS [113]. Vitamin K2 supplementation has been demonstrated to improve experimental autoimmune encephalomyelitis in a multiple sclerosis animal model [114].

Vitamin K2 has been proposed for therapeutic use in MS patients to lower the intensity or to slow down the progression of the disease [89]. Since arachidonic acid release and oxidative stress are linked to ischemia damage and a variety of neurological illnesses, the functional efficiency of original forms of VK2 in avoiding oxidative stress and influencing MS clinical progression should be of interest [113].

The occurrence of Vitamin K2 in myelin fragments and a significant relation between vitamin K2 and sulfatides in brain myelin has been demonstrated [115].

Vitamin K2 serum concentrations declined by more than three-fold in multiple sclerosis patients, according to an observational research of 45 multiple sclerosis patients and 29 healthy controls, and lower levels of vitamin K2 were linked to a higher frequency of multiple sclerosis attacks among individuals with multiple sclerosis [116].

Accordingly, there is adequate information of Vitamin K2's positive effect on the central nervous system to warrant clinical and experimental research into the function of Vitamin K2 in MS [117].

Future directions

Age-related neurodegenerative disorders may be prevented or delayed by a healthy nutritional diet and modifiable lifestyle variables. Accordingly, for the prevention or treatment of age-related neurodegenerative disorders, older persons may be recommended to consume foods that are high in Vitamin K and other vitamins, minerals, and polyphenols with potent antioxidant capabilities [118].

Vitamin K's mechanism of action has been generally linked to its anti-demyelinating and anti-inflammatory properties. Although the effect of vitamin K in neuropathology is not entirely understood, oxidative stress is widely established to play a role in neurodegenerative illnesses. The physiological role for Vitamin K2 as a cofactor for the γ -carboxylation reactions is critical, but, Vitamin K2's role in tissues and cells needs to be clarified.

Given that Vitamin K2 is linked to the advancement of PD, AD, as well as MS, the paucity of human clinical trials is particularly surprising. Although the relationship of vitamin K with other neurodegenerative diseases other than PD and AD has not been established sufficiently, we can say that its role in diseases including Huntington's disease and amyotrophic

lateral sclerosis will attract more attention in the future, considering its role in improving cognitive functions.

In the coming periods, the potential of vitamin K to improve mitochondrial functions and ATP production will garner greater interest in the development of individual treatment methods according to the genetic background of neurodegenerative diseases.

Data Availability Not applicable.

Declarations

Disclosure statement The authors report no conflicts of interest.

Consent to participate All the authors have agreed for authorship, read and approved the manuscript, and given consent to participate.

Consent for publication All the authors have agreed for authorship, read and approved the manuscript, and given consent for publication.

Ethics approval Not applicable.

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