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Vitamin K2 As A Non-Pharmacological Approach To Alzheimer' S Disease : Mechanisms And Clinical Prospects.

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ABSTRACT:
Background: Since its discovery in 1935, vitamin K, a fat-soluble nutrient, has been known to play a part in blood clotting. Recent research on animals and in vitro is illuminating its important role in brain health. The vitamin has anti-inflammatory and anti-apoptotic properties, which may aid in the growth and survival of brain cells. It appears that the triggering of halted development fixed cistron 6, and protein S mediates these effects. Additionally, sphingolipid metabolism, which is essential for brain cell survival, differentiation, and proliferation, is facilitated by vitamin K. **Methodology:** The bond allying menaquinone levels in the brain and cognitive loss, including dementia, was investigated in this study. Researchers assessed 325 people's levels of vitamin K (MK4), the main appearance of vitamin K in the brain, in four distinct cerebrum regions. Higher brain MK4 attention was shown to be substantially linked with a 17% to 20% reduced risk of mental illness or moderate cognitive impairment (MCI), indicating that this nutrient may have a protective function in brain health. **Results and Discussion:** By directly analyzing vitamin K levels in the brain, this study offers information that goes beyond merely linking food intake with cognition. **Conclusion:** We have discovered a developing body of proof showing that VK2 is useful to prevent AD and reduce the speed of its formation of AD and leads to its avoidance. After evaluating fundamental science research and clinical trials, it has linked VK2 to causes that affect AD development.

INTRODUCTION:
The important source of vitamin K, also called as vitamin K1, is green leafy vegetables. The pro-coagulant effects of this phylloquinone vitamin are well known. It is used as a cofactor by the enzyme that makes it possible for the activation of vitamin K-dependent factors One of the recently identified effects of the vitamin is the enzyme is positively regulated protein S and Gas-6. The former has anti-apoptotic, mitogenic, and myelinating properties, while the latter protect the brain against ischemic/hypoxic injury in both in vitro and in

vivo conditions. Furthermore, it is known that vitamin K stimulates the production of sphingolipids [1]. According to research, the number of dementia cases will quadruple between 2020 and 2040, reaching 81 million, as a result of the world's population aging. This will place a significant burden on both national health systems and society. For instance, by the middle of the century, there will be 13.8 million cases of Alzheimer's disease (AD) in the US, up from 5.4 million now. Finding modifiable factors that may influence the progression of neurodegenerative diseases is therefore crucial. This vitamin K activity is believed to be distinct from the carboxylase function and was actually described more than 40 years ago by the Meir Lev team. Fat-soluble vitamins K and D have been linked to Alzheimer's disease and associated dementia (ADRD) [2]. 25-dihydroxyvitamin D3 inhibited excitotoxicity, increased neurotrophic factors, and had anti-inflammatory effects on brain tissue in mouse tests. Human brain tissue also contains vitamin K, primarily in the form of menaquinone-4 (MK4), which is an enzymatic cofactor for vitamin K-dependent proteins as neural tissue. An increasing amount of data from observational and interventional trials illustrates how crucial vitamin K2 is for controlling arterial calcification it may establish an association across cognitive performance and vascular health, indicating that vitamin K2 may be essential in preventing cognitive decline in older individuals [3].

Vitamin K:

The structurally identical vitamins K1 and K2 are members of the vitamin K family of fat-soluble chemicals. Though historically recognized for its activity in blood clotting, new research has expanded vitamin K's clinical usefulness and understanding to include bone and vascular health. For their biological activity, vitamin K-dependent proteins (VKDPs) must undergo γ-glutamyl carboxylation, which is dependent on vitamin K [4]. Leafy green vegetables and other plant-based foods are the finest dietary sources of vitamin K. Natto (fermented soy) and cheese are examples of fermented foods and foods originating from animals that include vitamin K2 this is primarily made by bacteria [5]. Menaquinone-7 (MK-7) is a K2 sub type of vitamin K1 that has a substantially longer half-life, accumulates in the blood more quickly, and has more biological activity, particularly when it comes to aiding in the carboxylation of extrahepatic VKDPs. Vitamin K's current daily recommended intake (DRI) is only intended to prevent bleeding because it is involved in blood coagulation, according to recent research, and their activation needs a sufficient intake of vitamin K [6].

Vitamin K evaluation:

Evaluating vitamin K status and intake in clinical and community surveys presents multiple challenges, and several methods are taken, each with specific limitations. The food frequency questionnaire (FFQ), which is widely used, frequently fails to detect vitamin K2 intake because food composition databases are not complete [7]. There isn't a single reliable test to determine vitamin K levels, though. VKDPs are used as indicators of vitamin K status and have been connected to certain health consequences. These markers have also been linked in recent studies to cognitive decline. Since each biomarker has a unique purpose,utilizing numerous biomarkers or combining them with data concerning dietary intake may improve the reliability in evaluating vitamin K status [8].

Distribution of vitamin K in the brain:

In the last 20 years, research has confirmed that vitamin K is present in the brain. But whereas vitamin-K1 and menaquinone-4 are found in most extrahepatic organs, vitamin K predominantly expresses in the brain as MK-4. In the brains of 6- and 21-month-old rats, MK-4 was found to account for above the 95% of the total vitamin K, regardless of age [9]. Every region of the brain contained MK-4, albeit in varying amounts, according to a thorough analysis of the anatomic distribution of vitamin K. Age and sex have also been demonstrated to have an impact on MK-4 concentrations in the brain. Despite possessing equal diets,female Brown Norway rats had higher amounts of MK-4 in their cortex and cerebellum than male rats, and by the time they were between 12 and 24 months old, concentrations had dropped. Diet also affects brain vitamin K concentrations in a way that corresponds to intake [10].

The role vitamin K in brain function:

According to recent research, vitamin K is crucial for brain function in addition to its well-established role in bleeding. Vitamin K affects neurological and cognitive processes through a number of pathways, including the activation of several VKDPs. Interestingly, protein S improves neuron protection and anti-thrombotic effects by modifying the BBB, Gas6 controls cell survival and myelination, and MGP has been linked to cognitive function and is a strong inhibitor of vascular calcification. In these circumstances, MK-7 performs admirably [11]. Vitamin K's antioxidant and anti-inflammatory qualities provide a promising preventive treatment. The function and viability of brain cells heavily depend on maintaining optimal glucose metabolism [12]. G-MK-7 might

therefore affect brain structure and function via regulating glucose metabolism. With the inhibition of enzymes involved in sphingolipid formation, vitamin K also affects sphingolipid metabolism, which is crucial for brain function. In contrast to vitamin K, vitamin K2 has distinct roles as a transcriptional regulator and mitochondrial electron carrier through the steroid and xenobiotic receptor (SXR). Further investigation is required to determine whether increased mitochondrial activity correlates with improved human cognitive function, yet mitochondrial dysfunction is strongly related to cognitive decline[13]. Studies conducted in vitro have shown that MK-4 protects against oxidative damage and the activation of the inflammatory cascade. In murine models, decreased cognitive function has also been associated with MK-4 depletion. An association with neurodegenerative disorders surfaced in certain situations, which may be investigated further through human examination.

Gas-6:
Gas-6, which is named for the growth arrest-specific gene that generates it, was discovered in 1993. It is a secreted protein that weighs 75 kDa and has 11–12 gamma-carboxyglutamic acid residues. A structural link is indicated by the 44% amino acid similarity it has with the vitamin K-dependent anti-coagulation factor protein S. The growth and survival of the neuronal system based on Gas-6. Furthermore, it has myelinating, mitogenic, and anti-apoptotic activities in glial and neuronal cells. Gas-6 binds to Tyro3, Axl, and Mer (TAM) receptor tyrosine kinase and activates it [14]. Gonadotropin-releasing hormone (GnRH) neurons are sustained, and several cell types multiply because of Axl, which allows them to go from the olfactory bulb to the hypothalamus. Mer inhibits the apoptosis of primary macrophages brought on by oxidative stress. Based on in-vitro research, recombinant Gas-6 suppresses apoptosis in the neurons of hippocampus rats, highlighting the protein's pro-survival function by activating TAM proteins. For the reason of its immune-regulatory activity, Gas-6 is associated with autoimmune disorders like the pathophysiology of multiple sclerosis (MS) according to research done on microglial cells cultured in mice, Gas-6 suppresses the production of nitric oxide synthase created by interleukin-1, which lessens the pro-inflammatory response [15]. The recruitment of microglial cells to damaged neuronal areas was decreased in two recent mouse models that used Mer and Axl knockout animals. These models also showed mutations in the cytoskeleton that affected phagocytic activity. Gas-6 has also been demonstrated to inhibit low-voltage Ca^{2+} influx channels, which reduces β-amyloid-induced apoptosis, a defining feature of Alzheimer's disease. Nevertheless, a more recently conducted study revealed that Tyro3 is inhibited by Gas-6, which stops ß-amyloid production [16].

Protein S:
Though the anticoagulant action of protein S has long been known, a novel study is exploring extra consequences, including a potential involvement in inflammation, angiogenesis, and cancer. Furthermore, in improving cerebral blood flow following ischemia. As Gas-6 and Protein S share almost fifty percent of their amino acid structure (44%) (3), Protein S serves partially as a TAM receptor ligand on Gas-6 [17]. Through the Tyro3/Akt pathway, protein S specifically guards against toxicity and apoptosis brought on by NMDA. Protein S may act as a tissue plasminogen activator amplifier when administered in large doses to stroke animal models, reducing cerebral post-ischemic damage while lowering the risk of bleeding. The blood-brain barrier (BBB), which protects against chronic ischemia damage and BBB-related diseases, is formed and maintained by protein S [18].

The metabolism of sphingolipids:
Sphingolipids are one of the key groups of eukaryotic lipids, are crucial for cell membranes, and vitamin K is known to promote their synthesis. In nerve cell membranes, gangliosides, sulfatides, cerebrosides, ceramides, and sphingomyelin are the most prevalent sphingolipids. It appears that this class of lipids is an essential regulator of cell survival, differentiation, and multiplication. The pathogenesis of brain disorders is increasingly being linked to the metabolism of sphingolipids. Amyloid precursor protein (APP) buildup and microglial activation have linked these polar lipids to neuroinflammatory and neurodegenerative conditions [19]. These provide the basis of the development of many illnesses, such as AD, where β-amyloid plaques induce microglial activation, which in turn causes inflammation. Lastly, sphingolipids are important constituents of the oligodendrocyte membrane and direct the myelination process in the CNS. Serum and CSF fluid from MS patients contain antibodies against myelinic sphingolipids, and active lesions have been shown to include ceramide deposits [20].

Vitamin K2:
Last few years have saw a marked increase in the incidence of Alzheimer's disease (AD), which remains a major

cause of death and continuous disability. The estimated 6.2 million Americans who suffer from AD, the most prevalent form of dementia, are expected to more than quadruple in number by 2050. 50 million people globally suffered from dementia in 2018. In addition to having no known cure or way to slow its course, AD has a financial, emotional, and physical toll that affects not just people and families but also society at large. AD has been described by two important features the formation of Neurofibrillary tangles (NFTs) in neurons and the outer cellular appearance of neurotoxic ß-amyloid (Aβ) in the brain [21]. Its pathogenesis has also been connected to other non-genetic and genetic factors. The apolipoprotein E (APOE) gene's alleles are one example of a known gene factor. While the e2 allele largely protects against AD, the e4 allele, especially two copies, increases the risk of the illness [22].

Our focus is on the potential for VK2 to mitigate the result of these factors and, consequently, reduce the risk of AD. We think that VK2 is relevant to AD study because of its numerous physiological functions, which have been validated by recent investigations. We examine basic science research and clinical investigations, such as randomized controlled trials and population-based cohort studies. One of our search's distinctive criteria was that we preferred VK2 over vitamin K1 (VK1) or vitamin K in normally [23]. According to our research, VK1 and VK2 have different links to human health, despite their similarities. After our first PubMed searches for "Menaquinones and Alzheimer" and "Vitamin K2 and Alzheimer" produced only 6 relevant publications, we expanded our search to look at how VK2 and pathophysiological factors for AD interact (figure 1). Suppose we evaluated population research studies that looked into the relation of CV health and AD and then these that examined the relationship between CV health and VK2 analysis. We examine clinical and fundamental science research, including randomized controlled trials and population-based cohort studies. Our search was unique in part because we were interested in VK2 rather than vitamin K1 (VK1) or vitamin K in normal [24].

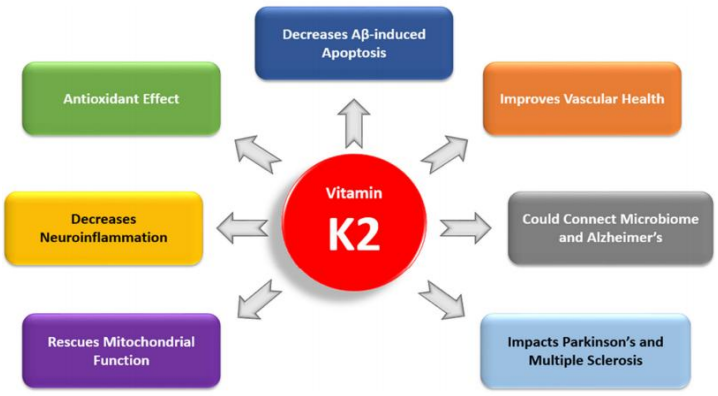

Figure 1. The roles of vitamin K2 in AD

To the best of our knowledge, our review is the first to examine this relation, and it is significant since it brought to light recent, developing evidence that links VK2 with AD. We intend to convey the necessity of more research examining VK2's role in AD prevention by bringing attention to this relationship.

Cognitive Decline and Vitamin K:

Given the various functions that vitamin K has been shown to play in earlier studies, several researchers have begun looking at a potential connection between vitamin K and cognitive impairment in recent years. It is yet unclear how vitamin K deficiency and cognitive decline are related.We added seven human studies from the literature search, all except one of which supported a connection of vitamin K and cognitive function in older adults. Among a group of individuals aged 65 and over, six studies found a direct link between a small amount of vitamin K food consumed or blood serum concentration and poor cognitive and behavioral performance [25]. The findings of a cross-sectional study conducted on 320 elderly participants, ages 70 to 85, from the NuAge study cohort, who did not suffer from cognitive impairment, were published by Presse et al. in 2013. HPLC was used to find the serum content of phylloquinone. HPLC has been proven to be a reliable indication of dietary phylloquinone intake for an extensive amount of time. HPLC must also be used to evaluate the blood lipid profile, which is a condition of circulating phylloquinone concentrations. Each cognitive domain has been

cognitively assessed using a different set of activities, including processing speed, executive functioning, and verbal and nonverbal episodic memory [26]. Higher blood phylloquinone levels were associated with greater verbal episodic memory in recruited persons, but not with non-verbal episodic memory, executive functioning, or processing speed. This demonstrates how important vitamin K is for memory consolidation. Among older persons, higher vitamin K intake was linked to better cognition, fewer behavioral issues, and a less severe subjective memory complaint. Vitamin K food intake is measured using the FFQ, a 50-item questionnaire [27]. As you examine individuals who have cognitive impairment, it may lead to an underestimation even though it has been validated in older individuals. In keeping with previous investigations, Kiely et al. observed that older people with poor cognitive skills, as measured by the MMSE, consumed the least amount of vitamin K from their diet (as measured by the FFQ). Correlations between MMSE scores and HPLC-measured phylloquinone blood levels showed similar findings [28]. Later studies highlighted the possible significance of this vitamin in individuals with dementia associated with Alzheimer's disease, who had significantly decreased vitamin K levels even if caloric intakes were taken into account. In a more recent investigation, our team examined the phylloquinone intake of 31 patients with early-stage AD who lived in the community vs 31 controls who were age- and sex-matched and had normal cognitive function [29]. The primary source of vitamin K, green vegetables, made up 33% and 49% of the patients' and controls' overall phylloquinone diet, respectively. Fruits, vegetables, and fatty substances contributed over 70% of the total amount consumed in both groups. The group's overall lesser vitamin K intake was explained by their lower consumption of green vegetables. Patients' plasma phylloquinone levels were considerably lower than controls' in a previous study that included 100 women [30].

Vitamin K2 and Alzheimer's Disease:

The Anti-apoptotic and Antioxidant Effects of Vitamin k2:

The impact of VK2 and Gas6 on β-amyloid (Aβ) will be our primary focus. Aβ causes neuronal death through direct toxicity as well as by encouraging apoptosis. There are several ways that neurotoxicity can happen, such as when mitochondrial malfunction, oxidative stress, or calcium homeostasis is upset. VK2 inhibited Aβ-induced neuronal death in PC12 cells originating from a rat pheochromocytoma, the most neurotoxic type of Aβ. The cells pre-treated with VK2 showed much less death as determined by flow cytometry when exposed to either H_2O_2 or Aβ [31]. Moreover, VK2 pretreatment lowers the quantity of apoptotic signaling proteins, including a lower Bax/Bcl-2 ratio, reduced reactive oxygen species (ROS), and raised glutathione, an effective antioxidant. The authors discovered that one mechanism for the possible protective function of VK2 in AD is the inhibition of the p38 MAP kinase pathway [32].

A 2021 study that made use of a transfected C6 cell line of rat astroglia to express Aβ came to similar conclusions. The researcher team also discovered that Gas6 contributes to VK2 defense against Aβ cytotoxicity, which is consistent with results from previous investigations. In that 2002 work, in rat embryo brain cell cultures, chromatin condensation, DNA fragmentation, and Ca(2+) influx were markers of Aβ neurotoxicity and mortality. The quantity of chromatin condensation and DNA breaks caused by Aβ was significantly decreased by Gas6, which also demonstrated dose-dependent reduction of the influx of Ca(2+). Each of these investigations provides strong evidence for VK2's anti-apoptotic and antioxidant qualities.

Vitamin K2 and Neuroinflammation:

It becoming known that neurodegeneration and AD are caused by neuroinflammation and persistent glial hyperactivity. A neuroprotective impact of astrocytes and microglia can be achieved by eliminating Aβ, but prolonged, excessive activity may accelerate or even cause dementia.While one study suggested neuroinflammation leads to neuronal dysfunction in AD and Parkinson's disease, as identified by MRI scans, another study showed that glial activation happens before the formation of Aβ plaques in animal models [33]. When microglia are activated, a variety of pro-inflammatory mediators are produced. The inflammatory cytokines TNF-α, IL-1β, and IL-6 were elevated at the mRNA level, while NF-κB signaling was decreased by the pretreatment with MK-4. MK-7 also prevented glial activation in rat astrocytes from producing more pro-inflammatory cytokines. In cells grown under both normal and hypoxic circumstances, MK-7 pretreatment decreased the generation of TNF-α and IL-6 that was brought on by hypoxia. MK-7 confirmed the antioxidant qualities of VK2 as shown by suppressing the generation of ROS in the hypoxic astrocytes. Both studies found that VK2 inhibits the synthesis of pro-inflammatory cytokines, indicate that VK2 may have the properties to lower neuroinflammation and neurodegeneration, despite using different glial cell types (microglia and astrocytes), and different activation techniques (LPS and hypoxia) [34].

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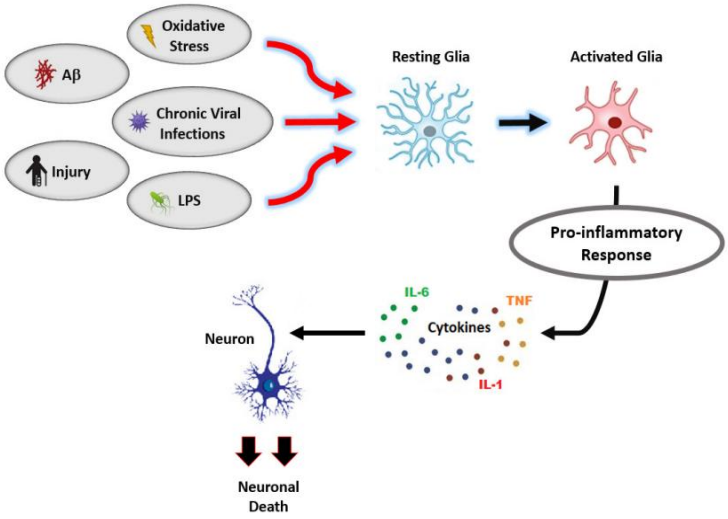

Figure.2 Glial activation leads to neurodegeneration

Vitamin K2 and Mitochondrial Dysfunction:
Multiple sclerosis, Parkinson's disease, and AD have been linked to neurodegeneration, neuroinflammation, and mitochondrial failure throughout decades of research. According to the aforementioned study, an astrocyte culture is subjected to hypoxia. Furthermore, MK-7 pretreatment stopped the hypoxic astrocytes from producing ROS, increased the generation of ATP, and decreased neuroinflammation. In another study, MK-4 was able to fix serious mitochondrial issues with fruit flies using a mutant variant of the pink1 gene, which causes familial Parkinson's disease in people [35]. Time- and dose-dependent improvements in flight and ATP generation were found in pink1 mutants fed with MK-4. After being given to transgenic Drosophila flies for AD for 28 days, VK2 enhanced climbing ability, restored mitochondrial dysfunction, enhanced ATP synthesis, and decreased brain Aβ levels. We think VK2 has promise as a novel therapy for AD given its capacity to ameliorate Aβ neurotoxicity and restore mitochondrial dysfunction [36].

Vitamin K2 and Anesthesia-Induced Cognitive Deficits:
The results of anesthesia on animal model [mice] with phosphorylated tau proteins or Aβ expression were examined in both investigations. VK2 increased ATP levels and lessened the cognitive deficit caused by anesthesia. When transgenic mice with mutant versions of the APP gene linked to familial AD are given isoflurane, they develop dementia [37].

An examination of their brain tissue revealed that their hypothalamus produced less ATP and had fewer synapses their negative effects were alleviated by VK2 therapy. In 2020, a study explains that VK2 reduced tau phosphorylation and the dementia it produced in neonatal mice, which supported our findings. Both studies showed the neuronal protection advantages of VK2, which implies that VK2 may be important in treating AD even though they show various AD biomarkers in mice [38].

Vitamin K2 and Cardiovascular Health:
Atherosclerosis, arterial calcification, and arterial stiffness have each been linked to an heightened threat of dementia and cognitive impairment in several types of population studies. The amount of atherosclerotic calcification correlated to brain tissue volume and was directly related to cognitive impairment in a sample-based cohort study involving 844 patients. More calcification found by a CT scan has also been associated with decreased white matter microstructural integrity. More population research that followed 2364 people for 5 years identified that Three years later, atherosclerotic calcification was associated to an more risk of dementia [39]. A similar conclusion was reached by a cohort study of 1732 participants, which revealed an association between mild cognitive impairment and widespread atherosclerosis. Furthermore, a higher incidence of dementia has been linked to aortic stiffness. Also, we have strong evidence that AD & vascular health are closely linked. AD is associated with blood-brain barrier failure, cerebral amyloid angioplasty, small vessel disease, and cerebral atherosclerosis[40]. Cerebrovascular disease is defined by arterial stiffness, atherosclerosis,

and endothelial dysfunction, all of which contribute to the development of cerebral Aβ, brain atrophy, and neurovascular disintegration.Cardiovascular disease have the link to the pathogenesis of AD and has been discover to raise the risk of AD in epidemiological studies. Interventions that increase vascular function also lessen AD pathology. A genetic association between AD and vascular illness is the APOE gene, according to a study of 2907 elderly people [41].

Additional pathological data indicates that AD can be defined in both neurodegenerative and vascular processes. Based on the autopsy results of dementia patients, AD accounted for 80% of cases, vascular dementia for 7%–10%, and mixed dementia for 35%. Between 20 and 40 percent of AD patients exhibited vascular lesions. Vascular lesions include hemorrhages, white matter lesions, cortical microinfarcts, and cortico-subcortical infarcts. Compared to those who have vascular dementia or mixed dementia, people with AD usually have lesser vascular lesions [42]. In another autopsy investigation, 5715 patients had a correlation between AD, cerebrovascular illness, and vascular risk factors. We will now discuss studies showing the significance of VK2 for vascular health. Those in the more tercile of VK2 intake had a 41% decrease risk of CVD than those in the lowest tercile, based on an analysis that tracked 4807 men and women aged 55 and over for more than 7years. CVD risk was not impacted by VK1 [43].

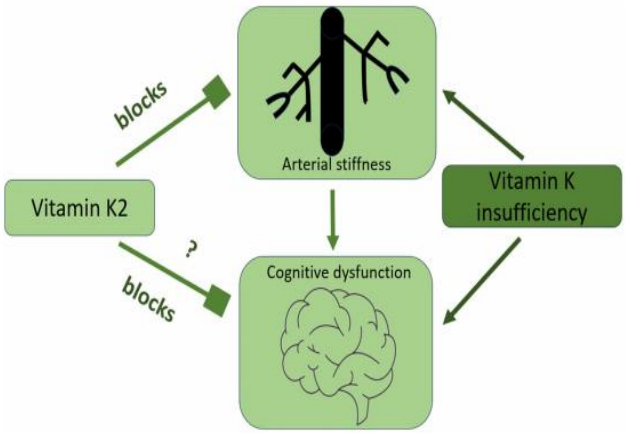

Figure 3: The connection between the arterial stiffness, cognitive function, and optimal vitamin k in take.

CONCLUSION:

The enhanced interest in the function of vitamin K in the brain, particularly for cognition, is what spurred this review. According to recent research, vitamin K2 and vitamin K-dependent proteins (VKDPs) may have a significant role in delaying or possibly stopping the advancement of AD. More recently, VK2 has been recognized as a vitamin that is critical to human health. VK2 enhances neuronal health in a number of ways, since many pharmacological studies have ineffective to produce an effective treatment to treat or prevent AD, research on the disease has shifted to non-pharmacological approaches. The National Institute of Aging supported 270 clinical trials that focused on AD and related dementia's.While research has examined the connection between VK2 and other conditions like cardiovascular disease and osteoporosis, there aren't many studies examining the relation between VK2 and AD.

Vascular calcification and arterial stiffness may be characteristics of the physiological processes that underlie the development and progression of cognitive issues. A key component in vascular health is vitamin K deficiency; it can therefore have an influence on elderly people' cognitive abilities. In conclusion, further study on the topic may prove beneficial, and helpful results may be expected provided the rising societal and financial burden associated with the growing number of patients with dementia and cognitive impairment.

CONFLICT OF INTEREST:

The author declares no conflict of interest, financial or otherwise.

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