*Systematic Review*

# Exploring the Link Between Vitamin K and Depression: A Systematic Review

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**Abstract:** *Background and Objectives:* Depression is a multifactorial mental health disorder involving inflammation, oxidative stress, neuroplasticity deficits, and metabolic dysfunction. Emerging research suggests that vitamin K, beyond its classical roles in coagulation and bone metabolism, may influence neurobiological processes relevant to mood regulation. This systematic review evaluates the association between vitamin K and depressive symptoms and explores potential underlying mechanisms. *Materials and Methods:* A systematic search was conducted across PubMed, Scopus, Cochrane Library, ScienceDirect, and Google Scholar, following PRISMA 2020 guidelines. Eligible studies included human or animal research examining associations between vitamin K status (dietary intake or serum levels) and depression-related outcomes. Fourteen studies met the inclusion criteria: eleven observational studies, one randomized controlled trial (RCT), and two preclinical animal studies. *Results:* Most observational studies reported an inverse association between vitamin K intake or serum levels and depressive symptoms across diverse populations. One small RCT demonstrated modest improvements in depression scores following vitamin K2 (menaquinone-7) supplementation in women with polycystic ovary syndrome. Two preclinical studies using non-depression models reported behavioral improvements and reduced oxidative stress following vitamin K2 administration. *Conclusions:* While preliminary findings suggest a potential role for vitamin K in pathways relevant to depression, the current evidence is limited by cross-sectional designs, lack of isoform-specific analyses, and the absence of depression-focused preclinical models. Mechanisms including inflammation reduction, oxidative stress modulation, sphingolipid regulation, and vitamin K-dependent protein signaling (e.g., GAS6 and osteocalcin) were discussed based on indirect evidence and require further investigation in depression-specific contexts.

**Keywords:** vitamin K; depression; oxidative stress; osteocalcin; neuroinflammation

## 1. Introduction

Depression is one of the most prevalent and debilitating mental health disorders worldwide, affecting millions of individuals. According to recent estimates from the World Health Organization (WHO), approximately 280 million people suffer from depression. In

2021, an estimated 3.8% of the global population experienced depression, including 5% of adults—4% among men and 6% among women—and 5.7% of individuals over the age of 60 years [1]. Furthermore, depression is a significant concern among women during pregnancy and postpartum, with more than 10% experiencing depressive episodes [2]. Alarmingly, more than 700,000 people die by suicide annually, making it the fourth leading cause of death among individuals aged 15–29 years [1]. Despite the availability of effective treatments, over 75% of people in low- and middle-income countries receive no intervention, underscoring the urgent need for alternative therapeutic approaches [3].

Depression is characterized by persistent sadness, fatigue, cognitive impairments, and a loss of interest in daily activities [4]. It is a leading cause of disability and contributes significantly to the global burden of disease. Its etiology is complex and multifactorial, involving biological, genetic, psychological, and environmental factors. Conventional treatments, such as pharmacotherapy and psychotherapy, often have limited effectiveness, particularly in cases of treatment-resistant depression. As a result, there is growing interest in alternative and complementary interventions, including dietary modifications and micronutrient supplementation, natural product-derived compounds with potential health-promoting properties [5–8].

Among the micronutrients under investigation, vitamin K has emerged as a promising candidate in the context of mental health. Traditionally recognized for its role in blood clotting through the activation of clotting factors, vitamin K has also been implicated in a range of physiological processes beyond coagulation [9]. It plays a crucial role in bone health by activating osteocalcin and matrix Gla-protein, essential for bone mineralization. Additionally, vitamin K possesses significant anti-inflammatory and antioxidative properties, which are vital for cellular health and the regulation of oxidative stress. These functions are particularly relevant in depression, as chronic inflammation and oxidative imbalance are increasingly identified as key contributors to its pathophysiology [10,11].

Vitamin K exists in two main forms: vitamin K1 (phylloquinone) and vitamin K2 (menaquinones, MKs), which differ in their chemical structures, tissue distribution, and biological functions [12]. Vitamin K1, primarily found in green leafy vegetables, is mainly involved in the hepatic activation of clotting factors and has limited bioavailability in extrahepatic tissues. In contrast, vitamin K2, which is found in fermented foods and animal products, exhibits greater bioavailability outside the liver and exists in multiple subtypes (e.g., MK-4, MK-7) that vary in half-life and tissue distribution. Notably, MK-4, a subtype of vitamin K2, is present in high concentrations in the brain and has been implicated in neuronal health, sphingolipid metabolism, and neuroprotection. Vitamin K is also known to assist in the production of gamma-carboxyglutamic acid protein known as osteocalcin, which has been largely associated with bone health [13].

However, to date, no systematic review has comprehensively synthesized the available evidence on the relationship between vitamin K and depression. It remains unclear whether a consistent association exists, what types of populations have been studied, and which mechanisms may underlie this potential link. The aim of this review is therefore to identify, collate, and critically evaluate studies that explore this relationship. By incorporating findings from observational studies, clinical trials, and preclinical models, we seek to map the current state of research, highlight emerging mechanistic insights, and inform future directions in nutritional psychiatry. This exploratory synthesis is intended to establish whether a credible association exists and to describe the biological pathways that may explain the role of vitamin K in depression.

## 2. Materials and Methods

This systematic review was conducted in accordance with the PRISMA 2020 guidelines to ensure rigor and transparency throughout the process [14]. The review aimed to identify and synthesize high-quality evidence related to vitamin K and depression. The methodology comprised four key stages: identification, screening, eligibility assessment, and inclusion (Figure 1).
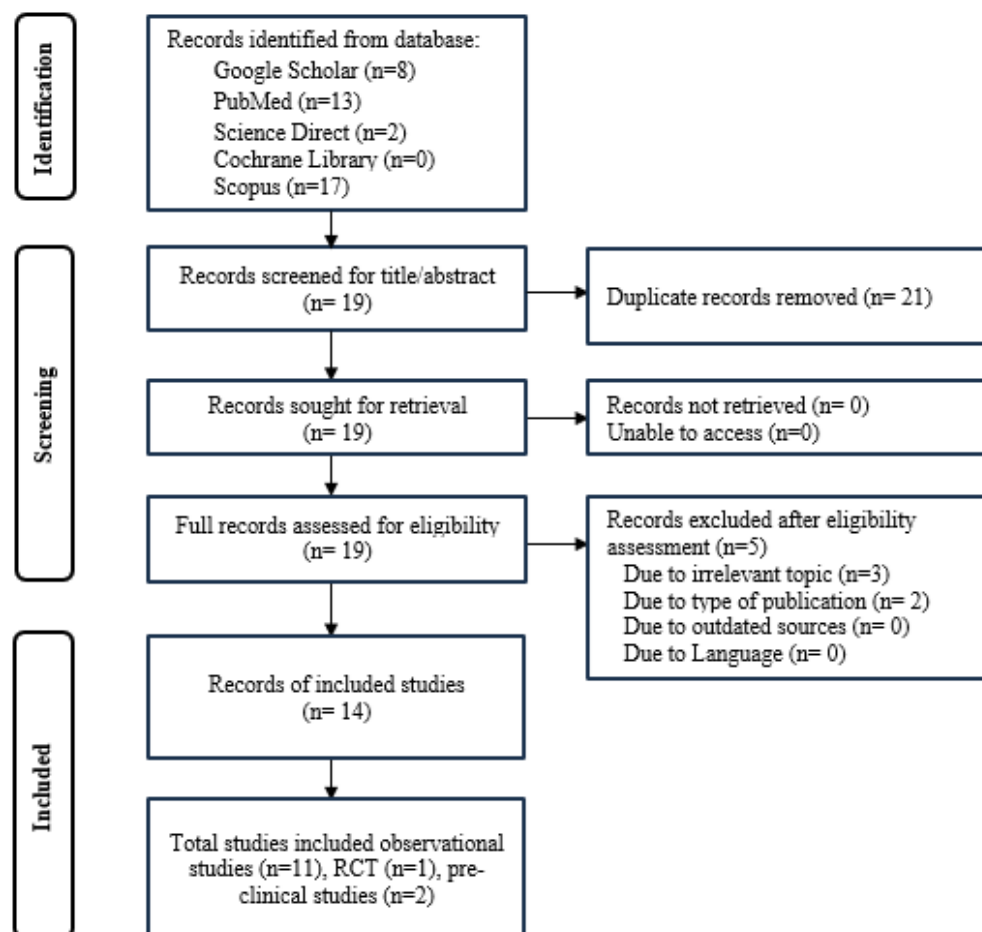


**Figure 1.** Prisma flow diagram.

*2.1. Search Strategy and Identification*

A comprehensive literature search was performed across five electronic databases: PubMed, Scopus, Cochrane Library, ScienceDirect, and Google Scholar. The search strategy incorporated combinations of the following keywords: "Vitamin K", "depression", "major depressive disorder", "menaquinone", "phylloquinone", "Vitamin K1", "Vitamin K2", "Vitamin K3", "MK4", and "MK7". The initial search yielded 40 unique records, distributed as follows: Google Scholar (n = 8), PubMed (n = 13), ScienceDirect (n = 2), Cochrane Library (n = 0), and Scopus (n = 17).

*2.2. Screening and Eligibility Criteria*

Titles and abstracts of the 40 identified records were screened for relevance. During this process, 21 duplicate records were removed. Two additional records were excluded because they were non-original research articles, specifically letters to the editor. Full-text articles were then retrieved for detailed eligibility assessment.

Inclusion and Exclusion Criteria

Studies were included if they were original human observational studies, randomized controlled trials, or preclinical animal studies that individually assessed vitamin K intake or serum levels in relation to depression or depressive symptoms and employed validated depression assessment tools. Only peer-reviewed articles published in English were considered eligible. Studies were excluded if vitamin K was analyzed only as part of a broader nutrient pattern without specific isolation, if the study design was a machine learning exploratory model without direct hypothesis testing of vitamin K's relationship to depression, or if the study explored other specific psychiatric diseases than depression.

Subsequently, 19 full-text articles were assessed for eligibility. During this assessment, three studies were excluded: two studies evaluated vitamin K only within broader nutrient patterns without individual vitamin K analysis, and one study used a machine learning exploratory model without directly testing the association between vitamin K and depression. No studies were excluded due to language barriers or inability to retrieve the full text.

### 2.3. Study Inclusion

Following full-text assessment, a total of 14 studies met the inclusion criteria. The eligible studies investigated the association between vitamin K, through either dietary intake or serum measurement, and depression or depressive symptoms, and used validated tools to assess depression outcomes. These 14 studies formed the basis of the final synthesis, comprising 11 observational studies, 1 RCT, and 2 preclinical animal studies.

### 2.4. Risk of Bias Assessment

The risk of bias for each included study was evaluated according to the study design. Randomized controlled trials were assessed using the Cochrane Risk of Bias tool 2.0 (ROB 2.0). Observational studies with control groups were evaluated using the Newcastle–Ottawa Scale (NOS), while preclinical animal studies and observational studies without control groups were assessed using the Agency for Healthcare Research and Quality (AHRQ) checklist. Most studies were rated as having a low risk of bias. However, five studies were judged to have a moderate risk of bias or some concerns, primarily due to limitations in comparability, methodological transparency, or incomplete blinding. A detailed summary of the risk of bias assessments is presented in Table 1. This review was not prospectively registered in a database such as PROSPERO, and no separate protocol was published prior to conducting the review. The identified risk of bias across studies was taken into consideration during the synthesis and interpretation of findings, with particular caution applied to studies assessed as having moderate risk.

**Table 1.** Risk of bias assessment table.

| Study | First Author | Year | Study Type | ROB Tool Used | Overall Risk of Bias |
|---|---|---|---|---|---|
| 1 | Rubio-López et al. [15] | 2016 | Observational Study | Newcastle–Ottawa Scale | Low Risk |
| 2 | Nguyen et al. [16] | 2017 | Observational Study | Newcastle–Ottawa Scale | Moderate Risk |
| 3 | Bolzetta et al. [17] | 2019 | Observational Study | Newcastle–Ottawa Scale | Low Risk |
| 4 | Zhang et al. [18] | 2023 | Observational Study | Newcastle–Ottawa Scale | Low Risk |
| 5 | Wang et al. [19] | 2024 | Observational Study | Newcastle–Ottawa Scale | Moderate Risk |
| 6 | Wang et al. [20] | 2024 | Observational Study | Newcastle–Ottawa Scale | Low Risk |
| 7 | Hayashi et al. [21] | 2020 | Observational Study | AHRQ Checklist | Moderate Risk |
| 8 | Yu et al. [22] | 2025 | Observational Study | Newcastle–Ottawa Scale | Low Risk |
| 9 | Kaner et al. [23] | 2015 | Observational Study | Newcastle–Ottawa Scale | Low Risk |

**Table 1.** *Cont.*

| Study | First Author | Year | Study Type | ROB Tool Used | Overall Risk of Bias |
|---|---|---|---|---|---|
| 10 | Khosravi et al. [24] | 2019 | Observational Study | Newcastle–Ottawa Scale | Low Risk |
| 11 | Mohtashamian et al. [25] | 2024 | Observational Study | AHRQ Checklist | Moderate Risk |
| 12 | Tarkesh et al. [26] | 2022 | Randomized Controlled Trial (RCT) | ROB 2.0 | Moderate Risk |
| 13 | Gancheva & Zhelyazkova-Savova [27] | 2016 | Preclinical Animal Study | AHRQ Checklist | Low Risk |
| 14 | Mansour et al. [28] | 2023 | Preclinical Animal Study | AHRQ Checklist | Low Risk |

## 3. Results

The initial database search identified 40 potentially relevant articles. After removing 21 duplicates and screening titles and abstracts, 19 full-text articles were assessed for eligibility. Of these, 14 studies met the predefined inclusion criteria and were included in the final synthesis. These comprised 11 observational studies, 1 RCT, and 2 preclinical animal studies. The studies selected are detailed in Table 2.

The included studies varied in design, population, and methodology. Observational studies were conducted across diverse demographic groups, including children, adults, older adults, pregnant women, and individuals with chronic health conditions, such as polycystic ovary syndrome (PCOS) and chronic kidney disease (CKD). Sample sizes ranged from 59 to over 30,000 participants. Vitamin K intake was assessed primarily through dietary recalls or food frequency questionnaires, while serum levels were measured using enzyme-linked immunosorbent assay (ELISA) or liquid chromatography–mass spectrometry (LC-MS/MS). Depression was evaluated using validated tools, including the Patient Health Questionnaire-9 (PHQ-9), the Center for Epidemiologic Studies Depression Scale (CES-D), the Geriatric Depression Scale (GDS), the Beck Depression Inventory-II (BDI-II), and clinical interviews based on the DSM-IV or DSM-IV-TR criteria.

Among the 11 observational studies, there was a consistent inverse association between vitamin K status and depressive symptoms. For instance, in a large cross-sectional study of U.S. adults using NHANES data, Zhang et al. [18] found that participants in the highest quartile of vitamin K intake had significantly lower odds of depression compared to those in the lowest quartile (odds ratio [OR] = 0.68; 95% confidence interval [CI]: 0.52–0.89; $p$-trend < 0.05). Similarly, Nguyen et al. [16] reported significant associations between lower dietary vitamin K intake and depressive symptoms among older Japanese adults, with ORs of 0.998 and 0.997 in men and women, respectively ($p < 0.05$). Hayashi et al. [21] observed a moderate inverse correlation between dietary vitamin K intake and CES-D scores in pregnant women (r = −0.496, $p = 0.019$). These findings remained statistically significant after adjusting for common confounders, including age, body mass index, comorbidities, and dietary quality. However, one study did not report on depression outcomes, instead noting an inverse relationship between vitamin K intake and anxiety levels in adults with CKD [25].

Experimental evidence from a randomized controlled trial by Tarkesh et al. [26] provided preliminary support for a causal relationship. In this study, women with PCOS who received 90 μg/day of vitamin K2 (MK-7) for eight weeks exhibited a significant reduction in depressive symptoms compared to those receiving placebo. BDI-II scores decreased from 16.9 to 15.0 in the intervention group, whereas scores slightly increased in the control group (from 13.8 to 14.0), with $p < 0.05$.

**Table 2.** A systematic review analysis on vitamin K and depression studies.

| | | | **Observational Studies** | | | |
|---|---|---|---|---|---|---|
| No. | Study | Population | Depression Tool | Vitamin K Measure | Key Finding | Effect Size/Statistics |
| 1 | Rubio-López et al. [15] | Children (6–9 years), Spain, n = 710 | CES-DC | 3-day dietary recall | Lower vitamin K intake in children with depressive symptoms | $p < 0.05$ (between-group difference) |
| 2 | Nguyen et al. [16] | Adults ≥ 65 years, Japan, n = 1634 | GDS | BDHQ (dietary intake) | Lower K intake associated with depressive symptoms | OR = 0.998 (m), 0.997 (f), $p < 0.05$ |
| 3 | Bolzetta et al. [17] | Adults 45–79 years, USA, n = 4375 | CES-DC | FFQ | Higher K intake linked to lower depression | β = −0.10, 95% CI: −0.17 to −0.03, $p = 0.02$ |
| 4 | Zhang et al. [18] | Adults ≥ 18 years, USA, n = 11,687 | PHQ-9 | 24-h dietary recall | Higher K intake inversely associated with depression | OR = 0.68, 95% CI: 0.52–0.89, p-trend < 0.05 |
| 5 | Wang et al. [19] | Adults 18–80 years, USA, n = 30,408 | PHQ-9 | 2 × 24-h dietary recall | Non-linear inverse association; mediated by oxidative balance | OR Q4 vs. Q1 = 0.64, 95% CI: 0.52–0.78, $p < 0.001$ |
| 6 | Wang et al. [20] | Adults 18–65 years, China, n = 295 | SCID | Serum vitamin K (LC-MS/MS) | Lower serum K in the suicide attempt group | OR = 0.61, 95% CI: 0.15–0.90, $p = 0.004$ |
| 7 | Hayashi et al. [21] | Pregnant women, Japan, n = 776 | CES-D | BDHQ | Higher K intake is associated with fewer depressive symptoms | r = −0.496, $p = 0.019$ |
| 8 | Yu et al. [22] | Adults ≥ 18 years with CKD, USA, n = 5381 | PHQ-9 | 24-h dietary recall + supplements | Higher K intake reduced depression risk | OR = 0.61, 95% CI: 0.44–0.85, $p < 0.05$ |
| 9 | Kaner et al. [23] | Adults 18–60 years, Turkey, n = 59 | DSM-IV-TR diagnosis | 24-h dietary recall | Lower K intake in depressed patients | 1353.9 mg vs. 2063.9 mg, $p < 0.001$ |
| 10 | Khosravi et al. [24] | Adults 18–65 years, Iran, n = 330 | DSM-IV/BDI | FFQ | Lower K intake associated with depression | OR = 0.99, 95% CI: 0.99–0.99, $p < 0.05$ |
| 11 | Mohtashamian et al. [25] | Adults with CKD, Iran, n = 90 | DASS-21 | 3 × 24-h dietary recall | Inverse correlation for anxiety; not reported for depression | β = −0.26, $p = 0.015$ (anxiety only) |
| | | | **Clinical Trial** | | | |
| 12 | Tarkesh et al. [26] | Women with PCOS, Iran, n = 84 (RCT, 8 weeks) | BDI-II | Serum K (ELISA) | MK-7 improved depression scores vs. placebo | 16.9 → 15.0 vs. 13.8 → 14.0, $p < 0.05$ |
| | | | **Pre-clinical Animal Studies** | | | |
| No. | Study | Model | Depression Measures | Key Finding | Effect Size/Statistics | |
| 13 | Gancheva & Zhelyazkova-Savova [27] | Male Wistar rats, metabolic syndrome model | FST, Social Interaction Test | K2 reduced depression-like and anxiety-like behavior | FST immobility reduced to 162.9 s, $p < 0.05$ vs. MS group | |
| 14 | Mansour et al. [28] | Female rats, OVX model | Modified FST, Open Field, Biochemical markers | K2 improved mood, behavior, and oxidative markers | All behavioral outcomes improved, $p < 0.05$ vs. OVX | |

Two preclinical studies further supported the potential neurobiological role of vitamin K. Gancheva and Zhelyazkova-Savova [27] found that vitamin K2 supplementation significantly reduced depression- and anxiety-like behaviors in rats with diet-induced metabolic syndrome, as demonstrated by decreased immobility in the forced swim test and improved social interaction times ($p < 0.05$). Similarly, Mansour et al. [28] showed that vitamin K2 (MK-7) improved behavioral outcomes and reduced oxidative stress markers in ovariectomized female rats, a model of estrogen-deficiency-related mood disturbances.

Overall, the findings across human and animal studies indicate a consistent inverse relationship between vitamin K status and depressive symptoms. While the observational data suggest a robust association, causal inference is limited due to study design. Only one RCT was identified, and though supportive, further high-quality trials are needed to confirm efficacy and clarify the distinct roles of vitamin K1 versus K2. Additionally, considerable heterogeneity in population characteristics, outcome measures, and vitamin K assessment methods highlights the need for more standardized and targeted investigations.

## 4. Discussion

### 4.1. Insights from the Reviewed Articles

This review found a consistent inverse association between vitamin K status and depressive symptoms across diverse human populations. These associations, observed in large-scale observational cohorts and supported by preliminary causal signals from a small randomized controlled trial, suggest a biologically meaningful relationship rather than a chance finding. However, several critical gaps must be addressed before considering translational applications.

First, nearly all observational studies aggregated phylloquinone (vitamin K1) and menaquinones (vitamin K2) into a single exposure metric, obscuring key differences in isoform-specific bioavailability, tissue distribution, and the activation of vitamin K-dependent proteins such as Gas6 and osteocalcin. Given that MK-7, a form of vitamin K2, crosses the blood–brain barrier more efficiently and has a longer half-life than K1 [29], future studies must disaggregate isoforms to determine which molecular species are most relevant to neuroprotection and mood regulation. Second, the reliance on cross-sectional dietary recall data introduces recall bias and limits the ability to distinguish between acute and chronic vitamin K exposure. Integrating longitudinal biomarker panels—such as serum phylloquinone, MK-4/7 concentrations, and carboxylated osteocalcin—into cohort studies would help establish temporal relationships and clarify dose-response effects.

Although most studies reported statistically significant associations, the observed effect sizes were modest (ORs ~0.6–0.7), indicating that vitamin K is unlikely to function as a standalone antidepressant. Rather, it may act as a modulatory cofactor within a broader nutritional and metabolic framework. Interactions with other micronutrients (e.g., vitamins D and B), gut microbiome-derived menaquinone production, and individual genetic variations in vitamin K metabolism (e.g., VKORC1, GGCX polymorphisms) warrant systematic investigation. Future randomized trials should consider factorial designs that test vitamin K alongside established anti-inflammatory or neurotrophic agents. Concurrently, preclinical research should move beyond behavioral assessments to include molecular endpoints that are known to be implicated in depression pathophysiology.

In addressing the second aim of this review—exploring the underlying biological mechanisms linking vitamin K to depression—the available evidence remains limited. Only two preclinical studies met the inclusion criteria, both conducted in non-psychiatric disease models: one in rats with metabolic syndrome and the other in ovariectomized rats. Although both studies reported behavioral improvements with vitamin K2 supplementation, mechanistic insights were limited to general markers of oxidative stress. These included reductions in hippocampal malondialdehyde (MDA) and hydrogen peroxide levels, increased catalase (CAT) activity and total antioxidant capacity, and histological findings of preserved hippocampal pyramidal cell morphology, with minimal nuclear degeneration [28]. However, no studies directly examined central neurobiological mediators such as BDNF, TAM receptor activation, or neurotransmitter regulation. Thus, while these findings support the plausibility of a neuroprotective role for vitamin K, the current mechanistic evidence remains preliminary and indirect.

### 4.2. The Link: Potential Mechanism of Action (MOA) of Vitamin K on Depression

While the studies reviewed consistently suggest a link between vitamin K and depression, significant gaps remain in understanding the specific biological mechanisms underlying this association. To date, no preclinical studies have directly examined the effects of vitamin K in animal models of depression. Nevertheless, a broader neurobiological approach is warranted. Depression is increasingly recognized as a heterogeneous disorder involving multiple overlapping pathophysiological domains—including inflam-

mation, oxidative stress, neurotrophic signaling, and myelin integrity—all of which are modulated by vitamin K in other disease contexts. The following mechanisms are therefore extrapolated from neurophysiological and disease models with shared features relevant to depression. These pathways should be interpreted as hypothesis-generating rather than definitive (Figure 2).
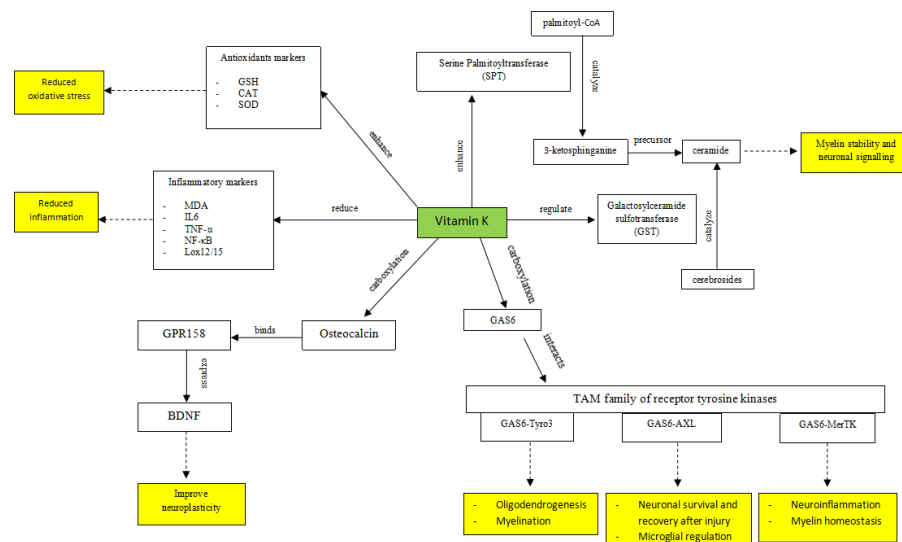


**Figure 2.** Potential mechanism of action (MOA) of vitamin K on depression.

### 4.2.1. Mechanism of Action 1: Antioxidant and Anti-Inflammatory Potential of Vitamin K

A growing body of evidence supports the antioxidant and anti-inflammatory roles of vitamin K in protecting the brain against oxidative stress and neuroinflammation. In vitro studies have demonstrated that vitamin K1 and MK-4 protect neural precursor cells from oxidative stress by reactive oxygen species (ROS) accumulation. This effect is partly mediated by the inhibition of 12-lipoxygenase (12-LOX), an enzyme involved in ROS production during lipid peroxidation [30,31]. Additionally, the antioxidant effect is enhanced through the activity of the vitamin K cycle, particularly the regeneration of vitamin K-hydroquinone, a potent radical-scavenging form of the vitamin that suppresses lipid peroxidation [32]. These findings highlight the role of vitamin K in modulating ROS-related damage through both enzymatic regulation and redox cycling.

In animal studies, Gancheva & Zhelyazkova-Savova [27] investigated vitamin K2 effects in rats with metabolic syndrome and found that vitamin K2 improved glucose metabolism and reduced anxiety and depression. Building on this, Chatterjee et al. have consistently explored its role across multiple rodent models of cognitive decline—induced by diabetes [33], D-galactose administration [34], aluminum chloride exposure [35], and gut dysbiosis [36]—concluding that vitamin K2 exerts neuroprotective effects. These studies collectively show that vitamin K2 enhances endogenous antioxidant systems (SOD, GSH, catalase, and NRF2) while mitigating neuroinflammatory responses through the downregulation of key proinflammatory markers such as TNF-$\alpha$, IL-1$\beta$, MCP-1, NF-$\kappa$B, and SIRT1.

Given that oxidative stress plays a significant role in the pathophysiology of both neurodegeneration and depression—largely through excessive ROS production and impaired antioxidant defense—vitamin K's observed antioxidant and anti-inflammatory effects in preclinical models suggest potential therapeutic relevance. However, further research, particularly in clinical settings, is needed to confirm its efficacy and translational value in these conditions.

4.2.2. Mechanism of Action 2: Vitamin K Regulation of Sphingolipid Biosynthesis

Vitamin K is essential for sphingolipid metabolism, supporting myelin integrity, neuronal function, and cognitive health. It regulates key sphingolipids like sulfatides and sphingomyelin, which are crucial for white matter stability, while also influencing gangliosides, which contribute to neuronal signaling. The enzymes serine palmitoyltransferase (SPT) and galactosylceramide sulfotransferase (GST) play central roles in this pathway and are influenced by vitamin K availability [37].

Studies show that higher MK-4 levels correlate with increased sulfatide concentrations in the hippocampus and cortex, regions vital for learning and memory, though this effect is region-specific [38]. In a demyelination animal model of multiple sclerosis, vitamin K supplementation enhances sulfatide production and supports myelin repair, highlighting its potential in remyelination therapies [39].

Beyond sulfatides, vitamin K—particularly its MK-4 form—has been associated with sphingomyelin biosynthesis, with deficiency leading to reduced levels of ceramides, sphingomyelin, and sulfatides, all critical for maintaining myelin integrity. An animal study showed that MK-4 concentrations are higher in myelinated brain regions and positively correlate with sulfatide and sphingomyelin levels, while showing a negative correlation with gangliosides [40]. Meanwhile, its deficiency has been linked to lower ganglioside levels, impaired cognition, and reduced exploratory behavior, reinforcing its role in neuronal communication [41].

Disruptions in sphingolipid metabolism have been implicated in various neuropsychiatric disorders, including major depression. Altered sphingolipid levels can impair synaptic transmission and neuronal plasticity—processes essential to mood regulation—while dysregulation may also compromise myelin integrity, contributing to the neurobiological changes observed in depressive disorders [42]. Given vitamin K's role in sphingolipid metabolism, particularly in the biosynthesis of sulfatides and sphingomyelin, maintaining adequate vitamin K levels may support neuronal health and resilience against mood disorders. However, this mechanism has not yet been demonstrated in depression-specific models and requires further validation.

4.2.3. Mechanism of Action 3: Vitamin K-Dependent Protein, GAS6

Vitamin K is essential for the γ-carboxylation of Growth Arrest-Specific 6 (Gas6), a vitamin K-dependent protein that interacts with the TAM family of receptor tyrosine kinases—Tyro3, Axl, and MerTK—to regulate various physiological processes, including those in the nervous system. While Gas6 can bind to all three receptors, it has the highest affinity for Axl, followed by Tyro3, and the lowest for MerTK [43].

In the brain, Tyro3 is predominantly expressed in neurons and oligodendrocytes, indicating a crucial role in neural function. Gas6-Tyro3 signaling has been shown to promote oligodendrogenesis and myelination in the adult central nervous system by enhancing oligodendrocyte generation and myelin production. These processes are vital for repairing demyelinating injuries, such as those seen in multiple sclerosis [44].

Although Axl and MerTK are part of the same receptor family, their functions in the brain differ from Tyro3. GAS6-Axl signaling plays a key role in neuronal survival and recovery after injury by regulating inflammatory responses and apoptosis. Additionally, this pathway is involved in microglial regulation, which is essential for maintaining central nervous system homeostasis [45].

GAS6-MerTK contributes to neuroprotection through distinct mechanisms, primarily by modulating neuroinflammation and supporting myelin homeostasis. Its activation suppresses the NLRP3 inflammasome via autophagy induction, leading to reduced neuroinflammation and improved neurological recovery following subarachnoid hemorrhage [46].

Additionally, GAS6-MerTK signaling inhibits Toll-like receptor-mediated inflammatory pathways in microglia, reducing pro-inflammatory cytokine production, while also playing a key role in myelin phagocytosis to support myelin maintenance and repair [47].

However, it is important to note that, while these mechanisms are well-supported in models of demyelination, injury, and neuroinflammation, they have not yet been demonstrated in depression-specific models. Future studies are needed to determine whether GAS6–TAM signaling plays a direct role in mood regulation or depressive pathophysiology.

### 4.2.4. Mechanism of Action 4: Vitamin K-Dependent Protein, Osteocalcin

Vitamin K plays an essential role in activating osteocalcin, a hormone secreted by bone, by enabling its carboxylation through $\gamma$-glutamyl carboxylase—an enzymatic process necessary for osteocalcin's calcium-binding function and biological activity. Emerging evidence from multiple lines of research points to a potential link between low osteocalcin levels and a wide array of psychiatric symptoms and disorders. Preclinical studies have shown that osteocalcin is capable of crossing the blood–brain barrier, where it contributes to several neurobiological processes critical for mental health, including enhanced learning and memory, increased neurogenesis, stimulation of monoamine neurotransmitter production, and balances GABA synthesis [48]. These processes are known to counteract mechanisms underlying various psychiatric conditions. Notably, osteocalcin-deficient mice exhibit pronounced anxiety- and depression-like behaviors, effects that are reversed upon the administration of osteocalcin [48]. Extending this work, Khrimian et al. [49] found that osteocalcin also promotes neuroplasticity by upregulating hippocampal BDNF expression and facilitating the intracellular transport of BDNF-containing vesicles, an effect mediated by the GPR158 receptor—further implicating osteocalcin in the modulation of mood and cognition.

Building on this, a recent study by Rnic et al. [50] provided human evidence by demonstrating both cross-sectional and longitudinal associations in youth: lower osteocalcin levels were linked to current psychiatric disorders and predicted greater increases in psychopathology symptoms over time. While these results point to a promising connection between osteocalcin and BDNF-mediated neuroplasticity, further research is necessary to confirm the role of vitamin K on these effects and assess their therapeutic potential for cognitive and emotional disorders.

## 5. Limitations

This systematic review has several limitations that should be acknowledged. First, the literature search was limited to studies published in English, which may have introduced language bias and restricted the inclusion of potentially relevant findings from non-English sources. This decision was made to ensure the accuracy of data interpretation, as automated or secondary translation tools may compromise the reliability of nuanced clinical data. Nonetheless, this may reduce the global generalizability of our findings, especially considering regional variations in dietary vitamin K intake and depression prevalence. In future updates, expanding the search to include non-English publications with appropriate translation support would help mitigate this limitation.

Second, many of the included studies did not differentiate between the two primary forms of vitamin K—phylloquinone (vitamin K1) and menaquinones (vitamin K2)—which may have distinct biological effects, particularly in the brain. While some experimental studies emphasized vitamin K2, most observational studies assessed total dietary intake or serum vitamin K without specifying the isoform. As a result, the relative contributions of K1 and K2 to mood regulation remain unclear. This represents an important gap in the literature that should be addressed through future studies focusing specifically on isoform-

specific effects. Additionally, the majority of the included studies were cross-sectional in design, which limits causal inference and increases susceptibility to residual confounding. Although one randomized controlled trial and a few animal studies provided preliminary mechanistic support, these findings may not be fully generalizable to human populations. Sensitivity analyses were not conducted, which may limit the ability to assess the robustness of the findings across different subgroups or study designs. Certainty of evidence was not formally assessed using GRADE. Given the predominance of cross-sectional studies and variability in study designs, the overall certainty is likely low to moderate.

## 6. Conclusions

This systematic review synthesizes emerging evidence indicating a consistent inverse association between vitamin K status and depressive symptoms across diverse human populations. While most available data derive from observational studies, one randomized controlled trial and supporting preclinical research suggest that vitamin K—particularly menaquinones—may influence neurobiological pathways relevant to mood regulation. Proposed mechanisms include the modulation of oxidative stress, inflammatory signaling, sphingolipid metabolism, and neurotrophic support via vitamin K-dependent proteins such as GAS6 and osteocalcin.

However, key limitations constrain current interpretations. The majority of studies are cross-sectional in design, precluding causal inference, and often fail to distinguish between vitamin K isoforms. Mechanistic insights are derived primarily from non-depression models and remain hypothesis-generating rather than conclusive. As depression is increasingly recognized as a heterogeneous disorder with systemic underpinnings, vitamin K may represent a biologically plausible, upstream modulator within this broader pathophysiological framework.

To clarify its role in mental health, future research should prioritize longitudinal cohort studies with validated biomarkers, randomized trials stratified by vitamin K form, and targeted preclinical investigations using depression-relevant models. A more precise understanding of the neurobiological effects of vitamin K could ultimately support the development of novel nutritional strategies or adjunctive interventions in the prevention and treatment of depressive disorders.

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## Abbreviations

The following abbreviations are used in this manuscript:

| | |
|---|---|
| RCT | Randomized Controlled Trial |
| WHO | World Health Organization |

| | |
|---|---|
| MK | Menaquinone |
| MK-4 | Menaquinone-4 |
| MK-7 | Menaquinone-7 |
| ROB 2.0 | Risk of Bias tool 2.0 |
| NOS | Newcastle–Ottawa Scale |
| AHRQ | Agency for Healthcare Research and Quality |
| CES-DC | Center for Epidemiological Studies Depression Scale for Children |
| GDS | Geriatric Depression Scale |
| PHQ-9 | Patient Health Questionnaire-9 |
| SCID | Structured Clinical Interview for DSM |
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders |
| DSM-IV-TR | Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision |
| BDI | Beck's Depression Inventory |
| DASS-21 | Depression, Anxiety, and Stress Scale-21 items |
| BDI-II | Beck's Depression Inventory, Second Edition |
| BDHQ | Brief Self-Administered Diet History Questionnaire |
| FFQ | Food Frequency Questionnaire |
| LC-MS/MS | Liquid Chromatography-Mass Spectrometry |
| ELISA | Enzyme-Linked Immunosorbent Assay |
| FST | Forced Swim Test |
| MS | Mass Spectrometry |
| OVX | Ovariectomized |
| PCOS | Polycystic Ovary Syndrome |
| NHANES | National Health and Nutrition Examination Survey |
| CKD | Chronic Kidney Disease |
| OR | Odds Ratio |
| CI | Confidence Interval |
| μg | Microgram |
| MDA | Malondialdehyde |
| CAT | Catalase |
| BDNF | Brain-Derived Neurotrophic Factor |
| TAM | Tyro3, Axl, MerTK |
| GSH | Glutathione |
| SOD | Superoxide Dismutase |
| IL6 | Interleukin-6 |
| TNF-$\alpha$ | Tumor Necrosis Factor-alpha |
| NF-kB | Nuclear Factor Kappa-Light-Chain Enhancer of Activated B Cells |
| Lox12/15 | 12/15-lipoxygenase |
| GPR158 | G-Coupled Protein Receptor 158 |
| SPT | Serine Palmitoyltransferase |
| GAS6 | Growth-Arrest-Specific 6 |
| GST | Galactosylceramide Sulfotransferase |
| MOA | Mechanism of Action |
| ROS | Reactive Oxygen Species |
| NRF2 | Nuclear factor erythroid 2-related factor 2 |
| IL-1$\beta$ | Interleukin-1 Beta |
| MCP-1 | Monocyte Chemoattractant Protein-1 |
| SIRT1 | Silent Information Regulator Sirtuin 1 |
| NLRP3 | Nucleotide-Binding Domain, Leucine-Rich-Containing Family, Pyrin Domain-Containing-3 |
| GABA | Gamma-Aminobutyric Acid |
| GRADE | Grading of Recommendations Assessment, Development, and Evaluation |
| MOHE | Ministry of Higher Education |
| FRGS | Fundamental Research Grant Scheme |
| APC | Article Processing Charge |
| MPCG | Management and Science University Publication and Conference Grant |

# References

1.　World Health Organization. Depressive Disorder (Depression). Available online: https://www.who.int/news-room/fact-sheets/detail/depression/?gad_source=1&gclid=Cj0KCQiApNW6BhD5ARIsACmEbkX2Jos93Q57OLzJsjVx98e3JKEq3DD0a8g_hq4SGDy4vGj-oajo6WcaAjm_EALw_wcB (accessed on 31 March 2023).

2.　Woody, C.A.; Ferrari, A.J.; Siskind, D.J.; Whiteford, H.A.; Harris, M.G. A systematic review and meta-regression of the prevalence and incidence of perinatal depression. *J. Affect. Disord.* **2017**, *219*, 86–92. [CrossRef] [PubMed]

3.　Evans-Lacko, S.; Aguilar-Gaxiola, S.; Al-Hamzawi, A.; Alonso, J.; Benjet, C.; Bruffaerts, R.; Chiu, W.T.; Florescu, S.; de Girolamo, G.; Gureje, O.; et al. Socio-economic variations in the mental health treatment gap for people with anxiety, mood, and substance use disorders: Results from the WHO World Mental Health (WMH) surveys. *Psychol. Med.* **2018**, *48*, 1560–1571. [CrossRef]

4.　Zainal Abidin, Z.; Kamaruddin, N.S.; Hein, Z.M.; Che Mohd Nassir, C.M.N.; Ramli, M.D.C. The Gut-Brain Axis and Depression: Understanding Microbiota-Driven Mechanisms and Novel Therapeutic Strategies. *Preprints*, 2025. [CrossRef]

5.　Dobrek, L.; Głowacka, K. Depression and Its Phytopharmacotherapy—A Narrative Review. *Int. J. Mol. Sci.* **2023**, *24*, 4772. [CrossRef]

6.　Aidiel, M.R.; Maisarah, A.M.; Khalid, K.; Nik Ramli, N.N.; Tang, S.G.H.; Adam, S.H. Polymethoxyflavones transcends expectation, a prominent flavonoid subclass from Kaempferia parviflora: A critical review. *Arab. J. Chem.* **2023**, *17*, 105364. [CrossRef]

7.　Mutalib, M.A.; Shamsuddin, A.S.; Nik Ramli, N.N.; Tang, S.G.H.; Adam, S.H. Antiproliferative activity and polyphenol analysis in tomato (*Solanum lycopersicon*). *Malays. J. Microsc.* **2023**, *19*, 282–294. Available online: https://malaysianjournalofmicroscopy.org/ojs/index.php/mjm/article/view/737 (accessed on 2 May 2025).

8.　Nik Ramli, N.N.; Shamsul Adzmi, N.A.; Nasarudin, S.N.A.Z.; Hashim, M.H.; Abdul Mutalib, M.; Mohamad Alwi, M.N.; Abd Rashed, A.; Ramasamy, R. Environmental enrichment preconditioning prevents chronic social defeat stress-induced memory impairment and hippocampal neurodegeneration. *Asia-Pac. J. Mol. Biol. Biotechnol.* **2024**, *32*, 29–38. [CrossRef]

9.　Sadler, R.A.; Shoveller, A.K.; Shandilya, U.K.; Charchoglyan, A.; Wagter-Lesperance, L.; Bridle, B.W.; Mallard, B.A.; Karrow, N.A. Beyond the Coagulation Cascade: Vitamin K and Its Multifaceted Impact on Human and Domesticated Animal Health. *Curr. Issues Mol. Biol.* **2024**, *46*, 7001–7031. [CrossRef] [PubMed]

10.　Wei, Y.; Gao, H.; Luo, Y.; Feng, J.; Li, G.; Wang, T.; Xu, H.; Yin, L.; Ma, J.; Chen, J. Systemic inflammation and oxidative stress markers in patients with unipolar and bipolar depression: A large-scale study. *J. Affect. Disord.* **2024**, *346*, 154–166. [CrossRef]

11.　Rawdin, B.J.; Mellon, S.H.; Dhabhar, F.S.; Epel, E.S.; Puterman, E.; Su, Y.; Burke, H.M.; Reus, V.I.; Rosser, R.; Hamilton, S.P.; et al. Dysregulated relationship of inflammation and oxidative stress in major depression. *Brain Behav. Immun.* **2013**, *31*, 143–152. [CrossRef]

12.　Halder, M.; Petsophonsakul, P.; Akbulut, A.C.; Pavlic, A.; Bohan, F.; Anderson, E.; Maresz, K.; Kramann, R.; Schurgers, L. Vitamin K: Double Bonds beyond Coagulation Insights into Differences between Vitamin K1 and K2 in Health and Disease. *Int. J. Mol. Sci.* **2019**, *20*, 896. [CrossRef]

13.　Mladěnka, P.; Macáková, K.; Kujovská Krčmová, L.; Javorská, L.; Mrštná, K.; Carazo, A.; Protti, M.; Remião, F.; Nováková, L.; OEMONOM Researchers and Collaborators. Vitamin K—Sources, physiological role, kinetics, deficiency, detection, therapeutic use, and toxicity. *Nutr. Rev.* **2022**, *80*, 677–698. [CrossRef] [PubMed]

14.　Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Moher, D.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, n71. [CrossRef]

15.　Rubio-López, N.; Morales-Suárez-Varela, M.; Pico, Y.; Livianos-Aldana, L.; Llopis-González, A. Nutrient Intake and Depression Symptoms in Spanish Children: The ANIVA Study. *Int. J. Environ. Res. Public Health* **2016**, *13*, 352. [CrossRef]

16.　Nguyen, T.T.T.; Tsujiguchi, H.; Kambayashi, Y.; Hara, A.; Miyagi, S.; Yamada, Y.; Nakamura, H.; Shimizu, Y.; Hori, D.; Suzuki, F.; et al. Relationship between Vitamin Intake and Depressive Symptoms in Elderly Japanese Individuals: Differences with Gender and Body Mass Index. *Nutrients* **2017**, *9*, 1319. [CrossRef]

17.　Bolzetta, F.; Veronese, N.; Stubbs, B.; Noale, M.; Vaona, A.; Demurtas, J.; Celotto, S.; Cacco, C.; Cester, A.; Caruso, M.G.; et al. The Relationship between Dietary Vitamin K and Depressive Symptoms in Late Adulthood: A Cross-Sectional Analysis from a Large Cohort Study. *Nutrients* **2019**, *11*, 787. [CrossRef]

18.　Zhang, Y.; Tan, W.; Xi, X.; Yang, H.; Zhang, K.; Li, S.; Chen, X.; Zuo, H. Association between vitamin K intake and depressive symptoms in US adults: Data from the National Health and Nutrition Examination Survey (NHANES) 2013–2018. *Front. Nutr.* **2023**, *10*, 1102109. [CrossRef] [PubMed]

19.　Wang, S.T.; He, X.Y.; Le, J.; Sun, T.; Peng, R. Associations Between Vitamin K and Suicide Attempts in Patients with Depression: A Case-Control Study. *J. Inflamm. Res.* **2024**, *17*, 3423–3431. [CrossRef]

20.　Wang, L.; Huang, S.; Feng, Z.; Xiao, J.; Luo, G.; Zhang, Y. Assessing the role of antioxidant and pro-oxidant balance in mediating the relationship between vitamin K intake and depressive symptoms in adults. *Front. Nutr.* **2024**, *11*, 1384489. [CrossRef] [PubMed]

21.　Hayashi, A.; Oguchi, H.; Kozawa, Y.; Ban, Y.; Shinoda, J.; Suganuma, N. Factors associated with symptoms of depression among pregnant women with gestational diabetes mellitus in Japan. *Drug Discov. Ther.* **2020**, *14*, 232–238. [CrossRef]

22. Yu, C.; Liu, K.; Yao, W.; Tang, D. Associations between the intake of single and multiple dietary vitamins and depression risk among populations with chronic kidney disease. *Front. Nutr.* **2025**, *12*, 1492829. [CrossRef]

23. Kaner, G.; Soylu, M.; Yüksel, N.; Inanç, N.; Ongan, D.; Başmısırlı, E. Evaluation of Nutritional Status of Patients with Depression. *BioMed Res. Int.* **2015**, *2015*, 521481. [CrossRef] [PubMed]

24. Khosravi, M.; Hosseinzadeh, M.; Golzar, M.; Majdzadeh, R.; Sotoudeh, G. Comparison between Macro & Micro Nutrient Intake in Depressed Patients with Healthy People. *J. Nutr. Food Secur.* **2019**, *4*, 83–92. [CrossRef]

25. Mohtashamian, A.; Soleimani, A.; Gilasi, H.R.; Taba, S.M.M.; Kheiripour, N.; Sharifi, N. Is There any Correlation Between Nutrient Intake and Mental Health in Patients with Chronic Kidney Disease? A Cross-Sectional Study. *Jundishapur J. Chronic Dis. Care* **2024**, *13*, e138367. [CrossRef]

26. Tarkesh, F.; Namavar Jahromi, B.; Hejazi, N.; Hoseini, G. Effect of vitamin K2 administration on depression status in patients with polycystic ovary syndrome: A randomized clinical trial. *BMC Women's Health* **2022**, *22*, 315. [CrossRef]

27. Gancheva, S.M.; Zhelyazkova-Savova, M.D. Vitamin K2 Improves Anxiety and Depression but not Cognition in Rats with Metabolic Syndrome: A Role of Blood Glucose? *Folia Med.* **2016**, *58*, 264–272. [CrossRef] [PubMed]

28. Mansour, S.W.; Selim, S.A.; Salama, S.A.; Hussein, S.; Abozaid, E.R. Anti-apoptotic effect of menaquinone-7 protects the brain of ovariectomized rats. *Beni-Suef Univ. J. Basic Appl. Sci.* **2023**, *12*, 22. [CrossRef]

29. Schurgers, L.J.; Teunissen, K.J.; Hamulyák, K.; Knapen, M.H.; Vik, H.; Vermeer, C. Vitamin K-containing dietary supplements: Comparison of synthetic vitamin K1 and natto-derived menaquinone-7. *Blood* **2007**, *109*, 3279–3283. [CrossRef]

30. Li, J.; Wang, H.; Rosenberg, P.A. Vitamin K prevents oxidative cell death by inhibiting activation of 12-lipoxygenase in developing oligodendrocytes. *J. Neurosci. Res.* **2009**, *87*, 1997–2005. [CrossRef]

31. Li, J.; Lin, J.C.; Wang, H.; Peterson, J.W.; Furie, B.C.; Furie, B.; Booth, S.L.; Volpe, J.J.; Rosenberg, P.A. Novel role of vitamin k in preventing oxidative injury to developing oligodendrocytes and neurons. *J. Neurosci. Off. J. Soc. Neurosci.* **2003**, *23*, 5816–5826. [CrossRef]

32. Vervoort, L.M.; Ronden, J.E.; Thijssen, H.H. The potent antioxidant activity of the vitamin K cycle in microsomal lipid peroxidation. *Biochem. Pharmacol.* **1997**, *54*, 871–876. [CrossRef]

33. Chatterjee, K.; Pal, A.; Padhy, D.S.; Saha, R.; Chatterjee, A.; Bharadwaj, M.; Sarkar, B.; Mazumder, P.M.; Banerjee, S. Vitamin K2 Ameliorates Diabetes-Associated Cognitive Decline by Reducing Oxidative Stress and Neuroinflammation. *J. Neuroimmune Pharmacol.* **2024**, *19*, 56. [CrossRef] [PubMed]

34. Chatterjee, K.; Mazumder, P.M.; Banerjee, S. Vitamin K2 protects against D-galactose induced ageing in mice. *Eur. J. Pharmacol.* **2025**, *990*, 177277. [CrossRef] [PubMed]

35. Chatterjee, K.; Mazumder, P.M.; Banerjee, S. Vitamin K2 protects against aluminium chloride-mediated neurodegeneration. *Inflammopharmacology* **2023**, *31*, 2675–2684. [CrossRef]

36. Chatterjee, K.; Mazumder, P.M.; Sarkar, S.R.; Saha, R.; Chatterjee, A.; Sarkar, B.; Banerjee, S. Neuroprotective effect of Vitamin K2 against gut dysbiosis associated cognitive decline. *Physiol. Behav.* **2023**, *269*, 114252. [CrossRef]

37. Denisova, N.A.; Booth, S.L. Vitamin K and sphingolipid metabolism: Evidence to date. *Nutr. Rev.* **2005**, *63*, 111–121. [CrossRef]

38. Crivello, N.A.; Casseus, S.L.; Peterson, J.W.; Smith, D.E.; Booth, S.L. Age- and brain region-specific effects of dietary vitamin K on myelin sulfatides. *J. Nutr. Biochem.* **2010**, *21*, 1083–1088. [CrossRef]

39. Popescu, D.C.; Huang, H.; Singhal, N.K.; Shriver, L.; McDonough, J.; Clements, R.J.; Freeman, E.J. Vitamin K enhances the production of brain sulfatides during remyelination. *PLoS ONE* **2018**, *13*, e0203057. [CrossRef] [PubMed]

40. Carrié, I.; Portoukalian, J.; Vicaretti, R.; Rochford, J.; Potvin, S.; Ferland, G. Menaquinone-4 concentration is correlated with sphingolipid concentrations in rat brain. *J. Nutr.* **2004**, *134*, 167–172. [CrossRef]

41. Tamadon-Nejad, S.; Ouliass, B.; Rochford, J.; Ferland, G. Vitamin K Deficiency Induced by Warfarin Is Associated With Cognitive and Behavioral Perturbations, and Alterations in Brain Sphingolipids in Rats. *Front. Aging Neurosci.* **2018**, *10*, 213. [CrossRef]

42. Bernal-Vega, S.; García-Juárez, M.; Camacho-Morales, A. Contribution of ceramides metabolism in psychiatric disorders. *J. Neurochem.* **2023**, *164*, 708–724. [CrossRef]

43. Lemke, G.; Rothlin, C.V. Immunobiology of the TAM receptors. *Nat. Rev. Immunol.* **2008**, *8*, 327–336. [CrossRef]

44. Goudarzi, S.; Rivera, A.; Butt, A.M.; Hafizi, S. Gas6 Promotes Oligodendrogenesis and Myelination in the Adult Central Nervous System and After Lysolecithin-Induced Demyelination. *ASN Neuro* **2016**, *8*, 1759091416668430. [CrossRef]

45. Fourgeaud, L.; Través, P.G.; Tufail, Y.; Leal-Bailey, H.; Lew, E.D.; Burrola, P.G.; Callaway, P.; Zagórska, A.; Rothlin, C.V.; Nimmerjahn, A.; et al. TAM receptors regulate multiple features of microglial physiology. *Nature* **2016**, *532*, 240–244. [CrossRef]

46. Du, Y.; Lu, Z.; Yang, D.; Wang, D.; Jiang, L.; Shen, Y.; Du, Q.; Yu, W. MerTK inhibits the activation of the NLRP3 inflammasome after subarachnoid hemorrhage by inducing autophagy. *Brain Res.* **2021**, *1766*, 147525. [CrossRef]

47. Gilchrist, S.E.; Goudarzi, S.; Hafizi, S. Gas6 Inhibits Toll-Like Receptor-Mediated Inflammatory Pathways in Mouse Microglia via Axl and Mer. *Front. Cell. Neurosci.* **2020**, *14*, 576650. [CrossRef]

48. Oury, F.; Khrimian, L.; Denny, C.A.; Gardin, A.; Chamouni, A.; Goeden, N.; Huang, Y.Y.; Lee, H.; Srinivas, P.; Gao, X.B.; et al. Maternal and offspring pools of osteocalcin influence brain development and functions. *Cell* **2013**, *155*, 228–241. [CrossRef]

49.    Khrimian, L.; Obri, A.; Ramos-Brossier, M.; Rousseaud, A.; Moriceau, S.; Nicot, A.S.; Mera, P.; Kosmidis, S.; Karnavas, T.; Saudou, F.; et al. Gpr158 mediates osteocalcin's regulation of cognition. *J. Exp. Med.* **2017**, *214*, 2859–2873. [CrossRef]

50.    Rnic, K.; Jopling, E.; Tracy, A.; Battaglini, A.; Grocott, B.; Lam, R.W.; LeMoult, J. Osteocalcin: A novel biomarker of adolescent psychopathology. *Psychoneuroendocrinology* **2024**, *169*, 107136. [CrossRef]