The Role of Vitamins in Neurodegenerative Disease: An Update

Sachchida Nand Rai 1, Payal Singh 2, Harry W.M. Steinbusch 3,4, Emanuel Vamanu 5,*, Ghulam Ashraf 6,7 and Mohan Prasad Singh 1,*

1 Centre of Biotechnology, University of Allahabad, Prayagraj 211002, India; raibiochem@gmail.com
2 Department of Zoology, MMV, Banaras Hindu University, Varanasi 221005, India; payalsingh200012@gmail.com
3 Department of Cellular Neuroscience, Faculty of Health, Medicine & Life Sciences, Maastricht University, 6211 LK Maastricht, The Netherlands; h.steinbusch@maastrichtuniversity.nl
4 Department of Cognitive Neuroscience, DGIST, Daegu 42988, Korea
5 Faculty of Biotechnology, The University of Agronomic Science and Veterinary Medicine, 59 Manasti bd, 1 District, 011464 Bucharest, Romania
6 Pre-Clinical Research Unit, King Fahd Medical Research Center, King Abdulaziz University, Jeddah 21589, Saudi Arabia; ashraf.gm@gmail.com
7 Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah 21589, Saudi Arabia
* Correspondence: email@emanuelvamanu.ro (E.V.); mpsingh.16@gmail.com (M.P.S.); Tel.: +07-4221-8240 (E.V.)

Abstract: Acquiring the recommended daily allowance of vitamins is crucial for maintaining homeostatic balance in humans and other animals. A deficiency in or dysregulation of vitamins adversely affects the neuronal metabolism, which may lead to neurodegenerative diseases. In this article, we discuss how novel vitamin-based approaches aid in attenuating abnormal neuronal functioning in neurodegeneration-based brain diseases such as Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, Amyotrophic lateral sclerosis, and Prion disease. Vitamins show their therapeutic activity in Parkinson’s disease by antioxidative and anti-inflammatory activity. In addition, different water- and lipid-soluble vitamins have also prevented amyloid beta and tau pathology. On the other hand, some results also show no correlation between vitamin action and the prevention of neurodegenerative diseases. Some vitamins also exhibit toxic activity too. This review discusses both the beneficial and null effects of vitamin supplementation for neurological disorders. The detailed mechanism of action of both water- and lipid-soluble vitamins is addressed in the manuscript. Hormesis is also an essential factor that is very helpful to determine the effective dose of vitamins. PubMed, Google Scholar, Web of Science, and Scopus were employed to conduct the literature search of original articles, review articles, and meta-analyses.

Keywords: vitamins; neurodegenerative disease; Parkinson’s disease; Alzheimer’s disease; Huntington’s disease; Prion disease

1. Introduction

In infants and elderly people, vitamin deficiency is common [1]. Prolonged deficiencies in vitamins lead to malnutrition and severe health issues [2,3]. Interestingly, the typical balanced diet of a healthy population has a rich number of vitamins, which prevent several diseases [4,5]. This has prompted researchers to explore the role of different vitamins in the development and progression of diseases. For this review, we focus on vitamins relative to neurodegenerative diseases.

In general, vitamins are considered organic compounds that are required for the development and normal functioning of the body. The body cannot synthesize vitamins, either at all or not in sufficient quantities. As such, they must be obtained through the diet. Importantly, vitamins commonly function as antioxidants or enzymatic cofactors [6,7]. There are two main categories of vitamins: fat-soluble vitamins, which are stored in the
body until your body needs them, and water-soluble vitamins, which are not stored in the body, so a continuous exogenous daily supply is required [8,9].

Generally, vitamins offer a significant advantage for neurodegenerative diseases. Both water- and lipid-soluble vitamins prevent Parkinson’s and Alzheimer’s disease in a substantial manner. The α-synuclein toxicity has been prevented by vitamin supplementation. In addition, vitamins also exert their protective effects on the dopamine transporter. Amyloid and tau pathologies are also progressively prevented by a higher dose of vitamins. Vitamins also show their therapeutic properties for Huntington’s, Prion, and multiple sclerosis diseases. However, some studies show the contrasting activity of vitamins too for the diseases mentioned above. Some vitamins also show toxicity too. Therefore, there is a solid need for the role of vitamins in neurodegenerative diseases to be described clearly. The role of different vitamins and their detailed mechanisms of action are included in their respective sections.

2. Water-Soluble Vitamins

Water-soluble vitamins (WSVs) are structurally and functionally distinct compounds vital for normal cellular functions, growth, and development. The WSV is generally considered as a micronutrient, and the deficiency of which causes severe diseases such as neurological diseases, growth retardation, or intestinal diseases [10,11]. The essential WSVs are vitamin B1 (Thiamine), vitamin B2 (Riboflavin), vitamin B3 (Niacin, Nicotinic Acid), vitamin B5 (Pantothenic Acid), vitamin B6 (Pyridoxine and derivatives), vitamin B7 (Biotin, Vitamin H), vitamin B9 (Folate, Folacin), vitamin B12 (Cobalamin), and vitamin C (Ascorbate, Dehydroascorbate). Thiamine is also known as the Anti-beriberi factor and Aneurin. The molecular weight of thiamine is 265.36 g/mol. The reaction between ATP and thiamine forms active coenzyme thiamine pyrophosphate. Thiamine pyrophosphate plays a very important role in carbohydrate metabolism. Thiamine is a colorless compound with a chemical formula C12H17N4OS. It is insoluble in the organic solvent while soluble in polar solvents such as water. For the proper maintenance of the heart, nervous system, and digestive system, thiamine plays a crucial role [12]. The molecular formula of riboflavin (Vitamin B2) is C17H20N4O6, and the molecular weight is 376.4 g/mol. Riboflavin is the precursor of two vital coenzymes, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). FAD and FMN are involved in the oxidation/reduction reaction. These coenzymes also take part in the metabolism of proteins, carbohydrates, and lipids. For healthy hair, skin, and nails, riboflavin is very important because it can also modulate the antioxidant enzyme glutathione reductase [13]. The chemical formula of nicotinic acid (Vitamin B3) is C6H5NO2 or C5H4NCOOH, and its molecular weight is 123.11 g/mol. It is also called niacin, pyridine-3-carboxylic acid, and 3-pyridinecarboxylic acid. It is essential for reducing the bad cholesterol (LDL) and enhancing the good cholesterol (HDL) in our body. That is why it is used to manage dyslipidemia. The level of serum aminotransferases might elevate because niacin and its high dose might be responsible for acute liver injury. The taste of vitamin B3 is feebly acidic, and it is an odorless crystalline powder. Niacin is used as a vasodilator agent, antilipemic drug, and also an antidote [14]. The chemical formula and molecular weight of pantothenic acid (Vitamin B5) are C9H17NO5 and 219.23 g/mol, respectively. Pantothenic acid exhibits strong antioxidative properties and is widely found in both animal and plant tissues. This vitamin is the main part of the Vitamin B2 complex and coenzyme A. It is involved in the metabolism of lipid, carbohydrates, and proteins. This vitamin also takes part in the synthesis of hormones, various neurotransmitters, hemoglobin, and lipids [15]. The molecular weight and chemical formula of pyridoxine (Vitamin B6) are 169.18 g/mol and C18H11NO3. It is also called Pyridoxol and Gravidox. Pyridoxine is converted into pyridoxal phosphate (PLP) that plays a significant contribution in the transamination reaction. PLP also helps in the synthesis of essential neurotransmitters such as serotonin and norepinephrine. Pyridoxine is involved in the metabolism of glycogen and amino acids [16]. Biotin (Vitamin B7) is also called Vitamin H, and C10H16N2O5S and 244.31 g/mol are the chemical formula and molecular weight of...
this enzyme. This is involved in the carboxylation reaction. This enzyme is required for proper growth and metabolism [17]. Folate (Vitamin B9) is also considered as folic acid and vitamin M. The chemical formula and molecular weight of this enzyme are $C_{19}H_{19}N_7O_6$ and 441.4 g/mol, respectively. This enzyme plays a role in the metabolism of amino acids and carbon transfer reactions. Moreover, folate is utilized in the production of red blood cells and hematopoiesis [18]. Cobalamin (Vitamin B12) is also called cyanocobalamin. Its molecular weight and chemical formula are 1355.4 g/mol and $C_{63}H_{80}CoN_{14}O_{14}P$, respectively. It is a cobalt-containing coordination compound synthesized by intestinal microbes and requires intrinsic factors for absorption through the intestine. Its deficiency caused megaloblastic anemia and pernicious anemia. In addition, several neurological lesions have been observed due to the lack of this enzyme [19]. Vitamin C or ascorbic acid is one of the important antioxidants taken in the diet. The molecular weight and chemical formula of this enzyme are 176.12 g/mol and $C_6H_8O_6$ or $HC_6H_7O_6$. It is found in lemons, oranges, and other citrus fruits. This enzyme is essential in the diet and cannot be produced by humans. It is involved in the synthesis of collagen. Its deficiency causes several complications such as scurvy. Its overdose is also responsible for jaundice and acute liver injury [20]. WSVs mainly function as cofactors for an associated enzyme and ultimately modulate the biological activity of specific enzymes [21,22].

3. Fat-Soluble Vitamins

As the name implies, fat-soluble vitamins (FSVs) dissolve in fats and oils. FSVs, namely A, D, E, and K, are absorbed in the intestine [8,23]. Vitamin A is also called retinol or all-trans-Retinol. The molecular weight and chemical formula of this vitamin are 286.5 g/mol and $C_{20}H_{30}O$, respectively. This vitamin is required for the normal functioning of the eyes, and it is also involved in the modulation of immune function. Reproductive organ functioning is also mediated by this enzyme. Totals of 300 to 700 µg for children and 700 to 900 µg for adults are recommended in the diet. A higher dose might cause several complications such as cirrhosis and portal hypertension, etc. [24]. Vitamin D3 (cholecalciferol) is the active form of Vitamin D. The chemical formula and molecular weight of vitamin D3 are $C_{27}H_{44}O$ and 384.6 g/mol, respectively. It is produced in the skin by ultraviolet light and also is obtained in the diet and belongs to the steroid hormones category. This vitamin regulates the level of calcium and phosphorus in the body by bone mineralization and demineralization. It also affects gene expression by binding on the receptor of vitamin D [25]. Vitamin E is also considered as alpha-Tocopherol and 5,7,8-Trimethyltolco. The molecular weight and chemical formula of this enzyme are 430.7 g/mol and $C_{29}H_{50}O_2$, respectively. It shows potent cytoprotective and vital antioxidant properties. This vitamin protects our body from harmful oxidative damage. It maintains the permeability of the cell membrane by neutralizing the reactive oxygen species. It is also involved in the regulation of reproductive functions [26]. Vitamin K is also considered as Kinadion, Konakion, Mephyton, Monodion. The chemical formula and molecular weights are $C_{31}H_{46}O_2$ and 450.7 g/mol. This enzyme is required for the normal blood clotting reaction. Multiple forms of this vitamin are known as Vitamin K2 (menaquinone), Vitamin K1 (phytomenadione), and Vitamin K3 (menadione). Butter, egg yolk, green leafy vegetables, cheese, and liver are good sources of this vitamin [27]. Clinically, the deficiency in FSV is described as night blindness (vitamin A), osteomalacia (vitamin D), increased oxidative cell stress (vitamin E), and hemorrhage (vitamin K). In the last few decades, additional potential actions for FSVs have been suggested, such as vitamin A and D deficiencies being indirectly linked to cancer, diabetes mellitus, and several immune disorders [28–32]. The FSVs, vitamin A and vitamin D, mainly act through nuclear receptors to control the expression of different genes [21,33]. Vitamin E is a powerful antioxidant, and vitamin K plays a key role in blood clotting. As research progresses, additional roles and mechanisms of action of FSVs will be further described.

In this review, we will discuss the role of WSVs and FSVs in the progression of neurodegenerative diseases. In general, vitamins play a neuroprotective role; several derivatives
of vitamins have been tested to treat various neurological diseases and have produced significant findings [34–39]. Therefore, in the following sections, we will reveal the role of different vitamins one by one in the context of specific neurodegenerative diseases.

4. Vitamins in Parkinson’s Disease

Parkinson’s disease (PD), characterized by several motor and non-motor symptoms, arises due to the degeneration of dopaminergic neurons in the midbrain region [40–44]. This disease has a high incidence in the aging population [45]. Effective treatments, which can stop the initiation or prevent the progression of PD, are not currently available. Only therapies to alleviate the symptoms are available. However, symptoms become worse following prolonged treatment [46]. Now, research is focused on identifying different compounds that can prevent the progression and initiation of PD [47]. Accordingly, in recent years, a role for several vitamins has been suggested for the treatment of PD [48,49]. These vitamin treatments may offer fewer if any side effects and may improve on currently available therapies for PD.

One of the major causative factors responsible for the progression of PD is oxidative stress, and vitamin A (VitA), along with its derivatives such as retinoic acid (RA), exhibits strong antioxidative activity [30,50]. VitA is obtained from both animal and plant sources [51]. Fish, meat, and dairy products are animal sources of preformed VitA (retinol and retinyl ester) (Figure 1) [51]. On the other hand, plant sources provide the precursors of VitA in the form of carotenoids (β-carotene, α-carotene, and β-cryptoxanthin) [51,52]. VitA is involved in multiple signaling pathways that regulate gene expression [30,53]. Specifically, in the central nervous system (CNS), VitA regulates several vital processes such as controlling neural cell differentiation and patterning in neural tube formation [54,55].

![Figure 1. Animal and plant sources of vitamin A (Retinoic acid). Vitamin A shows potent antioxidant activity. Gene regulation and neural differentiation are affected by vitamin A supplementation.](image)

4.1. Vitamins Based Clinical Studies in Parkinson’s Disease

One study demonstrated high concentrations of VitA and its derivatives in the human post-mortem frontal lobe cortex [56]. This is a biomarker-based clinical study that assessed the therapeutic impact of VitA in the frontal lobe cortex. The frontal lobe cortex showed an age-related decline in retinol and its derivatives compared to the occipital cortex. Further studies will be needed to explore and compare other brain areas for a similar type of activity. Additionally, a Singaporean Chinese cohort-based study also suggested no correlation between dietary antioxidants, such as carotenoids and vitamins (vitamin A, C, and E), and risk of developing PD [57]. A comparative study suggested the relation between risk
of PD and intake of carotenoids, VitE and VitC. This is a follow-up study on both male and female PD patients. A total of 47,331 men and 76,890 women were followed up to 12 and 14 years, respectively. Food frequency questionnaires on these PD patients were also noted in this study. None of these vitamins and even multivitamins were scientifically associated with the risk of PD in these patients. On the other hand, a food-derived high intake of VitE leads to a reduced risk of PD in both male and female patients. The risk of PD also gets reduced after the consumption of nuts. A multivitamin study showed that PD risk is not significantly reduced after intake of vitamins E and C, carotenoids. A multivitamin approach rich in vitamin E showed a better therapeutic effect than carotenoids and vitamin C. Therefore, this study suggested that dietary food rich in VitE reduces the risk for PD compared to carotenoids or VitC. Thus, VitE supplementation is protective for PD [58]. Therefore, a broader level study is needed regarding the therapeutic potential of VitA, VitC, VitE, and its derivatives in PD.

In many neurodegenerative diseases including PD, increased homocysteine levels, a sulphur-containing metabolite of methionine biosynthesis, were found to have multiple neurotoxic effects [59]. As such, in PD patients with enhanced homocysteine levels, there was a strong correlation between homocysteine level and PD pathogenesis [60–62]. Enhanced levels of homocysteine were responsible for the death of nigrostriatal dopaminergic neurons in PD patients. Thus, regulating the level of homocysteine may prevent PD progression [63,64]. Vitamin B (VitB) acts as a cofactor in the synthesis of methionine from homocysteine, and researchers have suggested that the level of homocysteine was strongly correlated with VitB levels [22,65]. Supplementary VitB has been shown to reduce the level of homocysteine in blood plasma [66,67]. Regardless, limited studies regarding the roles of the different types of VitB in PD pathologies were performed. Of interest, Vitamin B12 (VitB12) levels were decreased in PD patients as compared to normal healthy controls. In addition, a reduced risk of PD was found in those who consumed sufficient amounts of dietary Vitamin B6 (VitB6) [68,69]. No significant change was observed regarding folate (VitB9) concentration in PD patients versus normal healthy controls [69,70].

Interestingly, most research on VitB and homocysteine in brain function has mainly focused on three of the eight B-vitamins (VitB9, VitB12, VitB6), and, thus far, the results have been equivocal [22,66]. However, it has been suggested that treatments utilizing a combination of all might yield better results because of the inter-related cellular functions of the eight VitB types [71]. Thiamine deficiency causes death of the dopaminergic neurons in PD. Supplementation of thiamin was responsible for the delay in the progression and death of dopaminergic neurons in PD [72]. An open level study suggested that Parkinsonian symptoms become reversed significantly by the intramuscular administration of a high dose of thiamine to PD patients without any side effects [73].

Of additional interest, PD patients with olfactory dysfunction observed 2–8 years before the display of symptoms demonstrated low dietary thiamine (VitB1) and folate (VitB9) density [74,75]. Thus, at the early stage of PD, thiamine and folate levels effectively regulate the olfactory system and might serve as an important screening tool for detecting PD risk. A case report shows that bradykinesia and rigidity were significantly improved by niacin treatment for those with rashes in the skin and unacceptable nightmares [76]. In conclusion, because of the limited number of studies on the various types of VitB for treatments and/or the diagnosis of PD, more research is needed before advocating their usage in PD therapies.

Humans show a dose-response towards VitC as high levels can be toxic [77,78], but when VitC is maintained at homeostatic concentrations, there is the positive effect of reducing oxidative stress, one of the leading causes of neurodegenerative diseases (Figure 2) [79].
Figure 2. Vitamins prevent the oligomerization of alpha-synuclein into Lewy bodies. Neuroinflammation and oxidative stress are mainly responsible for the death of dopaminergic neurons via the NF-κB pathway. Vitamins ultimately prevent the death of dopaminergic neurons by inhibiting the neuroinflammation and oxidative stress in Parkinson’s disease. Vitamins prevent the nuclear translocation of NF-κB and associated activation of proinflammatory cytokines.

A clinical trial shows that ascorbic acid (200 mg) is very effective for elderly PD patients. In this clinical trial, the authors have suggested that ascorbic acid improves the absorption of levodopa (100 mg levodopa and 10 mg carbidopa) in a significant manner in PD patients. Therefore, the combinatorial therapy of ascorbic acid with levodopa might get a better result than treatment of one alone [80]. However, there is still controversy in the potential use of VitC for the treatment of PD, and further studies are desired [21].

Researchers have also suggested a link between vitamin D (VitD) and PD, and despite all efforts, it is not clear yet if a deficiency in VitD is responsible for PD or a consequence of PD [81]. Cutaneous levels of VitD are directly correlated to sunlight exposure [82,83], and ultraviolet exposure enhances the level of VitD in our body [84,85]. Bone density is directly associated with the concentration of VitD and consequently postural stability [86]; however, the role of VitD in the brain is less understood. Calcitriol (1,25-dihydroxy vitamin D3) is an active metabolite and the most studied form of VitD [87]. Compared to age-matched healthy controls, PD patients have a much lower concentration of calcitriol in their blood plasma, which may be related to bone health and fracture risk [88,89]. Interestingly, the receptor of calcitriol is also expressed in the CNS [90]. Thus, VitD mediates its effects in PD through its active form, calcitriol, and associated receptors present in the CNS [86,91]. One study shows an inverse association and toxic activity of vitamin D in PD [92]. Another study also indicates the toxicity of VitD as responsible for reversible symptoms of Parkinsonism [93].

Regrettably, a recent meta-analysis found few studies focusing on vitamin D supplementation in PD treatments. This study shows an inverse relationship between VitD level and risk and severity of PD in 2866 PD patients [94]. There is a limited response of VitD supplementation (≥400 IU/day) in early PD patients, and this warrants further study to justify its therapeutic potential [95]. Therefore, more cohort studies of early and late PD patients are needed to illuminate the connection between VitD and PD further.

Vitamin E (VitE) is a well-known antioxidant found in vegetables, and it has multiple therapeutic uses [96]. From the mid-1990s, the role of VitE has been demonstrated in several neurological diseases including PD [97]. Similar to other vitamins, VitE exhibits a
strong connection with PD [97]. Results from a recent study demonstrated that the effect of VitE was age- and sex-independent and showed an inverse relation between VitE intake and PD occurrence [97]. Consequently, diets rich in VitE may minimize the risk associated with PD [98,99].

The progression of PD might be controlled by high-dose alpha-tocopherol and ascorbate as shown by a pilot study. Further clinical trials at a broader level will be needed to confirm the protective efficacy of alpha-tocopherol and ascorbate [100]. As shown by a clinical trial, high dose vitamin E (2000 IU vitamin E orally per day) treatment enhanced its concentration in the cerebrospinal fluid (CSF) of an early untreated PD patient. High CSF and a high brain concentration of alpha-tocopherol show a protective effect on the PD patients [101]. One study also shows that there is not any relation between serum VitE and risk of PD [102]. Another study recommended daily multivitamin supplementation that should contain at least 30 IU of alpha-tocopherol instead of 400 IU of alpha-tocopherol in the affected individuals. This combination showed an improved therapeutic response in PD patients [103]. A multivitamin approach by using vitamin E, vitamin C, and carotenoids is not beneficial in reducing PD risk. Instead, dietary vitamin supplementation rich in VitE shows enhanced therapeutic potential to reduce the PD risk. A very high dose might lead to losses in the therapeutic activity of Vitamin E [104]. Therefore, care should be taken, and a broader level of clinical study is needed to prove the therapeutic potential of VitE. A case report on an old PD patient shows the enhanced therapeutic activity of multivitamin-multimineral supplementation with Ginkgo biloba [105]. A large population-based study is necessary to confirm the same.

4.2. Vitamin Based Animal Studies in Parkinson’s Disease

The cellular retinol-binding protein found on the blood-brain barrier (BBB) allows the brain easy access to VitA and its derivatives [106]. In the CNS, the prominent target of RA action is the nigrostriatal dopaminergic system [107,108]. RA-receptor heterodimers bind to the RA-response element within the promoter region and drive the transcription of the dopamine 2 receptor gene. As such, RA receptor knockout mice exhibited reduced expression of the D2 dopamine receptors [60]. Thus, the RA receptor effectively regulates the homeostatic regulation of the nigrostriatal dopaminergic system as supported by multiple pieces of evidence [108–111]. Therefore, further investigation into the incorporation of VitA in prospective PD therapies may prove fruitful. A recent study suggested that there is no effect of oral supplementation of retinol in the 6-hydroxydopamine intoxicated Wistar rat model [112]. RA receptor based therapeutic approaches might be beneficial in preventing the progression of PD and suggest the mechanism of action behind it [113]. Lycopene is an important carotenoid that also exhibits its effectiveness in the MPTP-induced Parkinsonian mouse model. The lycopene treatment reversed physiological anomalies, oxidative stress, neurochemical abnormalities, and apoptosis. Lycopene shows anti-apoptotic and antioxidative properties in this PD mouse model [114]. Lycopene also protects the cognitive decline in the rotenone-induced PD model [115].

Vitamin C (VitC), which humans cannot synthesize due to the absence of the enzyme L-gulonolactone oxidase, has many health benefits including essential antioxidant activities [116]. For example, treatments with VitC mitigated the PD-like phenotype of dopaminergic neuron degeneration and locomotor deficits in a UCH-L1 gene knockdown Drosophila PD model (Figure 2) [117]. Recently, a study explored the dose-dependent effects of VitC using this knockdown fly model. The authors suggested that for PD treatment, VitC dose-response activity should not be ignored as high concentrations of VitC had adverse effects on behavior and locomotion [118]. Ascorbic acid (100 mg/kg) administration just before the 20 min of MPTP intoxication showed a protective effect by its antioxidative activity in the BALB/c PD model (Figure 2) [119].

In an animal model of PD, VitD inhibits neuroinflammation by regulating microglial activity and protects the death of dopaminergic neurons (Figure 2) [120]. In a hemiparkin-
sonian rat model, VitD protects the death of dopaminergic neurons by inhibiting oxidative stress and neuroinflammation [121].

The PD-like symptoms and associated pathology regarding mitochondrial abnormalities and synaptic impairment in a PD knockdown model were significantly improved by VitE supplementation [97]. Chronic intake of VitE (500 mg/kg-diet) lowers the death of dopaminergic neurons in the substantia nigra of the zitter mutant rat model of PD [122]. However, many researchers have shown contrasting findings regarding the dietary intake of VitE for treatment of PD [123]. Tocotrienols (T3s) are well-known members of the VitE family that also offer neuroprotective potential through their antioxidantive activity [124]. Biochemical and behavioral evidence have suggested that the PD progression induced by intrastrital injection 6-OHDA was ameliorated by VitE treatment in the PD rat model [125]. Similarly, behavioral, neurochemical, and biochemical studies proved that VitE benefits the rotenone-induced rat model [126]. Histochemical and biochemical evidence also suggested that the repeated intramuscular administration of vitamin E (24 I.U./kg, i.m) offers the significant neuroprotective property in an early rat PD model induced by unilateral intrastrial 6-hydroxydopamine (12.5 microg/5 microl) [127]. Alpha-tocopherol also exhibited a similar neuroprotective activity in the unilateral 6-OHDA model and might be used as an effective PD drug [128].

Results from a study demonstrated that a combination of a higher dose of Coenzyme Q10 (CoQ10) (600 mg/kg/day) with levodopa (10 mg/kg/day) significantly protected subjects from neurodegeneration in a rotenone-induced rat model of Parkinsonism as compared to a low dose combination of CoQ10 (200 mg/kg/day) with levodopa (10 mg/kg/day). The higher dose of CoQ10 with levodopa improved abnormalities in the electron transport chain and exhibited anti-apoptotic activity. Striatal dopamine levels were considerably restored by this treatment paradigm [129].

4.3. Vitamins in Cell-Based Parkinson’s Disease

A pluripotent stem-cell-based study shows that RA-γ is the most effective among α and β RA receptors in forming striatopallidal-like neurons in PD by affecting the dopamine 2 receptor gene [130]. Niacin (VitB3) shows potent anti-inflammatory activity through its receptor GPR109A by inhibiting the nuclear translocation of NF-κB in a lipopolysaccharide (LPS)-induced RAW264.7 cell model of PD. This nuclear inhibition of NF-κB prevented the upregulation of proinflammatory cytokines and the associated neurodegeneration in this PD model [131]. NADH is the active coenzyme of VitB3. NADH causes enhanced release of dopamine from the striatal slices at a 350 microM concentration in vitro. There is no effect of NADH (10 or 100 mg/kg) in vivo. For the synthesis and regeneration of tetrahydrobiopterin, NADH is needed. In addition, tetrahydrobiopterin is needed to synthesize Tyrosine hydroxylase, a rate-limiting enzyme in the synthesis of dopamine. A study will be required to validate the in vitro findings in an in vivo model [132]. In a cellular model of PD, the survival rate and energy activity were improved significantly by Nicotinamide mononucleotide (NMN). In the human neuroblastoma cell line SK-N-SH, ascorbic acid (200 microM) led to enhanced expression (three-fold) of tyrosine hydroxylase (TH) after 5 days of treatment. Consequently, dopamine synthesis was increased as a result of enhanced expression of TH. Therefore, ascorbic acid might be utilized in early PD as a potential anti-Parkinsonian agent [133]. In the cellular model, ascorbic acid also exhibits its therapeutic potential against levodopa-induced neurotoxicity [134]. MN ameliorated the process of apoptosis in this cellular model [135].

Further, studies have demonstrated that 1,25-dihydroxyvitamin D3 exhibited strong anti-inflammatory and neuroprotective effects, and reduced the neurotoxin-induced microglial activation and expression of proinflammatory cytokines in experimental models of inflammation-mediated neurodegenerative disease (Figure 2) [136,137].

In a cellular PD model, T3s exhibited cytoprotective activity through the estrogen receptor-activated β-PI3K/Akt pathway [124].
In conclusion, numerous cell-, animal-, and human-based studies have found that vitamins have beneficial effects in the prevention and/or treatment of PD due to their antioxidant properties and other biological functions such as regulating gene expression. However, some studies disagree [21]. Specifically, some studies also show that there is no impact regarding the therapeutic potential of vitamins. In addition, the dose is the very crucial factor that decides the efficacy of the action of vitamins in the PD. Therefore, more clinical studies are necessary to clarify the potential use of vitamin supplementation in PD therapeutics.

5. Vitamins in Alzheimer’s Disease

Worldwide, Alzheimer’s disease (AD) is ranked first in occurrence among all neurodegenerative diseases [105]. In the aging population, AD is the most common cause of dementia [138]. Clinical symptoms of AD begin with cognitive impairments, which further progress into dementia [139]. AD neuropathology includes the progressive degeneration of neurons, the formation of amyloid (Aβ) plaques, and neurofibrillary tangles (NFT) of the hyperphosphorylated tau protein [140,141]. As such, post-mortem analysis of AD patient brains reveals a reduction in the size of the cerebral cortex and abnormal deposits inside and around neurons [138]. Similar to other neurodegenerative diseases, one of the leading causes responsible for progressive neurodegeneration in AD is oxidative stress [142]. Accumulating evidence has shown that the antioxidative activity of vitamins may be beneficial in the treatment of AD. As such, vitamins have been used as adjuvants in AD therapy [6,143].

5.1. Vitamins Based Clinical Studies in Alzheimer’s Disease

In AD treatment, nicotinamide can be used as an adjuvant therapy because it is a potent inhibitor of Poly (ADP-ribose) polymerase 1 [144]. Multiple pieces of evidence have suggested that compared to healthy individuals with intact neurocognitive function, AD patients show reduced levels of VitA, VitB, and VitC in blood serum [145]. Meta-analytic studies have found reduced serum levels of VitA, VitB [6,9,21], VitC, VitD, VitE, and VitK in AD patients [146,147]. Moreover, reduced levels of VitA, VitC, and VitE were observed in dementia patients as compared to healthy controls [148,149]. Interestingly, a cross-sectional and prospective study reported that a combination of VitC and VitE supplements reduced the prevalence and incidence of AD; however, they made no report of VitA, and found no association of VitB intake with AD [150].

Cognitive function in US women was significantly improved by long-term treatment with retinoids [151]. Clinical trials on RA and associated derivatives might confirm its therapeutic efficacy and role as a biomarker in AD patients.

Gut microbiota also might affect retinoid signaling in AD. Dynamic gut microbiota may directly link with retinoic acid to mediate therapeutic responses in AD [152]. In the early AD stage, there is no correlation between Retinol binding protein 4 and AD. Therefore, RBP4 is not used as a clinical biomarker in early AD [153]. Failures of RA signaling and associated RA deficiency are linked with age-related cognitive decline in AD. Thus, RA therapeutic activity is directly linked with AD and associated symptoms [154].

Several types of B vitamins (VitB9, VitB12, VitB6, and VitB2) are involved in the metabolism of homocysteine [155]. Elevated levels of total plasma homocysteine lead to cognitive impairments, which may ultimately lead to dementia [66,156,157]. Several studies have demonstrated that VitB supplementation lowers total homocysteine in the treatment for cognitive decline [158–160]. In an unbiased analysis, Douaud et al. showed that AD pathology, characterized by atrophy of cerebral gray matter, was reduced by VitB supplementation, reducing the total homocysteine in serum plasma [156]. In contrast, a meta-analysis on randomized control trials suggests that no improvements in cognitive impairment have been observed in therapies that reduce total homocysteine with VitB supplementation [161–163]. As such, results from a 26-week randomized, double-blind, placebo-controlled study of Taiwanese AD patients given a multivitamin supplement
containing vitamins B6, B12, and B9 in addition to acetylcholinesterase inhibitor treatment demonstrated a decrease in the concentration of serum homocysteine but no beneficial effects on cognition or the daily living activity of the AD patients [164]. Another clinical study showed that a high dose of B vitamins (VitB9, VitB12, VitB6), while effectively lowering homocysteine levels, did not affect cognition in individuals with mild to moderate AD [165]. However, in older MCI patients, vitamin B prevented cognitive decline as demonstrated by a randomized placebo-controlled trial [166]. On the other hand, there is no effect of a 2-year treatment of vitamin B on the elevated level of homocysteine and cognitive performance as shown by secondary data from a RCT [167]. Higher vitamin B12 and folate exhibited potent therapeutic activity and improved cognitive performance in a cross-sectional study on AD [168]. The screening of presymptomatic AD cannot be diagnosed by measuring the serum folic and vitamin B12 levels as shown by a Turkish three-center based study [169]. Thus, the role of vitamin B and folic acid for MCI and AD is very speculative and needs a complete investigation. Therefore, a complete evaluation of the therapeutic efficacy of vitamin B and folate in MCI and AD on a broader population might solve the puzzle mentioned above. Significant cognitive impairment with progressive dementia is associated with thiamine deficiency. These symptoms have been improved by the supplementation of thiamine in affected individuals [170]. In elderly patients, reversible dementia is associated with a deficiency in cobalamin [171].

Vitamin B12 inhibits the tau fibrillization and formation of the neurofibrillary tangle. Thus, VitB12 prevents the tau aggregation and ultimately neurofibrillary tangle formation that might progress the severity of AD (Figure 3) [172]. A Havana, Cuba based study also suggests a relationship between the level of homocysteine and vitamins among older AD patients. In this study, a total of 424 peoples above or equal to the age of 65 were included in which 131 were MCI, 43 AD, and, in 250 individuals, no sign of cognitive impairment was detected. As compared to healthy participants, the level of vitamin A, C, and B2 was reduced significantly among AD patients. In addition, in the same AD patients and MCI patients, the homocysteine level was elevated significantly compared to healthy individuals. The level of vitamin B12, folic acid, and thiamine was unrelated in all groups. The authors concluded that in MCI and AD, various vitamin deficiencies are directly related to impairment in the metabolism of homocysteine [173]. Although this is a very small-scale study, a larger population-based study is needed to find any valid correlation between different B vitamins and hyperhomocysteinemia among AD and MCI patients. In patients with folate deficiency, cognitive impairment was ameliorated by folate supplementation for a short period [174]. Inflammation is one of the major factors that lead to progressive neurodegeneration in AD. A clinical trial suggested that folic acid shows anti-inflammatory solid activity and prevents neurodegeneration in AD. ChiCTR-TRC-13003246 is the registration number of this clinical trial conducted in China [175]. A greater understanding of the relevance of VitB and homocysteine metabolism to cognitive function is wanted.

The risk of AD also increases due to a low serum level of VitD [176,177]. Calcium levels and the parathyroid hormone, along with specific cytokines, regulate the concentration of the active form of VitD, calcitriol. The inactive form of VitD crosses the BBB, and, inside glial and neuronal cells, it is converted into the active form by the enzyme CYP27B1 [178,179]. Microglial cells are also responsible for converting provitamin D into the active form of VitD [180]. Calcitriol controls the synthesis of the nerve growth factor (NGF) and ultimately governs the process of neuronal cell differentiation and maturation. In addition, calcitriol regulates the synthesis of the glial cell-line-derived neurotrophic factor (GDNF) [181,182]. Both the NGF and GDNF regulate learning and memory through the septohippocampal pathway. With advancing age, the level of the NGF decreases [183]. NGF levels are also reduced in AD patients [184]. Amyloid precursor protein (APP) concentration is effectively modulated by the NGF [184]. NGF signaling interruption leads to an up-regulation of APP levels and an increased production of Abeta intracellular aggregates [185]. Of great interest
is that the active form of VitD and its analogs induce NGF expression [177,186], which presents a possible mechanism by which VitD could indirectly improve AD pathology.

Cognitive function is affected by the B12 levels as suggested by an elderly Korean population-based study [187].

VitE plays an important role in improving cognitive function along with memory deficits [188]. VitE can be combined with other antioxidants to promote the efficacy of the treatment strategies effectively [189]. Despite several pieces of evidence regarding the antioxidant activity of VitE, the role of VitE is controversial [190].

In contrast, clinical trials regarding the activity of VitE in AD showed conflicting findings [190]. One such trial, reporting the impact of VitE in conjunction with donepezil supplementation for mild cognitively impaired (MCI) patients (early stage of AD), found no added benefit for VitE supplementation [191]. This double-blinded study treated MCI patients with 2000 IU of VitE daily and 10 mg of donepezil daily or a placebo for three years. There was no effect of VitE for MCI; however, donepezil lowered the rate of progression of MCI towards AD for the first 12 months and longer for apolipoprotein E4 carriers [192]. Slower functional decline was observed as a result of 2000 IU/d of alpha-tocopherol in AD patients compared to controls in a collaborative randomized trial-based study [193]. In conclusion, as it is unclear whether prolonged and synergistic treatments with VitE are beneficial for the management of AD, broader population studies are needed [189].

5.2. Vitamins Based Animal and Cellular Studies in Alzheimer’s Disease

However, in a streptozotocin (STZ)-induced AD mouse model, beta-carotene, a form of VitA, significantly improved measures of cognitive function and oxidative stress and reduced levels of toxic B-amyloid fragments [194]. In vitro and in vivo animal studies show that VitA and beta-carotene inhibit the oligomerization and aggregation of Aβ (Figure 3) [146,195,196]. Furthermore, VitC attenuated the advancement of neurodegeneration and improved behavioral deficits in a mouse model of AD [197]. Thus, a combination of VitA, VitC, and VitE therapy may provide a synergistic effect and act as adjuvants in preventing the progression of neurodegeneration in AD [198]. In an AD mouse model, neu-
ronal dysfunction was significantly attenuated by intranasal administration of 9-cis retinoic acid (9-cis RA). This might be a novel therapeutic option for the preventive treatment of AD. The astrocyte activation, neuroinflammation, and Aβ aggregation were considerably reduced by 9-cis RA in the AD transgenic mouse model compared to controls (Figure 3). As a result, synaptic deficits were restored in the AD model compared to vehicle-treated mice [199]. Retinoids show strong therapeutic efficacy by preventing progressive neurodegeneration by inhibiting the neuroinflammatory processes in AD [200].

Although AD accounts for 60–80% of dementia, there are other types, such as vascular dementia (VD), frontotemporal dementia (FTD), and Wernicke-Korsakoff syndrome, etc. [201,202]. Interestingly, Wernicke-Korsakoff is a type of dementia caused by a lack of VitB1 (Thiamine), and VitB1 supplementation has been used to treat this type of dementia [203]. Similarly, symptoms of frontotemporal lobe degeneration appear in vascular dementia, and VitB1 supplementation significantly improves these symptoms [204]. VitB12 and folate (VitB9) deficiencies have also been seen in VD and AD patients [205]. Severe lack of niacin (VitB3) leads to pellagra, a disease characterized by diarrhea, dermatitis, and dementia, which is treated by niacin supplementation [159,206]. Thus, VitB shows therapeutic activity in AD and other dementias. In another study, pre-treatment with VitC prevented cognitive impairment and improved biochemical measures such as lowering proinflammatory cytokines, modulating anti-apoptotic activity, and contributing to the phosphorylation of p38 mitogen-activated protein kinase (MAPK) activation in the hippocampus of LPS-treated mice [207]. In an AlCl₃ (100 mg/kg) induced rat model of Alzheimer’s disease (AD), ascorbic acid (100 mg/kg daily for 15 days) alleviated the biochemical and behavioral deficits along with neuropathological alteration by its antioxidative activity. Ascorbic acid shows AChE inhibitory and anti-proteolytic activity. Thus, the progression of AD is inhibited by ascorbic acid supplementation [208]. Thus, VitC improved cognition by modulating oxidative stress and neuroinflammatory parameters.

A study indicated that a low dose of VitC (200 and 400 mg/kg BW) confers protection from colchicine-induced, neuroinflammation-mediated neurodegeneration and cognitive impairments by scavenging free radicals. However, on the other hand, a higher dose of VitC (600 mg/kg BW) was responsible for the generation of oxidative stress, neuroinflammation, and cognitive impairment. Therefore, VitC exhibited dual activity with protection at lower doses and damage at higher [209].

VitD3 improved cognitive function by inhibiting neuroinflammatory and oxidative stress responses and improved cholinergic function in the mouse model of STZ-induced AD [210]. VitD improved the age-related cognitive decline in a rat model by modulating the activity of proinflammatory cytokines. VitD also decreased the amyloid burden responsible for cognitive impairment [211]. A recent study demonstrated that maxacalcitol, an analog of the active form of VitD, improved cognitive function and inhibited neuroinflammation induced by LPS in a rat model of AD, through Keap1/Nrf2 and MAPK-38p/ERK signaling pathways [212]. Thus, VitD and its analogs effectively prevent AD pathology in animal models and AD patients [177,183]. The deficiency of VitD promotes AD-like pathology by reducing the antioxidative potential. Enhanced production of amyloid-beta, the elevated phosphorylation status of tau, enhanced inflammatory loads, and reflected VitD deficiency in mice. A reduced concentration of the active form of VitD might improve the AD and dementia risk in a significant way [213]. In the D-Galactose-induced memory impairment mouse model, neuroprotective activity is shown by VitD via SIRT1/Nrf-2/NF-kB signaling pathways [214]. Therefore, the VitD level should be checked and managed by the patients during AD treatment [215].

Extended administration of VitE provided better results as it counteracted effectively with Aβ plaques and NFT. Further, a type of VitE, α-tocopherol, prevented progressive neurodegeneration in animal models of AD [190]. In addition, α-tocopherol showed synergistic effects with antioxidative and anti-inflammatory compounds that are beneficial in treating AD [190,216].
In a retrospective study, a multivitamin exhibits its therapeutic potential to improve cognitive impairment. In this multivitamin retrospective study, higher folate concentration improved cognitive performance, as shown by its MMSE score. Folate deficiency is directly linked with hyperhomocysteinemia and is associated with worse cognitive performance. Further study will be needed to define the optimal vitamin status among affected individuals [191]. Another multivitamin-based study suggests a neuroprotective role of vitamin B6, B12, folate, and choline in hypoxia. This multivitamin treatment significantly alleviated hypoxia-induced memory deficits. Reduced tau hyperphosphorylation and decreased levels of homocysteine are detected by vitamin B6, B12, folate, and choline treatment. Memory functions were improved by this multivitamin approach [217]. Therefore, instead of a single vitamin-based approach, the multivitamin strategy might offer better therapeutic options for AD and MCI. Vitamin K2 prevents the Aβ induced neurotoxicity by the phosphatidylinositol 3-kinase (PI3K) associated signaling pathway [218].

In conclusion, vitamins have been studied for the treatment of AD and other types of dementia, and many of these studies have indicated vitamins’ beneficial role with evidence of VitA inhibiting the formation of Aβ plaques, and VitB, VitC, VitD, and VitE intervening with the progression of neurocognitive decline. As such, the role of many vitamins in adjuvant therapy treatments for AD has been underestimated [146]. Therefore, future clinical studies that employ vitamins in AD therapeutics might illuminate important details of how vitamins help alleviate AD symptoms.

6. Vitamins in Huntington’s Disease

Huntington’s disease (HD) is also an example of a progressive, neurodegenerative disease of the CNS. Similar to PD and AD, motor abnormalities, dementia, and psychiatric problems are the main characteristics of HD [219,220]. HD is caused by a dominantly inherited genetic mutation that elongates a section of the huntingtin gene by the repetition of trinucleotide (CAG) segments (more than 36 repeats), leading to toxic intracellular polyglutamine aggregates and neuronal degradation [221,222] (Figure 4). Alterations in vitamins are involved in the pathogenesis of HD [223]. Oxidative stress is one of the major causative factors responsible for progressive neurodegeneration. Antioxidative therapy targeting the reactive oxygen species shows the potential impact of reducing the stress burden in associated neuronal cells [224]. Similar to AD and PD, vitamins also offer strong antioxidative activity and prevent progressive neurodegeneration in HD [225].

RA is the most studied form of VitA, and its receptors are present in the CNS [226]. RA effectively regulates adult brain physiology through its receptors [227–229]. However, the mechanism of action is not clearly understood. One of the main locations of RA receptors is in the striatum, a brain region critical for planning and the execution of movement, cognition, reward, and motivation [230,231]. One isoform of the RA receptor, known as retinoic acid receptor β (RARβ), is widely studied in PD, AD, and HD [232]. The characterization of RARβ transcriptional targets through genome-wide analysis identified possible mechanisms of action for RARβ activity [230]. RARβ controls the striatal pathways through transcription, energy metabolism, and neurotransmission through G-protein, c-AMP, and calcium signaling [230]. In HD transgenic mouse models, striatal signaling genes induced by retinoids are downregulated [233]. In addition, the RARβ receptor is sequestered inside huntingtin protein aggregates in the R6/2 mouse striatum [230]. These studies indicate that RA signaling is compromised in HD and contributes to HD pathology. Therefore, drugs that target this signaling pathway may offer a potential treatment for HD. Similar to AD and PD, more studies will be needed to reach any definite conclusion regarding the mechanism of action behind RA and its receptor in HD therapy [230].
Figure 4. Etiology of oxidative stress behind Huntington’s disease (HD). In HD, reduced levels of ascorbate, cysteine, and antioxidants are observed. Excitatory amino acid transporter 3 (EAAT3/EAAC1) is the cysteine transporter, which is dysregulated and responsible for the reduced uptake of cysteine. Uptake of the oxidized form of cysteine is also reduced, which is mediated through the xCT and 4F2hc complex transporter. Sodium-dependent vitamin C transporters 2 (SVCT2)-mediated uptake of ascorbate (vitamin C), which is also reduced in HD, is responsible for the compromised antioxidant defense system in neurons. Cellular components are damaged because of metal deposition such as iron (Fe) and copper (Cu) in both cytoplasms and mitochondria, generating free radicals. Additional oxidative stress generates the mutant form of huntingtin aggregates (mHtt) in both the cytoplasm and nucleus. mHtt aggregates affect vital cellular processes such as mitochondrial dysfunction, proteostasis, and autophagy. In the nucleus, mHtt affects transcription factors involved in the cell’s antioxidant defense system. mHtt also affects DNA repair processes, which are responsible for damage and the error-prone repair system. Ascorbate (vitamin C) supplementation in HD improves the antioxidant defense system and prevents disease progression.

The direct association of thiamine (VitB1) with HD is far from clear, but results have demonstrated that a deficiency in thiamine causes oxidative stress and neuroinflammation, which could contribute to the progression of HD [234–236]. Researchers investigated the role of supplemented thiamine in HD pathogenesis by assessing the viability of human B lymphocytes with and without the abnormal huntingtin gene [237]. Results indicated that energy metabolism is a vital step in HD pathogenesis, and thiamine deficiency caused a reduction in the cellular energy metabolism by altering the expression of various genes. In the HD human B lymphocyte model, the genes affected were glyceraldehyde-3-phosphate dehydrogenase (GAPDH), isocitrate dehydrogenase gene (IDH1), and the solute carrier family 19, member 3 (SLC19A3) gene. GAPDH, IDH1, and SLC19A3 are involved in the synthetic process of ATP and other high-energy-containing molecules [237]. Thus, thiamine controls the expression of genes involved in energy metabolism and could provide effective therapy for HD.

Recent results demonstrated that nicotinamide (VitB3) improved motor functioning and prevented the progression of 3-nitropropionic acid (NPA)-induced HD-associated neurodegeneration by balancing the redox state in a rat model. In addition, nicotinamide also improved histopathological parameters by decreasing the expression of lactate dehydrogenase, a marker of tissue degradation [238]. Thus, nicotinamide exhibits potent neuroprotective activity in a chemical-induced rat model of HD.
VitC, the most prescribed vitamin by clinicians, is involved in many body functions, including postural stability and bone health. Postural stability is the most common motor abnormality observed during neurodegenerative diseases, and bone density is significantly related to serum VitC concentration [239–242]. Therefore, VitC activity in HD has been widely explored. HD transgenic mouse models display dysregulation of ascorbate (VitC) within the cortical and striatal pathways [243]. These pathways regulate the activity of ascorbate with the help of the neurotransmitter glutamate in HD pathogenesis. Glutamate transporters on astrocytes are responsible for the removal of extracellular glutamate [244]. Both ascorbate release and glutamate uptake were impaired in a transgenic model of HD [245]. External ascorbate was responsible for increased glutamate uptake and, consequently, the inhibition of HD progression [245]. Overactive glutamate receptors were responsible for dysregulation of the corticostriatal pathway and contributed to HD pathogenesis in the R6/2 mouse HD model [246]. Furthermore, ascorbate deficiency contributed to behavioral deficits in HD by influencing the striatal pathway in the R6/2 mice model, and intake of ascorbate alleviated behavioral abnormalities [245,246]. Further studies are needed to clarify the interactions between ascorbate and glutamate within the different signaling pathways and their influence on motor function.

Calcitriol (VitD) also plays an important role in muscle strength and bone density. As such, VitD deficiency is directly related to motor abnormalities [247,248]. A study of institutionalized HD patients found a high prevalence of VitD deficiency or insufficiency, and a positive association between calcifediol 25 (OH)D levels, an indicator of Vit D status, and ambulatory abilities was observed [221]. In a transgenic mouse HD model, supplementation of calcitriol significantly improved clinical symptoms and augmented the life span [249]. Thus, serum calcitriol is positively related to the treatment of HD.

In a localized and limited clinical trial, α-tocopherol, a major constituent of VitE, slowed the progression of motor abnormalities associated with HD [250]. Kasparová et al. studied the synergistic effects of CoQ10 and VitE in the NPA-induced rat model of HD. NPA-induced rat models exhibit reduced energy homeostasis. They found that creatine kinase (CK), an energy biomarker in brain diseases, was increased in their HD model. On the other hand, CoQ10, ATP, and the activity of the electron transport chain were reduced. Interestingly, supplementation of CoQ10 and VitE reversed these abnormalities [251].

In summary, for the treatment of HD, vitamins offer adjuvant therapeutic options. Both VitC and VitD prevent the progression of postural instability for HD patients. CoQ10, VitE, nicotinamide (VitB3), and VitB1 all show significant neuroprotective activity to minimize the load for HD patients. In addition, VitA and several intracellular mediators such as calcium and cyclic adenosine monophosphate are involved in the vitamin-mediated protection of HD. Large-scale clinical studies may be helpful to uncover the detailed mechanisms of action behind the neuroprotective effects of vitamins in HD pathogenesis.

7. Vitamins in Multiple Sclerosis

Multiple sclerosis (MS) is characterized by progressive neuroinflammation and subsequent neurodegeneration [252]. In the CNS, the body’s immune system attacks the myelin sheaths that coat and protect nerve fibers [253,254]. Movement abnormalities, vision problems, fatigue, and pain are common symptoms associated with MS. The etiology of MS is not clearly defined [255]. However, it is thought that both environmental and genetic factors are equally responsible for MS [256]. While there is no cure for MS, the usefulness of vitamins in MS therapeutics has been explored due to their antioxidant activities.

VitD has protective activity in MS that usually depends on the patient’s developmental stage. As such, VitD supplementation was more efficacious at ameliorating MS-like neuroinflammation in a juvenile/adolescent rat model of MS compared to adult aged animals [257]. Observational studies and clinical trials have shown that a reduced level of VitD in the blood is a risk factor for developing MS [258–260]. Supplementation with
VitD shows potent anti-inflammatory activity by increasing the oxidation of white matter. However, overdosing with VitD can lead to hypercalcaemia, a toxic build-up of calcium in the blood [259,261–264]. In MS patients, supplementation with VitD enhanced blood perfusion, which supports tissue oxygenation and, therefore, reduced neuroinflammation and neurodegeneration [265]. Several studies suggested that the level of apolipoprotein E and two isoforms of VitD binding protein (DBP) in the cerebrospinal fluid could be utilized as potential biomarkers for the diagnosis of MS [266,267]. In contrast, another study found no association between DBP, MS, and VitD in blood samples from MS patients [268]. Therefore, larger controlled clinical trials are needed to evaluate the efficacy of VitD supplementation in MS therapies.

There is significant evidence from in vitro and in vivo studies of the beneficial effects of VitA/retinoic acid in treating MS [269,270]. VitA exhibited anti-inflammatory and antioxidative activity in the brain, and VitA serum levels were reduced in MS patients [269,271–273]. VitA improved the function of astrocytes, led to remyelination, and suppressed immune function in MS patients [218,269,274–277]. In contrast, results from one study demonstrated no correlation between serum VitA concentration and the progression of MS [278].

To date, few studies have investigated the potential therapeutic effects of the antioxidative ability of VitC or VitE in treating MS [279]. However, several studies have shown that as compared to a healthy individual, MS patients exhibit reduced levels of VitC [280–282]. Direct intrahippocampal injections of VitC in a rat model of MS improved memory dysfunction on passive avoidance learning [283]. Studies investigating VitE showed the improved function of oligodendrocytes and inhibition of factors related to the necrosis process in MS [284]. Due to the limited amount of information currently available for VitC and VitE in MS [285].

The role of VitB in MS is very controversial. Some studies have found that VitB levels are reduced in MS patients, while others show no relation between VitB levels and MS [286]. However, VitB may still be useful in MS therapies. Vitamins B9 and B12 regulate the immune function in MS by effectively improving the uptake of homocysteine, which is responsible for the synthesis of myelin sheaths [287–291]. In addition, the roles of VitB1, VitB3, and VitB6 in MS have been explored. VitB3 showed a remyelination ability and may be effective in the treatment of MS [292]. High-dose thiamine (VitB1) therapy improved the fatigue commonly associated with MS [293]. More clinical trials are needed to validate the role of VitB in MS therapies.

Because many observational studies have related VitD levels to MS risk, and because of the anti-inflammatory activities of VitD, there has been much focus on the utilization of VitD for the prevention and/or intervention of MS (for a comprehensive review, see Sintzel 2018) [260]. In addition, other vitamins such as VitA and VitE, due to their anti-inflammatory and antioxidative effects, may be helpful for adjuvants in MS treatments [269,270,294,295]. The role of VitB in MS is still controversial. Future clinical trials are necessary to determine the role of each vitamin in the potential treatment of MS.

8. Vitamins in Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal form of motor neuron disease (MND) characterized by progressive degeneration of motor neurons in the brain and spinal cord. The loss of motor neurons leads to the deterioration of whole-body muscle mass [296–298]. Similar to MS, very few studies have been performed regarding the role of vitamins in ALS. However, as in MS, there is a strong correlation between ALS and VitD supplementation. The active form of VitD is reduced in ALS patients and animal models of ALS [81,299]. VitD was shown to be protective in motor neurons in vitro, and plasma levels of VitD were directly correlated to the severity of the disease in ALS patients [300]. Genetic studies have shown that VitD is linked to ALS pathology through the regulation of various immune components such as toll-like receptors, major histocompatibility complex (MHC) class II molecules, poly (ADP-ribose) polymerase 1 (PARP1), and heme oxygenase-1 (HO-1) [81]. In addition, VitD influences ALS pathology through cell-signaling mechanisms, including
Wnt/β-catenin, mitogen-activated protein kinase (MAPK), glutamate, prostaglandins, reactive oxygen species (ROS), matrix metalloproteinases, and nitric oxidase synthase [81]. In transgenic mouse models of ALS, VitD supplementation reduced symptoms of muscle weakness and improved motor functional capacity but did not prevent the final disease outcome [201–303]. In contrast, a recent study of ALS patients found no reduction in VitD levels, and no benefit for VitD supplementation for improving the prognosis of this disease [304]. Therefore, future studies are needed to determine the role of VitD in ALS pathophysiology.

The impact of VitE supplementation has been monitored in a clinical study. Results suggested that individuals who did not take the regular dose of VitE exhibited early death as compared to those who regularly took VitE supplementation. This study also concluded that VitE significantly improved motor functioning in ALS patients [305]. In a study focusing on transcriptional profiles, VitE prevented the death of NSC-34 motor neurons in ALS through the downregulation of the c-Jun N-terminal kinase (JNK) and p38 MAPK pathway (cell death), and upregulation of the extracellular signal-regulated kinase (ERK) pathways (cell survival) [306].

In summary, ALS is responsible for progressive muscular degeneration. VitD and VitE may have beneficial activities in ALS by protecting motor neurons and improving motor symptoms. However, more studies are needed to understand the roles of these vitamins fully and to uncover the potential use of other vitamins in the treatment of ALS.

9. Vitamins in Prion Disease

Prion disease (PRD), also known as transmissible spongiform encephalopathies, is a rare progressive neurodegenerative disorder caused by abnormal prion protein accumulation, which leads to subsequent brain damage [307]. Structural differences occur between two forms of a prion protein [308]. PrPC is the normal prion protein, while the misfolded PrPSc (scrapie) is the pathogenic form [309]. The difference between the two versions of the prion protein is in the secondary structure [310,311]. Secondary structure α-helix motifs within the normal protein are converted to β-sheet secondary structures, which leads to protein misfolding and toxicity. The molecular mechanisms for this conversion are unclear [312]. Vitamins prevent the transformation of the normal form of the prion protein towards the pathogenic form [313]. Various micronutrients, including copper (Cu) and iron (Fe), are also involved in the vitamin-mediated maintenance of the normal form of the prion protein [314]. In addition, it is thought that oxidative stress and inflammation lead to the formation of the pathogenic form of the prion protein. Therefore, compounds or vitamins with antioxidative and anti-inflammatory characteristics should be beneficial in decreasing the risk of PRD [313].

Cobalamin (Cbl, Vitamin B12) deficiency plays a major role in the disturbance of the connection between the CNS and the peripheral nervous system (PNS) [315,316]. Cbl deficiency mainly affects glial cells, myelin sheaths, and the interstitium of the nervous system [317,318]. In the rat CNS, Cbl deficiency causes a reduction in the epidermal growth factor (EGF) and an enhancement of the activity of tumor necrosis factor-α (TNF-α), which leads to myelin damage and glial activation in both the CNS and PNS [319]. Interestingly, Cbl inhibits the nuclear localization of the NF-κB pathway, which is responsible for the upregulation of cytokines such as TNF-α and affects the conversion of the normal form of PrPC to the diseased form [320]. Another vitamin relevant to PRD is VitD2, which effectively crossed the BBB and suppressed PrPc oligomerization, a required step before PrPSc formation [321].

Metal homeostasis plays an important role in the maintenance of CNS [322]. Metals participate as cofactors in the vitamin-mediated therapeutic processes. Thus, the efficiency of vitamins is reduced in the absence of ample amounts of metal ions. Metals also participate in various enzyme-mediated activities in the CNS. Abnormalities in metal homeostasis might be responsible for the formation of ROS, which could contribute to the progression of neurodegenerative disease. PRD is also regulated by metal ion concentrations [323].
Harmful metals from animal proteins might induce the risk of PRD. The Mediterranean diet may have a protective role in preventing PRD [324]. The foundation of the Mediterranean diet is vegetables, fruits, herbs, various nuts, beans, and whole grains, which are rich in polyphenols that can cross the BBB and act on multiple targets to inhibit the formation of the toxic form of prion proteins [313]. Polyphenols are responsible for regulating harmful metal ions and inhibit the aggregated form of the prion protein [323]. Thus, the Mediterranean diet controls the activity of harmful metals and proves its efficacy in preventing PRD progression [323].

10. Vitamins in Age-Related Macular Degeneration

Not only influential in PD, AD, and HD, vitamins also exert their therapeutic response against age-related macular degeneration (AMD). Oral supplementation and modifications in diet show significant protection against AMD [325]. The Age-Related Eye Disease Study 2 (AREDS2) research group suggested that lutein/zeaxanthin plays a very vital role in the protection against AMD [326]. In AMD, the cone cell abnormalities caused by oxidative stress were significantly improved by VitD supplementation [327]. A clinical study on the Korean population exhibits that the degeneration of AMD progresses due to a lower level of VitD [328]. In the pathogenesis of AMD, the VitD metabolism plays a very novel role as suggested by a system-biology-based analysis. Therefore, we can say that vitamins are also very effective against AMD. More study will be needed to confirm the applicability and suitability of vitamins in AMD.

11. Conclusions and Future Prospective

Oxidative stress and neuroinflammation are the two major factors involved in the progression of neurodegenerative diseases. As such, compounds having antioxidative and anti-inflammatory properties should provide significant neuroprotection. In recent years, accumulating evidence has suggested a beneficial role for vitamins in protecting CNS diseases, as both WSV and FSV can protect neurons from death [329,330]. PD, AD, HD, MS, ALS, and PRD are the major neurodegenerative diseases found in humans. Animal models for these diseases have been utilized to prove the therapeutic efficacy of vitamins. However, the utilization of vitamins in therapies has been delayed due to studies which suggest no correlation between vitamin levels and neurodegenerative diseases. Despite this, several clinical trials support a potential role for vitamins in future therapies of neurodegenerative diseases. Hormesis is an important factor and should be taken into consideration while designing the dose of vitamins. Hormesis differentiates between the beneficial and toxic activity of vitamins at a particular dose. Multivitamin supplementation shows therapeutic solid potential for neurodegenerative diseases as compared to a single vitamin-based option. Multiple signaling pathways are involved in the multivitamin approach that can boost the antioxidative response manifold.

Here, we discussed both beneficial and controversial studies involving the role of vitamins in neurodegenerative diseases. Future studies involving different drug-dose paradigms, diverse animal models, and various geographical locations are necessary to determine precisely the potential roles for vitamins in therapies to treat neurodegenerative diseases. Moreover, human clinical trials are desirable to prove the efficacy and the protective role of vitamins in neurodegenerative diseases.

Author Contributions: S.N.R. and P.S. wrote the manuscript. Editing of the manuscript was conducted by H.W.M.S., E.V., G.A. and M.P.S. All authors have read and agreed to the published version of the manuscript.

Funding: Not applicable.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: All of the authors have approved the contents of this paper and have agreed to submission policies.
Data Availability Statement: Each of the authors confirms that this manuscript has not been previously published and is not currently under consideration by any other journal. Additionally, all of the authors have approved the contents of this paper and have agreed to submission policies.

Acknowledgments: The authors also acknowledge the University grant Commission D.S. Kothari Postdoctoral Fellowship to Sachindra Nand Rai (Reference #: F4-2/2006 (BSR)/BL/19-20/0032) and The Deanship of Scientific Research (DSR) at King Abdulaziz University, Jeddah, Saudi Arabia has funded this project under grant no. (FP-81-42). The authors also would like to acknowledge Bio-render (https://app.biorender.com/biorender-templates (accessed on 20 April 2020)) for providing an efficient platform to create all the figures.

Conflicts of Interest: The authors declare no conflict of interest.

References
1. Darnton-Hill, I. Public health aspects in the prevention and control of vitamin deficiencies. Curr. Dev. Nutr. 2019, 3, nzz075. [CrossRef]
2. Shenkin, A. Micronutrients in health and disease. Postgrad. Med. J. 2006, 82, 559–567. [CrossRef] [PubMed]
3. Woteki, C.E.; Thomas, P.R. In eat for life: The food and nutrition board’s guide to reducing your risk of chronic disease. Clin. Nutr. Insight 1993, 19, 7. [CrossRef]
4. Heaney, R.P. The nutrient problem. Nutr. Rev. 2012, 70, 165–169. [CrossRef]
5. Shao, A.; Drewnowski, A.; Willcox, D.C.; Kramer, L.; Lausted, C.; Eggersdorfer, M.; Mathers, J.; Bell, J.D.; Randolph, R.K.; Witkamp, R.; et al. Optimal nutrition and the ever-changing dietary landscape: A conference report. Eur. J. Nutr. 2017, 56, 1–21. [CrossRef] [PubMed]
6. Kurutas, E.B. The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: Current state. Nutr. J. 2015, 15, 71. [CrossRef]
7. Sies, H.; Stahl, W.; Sundquist, A.R. Antioxidant functions of vitamins. Vitamins E and C, beta-carotene, and other carotenoids. Ann. N. Y. Acad. Sci. 1992, 669, 7–20. [CrossRef]
8. Albahrani, A.A.; Greaves, R.F. Fat-soluble vitamins: Clinical indications and current challenges for chromatographic measurement. Clin. Biochem. Rev. 2016, 37, 27. [PubMed]
9. Bruno, E.J.; Ziegenfuss, T.N. Water-soluble vitamins: Research update. Curr. Sports Med. Rep. 2005, 4, 207–213. [CrossRef] [PubMed]
10. Said, H.M.; Mohammed, Z.M. Intestinal absorption of water-soluble vitamins: An update. Curr. Opin. Gastroenterol. 2006, 22, 140–146. [CrossRef]
11. Lykstad, J.; Sharma, S. Biochemistry, Water Soluble Vitamins; StatPearls: Treasure Island, FL, USA, 2021.
12. National Center for Biotechnology Information. PubChem Compound Summary for CID 1130, Thiamine. Available online: https://pubchem.ncbi.nlm.nih.gov/compound/Thiamine (accessed on 17 September 2021).
13. National Center for Biotechnology Information. PubChem Compound Summary for CID 493570, Riboflavin. Available online: https://pubchem.ncbi.nlm.nih.gov/compound/Riboflavin (accessed on 17 September 2021).
14. National Center for Biotechnology Information. PubChem Compound Summary for CID 938, Nicotinic Acid. Available online: https://pubchem.ncbi.nlm.nih.gov/compound/Nicotinic-acid (accessed on 17 September 2021).
15. National Center for Biotechnology Information. PubChem Compound Summary for CID 6613, Pantothenic Acid. Available online: https://pubchem.ncbi.nlm.nih.gov/compound/Pantothenic-acid (accessed on 17 September 2021).
16. National Center for Biotechnology Information. PubChem Compound Summary for CID 1054, Pyridoxine. Available online: https://pubchem.ncbi.nlm.nih.gov/compound/Pyridoxine (accessed on 17 September 2021).
17. National Center for Biotechnology Information. PubChem Compound Summary for CID 171548, Biotin. Available online: https://pubchem.ncbi.nlm.nih.gov/compound/Biotin (accessed on 17 September 2021).
18. National Center for Biotechnology Information. PubChem Compound Summary for CID 135398658, Folic Acid. Available online: https://pubchem.ncbi.nlm.nih.gov/compound/Folic-acid (accessed on 17 September 2021).
19. National Center for Biotechnology Information. PubChem Compound Summary for CID 5311498, Cyanocobalamin. Available online: https://pubchem.ncbi.nlm.nih.gov/compound/Cyanocobalamin (accessed on 17 September 2021).
20. National Center for Biotechnology Information. PubChem Compound Summary for CID 54670067, Ascorbic Acid. Available online: https://pubchem.ncbi.nlm.nih.gov/compound/Ascorbic-acid (accessed on 17 September 2021).
21. Zhao, X.; Zhang, M.; Li, C.; Jiang, X.; Su, Y.; Zhang, Y. Benefits of vitamins in the treatment of Parkinson’s disease. Oxid. Med. Cell. Long. 2019, 2019, 1–14. [CrossRef] [PubMed]
22. Kennedy, D.O. B vitamins and the brain: Mechanisms, dose and efficacy—A review. Nutrients 2016, 8, 68. [CrossRef] [PubMed]
23. Goncalves, A.; Roi, S.; Nowicki, M.; Dhaussy, A.; Huertas, A.; Amiot, M.J.; Reboul, E. Fat-soluble vitamin intestinal absorption: Absorption sites in the intestine and interactions for absorption. Food Chem. 2015, 172, 155–160. [CrossRef]
24. National Center for Biotechnology Information. PubChem Compound Summary for CID 445354, Retinol. Available online: https://pubchem.ncbi.nlm.nih.gov/compound/Retinol (accessed on 17 September 2021).
55. Tafti, M.; Ghyselinck, N.B. Functional implication of the vitamin A signaling pathway in the brain. Arch. Neurol. 2007, 64, 1706–1711. [CrossRef]

56. Craft, N.E.; Haimela, T.B.; Garnett, K.M.; Fitch, K.A.; Dorey, C.K. Carotenoid, tocopherol, and retinol concentrations in elderly human brain. J. Nutr. Health Aging 2004, 8, 156–162.

57. Ying, A.F.; Khan, S.; Wu, Y.; Jin, A.; Wong, A.S.Y.; Tan, E.K.; Yuan, J.M.; Koh, W.P.; Tan, L.C.S. Dietary Antioxidants and Risk of Parkinson’s Disease in the Singapore Chinese Health Study. Mov. Disord. 2020, 35, 1763–1773. [CrossRef] [PubMed]

58. Zhang, S.M.; Hernán, M.A.; Chen, H.; Spiegelman, D.; Willett, W.C.; Ascherio, A. Intakes of vitamins E and C, carotenoids, vitamin supplements, and PD risk. Neurology 2002, 59, 1161–1169. [CrossRef]

59. Moretti, R.; Caruso, P. The controversial role of homocysteine in neurology: From labs to clinical practice. Int. J. Mol. Sci. 2019, 20, 231. [CrossRef]

60. Müller, T. Role of homocysteine in the treatment of Parkinson’s disease. Exp. Rev. Neurotherap. 2008, 8, 957–967. [CrossRef] [PubMed]

61. Rodríguez-Oroz, M.C.; Lage, P.M.; Sanchez-Mut, J.; Lamet, I.; Pagonabarraga, J.; Toledo, J.B.; García-Garcia, D.; Clavero, P.; Samaranch, L.; Iruzun, C. Homocysteine and cognitive impairment in Parkinson’s disease: A biochemical, neuroimaging, and genetic study. Mov. Disord. 2009, 24, 1437–1444. [CrossRef]

62. Saadat, F.; Ahmadi Ahangar, A.; Samaei, S.E.; Firozjaie, A.; Abbaspour, F.; Khafri, S.; Khodami, A. Serum homocysteine level in Parkinson’s disease and its association with duration, cardinal manifestation, and severity of disease. Park. Dis. 2018, 2018, 1–6. [CrossRef]

63. Martignoni, E.; Tassorelli, C.; Nappi, G.; Zangaglia, R.; Pacchetti, C.; Blandini, F. Homocysteine and Parkinson’s disease: A dangerous liaison? J. Neurol. Sci. 2007, 257, 31–37. [CrossRef] [PubMed]

64. Rozycka, A.; P Jagodziński, P.; Kozubski, W.; Lianeri, M.; Dorszewska, J. Homocysteine level and mechanisms of injury in Parkinson’s disease as related to MTHFR, MTR, and MTHFD1 genes polymorphisms and Ldopa treatment. Curr. Gen. 2013, 14, 534–542. [CrossRef]

65. Markišić, M.; Pavlović, A.M.; Pavlović, D.M. The impact of homocysteine, vitamin b12, and vitamin d levels on functional outcome after first-ever ischaemic stroke. BioMed Res. Int. 2017, 2017, 5489057. [CrossRef]

66. Kumar, A.; Palfrey, H.A.; Pathak, R.; Kadowitz, P.J.; Gettys, T.W.; Murthy, S.N. The metabolism and significance of homocysteine in nutrition and health. Nutr. Metab. 2017, 14, 78. [CrossRef]

67. Maruyama, K.; Eshak, E.S.; Kinuta, M.; Nagao, M.; Cui, R.; Imano, H.; Ohira, T.; Iso, H. Association between vitamin B group supplementation with changes in % flow-mediated dilatation and plasma homocysteine levels: A randomized controlled trial. J. Clin. Biochem. Nutr. 2019, 64, 243–249. [CrossRef]

68. De Lau, L.M.; Koudstaal, P.J.; Witemann, J.C.; Hofman, A.; Breteler, M.M. Dietary folate, vitamin B12 and vitamin B6 and the risk of Parkinson disease. Neurology 2006, 66, 315–318. [CrossRef] [PubMed]

69. Shen, L. Associations between B Vitamins and Parkinson’s Disease. Nutrients 2015, 7, 7197–7208. [CrossRef]

70. Dietiker, C.; Kim, S.; Zhang, Y.; Christine, C.W.; Investigators, N.N.-P. Characterization of Vitamin B12 Supplementation and correlation with clinical outcomes in a large longitudinal study of early Parkinson’s disease. J. Mov. Dis. 2019, 12, 91. [CrossRef]

71. Kennedy, D.O. Review: Power foods for the brain. Cerebrum 2015, 2015, 5. [PubMed]

72. Luong, K.V.; Nguyén, L.T. The beneficial role of thiamine in Parkinson disease. CNS Neurosci. Ther. 2013, 19, 461–468. [CrossRef]

73. Costantini, A.; Fancellu, R. An open-label pilot study with high-dose thiamine in Parkinson’s disease. Mov. Disord. 2013, 28, 461–468. [CrossRef]

74. Håglin, L.; Johansson, I.; Forsgren, L.; Bäckman, L. Intake of vitamin B before onset of Parkinson’s disease and atypical parkinsonism and olfactory function at the time of diagnosis. Eur. J. Clin. Nutr. 2017, 71, 97–102. [CrossRef]

75. Drouin, G.; Godin, J.R.; Page, B. The genetics of vitamin C loss in vertebrates. Curr. Genom. 2011, 12, 371–378. [CrossRef] [PubMed]

76. Alisky, J.M. Niacin improved rigidity and bradykinesia in a Parkinson’s disease patient but also caused unacceptable nightmares and skin rash—A case report. Nutr. Neurosci. 2005, 8, 327–329. [CrossRef] [PubMed]

77. McAllister, C.J.; Scowden, E.B.; Dewberry, F.L.; Richman, A. Renal failure secondary to massive infusion of vitamin C. JAMA 1984, 252, 1684. [CrossRef]

78. Wong, K.; Thomson, C.; Bailey, R.R.; McDiarmid, S.; Gardner, J. Acute oxalate nephropathy after a massive intravenous dose of vitamin C. Aust. N. Z. J. Med. 1994, 24, 410–411. [CrossRef]

79. Grosso, G.; Bei, R.; Mistretta, A.; Marventano, S.; Calabrese, G.; Masuelli, L.; Giganti, M.G.; Modesti, A.; Galvano, F.; Gazzolo, D. Effects of vitamin C on health. A review of evidence. Front. Biosci. 2013, 18, 1017–1029. [CrossRef]

80. Nagayama, H.; Hamamoto, M.; Ueda, M.; Nito, C.; Yamaguchi, H.; Katayama, Y. The effect of ascorbic acid on the pharmacokinetics of levodopa in elderly patients with Parkinson disease. Clin. Neuropharmacol. 2004, 27, 270–273. [CrossRef]

81. Luong, K.V.Q.; Nguyén, L.T.H. Roles of vitamin D in amyotrophic lateral sclerosis: Possible genetic and cellular signaling mechanisms. Mol. Brain 2013, 6, 16. [CrossRef] [PubMed]

82. Wacker, M.; Holick, M.F. Sunlight and vitamin D: A global perspective for health. Dermato-Endocrinology 2013, 5, 51–108. [CrossRef] [PubMed]

83. Ng, S.Y.; Bettyany-Saltikov, J.; Cheung, I.Y.K.; Chan, K.K.Y. The Role of vitamin D in the pathogenesis of adolescent idiopathic scoliosis. Asian Spine J. 2018, 12, 1127–1145. [CrossRef]
84. Engelsen, O. The relationship between ultraviolet radiation exposure and vitamin D status. *Nutrients* **2010**, *2*, 482–495. [CrossRef] [PubMed]

85. Shrestha, S.; Lutsey, P.L.; Alonso, A.; Huang, X.; Mosley, T.H., Jr.; Chen, H. Serum 25-hydroxyvitamin D concentrations in mid-adulthood and Parkinson’s disease risk. *Mov. Disord. 2016*, *31*, 972–978. [CrossRef]

86. Sleeman, I.; Aspray, T.; Lawson, R.; Coleman, S.; Duncan, G.; Khoo, T.K.; Schoenmakers, L.; Rochester, L.; Burn, D.; Yarnall, A. The role of vitamin D in disease progression in early Parkinson’s disease. *J. Park. Dis. 2017*, *7*, 669–675. [CrossRef]

87. Brandi, M. Indications on the use of vitamin D and vitamin D metabolites in clinical phenotypes. *Clin. Cases Miner. Bone Metab. 2010*, *7*, 243. [PubMed]

88. Sunyez, J.A. The use of calcium and vitamin D in the management of osteoporosis. *Therap. Clin. Risk Manag.* **2008**, *4*, 827. [CrossRef]

89. Ozturk, E.A.; Gundogdu, I.; Tonuk, B.; Koecher, B.G.; Tombak, Y.; Comoglu, S.; Cakici, A. Bone mass and vitamin D levels in Parkinson’s disease: Is there any difference between genders? *J. Phys. Ther. Sci. 2016*, *28*, 2204–2209. [CrossRef] [PubMed]

90. Rimmelzwaan, L.M.; van Schoor, N.M.; Lips, P.; Berendse, H.W.; Eekhoff, E.M. Systematic review of the relationship between vitamin D and Parkinson’s disease. *J. Park. Dis. 2016*, *6*, 29–37. [CrossRef] [PubMed]

91. Anjum, I.; Jaffery, S.S.; Fayyaz, M.; Samoo, Z.; Anjum, S. The role of vitamin D in brain health: A mini literature review. *Cureus 2018*, *10*, e2960. [CrossRef]

92. Fullard, M.E.; Duda, J.E. A Review of the Relationship between Vitamin D and Parkinson Disease Symptoms. *Front. Neurol. 2020*, *11*, 454. [CrossRef] [PubMed]

93. Chatterjee, R.; Chatterjee, K.; Sen, C. Reversible Parkinsonism Due to Vitamin D Toxicity. *J. Neurosci. Rural Pract. 2017*, *8*, 305–306. [CrossRef]

94. Luo, X.; Ou, R.; Dutta, R.; Tian, Y.; Xiong, H.; Shang, H. Association between serum vitamin D levels and Parkinson’s disease: A systematic review and meta-analysis. *Front. Neurol. 2018*, *9*, 909. [CrossRef]

95. Luthra, N.S.; Kim, S.; Zhang, Y.; Christine, C.W.; NINDS NET-PD Investigators. Characterization of vitamin D supplementation and clinical outcomes in a large cohort of early Parkinson’s disease. *J. Clin. Mov. Disord. 2018*, *5*, 7. [CrossRef]

96. Rizvi, S.; Raza, S.T.; Faizal Ahmed, A.A.; Abbas, S.; Mahdi, F. The role of vitamin E in human health and some diseases. *Sultan Qaboos Univ. Med. J. 2014*, *14*, e157.

97. Schirinzi, T.; Martella, G.; Imbriani, P.; Di Lazzaro, G.; Franco, D.; Colona, V.L.; Alwardat, M.; Salimei, P.S.; Mercuri, N.B.; Pierantozzi, M. Dietary vitamin E as a protective factor for Parkinson’s disease: Clinical and experimental evidence. *Front. Neurol. 2019*, *10*, 148. [CrossRef] [PubMed]

98. Etminan, M.; Gill, S.S.; Samii, A. Intake of vitamin E, vitamin C, and carotenoids and the risk of Parkinson’s disease: A meta-analysis. *Lancet Neurol. 2005*, *4*, 362–365. [CrossRef] [PubMed]

99. Ricciarelli, R.; Argellati, F.; Pronzato, M.A.; Domenicotti, C. Vitamin E and neurodegenerative diseases. *Mol. Aspects Med. 2007*, *28*, 591–606. [CrossRef] [PubMed]

100. Fahn, S. A pilot trial of high-dose alpha-tocopherol and aspirate in early Parkinson’s disease. *Ann. Neurol. 1992*, *32*, 28–32. [CrossRef] [PubMed]

101. Vatassery, G.T.; Fahn, S.; Kuskowski, M.A. Alpha tocopherol in CSF of subjects taking high-dose vitamin E in the DATATOP study. Parkinson Study Group. *Neurology 1998*, *50*, 1900–1902. [CrossRef] [PubMed]

102. Molina, J.A.; de Bustos, F.; Jiménez-Jiménez, F.J.; Benito-León, J.; Ortí-Pareja, M.; Gasalla, T.; Tallón-Barranco, A.; Navarro, J.A.; Arenas, J.; Enriquez-de-Salamanca, R. Cerebrospinal fluid levels of alpha-tocopherol (vitamin E) in Parkinson’s disease. *J. Neural Transm. 1997*, *104*, 1287–1293. [CrossRef]

103. Pham, D.Q.; Pakogiannis, R. Vitamin E supplementation in Alzheimer’s disease, Parkinson’s disease, tardive dyskinesia, and cataract: Part 2. *Ann. Pharmacother. 2005*, *39*, 2065–2072. [CrossRef] [PubMed]

104. Conrad, G.D. Is Ginkgo biloba and/or a Multivitamin-mineral supplement a therapeutic option for Parkinson’s disease? A case report. *Global Adv. Health Med. 2014*, *3*, 43–44. [CrossRef]

105. Dong, R.; Wang, H.; Ye, J.; Wang, M.; Bi, Y. Publication trends for Alzheimer’s disease worldwide and in China: A 30-year bibliometric analysis. *Front. Human Neurosci. 2019*, *13*, 259. [CrossRef]

106. MacDonald, P.N.; Bok, D.; Ong, D.E. Localization of cellular retinol-binding protein and retinol-binding protein in cells comprising the blood-brain barrier of rat and human. *Proc. Natl. Acad. Sci. USA 1990*, *87*, 4265–4269. [CrossRef]

107. Maden, M. Retinoic acid in the development, regeneration and maintenance of the nervous system. *Nat. Rev. Neurosci. 2007*, *8*, 755–765. [CrossRef] [PubMed]

108. Levesque, D.; Rouillard, C. Nurt77 and retinoid X receptors: Crucial factors in dopamine-related neuroadaptation. *Trends Neurosci. 2007*, *30*, 22–30. [CrossRef]

109. Samad, T.A.; Krezel, W.; Chambon, P.; Borrelli, E. Regulation of dopaminergic pathways by retinoids: Activation of the D2 receptor promoter by members of the retinoic acid receptor–retinoid X receptor family. *Proc. Nat. Acad. Sci. USA 1997*, *94*, 14349–14354. [CrossRef] [PubMed]

110. Esteves, M.; Cristóvão, A.C.; Saraiva, T.; Rocha, S.M.; Baltazar, G.; Ferreira, L.; Bernardino, L. Retinoic acid-loaded polymeric nanoparticles induce neuroprotection in a mouse model for Parkinson’s disease. *Front. Aging Neurosci. 2015*, *7*, 20. [CrossRef]

111. Yin, L.-H.; Shen, H.; Diaz-Ruiz, O.; Báckman, C.M.; Bae, E.; Yu, S.-J.; Wang, Y. Early post-treatment with 9-cis retinoic acid reduces neurodegeneration of dopaminergic neurons in a rat model of Parkinson’s disease. *BMC Neurosci. 2012*, *13*, 120. [CrossRef]
112. Kunzler, A.; Ribeiro, C.T.; Gasparotto, J.; Petiz, L.L.; da Rosa Silva, H.T.; da Silva, J.D., Jr.; Bortolin, R.; de Souza, P.O.; Barreto, F.; Espitia-Perez, P.; et al. The effects of retinol oral supplementation in 6-hydroxydopamine dopaminergic denervation model in Wistar rats. *Neurochem. Int.* 2019, 125, 25–34. [CrossRef]

113. Clark, J.N.; Whiting, A.; McCaffery, P. Retinoic acid receptor-targeted drugs in neurodegenerative disease. *Expert Opin. Drug Metab. Toxicol.* 2020, 16, 1097–1108. [CrossRef]

114. Prema, A.; Janakiraman, U.; Manivasagam, T.; Thenmozhi, A.J. Neuroprotective effect of lycopene against MPTP induced experimental Parkinson’s disease in mice. *Neurosci. Lett.* 2015, 599, 12–19. [CrossRef] [PubMed]

115. Kaur, H.; Chauhan, S.; Sandhir, R. Protective effect of lycopene on oxidative stress and cognitive decline in rotenone induced model of Parkinson’s disease. *Neurochem. Res.* 2011, 36, 1435–1443. [CrossRef]

116. Naidu, K.A. Vitamin C in human health and disease is still a mystery? An Overview. *Nutr. J.* 2003, 2, 7. [CrossRef]

117. Tran, H.H.; Dang, S.N.A.; Nguyen, T.T.; Huynh, A.M.; Dao, L.M.; Kamei, K.; Yamaguchi, M.; Dang, T.T.P. Drosophila Ubiquitin C-Terminal Hydrolase Knockdown Model of Parkinson’s Disease. *Sci. Rep.* 2018, 8, 4468. [CrossRef] [PubMed]

118. Man Anh, H.; Linh, D.M.; My Dung, V.; Thi Phuong Thao, D. Evaluating dose-and time-dependent effects of vitamin C treatment on a parkinsonian disease fly model. *Parkinson’s Dis.* 2019, 2019. [CrossRef] [PubMed]

119. Sershen, H.; Reith, M.E.; Hashim, A.; Lajtha, A. Protection against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine neurotoxicity by the antioxidant ascorbic acid. *Neuropsychopharmacology* 1985, 24, 1257–1259. [CrossRef]

120. Calvello, R.; Gianiucelli, A.; Nicolardi, G.; De Nuccio, F.; Giannotti, L.; Salvatore, R.; Porro, C.; Trota, T.; Panaro, M.A.; Lofrumento, D.D. Vitamin D Treatment Attenuates Neuroinflammation and Dopaminergic Neurodegeneration in an Animal Model of Parkinson’s Disease, Shifting M1 to M2 Microglia Responses. *J. Neuroimmune Pharmacol.* 2017, 12, 327–339. [CrossRef] [PubMed]

121. Lima, L.A.R.; Lopes, M.J.P.; Costa, R.O.; Lima, F.A.V.; Neves, K.R.T.; Calou, I.B.E.; Andrade, G.M.; Viana, G.S.B. Vitamin D protects dopaminergic neurons against neuroinflammation and oxidative stress in hemiparkinsonian rats. *J. Neuroinflamm.* 2018, 15, 249. [CrossRef]

122. Ueda, S.; Sakakibara, S.; Nakadate, K.; Noda, T.; Shinoda, M.; Joyce, J.N. Degeneration of dopaminergic neurons in the substantia nigra of zitter mutant rat and protection by chronic intake of Vitamin E. *Neurosci. Lett.* 2005, 380, 252–256. [CrossRef]

123. Olanow, C.W. Dietary vitamin E and Parkinson’s disease: Something to chew on. *Lancet Neurol.* 2003, 2, 74. [CrossRef]

124. Nakaso, K.; Tajima, N.; Horikoshi, Y.; Nakasone, M.; Hanaki, T.; Kamizaki, K.; Matsura, T. The estrogen receptor beta-PI3K/Akt pathway mediates the cytoprotective effects of tocotrienol in a cellular Parkinson’s disease model. *Biochim. Biophys. Acta* 2014, 1842, 1303–1312. [CrossRef]

125. Cadet, J.L.; Katz, M.; Jackson-Lewis, V.; Fahn, S. Vitamin E attenuates the toxic effects of intrastriatal injection of 6-hydroxydopamine (6-OHDA) in rats: Behavioral and biochemical evidence. *Brain Res.* 1989, 476, 10–15. [CrossRef]

126. Sharma, N.; Nehru, B. Beneficial Effect of Vitamin E in Rotenone Induced Model of PD: Behavioural, Neurochemical and Biochemical Study. *Exp. Neurol.* 2013, 22, 214. [CrossRef]

127. Roghani, M.; Behzadi, G. Neuroprotective effect of vitamin E on the early model of Parkinson’s disease in rat: Behavioral and histochemical evidence. *Brain Res.* 2001, 892, 211–217. [CrossRef]

128. Heim, C.; Kolasiewicz, W.; Kurz, T.; Sontag, K.H. Behavioral alterations after unilateral 6-hydroxydopamine lesions of the striatum. Effect of alpha-tocopherol. *Pol. J. Pharmacol.* 2001, 53, 435–448. [PubMed]

129. Abdin, A.A.; Hamouda, H.E. Mechanism of the neuroprotective role of coenzyme Q10 with or without L-dopa in rotenone-induced parkinsonism. *Neuropsychopharmacology* 2008, 55, 1340–1346. [CrossRef]

130. Podlesný-Drabiniok, A.; Sobaska, J.; de Lera, A.R.; Golembiowska, K.; Kamińska, K.; Dollé, P.; Cebrat, M.; Krężel, W. Distinct retinoic acid receptor (RAR) isotypes control differentiation of embryonal carcinoma cells to dopaminergic or striatopallidal medium spiny neurons. *Sci. Rep.* 2017, 7, 1–14. [CrossRef]

131. Giri, B.; Belanger, K.; Seamon, M.; Bradley, E.; Purohit, S.; Chong, R.; Morgan, J.C.; Baban, W.; Wakade, C. Niacin Ameliorates Neuro-Inflammation in Parkinson’s Disease via GPR109A. *Exp. Ther. Med.* 2014, 8, 943–950. [CrossRef] [PubMed]

132. Pearl, S.M.; Antion, M.D.; Stanwood, G.D.; Jamotte, J.D.; Kapatos, G.; Zigmond, M.J. Effects of NADH on dopamine release in rat striatum. *Synapse* 2000, 36, 95–101. [CrossRef]

133. Seitz, G.; Gebhardt, S.; Beck, J.F.; Böhm, W.; Lode, H.N.; Niethammer, D.; Bruchelt, G. Ascorbic acid stimulates DOPA synthesis and tyrosine hydroxylase gene expression in the human neuroblastoma cell line SK-N-SH. *Neurosci. Lett.* 1998, 244, 33–36. [CrossRef]

134. Pardo, B.; Mena, M.A.; Fahn, S.; de Yébenes, J.G. Ascorbic acid protects against levodopa-induced neurotoxicity on a catecholamine-rich human neuroblastoma cell line. *Mov. Disord.* 1993, 8, 278–284. [CrossRef] [PubMed]

135. Lu, L.; Tang, L.; Wei, W.; Hong, Y.; Chen, H.; Ying, W.; Chen, S. Nicotinamide mononucleotide improves energy activity and survival rate in an in vitro model of Parkinson’s disease. *Exp. Ther. Med.* 2014, 8, 943–950. [CrossRef] [PubMed]

136. Wang, Y.J.; Wu, J.N.; Cheng, T.L.; Hoffer, B.J.; Chen, H.H.; Borlongan, C.V.; Wang, Y. Vitamin D(3) attenuates 6-hydroxydopamine-induced neurotoxicity in rat brain. *Br. J. Neurosci.* 2001, 22, 904–910. [CrossRef]

137. Kim, J.S.; Ryu, S.Y.; Yun, I.; Kim, W.J.; Lee, K.S.; Park, J.W.; Kim, Y.I. 1alpha,25-Dihydroxyvitamin D(3) Protects Dopaminergic Neurons in Rodent Models of Parkinson’s Disease through Inhibition of Microglial Activation. *J. Clin. Neurol.* 2006, 2, 252–257. [CrossRef] [PubMed]

138. Serrano-Pozo, A.; Frosch, M.P.; Masliah, E.; Hyman, B.T. Neuropathological alterations in Alzheimer disease. *Cold Spring Harb. Perspect. Med.* 2011, 1, a006189. [CrossRef] [PubMed]
139. DeTure, M.A.; Dickson, D.W. The neuropathological diagnosis of Alzheimer’s disease. Mol. Neurodegen. 2019, 14, 1–18. [CrossRef]

140. Lacosta, A.-M.; Insua, D.; Badi, H.; Pesini, P.; Sarasa, M. Neurofibrillary tangles of βA x- 40 in Alzheimer’s disease brains. J. Alzheimers Dis. 2017, 58, 661–667. [CrossRef] [PubMed]

141. Castellani, R.J.; Lee, H.-G.; Zhu, X.; Nunomura, A.; Perry, G.; Smith, M.A. Neuropathology of Alzheimer disease: Pathognomonic but not pathogenic. Acta Neuropathol. 2006, 111, 503–509. [CrossRef] [PubMed]

142. Tönnies, E.; Trushina, E. Oxidative stress, synaptic dysfunction, and Alzheimer’s disease. J. Alz. Dis. 2017, 57, 1105–1121. [CrossRef] [PubMed]

143. Tan, B.L.; Norhaizan, M.E.; Liew, W.P.; Sulaiman Rahman, H. Antioxidant and oxidative stress: A mutual interplay in age-related diseases. Front. Pharmacol. 2018, 9, 1162. [CrossRef] [PubMed]

144. Salech, F.; Ponce, D.P.; Paula-Lima, A.C.; SanMartín, C.D.; Behrens, M.I. Nicotinamide, a Poly [ADP-Ribose] polymerase 1 (PARP-1) inhibitor, as an adjunctive therapy for the treatment of Alzheimer’s disease. Front. Aging Neurosci. 2020, 12, 255. [CrossRef] [PubMed]

145. De Wilde, M.C.; Vellas, B.; Girault, E.; Yavuz, A.C.; Sijben, J.W. Lower brain and blood nutrient status in Alzheimer’s disease: Results from meta-analyses. Alz. Dement. 2017, 3, 416–431. [CrossRef] [PubMed]

146. Bhatti, A.B.; Usman, M.; Ali, F.; Satti, S.A. Vitamin supplementation as an adjuvant treatment for Alzheimer’s disease. J. Clin. Diag. Res. 2016, 10, OE07–OE11. [CrossRef] [PubMed]

147. Da Silva, S.L.; Vellas, B.; Elemans, S.; Luchsinger, J.; Kamphuis, P.; Yaffe, K.; Sijben, J.; Groenendijk, M.; Stijnen, T. Plasma nutrient status of patients with Alzheimer’s disease: Systematic review and meta-analysis. Alz. Dement. 2014, 10, 485–502. [CrossRef] [PubMed]

148. Foy, C.; Passmore, A.; Vahidassr, M.; Young, J.; Lawson, J. Plasma chain-breaking antioxidants in Alzheimer’s disease, vascular dementia and Parkinson’s disease. QJM 1999, 92, 39–45. [CrossRef]

149. Lloret, A.; Esteve, D.; Monllor, P.; Cervera-Ferri, A.; Lloret, A. The effectiveness of vitamin E treatment in Alzheimer’s disease. Int. J. Mol. Sci. 2019, 20, 879. [CrossRef]

150. Zandi, P.P.; Anthony, J.C.; Khachaturian, A.S.; Stone, S.V.; Gustafson, D.; Tschanz, J.T.; Norton, M.C.; Welsh-Bohmer, K.A.; Breitner, J.C.S.; Cache County Study Group. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: The cache county study. Arch. Neurol. 2004, 61, 82–88. [CrossRef] [PubMed]

151. Yuan, C.; Fondeville, E.; Ascherio, A.; Ökereke, O.I.; Grodstein, F.; Hofman, A.; Willett, W.C. Long-term intake of dietary carotenoids is positively associated with late-life subjective cognitive function in a prospective study in US women. J. Nutr. 2020, 150, 1871–1879. [CrossRef]

152. Endres, K. Retinoic Acid and the Gut Microbiota in Alzheimer’s Disease: Fighting Back-to-Back? Curr. Alzheimer Res. 2019, 16, 405–417. [CrossRef] [PubMed]

153. Ishii, M.; Kamel, H.; Iadecola, C. Retinol Binding Protein 4 Levels Are Not Altered in Preclinical Alzheimer’s Disease and Not Associated with Cognitive Decline or Incident Dementia. J. Alzheimers Dis. 2019, 67, 257–263. [CrossRef] [PubMed]

154. Woloszynowska-Fraser, M.U.; Kouchmeshky, A.; McCaffery, P. Vitamin A and Retinoic Acid in Cognition and Cognitive Disease. Annu. Rev. Nutr. 2020, 40, 247–272. [CrossRef] [PubMed]

155. Refsum, H.; Ueland, P.M. Clinical significance of pharmacological modulation of homocysteine metabolism. Trends Pharmacol. Sci. 1990, 11, 411–416. [CrossRef]

156. Douaud, G.; Refsum, H.; de Jager, C.A.; Jacoby, R.; Nichols, T.E.; Smith, S.M.; Smith, A.D. Preventing Alzheimer’s disease-related gray matter atrophy by B-vitamin treatment. Proc. Natl. Acad. Sci. USA 2013, 110, 9523–9528. [CrossRef] [PubMed]

157. Price, B.R.; Wilcock, D.M.; Weekman, E.M. Hyperhomocysteinemia as a risk factor for vascular contributions to cognitive impairment and dementia. Front. Aging Neurosci. 2018, 10, 350. [CrossRef] [PubMed]

158. Durga, J.; van Bostel, M.P.; Schouten, E.C.; Kok, F.J.; Jolles, J.; Katan, M.B.; Verhoef, P. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: A randomised, double blind, controlled trial. Lancet 2007, 369, 208–216. [CrossRef] [PubMed]

159. Morris, M.C.; Schneider, J.A.; Tangney, C.C. Thoughts on B-vitamins and dementia. J. Alzheimers Dis. 2006, 9, 429–433. [CrossRef] [PubMed]

160. De Jager, C.A.; Oulhaj, A.; Jacoby, R.; Refsum, H.; Smith, A.D. Cognitive and clinical outcomes of homocysteine- lowering B-vitamin treatment in mild cognitive impairment: A randomized controlled trial. Int. J. Geriatr. Psychiatry 2012, 27, 592–600. [CrossRef] [PubMed]

161. Ford, A.H.; Almeida, O.P. Effect of homocysteine lowering treatment on cognitive function: A systematic review and meta-analysis of randomized controlled trials. J. Alzheimers Dis. 2012, 29, 133–149. [CrossRef] [PubMed]

162. Ford, A.H.; Almeida, O.P. Effect of vitamin B supplementation on cognitive function in the elderly: A systematic review and meta-analysis. Drugs Aging 2019, 36, 419–434. [CrossRef]

163. Wald, D.S.; Kasturiratne, A.; Simmonds, M. Effect of folic acid, with or without other B vitamins, on cognitive decline: Meta-analysis of randomized trials. Am. J. Med. 2010, 123, 522–527. [CrossRef] [PubMed]

164. Sun, Y.; Lu, C.J.; Chien, K.L.; Chen, S.T.; Chen, R.C. Efficacy of multivitamin supplementation containing vitamins B6 and B12 and folic acid as adjunctive treatment with a cholinesterase inhibitor in Alzheimer’s disease: A 26-week, randomized, double-blind, placebo-controlled study in Taiwanese patients. Clin. Ther. 2007, 29, 2204–2214. [CrossRef]

165. Aisen, P.S.; Schneider, L.S.; Sano, M.; Diaz-Arrastia, R.; van Dyck, C.H.; Weiner, M.F.; Bottiglieri, T.; Jin, S.; Stokes, K.T.; Thomas, R.G.; et al. High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: A randomized controlled trial. JAMA 2008, 300, 1774–1783. [CrossRef] [PubMed]
166. Kwok, T.; Wu, Y.; Lee, J.; Lee, R.; Yung, C.Y.; Choi, G.; Lee, V.; Harrison, J.; Lam, L.; Mok, V. Randomized placebo-controlled trial of using B vitamins to prevent cognitive decline in older mild cognitive impairment patients. *Clin. Nutr.* **2020**, *39*, 2399–2405. [CrossRef] [PubMed]

167. Van der Zwaluw, N.L.; Dhouxkes-Rutten, R.A.; van Wijngaarden, J.; Brouwer-Brolsma, E.M.; van de Rest, O.; In’t Veld, P.H.; Enneman, A.W.; van Dijk, S.C.; Ham, A.C.; Swart, K.M.; et al. Results of 2-year vitamin B treatment on cognitive performance: Secondary data from an RCT. *Neurology* **2014**, *83*, 2158–2166. [CrossRef]

168. Meng, H.; Li, Y.; Zhang, W.; Zhao, Y.; Niu, X.; Guo, J. The relationship between cognitive impairment and homocysteine in a B12 and folate deficient population: A cross-sectional study. *Medicine* **2019**, *47*, e17970. [CrossRef]

169. Ulusu, N.N.; Yilmaz, G.; Erbayraktar, Z.; Evlice, A.T.; Aras, S.; Yener, G.; Avci, A.A. Turkish 3-center study evaluation of serum folate acid and vitamin B12 levels in Alzheimer disease. *Turk. J. Med. Sci.* **2015**, *45*, 1159–1166. [CrossRef] [PubMed]

170. Lu’o’ng, K.V.Q.; Nguyen, T.H. Role of thiamine in Alzheimer’s disease. *Am. J. Alzheimer’s Dis. Other Dement.* **2011**, *26*, 588–598. [CrossRef] [PubMed]

171. Osimani, A.; Berger, A.; Friedman, J.; Porat-Katz, B.S.; Ababarbal, J.M. Neuropsychology of vitamin B12 deficiency in elderly dementia patients and control subjects. *J. Geriatr. Psychiatry Neurol.* **2005**, *18*, 33–38. [CrossRef]

172. Rafiee, S.; Asadollahi, K.; Riazi, G.; Ahmadian, S.; Saboury, A.A. Vitamin B12 inhibits tau fibrillation via binding to cysteine residues of tau. *ACS Chem. Neurosci.* **2017**, *8*, 2676–2682. [CrossRef]

173. Lanyau-Domínguez, Y.; Macías-Matos, C.; Jesús, J.; Pita-Rodríguez, G.M.; Suárez-Medina, R.; Quintero-Alejo, M.E.; Díaz-Domínguez, M. Levels of vitamins and homocysteine in older adults with Alzheimer disease or mild cognitive impairment in cuba. *MEDICC Rev.* **2020**, *2*, 40–47. [CrossRef]

174. Hama, Y.; Hamano, T.; Shirafuji, N.; Hayashi, K.; Ueno, A.; Enomoto, S.; Nagata, M.; Kimura, H.; Matsunaga, A.; Ikawa, M.; et al. Influences of folate supplementation on homocysteine and cognition in patients with folate deficiency and cognitive impairment. *Nutrients* **2020**, *12*, 3138. [CrossRef]

175. Chen, H.; Liu, S.; Ji, L.; Wu, T.; Ji, Y.; Zhou, Y.; Zheng, M.; Zhang, M.; Xu, W.; Huang, G. Folic acid supplementation mitigates Alzheimer’s disease by reducing inflammation: A randomized controlled trial. *Mediat. Inflamm.* **2016**, *2016*, 5912146. [CrossRef]

176. Littlejohns, T.J.; Henley, W.E.; Lang, I.A.; Annweiler, C.; Beauchet, O.; Chaves, P.H.; Fried, L.; Kestenbaum, B.R.; Kuller, L.H.; Langa, K.M. Vitamin D and the risk of dementia and Alzheimer disease. *Neurology* **2014**, *83*, 920–928. [CrossRef]

177. Banerjee, A.; K Them, V.K.; Ganguly, A.; Roy, D.; Ganguly, U.; Chakrabarti, S. Vitamin D and Alzheimer’s disease: Neurocognition to therapeutics. *Int. J. Alzheimers Dis.* **2015**, *2015*, 192747. [CrossRef] [PubMed]

178. Diesel, B.; Raderschall, J.; Burik, M.; Bernhardt, R.; Seifert, M.; Reichrath, J.; Fischer, U.; Meese, E. Vitamin D3 metabolism in human glioblastoma multiforme: Functionality of CYP27B1 splice variants, metabolism of calcidiol, and effect of calcitriol. *Clin. Cancer Res.* **2005**, *11*, 5370–5380. [CrossRef] [PubMed]

179. Holick, M. Vitamin D and brain health: The need for vitamin D supplementation and sensible sun exposure. *J. Int. Med.* **2015**, *277*, 90–93. [CrossRef] [PubMed]

180. Neveu, I.; Naveilhan, P.; Menaa, C.; Wion, D.; Brachet, P.; Garabedian, M. Synthesis of 1, 25-dihydroxyvitamin D3 by rat brain macrophages in vitro. *J. Neurosci. Res.* **1994**, *38*, 214–220. [CrossRef] [PubMed]

181. Brown, J.; Bianco, J.I.; McGrath, J.J.; Eyles, D.W. 1, 25-dihydroxyvitamin D3 induces nerve growth factor, promotes neurite outgrowth and inhibits mitosis in embryonic rat hippocampal neurons. *Neurosci. Lett.* **2003**, *343*, 139–143. [CrossRef]

182. Orme, R.P.; Bhangal, M.S.; Fricker, R.A. Calcitriol imparts neuroprotection in vitro to midbrain dopaminergic neurons by upregulating GDNF expression. *PLoS ONE* **2013**, *8*, e62040. [CrossRef]

183. Budni, J.; Bellittini-Santos, T.; Mina, F.; Garcez, M.L.; Zugno, A.I. The involvement of BDNF, NGF and GDNF in aging and Alzheimer’s disease. *Aging Dis.* **2015**, *6*, 331. [CrossRef]

184. Allen, S.J.; Watson, J.J.; Dawborn, D. The neurotrophins and their role in Alzheimer’s disease. *Curr. Neuropharmacol.* **2011**, *9*, 559–573. [CrossRef] [PubMed]

185. Calissano, P.; Matrone, C.; Amadoro, G. Nerve growth factor as a paradigm of neurotrophins related to Alzheimer’s disease. *Dev. Neurobiol.* **2010**, *70*, 372–383. [CrossRef] [PubMed]

186. Veenstra, T.D.; Fahnestock, M.; Kumar, R. An AP-1 site in the nerve growth factor promoter is essential for 1, 25-dihydroxyvitamin D3-mediated nerve growth factor expression in osteoblasts. *Biochemistry* **1998**, *37*, 5988–5994. [CrossRef]

187. Söh, Y.; Lee, D.H.; Won, C.W. Association between Vitamin B12 levels and cognitive function in the elderly Korean population. *Medicine* **2020**, *99*, e21371. [CrossRef]

188. La Fata, G.; Weber, P.; Mohajeri, M.H. Effects of vitamin E on cognitive performance during ageing and in Alzheimer’s disease. *Nutrients* **2014**, *6*, 5453–5472. [CrossRef] [PubMed]

189. Browne, D.; McGuinness, B.; Woodside, J.V.; McKay, G.J. Vitamin E and Alzheimer’s disease: What do we know so far? *Clin. Interv. Aging* **2019**, *14*, 1303. [CrossRef] [PubMed]

190. Gugliando, A.; Bramanti, P.; Mazzon, E. Role of vitamin E in the treatment of Alzheimer’s disease: Evidence from animal models. *Int. J. Mol. Sci.* **2017**, *18*, 2504. [CrossRef]

191. Baroni, L.; Bonetto, C.; Rizzo, G.; Bertola, C.; Cabrillo, L.; Bazzera, G. Association between cognitive impairment and vitamin B12, folate, and homocysteine status in elderly adults: A retrospective study. *J. Alzheimers Dis.* **2019**, *70*, 443–453. [CrossRef] [PubMed]
192. Petersen, R.C.; Thomas, R.G.; Grundman, M.; Bennett, D.; Doody, R.; Ferris, S.; Galasko, D.; Jin, S.; Kaye, J.; Levey, A. Vitamin E and donepezil for the treatment of mild cognitive impairment. N. Engl. J. Med. 2005, 352, 2379–2388. [CrossRef]

193. Dysken, M.W.; Sano, M.; Asthana, S.; Vertrees, J.E.; Pallaki, M.; Llorente, M.; Love, S.; Schellenberg, G.D.; McCarten, J.R.; Malphurs, J.; et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: The TEAM-AD VA cooperative randomized trial. JAMA 2014, 311, 33–44. [CrossRef]

194. Hira, S.; Saleem, U.; Anwar, F.; Sohail, M.F.; Raza, Z.; Ahmad, B. β-Carotene: A Natural Compound Improves Cognitive Impairment and Oxidative Stress in a Mouse Model of Streptozotocin-Induced Alzheimer’s Disease. Biomolecules 2019, 9, 441. [CrossRef]

195. Ono, K.; Yamada, M. Vitamin A and Alzheimer’s disease. Ger. Gerontol. Int. 2012, 12, 180–188. [CrossRef] [PubMed]

196. Takasaki, J.; Ono, K.; Yoshikie, Y.; Hirohata, M.; Ikeda, T.; Morinaga, A.; Takashima, A.; Yamada, M. Vitamin A has anti-oligomerization effects on amyloid-beta in vitro. J. Alzheimers Dis. 2011, 27, 271–280. [CrossRef] [PubMed]

197. Murakami, K.; Murata, N.; Ozawa, Y.; Kinoshita, N.; Irie, K.; Shirasawa, T.; Shimizu, T. Vitamin C restores behavioral deficits and amyloid-β oligomerization without affecting plaque formation in a mouse model of Alzheimer’s disease. J. Alzheimers Dis. 2011, 26, 7–18. [CrossRef]

198. Mehta, V.; Desai, N.; Perwez, A.; Nemade, D.; Dawoodi, S.; Zaman, S.B. ACE Alzheimer’s: The role of vitamin A, C and E (ACE) in oxidative stress induced Alzheimer’s disease. J. Med. Res. Innov. 2018, 2, e000086. [CrossRef]

199. Zhao, H.; Li, S.; Li, Z.; Yang, S.; Li, D.; Zheng, J.; Gao, H.; Yun, L.; Gu, Y.; Li, L.; et al. Intranasal delivery of 9-cis retinoic acid reduces beta-amyloid deposition via inhibiting astrocyte-mediated inflammation. Aging 2020, 12, 5469–5478. [CrossRef]

200. Das, B.C.; Dasgupta, S.; Ray, S.K. Potential therapeutic roles of retinoids for prevention of neuroinflammation and neurodegeneration in Alzheimer disease. Neuro Regen. Res. 2019, 14, 1880–1892. [PubMed]

201. Duong, S.; Patel, T.; Chang, F. Dementia: What pharmacists need to know. Can. Pharm. J./Rev. Pharm. Can. 2017, 150, 118–129. [CrossRef] [PubMed]

202. Cunningham, E.L.; McGuinness, B.; Herron, B.; Passmore, A.P. Dementia. Ulster Med. J. 2015, 84, 79–87.

203. Gibson, G.E.; Hirsch, J.A.; Fonzetti, P.; Jordon, B.D.; Cirio, R.T.; Elder, J. Vitamin B1 (thiamine) and dementia. Ann. N. Y. Acad. Sci. 2016, 1367, 21. [CrossRef] [PubMed]

204. Blundo, C.; Marin, D.; Ricci, M. Vitamin B12 deficiency associated with symptoms of frontotemporal dementia. Neurrol. Sci. 2011, 32, 101–105. [CrossRef]

205. Malaguarnera, M.; Ferri, R.; Bella, R.; Alagona, G.; Carnemolla, A.; Pennisi, G. Homocysteine, vitamin B12 and folate in vascular dementia and in Alzheimer’s disease. Clin. Chem. Lab. Med. 2004, 42, 1032–1035. [CrossRef]

206. Hegyi, J.; Schwartz, R.A.; Hegyi, V. Pellagra: Dermatitis, dementia, and diarrhea. Int. J. Dermatol. 2004, 43, 1–5. [CrossRef]

207. Zhang, X.Y.; Xu, Z.P.; Wang, W.; Cao, J.B.; Fu, Q.; Zhao, W.X.; Li, Y.; Huo, X.L.; Zhang, L.M.; Li, Y.F.; et al. Vitamin C alleviates dementia and in Alzheimer disease. J. Mol. Neurosci. 2018, 65, 438–447. [CrossRef]

208. Olajide, O.J.; Yawson, E.O.; Gbadamosi, I.T.; Arogundade, T.T.; Lambe, E.; Obasi, K.; Lawal, I.T.; Ibrahim, A.; Ogunrinola, K.Y. Ascorbic acid ameliorates behavioural deficits and neuropathological alterations in rat model of Alzheimer’s disease. Environ. Toxicol. Pharmacol. 2017, 50, 200–211. [CrossRef] [PubMed]

209. Sil, S.; Ghosh, T.; Gupta, P.; Ghosh, R.; Kabir, S.N.; Roy, A. Dual Role of Vitamin C on the Neuroinflammation Mediated Neurodegeneration and Memory Impairments in Colchicine Induced Rat Model of Alzheimer’s Disease. J. Mol. Neurosci. 2016, 60, 421–435. [CrossRef] [PubMed]

210. Yamini, P.; Ray, R.S.; Chopra, K. Vitamin D3 attenuates cognitive deficits and neuroinflammatory responses in IVC-STZ induced sporadic Alzheimer’s disease. Inflammopharmacology 2018, 26, 39–55. [CrossRef]

211. Briones, T.L.; Darwish, H. Vitamin D mitigates age-related cognitive decline through the modulation of pro-inflammatory state and decrease in amyloid. J. Neuroinflamm. 2012, 9, 244. [CrossRef] [PubMed]

212. El-Din, S.S.; Rashed, L.; Medhat, E.; Aboulhoda, B.E.; Badawy, A.D.; ShamsEldeen, A.M.; Abdelgawad, M. Active form of vitamin D analogue mitigates neurodegenerative changes in Alzheimer’s disease’s rats by targeting Keap1/Nrf2 and MAPK-38p/ERK signaling pathways. Steroids 2020, 156, 108586. [CrossRef] [PubMed]

213. Ertlilav, E.; Barcin, N.E.; Ozdem, S. Comparison of Serum Free and Bioavailable 25-Hydroxyvitamin D Levels in Alzheimer’s Disease and Healthy Control Patients. Lab. Med. 2020, 52, 219–225. [CrossRef] [PubMed]

214. Ali, A.; Shah, S.A.; Zaman, N.; Uddin, M.N.; Khan, W.; Ali, A.; Riaz, M.; Kamil, A. Vitamin D Exerts Neuroprotection via SIRT1/Nrf2- NF-kB Signaling Pathways against D-Galactose-induced Memory Impairment in Adult Mice. Neurochem. Int. 2020, 4, 104893. [CrossRef]

215. Fan, Y.G.; Pang, Z.Q.; Wu, T.Y.; Zhang, Y.H.; Xuan, W.Q.; Wang, Z.; Yu, X.; Li, Y.C.; Guo, C.; Wang, Z.Y. Vitamin D deficiency exacerbates Alzheimer-like pathologies by reducing antioxidant capacity. Free Radic. Biol. Med. 2020, 161, 139–149. [CrossRef]

216. Boccardi, V.; Baroni, M.; Mangialasche, F.; Mecocci, P. Vitamin E family: Role in the pathogenesis and treatment of Alzheimer’s disease. Alzheimers Dement. 2016, 2, 182–191. [CrossRef]

217. Yu, L.; Chen, Y.; Wang, W.; Xiao, Z.; Hong, Y. Multi-vitamin B supplementation reverses hypoxia-induced tau hyperphosphorylation and improves memory function in adult mice. J. Alzheimers Dis. 2016, 54, 297–306. [CrossRef]

218. Huang, J.K.; Jarjour, A.A.; Oumesmar, B.N.; Kerninon, C.; Williams, A.; Krezel, W.; Kagechika, H.; Bauer, J.; Zhao, C.; Baron-Van Evercooren, A. Retinoid X receptor gamma signaling accelerates CNS remyelination. Nat. Neurosci. 2011, 14, 45. [CrossRef]
Antioxid. Redox Sig.

241. Caron, N.S.; Wright, G.E.B.; Hayden, M.R. Huntington Disease; Adam, M.P., Ardinger, H.H., Pagon, R.A., Wallace, S.E., Bean, L.J.H., Stephens, K., Amemiya, A., Eds.; GeneReviews: Seattle, DC, USA, 1993. Available online: http://www.ncbi.nlm.nih.gov/books/nbki305/ (accessed on 17 September 2021).

242. Dayalu, P.; Albin, R.L. Huntington disease: Pathogenesis and treatment. Neur. Clin. 2015, 33, 101–114. [CrossRef]

243. Chel, V.G.; Ooms, M.E.; van der Bent, J.; Veldkamp, F.; Roos, R.A.; Achterberg, W.P.; Lips, P. High prevalence of vitamin D deficiency and insufficiency in patients with manifest Huntington disease: An explorative study. Dermat Endocrinol. 2013, 5, 348–351. [CrossRef]

244. Roos, R. Huntington’s disease: A clinical review. Orphanet J. Rare Dis. 2010, 5, 40. [CrossRef]

245. Petassini, S.; Begley, P.; Xu, J.; Church, S.J.; Kureishi, N.; Reid, S.J.; Waldvogel, H.J.; Faull, R.L.; Snell, R.G.; Unwin, R.D. Cerebral vitamin B5 (D-Pantothenic Acid) deficiency as a potential cause of metabolic perturbation and neurodegeneration in Huntington’s disease. Metabolites 2019, 9, 113. [CrossRef] [PubMed]

246. Utara, B.; Singh, A.V.; Zamboni, P.; Mahajan, R.T. Oxidative stress and neurodegenerative diseases: A review of upstream and downstream antioxidant therapeutic options. Curr. Neuropharmacol. 2009, 7, 65–74. [CrossRef] [PubMed]

247. Johri, A.; Beal, M.F. Antioxidants in Huntington’s disease. Biochim. Biophys. Acta 2012, 1822, 664–674. [CrossRef]

248. Maden, M.; Holder, N. The involvement of retinoic acid in the development of the vertebrate central nervous system. Dev. Suppl. 1991, 113, 87–94.

249. Chakrabarti, M.; McDonald, A.J.; Will Reed, J.; Moss, M.A.; Das, B.C.; Ray, S.K. Molecular signaling mechanisms of natural and synthetic retinoids for inhibition of pathogenesis in Alzheimer’s disease. J. Alzheimers Dis. 2016, 50, 335–352. [CrossRef] [PubMed]

250. Lane, M.A.; Bailey, S.J. Role of retinoid signalling in the adult brain. Prog. Neurobiol. 2005, 75, 275–293. [CrossRef]

251. Lee, H.-P.; Casadesus, G.; Zhu, X.; Lee, H.-G.; Perry, G.; Smith, M.A.; Gustaw-Rothenberg, K.; Lerner, A. All-trans retinoic acid as a novel therapeutic strategy for Alzheimer’s disease. Exp. Rev. Neurotherap. 2009, 9, 1615–1621. [CrossRef]

252. Niewiadomska-Cimicka, A.; Krzyzosiak, A.; Ye, T.; Podleśny-Drabinio, A.; Dembèle, D.; Doleł, P.; Krężel, W. Genome-wide analysis of RARβ transcriptional targets in mouse striatum links retinoic acid signaling with Huntington’s disease and other neurodegenerative disorders. Mol. Neurobiol. 2017, 54, 3859–3878. [CrossRef] [PubMed]

253. Rataj-Baniowska, M.; Niewiadomska-Cimicka, A.; Paschaki, M.; Szyszka-Niagolov, M.; Carramolino, L.; Torres, M.; Doleł, P.; Krężel, W. Retinoic acid receptor β controls development of striatonigral projection neurons through FGF-dependent and Meis1-dependent mechanisms. J. Neurosci. 2015, 35, 14467–14475. [CrossRef]

254. Moutinho, M.; Cardocedo, J.F.; Puntambekar, S.S.; Landreth, G.E. Nuclear Receptors as Therapeutic Targets for Neurodegenerative Diseases: Lost in Translation. Ann. Rev. Pharmacol. Toxicol. 2019, 59, 257–261. [CrossRef]

255. Li, J.Y.; Popovic, N.; Brunpin, P. The use of R6 transgenic mouse models of Huntington’s disease in attempts to develop novel therapeutic strategies. NeuroRx 2005, 2, 447–464. [CrossRef]

256. Liu, D.; Ke, Z.; Luo, J. Thiamine deficiency and neurodegeneration: The interplay among oxidative stress, endoplasmic reticulum stress, and autophagy. Mol. Neurobiol. 2017, 54, 5440–5448. [CrossRef]

257. Lonsdale, D. Thiamin and protein folding. Med. Hypotheses 2019, 129, 109252. [CrossRef] [PubMed]

258. Wang, X.; Xu, M.; Frank, J.A.; Ke, Z.J.; Luo, J. Thiamine deficiency induces endoplasmic reticulum stress and oxidative stress in human neurons derived from induced pluripotent stem cells. Toxicol. Appl. Pharmacol. 2017, 320, 26–31. [CrossRef]

259. Gruber-Bzura, B.M.; Krzysztoń-Russjan, J.; Bubko, I.; Syska, J.; Jaworska, M.; Zmysłowski, A.; Rosłół, P.; Krężel, W. Retinoic acid receptor β controls development of striatonigral projection neurons through FGF-dependent and Meis1-dependent mechanisms. J. Neurosci. 2015, 35, 14467–14475. [CrossRef] [PubMed]

260. Sidhu, A.; Diwan, V.; Kaur, H.; Bhatia, D.; Singh, C.K.; Sharma, S.; Padi, S.S. Nicotinamide reverses behavioral impairments and provides neuroprotection in 3-nitropropionic acid induced animal model of Huntington’s disease: Implication of oxidative stress-poly (ADP- ribose) polymerase pathway. Metab. Brain Dis. 2018, 33, 1911–1921. [CrossRef]

261. Blanchet, M.; Prince, F.; Chouinard, S.; Messier, J. Postural stability limits in manifest and premanifest Huntington’s disease under different sensory conditions. Neuroscience 2014, 279, 102–112. [CrossRef]

262. Montero-Odasso, M.; Puerucci-Faria, F.; Bartha, R.; Black, S.E.; Finger, E.; Freedman, M.; Greenberg, B.; Grimes, D.A.; Hegele, R.A.; Hudson, C.; et al. Motor phenotype in neurodegenerative disorders: Gait and balance platform study design protocol for the ontario neurodegenerative research initiative (ONDRI). J. Alzheimers Dis. 2017, 59, 707–721. [CrossRef]

263. Wilczynski, J.; Pedrycz, A.; Mucha, D.; Ambroz, T.; Mucha, D. Body posture, postural stability, and metabolic age in patients with Parkinson’s disease. BioMed Res. Int. 2017, 2017, 3975417. [CrossRef]

264. Aghajanian, P.; Hall, S.; Wongworawat, M.D.; Mohan, S. The roles and mechanisms of actions of vitamin C in bone: New developments. J. Bone Miner. Res. 2015, 30, 1945–1955. [CrossRef]

265. Rebec, G.V.; Barton, S.J.; Marseilles, A.M.; Collins, K. Ascorbate treatment attenuates the Huntington behavioral phenotype in mice. Neureport 2003, 14, 1263–1265. [CrossRef] [PubMed]

266. Mahmoud, S.; Gharagozloo, M.; Simard, C.; Gris, D. Astrocytes maintain glutamate homeostasis in the CNS by controlling the balance between glutamate uptake and release. Cells 2019, 8, 184. [CrossRef]

267. Rebec, G.V. Dysregulation of corticostratal ascorbate release and glutamate uptake in transgenic models of Huntington’s disease. Antiox. Redox Sig. 2013, 19, 2115–2128. [CrossRef]
246. Dorner, J.L.; Miller, B.R.; Klein, E.L.; Murphy-Nakhnikian, A.; Andrews, R.L.; Barton, S.J.; Rebec, G.V. Corticosteroidal dysfunction underlies diminished striatal ascorbate release in the R6/2 mouse model of Huntington’s disease. Brain Res. 2009, 1280, 111–120. [CrossRef] [PubMed]

247. Sahay, M.; Sahay, R. Rickets–vitamin D deficiency and dependency. Indian J. Endocrino. Metab. 2012, 16, 164. [CrossRef]

248. Rejnmark, L. Effects of vitamin d on muscle function and performance: A review of evidence from randomized controlled trials. Ther. Adv. Chronic. Dis. 2011, 2, 25–37. [CrossRef]

249. Molnar, M.F.; Tokor, R.; Szalardy, L.; Sumegi, E.; Vecsei, L.; Klivenyi, P. High-dose 1,25-dihydroxyvitamin D supplementation elongates the lifespan of Huntington’s disease transgenic mice. Acta Neurobiol. Exp. 2016, 76, 176–181. [CrossRef]

250. Peyser, C.E.; Folstein, M.; Chase, G.A.; Starkstein, S.; Brandt, J.; Cockrell, J.R.; Bylsma, F.; Coyle, J.T.; McHugh, P.R.; Folstein, S.E. Trial of d-l-alpha-tocopherol in Huntington’s disease. Am. J. Psychiatry. 1995, 152, 1771–1775. [CrossRef] [PubMed]

251. Kašparová, S.; Sumbalová, Z.; Bystrický, P.; Kucharská, J.; Liptaj, T.; Mlynárik, V.; Gvozdjaková, A. Effect of coenzyme Q10 and vitamin E on brain energy metabolism in the animal model of Huntington’s disease. Neurochem. Int. 2006, 48, 93–99. [CrossRef] [PubMed]

252. Fitzner, D.; Simons, M. Chronic progressive multiple sclerosis–pathogenesis of neurodegeneration and therapeutic strategies. Curr. Neuropharmacol. 2010, 8, 305–315. [CrossRef] [PubMed]

253. Correale, J.; Marrodan, M.; Ysrraelit, M.C. Mechanisms of neurodegeneration and axonal dysfunction in progressive multiple sclerosis. Biomedicines 2019, 7, 14. [CrossRef]

254. Miljković, D.; Spasojević, I. Multiple sclerosis: Molecular mechanisms and therapeutic opportunities. Antioxid. Redox Signal. 2013, 19, 2286–2334. [CrossRef]

255. Serra, A.; Chisari, C.G.; Matta, M. Eye movement abnormalities in multiple sclerosis: Pathogenesis, modeling, and treatment. Front. Neurol. 2018, 9, 31. [CrossRef]

256. Dobson, R.; Giovannoni, G. Multiple sclerosis—A review. Eur. J. Neurol. 2019, 26, 27–40. [CrossRef]

257. Adzemovic, M.Z.; Zeitelhofer, M.; Hochmeister, S.; Gustafsson, S.S.; Jagodic, M. Efficacy of vitamin D in treating multiple sclerosis-like neuroinflammation depends on developmental stage. Exp. Neurol. 2013, 249, 39–48. [CrossRef]

258. Munger, K.L.; Åivo, J.; Hongell, K.; Soilu-Hänninen, M.; Surcel, H.-M.; Ascherio, A. Vitamin D status during pregnancy and risk of multiple sclerosis in offspring of women in the Finnish maternity cohort. JAMA Neurol. 2016, 73, 515–519. [CrossRef]

259. Smolders, J.; Damaoiseaux, J.; Menheere, P.; Hupperts, R. Vitamin D as an immune modulator in multiple sclerosis, a review. J. Neuroimmun. 2008, 194, 7–17. [CrossRef]

260. Sintzel, M.B.; Rametta, M.; Reder, A.T. Vitamin D and multiple sclerosis: A comprehensive review. Neurol. Ther. 2018, 7, 59–85. [CrossRef]

261. Ascherio, A.; Weisskopf, M.G.; O’Reilly, E.J.; Jacobs, E.J.; McCullough, M.L.; Calle, E.E.; Cudkowicz, M.; Thun, M.J. Vitamin E intake and risk of amyotrophic lateral sclerosis. Ann. Neurol. 2005, 57, 104–110. [CrossRef]

262. Niino, M.; Fukazawa, T.; Kikuchi, S.; Sasaki, H. Therapeutic potential of vitamin D for multiple sclerosis. Curr. Med. Chem. 2008, 15, 499–505. [CrossRef] [PubMed]

263. Ramagopalan, S.V.; Dobson, R.; Meier, U.C.; Giovannoni, G. Multiple sclerosis: Risk factors, prodromes, and potential causal pathways. Lancet Neurol. 2010, 9, 727–739. [CrossRef] [PubMed]

264. Sandberg, L.; Biström, M.; Salzer, J.; Vägborg, M.; Svenningsson, A.; Sundström, P. Vitamin D and axonal injury in multiple sclerosis. Mult. Scler. J. 2016, 22, 1027–1031. [CrossRef] [PubMed]

265. Muller, T.; Lohse, L.; Blodau, A.; Frommholz, K. Vitamin D rise enhances blood perfusion in patients with multiple sclerosis. J. Neural Transm. 2019, 126, 1631–1636. [CrossRef] [PubMed]

266. Perga, S.; Albo, A.G.; Lis, K.; Minari, N.; Falvo, S.; Marneto, F.; Caldano, M.; Reviglione, R.; Berchilla, P.; Capobianco, M.A. Vitamin D binding protein isoforms and apolipoprotein E in cerebrospinal fluid as prognostic biomarkers of multiple sclerosis. PLoS ONE 2015, 10, e0129291. [CrossRef]

267. Disanto, G.; Ramagopalan, S.V.; Para, A.E.; Handunnetthi, L. The emerging role of vitamin D binding protein in multiple sclerosis. J. Neurol. 2011, 258, 353–358. [CrossRef]

268. Smolders, J.; Peelen, E.; Thewissen, M.; Menheere, P.; Damaoiseaux, J.; Hupperts, R. Circulating vitamin D binding protein levels are not associated with relapses or with vitamin D status in multiple sclerosis. Mult. Scler. J. 2014, 20, 433–437. [CrossRef] [PubMed]

269. Fragoso, Y.D.; Stoney, P.N.; McCaffery, P.J. The evidence for a beneficial role of vitamin A in multiple sclerosis. CNS Drugs 2014, 28, 291–299. [CrossRef]

270. Khosravi-Largani, M.; Pourvah-Talatatpeh, P.; Rousta, A.M.; Karimi-Kivi, M.; Noroozi, E.; Mahjoob, A.; Asadi, Y.; Shahmohammadi, A.; Sadeghi, S.; Shakeri, S.; et al. A review on potential roles of vitamins in incidence, progression, and improvement of multiple sclerosis. eNeurologicalsci 2018, 10, 37–44. [CrossRef] [PubMed]

271. Torkildsen, Ø.; Loken-Amrsrud, K.I.; Wergeland, S.; Myhr, K.M.; Holmøy, T. Fat-soluble vitamins as disease modulators in multiple sclerosis. Acta Neurol. Scand. 2013, 127, 16–23. [CrossRef] [PubMed]

272. Warren, T.R. The increased prevalence of multiple sclerosis among people who were born and bred in areas where goitre is endemic. Med. Hypotheses 1984, 14, 111–114. [CrossRef]

273. Miller, E.D.; Dziedzic, A.; Saluk-Bijak, J.; Bijak, M. A review of various antioxidant compounds and their potential utility as complementary therapy in multiple sclerosis. Nutrients 2019, 11, 1528. [CrossRef]
274. Jafarirad, S.; Siassi, F.; Harirchian, M.-H.; Sahraian, M.-A.; Eshraghian, M.-R.; Shokri, F.; Amani, R.; Bitarafan, S.; Mozafari, S.; Saboor-Yaraghi, A. The effect of vitamin A supplementation on stimulated T-cell proliferation with myelin oligodendrocyte glycoprotein in patients with multiple sclerosis. *J. Neurosci. Rural Pract.* 2012, 3, 294–298. [CrossRef] [PubMed]

275. Loken-Amsrud, K.; Myhr, K.-M.; Bakke, S.; Beiske, A.G.; Bjerve, K.S.; Bjørnå, B.T.; Hovdal, H.; Lilleås, F.; Midgard, R.; Pedersen, T. Retinol levels are associated with magnetic resonance imaging outcomes in multiple sclerosis. *Mult. Scler. J.* 2013, 19, 451–457. [CrossRef] [PubMed]

276. Mizee, M.R.; Nijland, P.G.; van der Pol, S.M.; Drexhage, J.A.; van het Hof, B.; Mebius, R.; van der Valk, P.; van Horssen, J.; Reijerkerk, A.; de Vries, H.E. Astrocyte-derived retinoic acid: A novel regulator of blood–brain barrier function in multiple sclerosis. *Acta Neuropathol.* 2014, 128, 691–703. [CrossRef] [PubMed]

277. Salzer, J.; Hallmans, G.; Nystrom, M.; Stenlund, H.; Wadell, G.; Sundstrom, P. Vitamin A and systemic inflammation as protective factors in multiple sclerosis. *Mult. Scler. J.* 2013, 19, 1046–1051. [CrossRef] [PubMed]

278. Runia, T.; Hop, W.; De Rijke, Y.; Hintzen, R. Vitamin A is not associated with exacerbations in multiple sclerosis. *Mult. Scler. Rel. Dis.* 2014, 3, 34–39. [CrossRef] [PubMed]

279. Evans, E.; Piccio, L.; Cross, A.H. Use of vitamins and dietary supplements by patients with multiple sclerosis: A review. *JAMA Neurol.* 2018, 75, 1013–1021. [CrossRef]

280. Besler, H.T.; Comoglu, S.; Okcu, Z. Serum levels of antioxidant vitamins and lipid peroxidation in multiple sclerosis. *Nutr. Neurosci.* 2002, 5, 215–220. [CrossRef]

281. Polachini, C.R.; Spanevolo, R.M.; Zanini, D.; Baldissarelli, J.; Pereira, L.B.; Schetinger, M.R.; da Cruz, I.B.; Assmann, C.E.; Bagatini, M.D.; Morsch, V.M. Evaluation of delta-aminolevulinic dehydratase activity, oxidative stress biomarkers, and vitamin D levels in patients with multiple sclerosis. *Neurotox. Res.* 2016, 29, 230–242. [CrossRef]

282. Tavazzi, B.; Batocchi, A.P.; Amorini, A.M.; Nociti, V.; D’Urso, S.; Longo, S.; Gullotta, S.; Picardi, M.; Lazzarino, G. Serum metabolic profile in multiple sclerosis patients. *Mult. Scler. Int.* 2011, 2011, 167156. [CrossRef]

283. Babri, S.; Mehrvash, F.; Mohaddes, G.; Hatami, H.; Mirzae, F. Effect of intrahippocampal administration of vitamin C and progesterone on learning in a model of multiple sclerosis in rats. *Adv. Pharm. Bull.* 2015, 5, 83. [CrossRef]

284. Hernandez-Pedro, N.Y.; Espinosa-Ramirez, G.; De La Cruz, V.P.; Pineda, B.; Sotelo, J. Initial immunopathogenesis of multiple sclerosis: Innate immune response. *Clin. Dev. Immunol.* 2013, 2013, 413465. [CrossRef] [PubMed]

285. Zhang, S.M.; Hernan, M.A.; Olek, M.J.; Spiegelman, D.; Willett, W.C.; Ascherio, A. Intakes of carotenoids, vitamin C, and vitamin E and MS risk among two large cohorts of women. *Neurology* 2001, 57, 75–80. [CrossRef]

286. Najafi, M.R.; Shagyanajad, V.; Mirpourian, M.; Gholamrezaei, A. Vitamin B12 deficiency and multiple sclerosis; is there any association? *Int. J. Prev. Med.* 2012, 3, 286. [PubMed]

287. Krum, I.; Culmsie, C.; Chan, S.L.; Krum, Y.; Guo, Z.; Penix, L.; Mattson, M.P. Homocysteine elicits a DNA damage response in neurons that promotes apoptosis and hypersensitivity to excitotoxicity. *J. Neurosci.* 2000, 20, 6920–6926. [CrossRef] [PubMed]

288. Moghaddasi, M.; Mamarbadi, M.; Mohebi, N.; Razjouyan, H.; Aghaei, M. Homocysteine, vitamin B12 and folate levels in Iranian patients with multiple sclerosis: A case control study. *Clin. Neurol. Neurosurg.* 2013, 115, 1802–1805. [CrossRef] [PubMed]

289. Reynolds, E.; Bottiglieri, T.; Laundy, M.; Crellin, R.; Kirker, S. Vitamin B12 metabolism in multiple sclerosis. *Arch. Neurol.* 1992, 49, 649–652. [CrossRef] [PubMed]

290. Reynolds, E.; Limnell, J.; Faludy, J. Multiple sclerosis associated with vitamin B12 deficiency. *Arch. Neurol.* 1991, 48, 808–811. [CrossRef]

291. Weinstein, S.J.; Hartman, T.J.; Stoltenberg-Solomon, R.; Pietinen, P.; Barrett, M.J.; Taylor, P.R.; Virtamo, J.; Albanes, D. Null association between prostate cancer and serum folate, vitamin B6, vitamin B12, and homocysteine. *Cancer Epid. Prev. Biomark.* 2003, 12, 1271–1272.

292. Lempiere, S. Vitamin B3 promotes remyelination. *Nat. Rev. Neurosci.* 2020, 16, 184–185. [CrossRef]

293. Costantini, A.; Nappo, A.; Pala, M.Z.; Zappone, A. High dose thiamine improves fatigue in multiple sclerosis. *BMJ Case Rep.* 2013, bcr2013009144. [CrossRef]

294. Bitalafan, S.; Saboor-Yaraghi, A.; Sahraian, M.A.; Nafissi, S.; Togha, M.; Moghadam, N.B.; Roostaei, T.; Siassi, F.; Eshraghian, M.R.; Ghanaati, H.; et al. Impact of vitamin A supplementation on disease progression in patients with multiple sclerosis. *Arch. Iran Med.* 2015, 18, 435–440. [CrossRef]

295. Loken-Amsrud, K.I.; Myhr, K.M.; Bakke, S.J.; Beiske, A.G.; Bjerve, K.S.; Bjornar, B.T.; Hovdal, H.; Lilleås, F.; Midgard, R.; Pedersen, T.; et al. Alpha-tocopherol and MRI outcomes in multiple sclerosis—Association and prediction. *PLoS ONE* 2013, 8, e54417. [CrossRef]

296. Talbot, K. Motor neuron disease: The bare essentials. *Pract. Neurol.* 2009, 9, 303–309. [CrossRef] [PubMed]

297. Martin, S.; Al Khleifat, A.; Al-Chalabi, A. What causes amyotrophic lateral sclerosis? *F1000Research* 2017, 6, 371. [CrossRef]

298. Zarei, S.; Carr, K.; Reiley, L.; Diaz, K.; Guerra, O.; Altamirano, P.F.; Pagani, W.; Lodin, D.; Orozco, G.; Chinea, A. A comprehensive review of amyotrophic lateral sclerosis. *Surg. Neurol. Int.* 2015, 6, 171. [CrossRef]

299. Cortese, R.; D’Errico, E.; Introna, A.; Schirini, G.; Scarafino, A.; Distaso, E.; Nazzaro, P.; Zoccolla, S.; Simone, I. Vitamin D levels in serum of amyotrophic lateral sclerosis patients. (P2. 069). *AAN Enterp.* 2015, 84, 14S.

300. Camu, W.; Tremblier, B.; Plassot, C.; Alphandery, S.; Salsac, C.; Pageot, N.; Juntas-Morales, R.; Scamps, F.; Daures, J.P.; Raoul, C. Vitamin D confers protection to motoneurons and is a prognostic factor of amyotrophic lateral sclerosis. *Neurobiol. Aging* 2014, 35, 1198–1205. [CrossRef]
301. Gianforcaro, A.; Hamadeh, M.J. Dietary vitamin D3 supplementation at 10 × the adequate intake improves functional capacity in the G93A transgenic mouse model of ALS, a pilot study. CNS Neurosci. Ther. 2012, 18, 547–557. [CrossRef] [PubMed]

302. Gianforcaro, A.; Solomon, J.A.; Hamadeh, M.J. Vitamin D(3) at 50 × AI attenuates the decline in paw grip endurance, but not disease outcomes, in the G93A mouse model of ALS, and is toxic in females. PLoS ONE 2013, 8, e30243. [CrossRef]

303. Solomon, J.A.; Gianforcaro, A.; Hamadeh, M.J. Vitamin D3 deficiency differentially affects functional and disease outcomes in the G93A mouse model of amyotrophic lateral sclerosis. PLoS ONE 2011, 6, e29354. [CrossRef]

304. Libonati, L.; Onesti, E.; Gori, M.C.; Ceccanti, M.; Cambieri, C.; Fabbri, A.; Frasca, V.; Inghilleri, M. Vitamin D in amyotrophic lateral sclerosis. Funct. Neurol. 2017, 32, 35. [CrossRef]

305. Ascherio, A.; Munger, K.L.; Simon, K.C. Vitamin D and multiple sclerosis. Lancet Neurol. 2010, 9, 599–612. [CrossRef]

306. Chiricoosta, L.; Gugliandolo, A.; Tardiolo, G.; Bramanti, P.; Mazzon, E. Transcriptomic analysis of MAPK signaling in NSC-34 motor neurons treated with vitamin E. Nutrients 2019, 11, 1081. [CrossRef] [PubMed]

307. Soto, C.; Satani, N. The intricate mechanisms of neurodegeneration in prion diseases. Trends Mol. Med. 2011, 17, 14–24. [CrossRef] [PubMed]

308. Kupfer, L.; Hinrichs, W.; Groschup, M. Prion protein misfolding. Curr. Mol. Med. 2009, 9, 826–835. [CrossRef] [PubMed]

309. Atkinson, C.J.; Zhang, K.; Munn, A.L.; Wiegmans, A.; Wei, M.Q. Prion protein scrapie and the normal cellular prion protein. Prion 2016, 10, 63–82. [CrossRef]

310. Terry, C.; Wadsworth, J.D. Recent Advances in Understanding Mammalian Prion Structure: A Mini Review. Front. Mol. Neurosci. 2019, 12, 169. [CrossRef] [PubMed]

311. Geschwind, M.D. Prion disease. Continuum 2015, 21, 1612–1638. [CrossRef] [PubMed]

312. Benetti, F.; Barnes, X.; Attanasio, F.; Giachin, G.; Rizzarelli, E.; Legname, G. Structural determinants in prion protein folding and stability. J. Mol. Biol. 2014, 426, 3796–3810. [CrossRef]

313. Prasad, K.N.; Bondy, S.C. Oxidative and inflammatory events in prion diseases: Can they be therapeutically targets? Curr. Aging Sci. 2019, 11, 216–225. [CrossRef]

314. Singh, N.; Singh, A.; Das, D.; Mohan, M.L. Redox control of prion and disease pathogenesis. Antioxid. Redox Signal. 2010, 12, 1271–1294. [CrossRef] [PubMed]

315. Briani, C.; Dalla Torre, C.; Citton, V.; Manara, R.; Pompanin, S.; Binotto, G.; Adami, F. Cobalamin deficiency: Clinical picture and radiological findings. Nutrients 2013, 5, 4521–4539. [CrossRef]

316. Calderon-Ospina, C.A.; Nava-Mesa, M.O. B Vitamins in the nervous system: Current knowledge of the biochemical modes of action and synergies of thiamine, pyridoxine, and cobalamin. CNS Neurosci. Ther. 2020, 26, 5–13. [CrossRef]

317. Rzępka, Z.; Respondek, M.; Pawlik, J.; Beberok, A.; Gryko, D.; Wrześniok, D. Cobalamin deficiency: Effect on homeostasis of cultured human astrocytes. Cells 2019, 8, 1505. [CrossRef]

318. Scalabrino, G. The multi-faceted basis of vitamin B12 (cobalamin) neurotrophy in adult central nervous system: Lessons learned from its deficiency. Prog. Neurobiol. 2009, 88, 203–220. [CrossRef] [PubMed]

319. Scalabrino, G.; Nicolini, G.; Buccellato, F.R.; Peracchia, A.; Tardiolo, G.; Bramanti, P. The association between the Mediterranean dietary pattern and cognitive health: A local mediator of the neurotrophic action of vitamin B(12) (cobalamin) in the rat central nervous system. FASEB J. 1999, 13, 2083–2090. [CrossRef]

320. Scalabrino, G.; Viver, D. Cobalamin and normal prions: A new horizon for cobalamin neurotrophy. Biochimie 2013, 95, 1041–1046. [CrossRef] [PubMed]

321. Suenaga, M.; Hiramoto, Y.; Matsunaga, Y. Vitamin D2 interacts with Human PrPc (90–231) and breaks PrPc oligomerization in vitro. Prion 2013, 7, 312–318. [CrossRef] [PubMed]

322. Kozlowski, H.; Janicka-Klos, A.; Brasun, J.; Gaggelli, E.; Valensin, D.; Valensin, G. Copper, iron, and zinc ions homeostasis and their role in neurodegenerative disorders (metal uptake, transport, distribution and regulation). Coord. Chem. Rev. 2009, 253, 2665–2685. [CrossRef]

323. Toni, M.; Massimino, M.L.; De Mario, A.; Angiulli, E.; Spisni, E. Metal dyshomeostasis and their pathological role in prion and prion-like diseases: The basis for a nutritional approach. Front. Neurosci. 2017, 11, 3. [CrossRef]

324. Aridi, Y.S.; Walker, J.L.; Wright, O.R. The association between the Mediterranean dietary pattern and cognitive health: A systematic review. Nutrients 2017, 9, 674. [CrossRef] [PubMed]

325. Broadhead, G.K.; Grigg, J.R.; Chang, A.A.; McCluskey, P. Dietary modification and supplementation for the treatment of age-related macular degeneration. Nutr. Rev. 2015, 73, 448–462. [CrossRef]

326. Chew, E.Y.; Clemons, T.E.; Sangiovanni, J.P.; Danis, R.P.; Ferris, F.L.; 3rd; Elman, M.J.; Antoszyk, A.N.; Ruby, A.J.; Orth, D.; Bressler, S.B.; et al. Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression: AREDS2 report No. 3. JAMA Ophtalmol. 2014, 132, 142–149. [CrossRef]

327. Tohari, A.M.; Zhou, X.; Shu, X. Protection against oxidative stress by vitamin D in cone cells. Cell Biochem. Funct. 2016, 34, 82–94. [CrossRef]

328. Kim, E.C.; Han, K.; Lee, D. Inverse relationship between high blood 25-hydroxyvitamin D and late stage of age-related macular degeneration in a re-pre-sentative Korean population. Investig. Ophtalmol. Vis. Sci. 2014, 55, 4823–4831. [CrossRef] [PubMed]

329. Di Somma, C.; Scarano, E.; Barrea, L.; Zhukouskaya, V.V.; Savastano, S.; Mele, C.; Scacchi, M.; Aimaretti, G.; Colao, A.; Marzullo, P. Vitamin D and neurological diseases: An endocrine view. Int. J. Mol. Sci. 2017, 18, 2482. [CrossRef] [PubMed]

330. Fricker, R.A.; Green, E.L.; Jenkins, S.I.; Griffin, S.M. The influence of nicotinamide on health and disease in the central nervous system. Int. J. Trypt. Res. 2018, 11, 117864619877658. [CrossRef] [PubMed]