Review Article

Benefits of Vitamins in the Treatment of Parkinson’s Disease

Xiuzhen Zhao,1 Ming Zhang,2 Chunxiao Li,3 Xue Jiang,1 Yana Su,1 and Ying Zhang1

1Department of Neurology and Neuroscience Center, First Hospital of Jilin University, Xinmin Street No. 71, Changchun 130000, China
2Department of Pharmacology, College of Basic Medical Sciences, Jilin University, 126 Xin Min Street, Changchun, Jilin 130021, China
3Department of Neurology and Neuroscience Center, The Affiliated Hospital of Qingdao University, Qingdao, Shandong 266000, China

Correspondence should be addressed to Ying Zhang; zhang_ying99@jlu.edu.cn

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Parkinson’s disease (PD) is the second most common neurodegenerative disease in the elderly, which is clinically characterized by bradykinesia, resting tremor, hypermyotonia, postural instability, and dementia [1]. Additionally, patients with PD can also manifest with nonmotor symptoms such as cognitive decline, olfactory dysfunction, constipation, sleep disorders, and autonomic symptoms [2], and these nonmotor symptoms usually occur prior to the onset of motor symptoms [3]. PD severely affects the quality of life of the individual with the disease and also creates a great burden on the caregivers. The typical pathological hallmark of PD is degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and eosinophilic inclusion bodies (Lewy bodies) in the remaining neurons, which is the major contributor to the deficiency of dopamine in the basal ganglia [4, 5]. The exact pathogenetic mechanisms of PD is not yet fully understood. Current theories regard PD as a multifactorial disease, involving various genetic and environmental factors, among which mitochondrial dysfunction and oxidative stress play an important role in the pathogenesis and development of PD [6, 7]. The treatment for PD is challenging, and the existing therapeutic strategies can only relief clinical symptoms but fail to control the progression of PD.

Vitamins are natural bioactive products with antioxidant properties, which are necessities for maintaining the normal functions of human organisms. Essential vitamins cannot be endogenously synthesized in the organism and therefore must be obtained through the diet. Clinically, vitamin deficiency is quite common, especially in infants and elderly. Vitamins are generally divided into fat-soluble variants (vitamins A, D, E, and K) and water-soluble variants (vitamins B and C). The former mainly bind to cellular nuclear receptors and affect the expression of specific genes [8]. The latter

1. Introduction

Parkinson’s disease (PD) is the second most common neurodegenerative disorder following Alzheimer’s disease. Clinically, PD is characterized by resting tremor, hypermyotonia, postural instability, and bradykinesia [1]. Additionally, patients with PD can also manifest with nonmotor symptoms such as cognitive decline, olfactory dysfunction, constipation, sleep disorders, and autonomic symptoms [2], and these nonmotor symptoms usually occur prior to the onset of motor symptoms [3]. PD severely affects the quality of life of the individual with the disease and also creates a great burden on the caregivers. The typical pathological hallmark of PD is degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and eosinophilic inclusion bodies (Lewy bodies) in the remaining neurons, which is the major contributor to the deficiency of dopamine in the basal ganglia [4, 5]. The exact pathogenetic mechanisms of PD is not yet fully understood. Current theories regard PD as a multifactorial disease, involving various genetic and environmental factors, among which mitochondrial dysfunction and oxidative stress play an important role in the pathogenesis and development of PD [6, 7]. The treatment for PD is challenging, and the existing therapeutic strategies can only relieve clinical symptoms but fail to control the progression of PD.

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mainly constitute a cofactor for the enzyme, affecting the enzymatic activity [9].

Numerous clinical studies as well as animal and cell experiments have found a certain relationship between the vitamin family and PD [10]. The antioxidant properties of vitamins and their biological functions of regulating gene expression may be beneficial for the treatment of PD. Current clinical evidence indicates that proper supplementation of various vitamins can reduce the incidence of PD in the general population and improve the clinical symptoms of patients with PD; nevertheless, the safety of regular vitamin supplements still needs to be highlighted. Vitamin supplementation may represent an effective adjuvant treatment for PD. In this review, we summarized the biological correlations between vitamins and PD as well as the underlying pathophysiological mechanisms. Additionally, we elaborated the therapeutic potentials of vitamins for PD.

2. The Pathogenesis of Oxidative Stress in PD

Oxidative stress refers to the imbalance between the oxidation system and antioxidant system, resulting in excessive accumulation of oxidative substances, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) [11]. ROS include superoxide anion radical (O$_2^-$), hydroxyl radical (OH$^-$), and hydrogen peroxide (H$_2$O$_2$); RNS include nitric oxide (NO), nitrogen dioxide (NO$_2$), and peroxynitrite (ONOO$^-$). The antioxidant system mainly consists of two subtypes: (1) enzymatic antioxidant system, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px), and (2) nonenzymatic antioxidant system, including vitamin C, vitamin E, glutathione, melatonin, alpha-lipoic acid, carotenoids, and trace elements copper, zinc, and selenium.

Oxidative stress plays an important physiological role in the organism. For example, phagocytic cells kill pathogenic microorganisms, participate in detoxification and enzymatic reactions, and synthesize some essential biologically active substances. Meanwhile, it can as well cause damage to the body, such as cell membrane destruction, protein denaturation, and nucleic acid changes.

There is increasing evidence that oxidative stress represents a pathophysiological characteristic of PD, and the production of reactive oxygen species can result in neuronal death [12, 13]. The mitochondrial respiratory chain is regarded as the major source of ROS [14]. Additionally, previous studies have found that mitochondrial dysfunction exists in the substantia nigra of patients with PD [15]. Reduced glutathione (GSH) can enhance the production of ROS and RNS [16], and oxidation of dopamine and dopamine metabolites such as 3,4-dihydroxyphenylacetic acid (DOPAC) can inhibit the activity of complex I [17]. These findings indicate that the downstream metabolites of dopamine may make dopamine neurons more susceptible. Moreover, iron accumulation in the substantia nigra is common in patients with PD, leading to overproduction of hydrogen peroxide and molecular oxygen in the Fenton reaction from Fe$^{2+}$ to Fe$^{3+}$; hydrogen peroxide generates a highly toxic hydroxyl radical through the Haber-Weiss reaction in the presence of Fe$^{3+}$, which causes severe oxidative damage to the cellular components [18]. From the above, the oxidant stress is closely associated with the pathogenesis of PD. Oxidative stress can cause neuronal loss through some underlying intracellular damage, such as protein aggregation, mitochondrial dysfunction, and DNA rupture. Therefore, antioxidant damage has become a potential target for the treatment of PD.

3. Vitamin B and PD

The B family of vitamins is water-soluble, which includes thiamine (vitamin B$_1$), riboflavin (vitamin B$_2$), niacin (vitamin B$_3$), pantothenic acid (vitamin B$_5$), pyridoxine (vitamin B$_6$), biotin (vitamin B$_7$), folate (vitamin B$_9$), and cobalamin (vitamin B$_12$) [19]. These vitamins play an important role as enzyme cofactors in multiple biochemical pathways in all tissues, such as regulating metabolism, improving the function of the immune system and nervous system, and promoting cell growth and division [20].

Almost all of these B family vitamins are essential variants dependent on diet supply, except niacin which can also be synthesized from tryptophan. Vitamin B deficiencies are frequent in the children, elderly, vegetarians, pregnant women, and patients with gastrointestinal diseases. Recently, the association with vitamin B and PD is getting more and more attention. Herein, we use vitamin B$_3$ as a representative to discuss the relationship between vitamin B and PD.

3.1. Vitamin B$_3$. Nicotinamide is the active form of niacin, and it is the precursor of coenzymes NADH and NADPH, which are essential for over 200 enzymatic reactions in the organism, especially the production of adenosine triphosphate (ATP). Meat, fish, and wheat are generally rich in nicotinamide, while vegetables have a low nicotinamide content [21]. Deficiency of nicotinamide/niacin can lead topellagra, causing dermatitis, diarrhea, and depression [22]. Nicotinamide has neuroprotective and antioxidant functions at low doses but exhibits neurotoxicity, especially dopaminergic toxicity, at high doses [23]. Fukushima also suggests that excessive nicotinamide is related to the development of PD [24]; excessive nicotinamide can induce overproduction of 1-methylnicotinamide (MNA), which is increased in patients with PD [25]. In an in vitro study, Griffin et al. found that low-dose nicotinamide (10 mM) has a significant effect on inducing differentiation from embryonic stem cells into neurons; however, higher doses (>20 mM) of nicotinamide induce cytotoxicity and cell death [26]. The definitive protective dose of vitamin B$_3$ still needs further researches.

3.2. Possible Neuroprotective Mechanisms of Vitamin B$_3$ in PD. Firstly, numerous studies have demonstrated that mitochondrial dysfunction and cellular energy failure are pathophysiological features of PD. Nicotinamide participates in the biosynthesis of nicotinamide adenine dinucleotide (NAD; oxidized form: NAD$^+$; reduced form: NADH) via various metabolic pathways [27]. NADH is an essential cofactor assisting the tetrahydrobiopterin functioning in tyrosine
hydroxylase, which can hydroxylate tyrosine and produce dopamine; NADH deficiency is common in PD [28].

Secondly, NADH is indispensable for the physiological function of mitochondrial complex I in ATP synthesis, and the corresponding dysfunction is involved in PD patients and animal models [15, 29, 30]. Nicotinamide mononucleotide (NMN) constitutes one of the key precursors of NAD⁺. In previous in vitro studies, the scholars have established a cellular model of PD using rotenone-treated PC12 cells, and they found the NMN (0.1 mM or 1 mM) treatment was associated with a significantly higher survival rate in the rotenone-treated (0.5 μM) PC12 cells. NMN is assumed to enhance the intracellular levels of NAD⁺ and ATP in the cellular model of PD [31].

In addition, nicotinamide can act a neuroprotective role by inhibiting the oxidative stress. In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine- (MPTP-) induced mouse models of PD, nicotinamide (500 mg/kg) was injected before subacute (30 mg/kg/d for 5 days) MPTP administration. This study showed that cotreatment with MPTP and nicotinamide significantly improved the locomotor activity compared to single-agent treatment with MPTP. Nicotinamide administration significantly attenuated the MPTP-induced dopamine depletion (47.11 ± 21.06 vs. 12.77 ± 8.06). Meanwhile, nicotinamide pretreatment markedly inhibited MPTP-induced lactate dehydrogenase (LDH) and NOS activities, which prevented the oxidative stress and alleviated the oxidative damage.

Sirtuins (SIRTs) are NAD⁺-dependent protein deacetylasers involved in vital biological processes [32]. Recently, sirtuin 5 (SIRT5) has received considerable attention. Liu et al. investigated the role of SIRT5 in MPTP-induced mouse PD models [33]. They found that deletion of SIRT5 exacerbated motor deficits, nigrostriatal dopaminergic degeneration in the compact part of substantia nigra (SNc), and mitochondrial antioxidant activities in the PD models. These findings provide new insight into the therapeutic strategies for PD. However, the protective effects of nicotinamide are still controversial, and further researches are needed to clarify the biological function of vitamin B₃ in PD.

3.3. Clinical Studies regarding Vitamin B₃ in PD. Current existing clinical studies have shown that a high-niacin diet can reduce the risk of PD [34, 35]. A previous case report also demonstrated that oral niacin (500 mg twice daily for three months) significantly improved rigidity and bradykinesia in a patient with idiopathic PD, though the original purpose was to treat hypertriglyceridemia; after the cessation of oral dopamine depletion ([glucose transporter type 1] and GLUT3 (glucose transporter type 3) [46].

Dopamine metabolism can produce oxidative stress products, which in return induce accumulation of abnormal proteins in PD [42]. Vitamin C has potentials for the treatment of PD considering the following reasons. Firstly, vitamin C is mainly distributed in areas that are rich in neurons [43, 44]. Secondly, vitamin C can be transported to the brain by SVCT2 (vitamin C transporter type 2) [45], and DHA can be transported to the brain by GLUT1 (glucose transporter type 1) and GLUT3 (glucose transporter type 3) [46].

4.1. Possible Neuroprotective Mechanisms of Vitamin C in PD. There is evidence that ascorbic acid can protect against both levodopa toxicity and the MPTP neurotoxicity [47, 48]. Vitamin C can increase the production of dihydroxyphenylalanine (DOPA). Seitz et al. noted overproduction of DOPA in a dose-dependent manner after incubation of the human neuroblastoma cell line SK-N-SH with ascorbic acid (100-500 mM) for 2 hours. Additionally, the gene expression of tyrosine hydroxylase increased three-fold after incubation with ascorbic acid (200 mM) for 5 days. The scholars speculated that ascorbic acid may be effective in the treatment of early-stage PD [49].

Vitamin C can improve the absorption of levodopa in elderly PD patients with a poor levodopa bioavailability [50]. Previous studies showed that ascorbic acid can reduce the levodopa dosage under the premise of equal efficacy [51]. Combination of anti-PD drugs and vitamin C may be more effective for alleviating the symptoms of PD.

Vitamin C is essential for the brain development. A study showed that ascorbic acid treatment can promote a 10-fold increase of dopaminergic differentiation in CNS precursor cells derived from the E12 rat mesencephalon [52]. Soon after, another in vitro study also reported that AA can stimulate the CNS precursor cells differentiating into CNS neurons and glia [53]. Recently, He et al. proposed that vitamin C can greatly enhance the embryonic midbrain neural stem cells differentiating into midbrain dopaminergic neurons in vitro. Vitamin C induces the gain of 5-hydroxymethylcytosine (5HMC) and loss of H3K27m3 in dopaminergic phenotype gene promoters, which are catalysed by ten-eleven translocation 1 methylcytosine dioxygenase 1 (TET1) and histone H3K27 demethylase (JMJD3), respectively. However, subsequent TET1 and JMJD3 knockdown/inhibition experiments did not show this effect of vitamin C, and the epigenetic role of vitamin C
may be associated with the midbrain dopaminergic neuron development [54, 55].

4.2. Clinical Studies regarding Vitamin C in PD. Although vitamin C has many potential positive effects on PD, the serum level of vitamin C in patients with PD remains controversial [56, 57]. Noteworthily, the vitamin C level in lymphocytes has been found significantly lower in patients with severe PD [58]. Theoretically, vitamin C supplementation may be beneficial for the treatment of PD. A cohort study involving 1036 patients with PD supported this hypothesis, which found that dietary vitamin C intake significantly reduced the risk of PD, but this effect is invalid for a 4-year-lag analysis [59]. Controversially, many studies did not support that vitamin C supplementation can reduce the risk of PD [10, 60, 61]. We speculate this contradiction may be related to the timing of vitamin application.

5. Vitamin E and PD

Vitamin E is a fat-soluble vitamin with high antioxidant properties. Natural vitamin E includes two subgroups: tocopherols and tocotrienols; and they can further be divided into four lipophilic molecules, respectively: α-, β-, γ-, and δ-tocopherol (αT, βT, γT, and δT) and α-, β-, γ-, and δ-tocotrienol (αTE, βTE, γTE, and δTE). The major difference between tocopherols and tocotrienols is the side chain. Tocopherols have a saturated phytyl tail, while tocotrienols possess an unsaturated isoprenoid side chain [62]. Because of this unsaturated side chain, the tocotrienol is superior to the tocopherol as an antioxidant by increasing the molecular mobility through lipid membranes and by accepting electrons readily. Overt vitamin E deficiency is relatively rare, mainly in infants and premature babies.

In addition to its potent antioxidant capacity, vitamin E is involved in many physiological processes such as immune function [63], cognitive function, physical performance [64, 65], and regulation of gene expression. In humans, deficiency of vitamin E is clinically characterized by peripheral neuropathy, ataxia, and anemia [66, 67].

5.1. Possible Neuroprotective Mechanisms of Vitamin E in PD. Unilateral 6-hydroxydopamine (6-OHDA) injections into the striatum can cause circling behaviours and biochemical abnormalities in rats. Cadet et al. found that pretreatment with either D-alpha-tocopherol or all-racemic-alpha-tocopherol significantly attenuated these pathological changes [68]. Roghani and Behzadi [69] and Sharma and Nehru [70] also demonstrated the similar phenomenon in 6-OHDA-induced PD models and in rotenone-induced PD models, respectively. However, some studies have shown that vitamin E did not completely protect dopaminergic neurons from MPTP-mediated damage in PD models [71, 72]. The protective effects of vitamin E may be achieved through preventing oxidative stress in cells and inhibiting apoptosis. Moreover, one study has found that tocotrienol participates not only in antioxidant stress but also in estrogen receptor beta (ERβ) signal transduction [73]. Then, Nakaso’s team demonstrated a protective effect of vitamin E via this signaling pathway. Firstly, they reported that γ-tocotrienol/δ-tocotrienol exerts neuroprotective effects through the ERβ-PI3K/Akt signaling pathways in SH-SY5Y cells by resisting 1-methyl-4-phenylpyridinium ion- (MPP+ -)-induced toxicity [74]. Secondly, they verified this mechanism in a mouse model of PD. Meanwhile, they found δ-tocotrienol administration can reduce the loss of dopaminergic neurons in the substantia nigra and ER inhibitors can attenuate this neuroprotective effect [75]. These findings indicate vitamin E may be potential therapeutic agents for PD.

5.2. Clinical Studies regarding Vitamin E in PD. The DATA-TOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) experiment is a multicentre-controlled clinical trial to investigate the long-term efficacy of treatment with deprenyl and/or tocopherol (vitamin E) and to explore whether it is possible to extend the time before the application of levodopa treatment. At 28 US and Canadian sites, 800 eligible patients with untreated early-stage PD were enrolled in DATATOP and randomized to four groups: (1) deprenyl 10 mg/d, (2) cotherol 2000 IU/d, (3) placebo-controlled, and (4) deprenyl 10 mg/d and coherol 2000 IU/d. Deprenyl can delay the development of functional disorders, delay the application of levodopa, and improve motor symptoms, but vitamin E is disappointing [76]. Similarly, another two population-based studies also did not find the association between vitamin E intake and risk of PD [10, 77].

However, a large community-based study showed that high intake of dietary vitamin E (10 mg/day) may reduce the occurrence of PD [78]. Another pilot trail suggests that long-term treatment with vitamin E may delay the use of levodopa in patients with PD [79]. Further research is needed to verify these results.

Although there seems to be no difference in the level of alpha-tocopherol (vitamin E) in serum, cerebrospinal fluid, and brains between PD and normal controls [80–82], there is evidence showing that high-dose vitamin E (2000 IU/day) can significantly elevate the vitamin E level in cerebrospinal fluid [83]. At present, the protective mechanism of vitamin E in PD is still unclear and may be related to the strong antioxidant effect of vitamin E. Further research is needed to determine whether vitamin E can be used as a potential treatment for PD.

6. Vitamin D and PD

Vitamin D, a steroid hormone, is crucial for calcium homeostasis and skeletal health. This nutrient mainly includes two forms: vitamin D$_3$ and vitamin D$_2$; the latter is endogenously produced when skin is exposed to UV-B rays from the sun. Both of the above forms are inactive, and they are transformed into the active form 1,25-dihydroxy vitamin D$_3$ (1,25-(OH)$_2$-D$_3$) after being hydroxylated twice [84, 85]. 1,25-(OH)$_2$-D$_3$ were secreted into the blood system by the kidney, having a direct effect on gene regulation by binding to the nuclear vitamin D receptor (VDR) [86, 87]. Vitamin D deficiency is prevalent at all ages, especially in elderly. Vitamin D not only regulates the calcium homeostasis...
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<td>Vitamin B&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Abbott et al. [37]</td>
<td>A Honolulu-Asia Aging Study in Japanese-American</td>
<td>Total 8006 and observed 137 PD</td>
<td>Niacin has no obvious relationship with clinical PD</td>
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<td></td>
<td>Johnson et al. [38]</td>
<td>A case-control study in US</td>
<td>126/432</td>
<td>Niacin has no relationship with PD</td>
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<td></td>
<td>Fall et al. [34]</td>
<td>A case-control study in Sweden</td>
<td>113/263</td>
<td>High-niacin diet can reduce the risk of PD</td>
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<td></td>
<td>Hellenbrand et al. [35]</td>
<td>A case-control study in German</td>
<td>342/342</td>
<td>PD patients with lower intake of niacin than controls</td>
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<td>Vitamin C</td>
<td>Yang et al. [61]</td>
<td>A prospective study in Sweden</td>
<td>Total 84,774 and observed 1329 PD cases</td>
<td>Intake of vitamin C has a negative correlation with PD risk in women at borderline significance ($P = 0.04$)</td>
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<td></td>
<td>Hughes et al. [59]</td>
<td>A prospective study in American</td>
<td>Total 129,422 and observed 1036 PD cases</td>
<td>Intake of vitamin C has no relationship with PD risk</td>
</tr>
<tr>
<td></td>
<td>Ide et al. [58]</td>
<td>A case-case study in Japan</td>
<td>62 PD</td>
<td>The severe PD patients with significantly lower lymphocyte vitamin C levels ($P &lt; 0.01$)</td>
</tr>
<tr>
<td></td>
<td>Miyake et al. [60]</td>
<td>A case-control study in Japan</td>
<td>249/368</td>
<td>Intake of vitamin C has no relationship with PD risk</td>
</tr>
<tr>
<td></td>
<td>Zhang et al. [10]</td>
<td>A prospective study in US</td>
<td>Total 124,221 and observed 371 PD cases</td>
<td>Intake of vitamin C has no relationship with PD risk</td>
</tr>
<tr>
<td></td>
<td>Férnandez-Calle et al. [56]</td>
<td>A case-control study in Spain</td>
<td>63/63</td>
<td>Vitamin C has no relationship with PD</td>
</tr>
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<td></td>
<td>King et al. [127]</td>
<td>A case-control study in United States</td>
<td>27/16</td>
<td>Vitamin C was higher in PD groups</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Yang et al. [61]</td>
<td>A prospective study in Sweden</td>
<td>Total 84,774 and observed 1329 PD cases</td>
<td>Dietary intake of vitamin E has negative correlation with the incidence of PD in women ($P = 0.02$)</td>
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<td></td>
<td>Zhang et al. [10]</td>
<td>A prospective study in US</td>
<td>Total 124,221 and observed 371 PD cases</td>
<td>Intaking foods containing more vitamin E can reduce the risk of Parkinson's disease</td>
</tr>
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<td></td>
<td>Molina et al. [82]</td>
<td>A case-control study in Spain</td>
<td>34/47</td>
<td>CSF and serum vitamin E levels have no difference between two groups</td>
</tr>
<tr>
<td></td>
<td>de Rijk et al. [78]</td>
<td>A cross-sectional study in Netherlands</td>
<td>5342 individuals including 31 PD cases</td>
<td>Intaking 10 mg dietary vitamin E daily may reduce the risk of PD</td>
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<td>Logroscino et al. [77]</td>
<td>A case-control study in USA</td>
<td>110/287</td>
<td>Vitamins A, C, and E were not associated with PD</td>
</tr>
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<td></td>
<td>Férnandez-Calle et al. [80]</td>
<td>A case-control study in Spain</td>
<td>42/42</td>
<td>Serum levels of alpha-tocopherol (vitamin E) have no difference between two groups</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Kim et al. [128]</td>
<td>A prospective, observational study in Korea</td>
<td>39 PD cases</td>
<td>The level of vitamin D might impact the olfactory dysfunction in PD</td>
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<td></td>
<td>Sleeman et al. [112]</td>
<td>A prospective observational study in England</td>
<td>145/94</td>
<td>Serum 25(OH)D concentrations are often lower in PD patients than controls and relate to the severity of motor symptoms</td>
</tr>
</tbody>
</table>
and skeletal health but also regulates the physiological and pathological processes, such as cell proliferation and differentiation, immunomodulatory, and antioxidative stress [88–90]. Children with a lack of vitamin D may suffer from rickets, and adults may develop osteomalacia. Additionally, vitamin D deficiency is also associated with cardiovascular diseases, muscle weakness, diabetes mellitus, cancers, and multiple sclerosis [91]. The relationship between vitamin D and PD has gradually attracted attention [92].

6.1. Possible Neuroprotective Mechanisms of Vitamin D in PD. VDR belongs to the intranuclear receptor superfamily, composing of eight coding exons and three alternative 5’ noncoding exons, spanning over 105 kb, on chromosome 12 [93]. The most widely studied biallelic polymorphic sites are BsmI, TaqI, Apal, and FokI. Substantial researches have been carried out to explore the relationship between these allelic variations and PD. Kim et al. detected VDR gene BsmI polymorphisms in over 300 Korean individuals (85 PD and

<table>
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<td>Wang et al. [110]</td>
<td>A case-control study in China</td>
<td>201/199</td>
<td>The serum 25(OH)D and sunlight exposure inversely correlated with PD occurrence</td>
<td></td>
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<td>Shrestha et al. [129]</td>
<td>A prospective study in USA</td>
<td>Total 12,762 participants and observed 67 PD cases</td>
<td>This study did not suggest that the vitamin D can reduce the risk of PD</td>
<td></td>
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<td>Liu and Zhang [111]</td>
<td>A case-control study in China</td>
<td>229/120</td>
<td>The 25(OH)D levels may be inversely associated with the PD severity</td>
<td></td>
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<tr>
<td>Lin et al. [130]</td>
<td>A case-control study in China</td>
<td>700/792</td>
<td>They have not found the associations between the genetic variants of VDR and PD occurrence</td>
<td></td>
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<tr>
<td>Zhu et al. [131]</td>
<td>A case-control study in China</td>
<td>209/210</td>
<td>Outdoor activity and total vitamin D intake may reduce the risk of PD</td>
<td></td>
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<tr>
<td>Petersen et al. [132]</td>
<td>A case-control study in Denmark</td>
<td>121/235</td>
<td>They have not found the association between PD and vitamin D polymorphisms and/or 25(OH)D levels</td>
<td></td>
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<tr>
<td>Török et al. [133]</td>
<td>A case-control study in Hungary</td>
<td>100/109</td>
<td>It showed the association between the FokI C allele and PD</td>
<td></td>
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<tr>
<td>Lv et al. [134]</td>
<td>A case-control study in China</td>
<td>483/498</td>
<td>The study did not support the relationship between VDR gene and PD</td>
<td></td>
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<tr>
<td>Peterson et al. [135]</td>
<td>A cross-sectional, observational study in USA</td>
<td>40 PD</td>
<td>Serum vitamin D levels are inversely related to the severity of Parkinson’s disease and play an important role in balance of PD</td>
<td></td>
</tr>
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<td>Suzuki et al. [96]</td>
<td>A prospective cohort study in Japan</td>
<td>137 PD</td>
<td>The 25-hydroxyvitamin D levels and the vitamin D receptor FokI CC genotype may be associated with the severity of the PD</td>
<td></td>
</tr>
<tr>
<td>Kenborg et al. [108]</td>
<td>A case-control study in Denmark</td>
<td>3819/19,282</td>
<td>This study supports that working outdoors can reduce the risk of PD</td>
<td></td>
</tr>
<tr>
<td>Evatt et al. [136]</td>
<td>A survey study in USA</td>
<td>199 PD (from DATATOP)</td>
<td>Vitamin D insufficiency is very common in early PD patients</td>
<td></td>
</tr>
<tr>
<td>Miyake et al. [137]</td>
<td>A case-control study in Japan</td>
<td>249/368</td>
<td>The study showed that vitamin D was not related to the PD</td>
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</tr>
<tr>
<td>Knekt et al. [106]</td>
<td>The Mini-Finland Health Survey in Finland</td>
<td>Total 3173 and observed 50 PD cases</td>
<td>The serum vitamin D concentrations were inversely correlated with the risk of PD</td>
<td></td>
</tr>
<tr>
<td>Kim et al. [94]</td>
<td>A case-control study in Korea</td>
<td>85/231</td>
<td>Vitamin D receptor gene polymorphism was associated with the PD</td>
<td></td>
</tr>
</tbody>
</table>
231 controls). The frequency of VDR genotype $bb$ was significantly increased in the PD patients (84.7%) than that in the controls (72.7%). The $bb$ genotype was more common in PD patients with postural instability and gait difficulty than in the PD patients with tremor (94.3% vs. 75.6%) [94]. A meta-analysis showed that VDR BsmI and FokI polymorphisms were associated with the risk of PD [95], and VDR FokI genotype was associated with the severity and cognitive decline of PD [96, 97]. Muscular and motor impairments, which can seriously affect the motor behaviour, were found in the VDR-knockout mice [98], indicating that vitamin D may be involved in the pathogenesis of PD.

Glial cell line-derived neurotrophic factor (GDNF) is a protein that is essential for the maintenance and survival of dopaminergic neurons and can inhibit microglial activation [99]. Many animal studies showed that 1,25-(OH)$_2$D$_3$ could enhance the endogenous GDNF expression in vitro and in vivo and inhibit the glial cell activation to protect dopaminergic neurons from immune inflammation [100–102].

Vitamin D$_3$ can protect dopaminergic neurons against 6-hydroxydopamine-mediated neurotoxicity and improve the motor performance in the 6-hydroxydopamine-induced PD rat [103]. It may be related to vitamin D’s properties of inhibiting oxidative stress and decreasing the production of reactive oxygen species and free radicals [104]. In addition, endothelial dysfunction may be associated with low vitamin D levels in patients with PD [105]. The definitive correlations between vitamin D and PD require more researches.

### Table 2: The clinical intervention trial of vitamins and Parkinson’s disease.

<table>
<thead>
<tr>
<th>Vitamins</th>
<th>Authors</th>
<th>Patients</th>
<th>Treatment</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin C</td>
<td>Nagayama et al. [50]</td>
<td>67 elderly PD patients</td>
<td>200 mg ascorbic acid</td>
<td>Ascorbic acid can improve levodopa absorption in elderly PD patients</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Parkinson Study Group (DATATOP study) [76]</td>
<td>800 untreated and early PD patients</td>
<td>Deprenyl 10 mg/d and/or tocopherol (vitamin E) 2000 IU/d</td>
<td>There was no effect of tocopherol on PD</td>
</tr>
<tr>
<td></td>
<td>Parkinson Study Group (DATATOP study) [124]</td>
<td>800 untreated and early PD patients</td>
<td>Deprenyl 10 mg/d and/or tocopherol (vitamin E) 2000 IU/d</td>
<td>Alpha-tocopherol did not improve clinical features in patients with Parkinson’s disease</td>
</tr>
<tr>
<td></td>
<td>Vatassery et al. (DATATOP study) [83]</td>
<td>$n = 18$ (vitamin E group)/$n = 5$ (placebo group)</td>
<td>Tocopherol (vitamin E) 2000 IU/d</td>
<td>Treatment with vitamin E significantly increased the alpha-tocopherol concentrations in cerebrospinal fluid</td>
</tr>
<tr>
<td></td>
<td>Taghizadeh et al. [125]</td>
<td>$n = 30$ (vitamin E group)/$n = 30$ (placebo group)</td>
<td>1000 mg omega-3 fatty acids plus 400 IU vitamin or placebo</td>
<td>Omega-3 and vitamin E cosupplementation in PD patients improved UPDRS compared with the placebo</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Suzuki et al. [113]</td>
<td>$n = 56$ (vitamin D3 group)/$n = 58$ placebo group</td>
<td>Vitamin D3 1200 IU/d or placebo for 12 months</td>
<td>Vitamin D3 prevented the deterioration of the PD and especially patients with FokI TT genes</td>
</tr>
<tr>
<td></td>
<td>Sato et al. [126]</td>
<td>$n = 43$ (vitamin D group)/$n = 43$ (placebo group)</td>
<td>1α(OH)D$_3$ 1 μg/d or placebo for 12 months</td>
<td>1alpha-hydroxyvitamin D3 supplements can reduce the risk of hip and other nonvertebral fractures in PD patients</td>
</tr>
</tbody>
</table>

6.2 Clinical Studies regarding Vitamin D in PD. Substantial epidemiological and clinical studies suggest that vitamin D has a positive effect on PD. In a cohort study, over 7000 Finnish’s serum samples were collected for measuring the 25-hydroxy vitamin D level, and meanwhile, the occurrence of PD was instigated over a 30-year follow-up period. The results showed that individuals with higher serum vitamin D concentrations had a lower risk of PD [106]. Evatt et al. also noted consistent findings [107].

As mentioned above, vitamin D$_3$ can be endogenously synthesized upon sunlight exposure in the skin. In a large case-control study of Danish men, involving 3819 PD patients and 19,282 controls, the scholars proposed that men working outdoors have a lower risk of PD [108]. Another nationwide ecologic study in France also suggests that vitamin D levels are negatively correlated with the risk of PD, but this result needs taking ages into account [109]. Wang et al. not only demonstrated a positive correlation between serum 25-hydroxy vitamin D and sunlight exposure but also noted that lower serum levels of 25-hydroxy vitamin D and sunlight exposure can increase the risk of PD [110].

Furthermore, PD patients with lower 25-hydroxy vitamin D levels may exhibit more severe symptoms compared with normal controls [111, 112]. Unsurprisingly, a randomized, double-blind, placebo-controlled trial found that vitamin D$_3$ supplementation (1200 IU/day for 12 months) significantly prevented the deterioration of PD [113].
<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Authors</th>
<th>Object of study</th>
<th>Treatment</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B₃ (nicotinamide)</td>
<td>Lu et al. [31]</td>
<td>Rotenone-PC12 cells</td>
<td>NMN (0.1 mM, 1.0 mM, 5 mM, and 10 mM coculture)</td>
<td>Attenuated apoptosis and improved energy metabolism</td>
</tr>
<tr>
<td></td>
<td>Xu et al. [114]</td>
<td>MPTP-C57BL/6 mice</td>
<td>500 mg/kg/day for 5 days i.p.</td>
<td>Nicotinamide can alleviate MPTP-induced damage to dopaminergic neurons through antioxidant stress</td>
</tr>
<tr>
<td></td>
<td>Jia et al. [115]</td>
<td>MPP(+) SK-N-MC human neuroblastoma cells and alpha-synuclein transgenic Drosophila PD model</td>
<td>Nicotinamide concentration (21, 51, 101, 301, and 501 mg/L and 3, 15, 30, and 60 mg/100 g)</td>
<td>High doses of nicotinamide can reduce oxidative stress and improve mitochondrial function</td>
</tr>
<tr>
<td></td>
<td>Anderson et al. [116]</td>
<td>MPTP-adult male C57BL/6 mice</td>
<td>Nicotinamide (125, 250, or 500 mg/kg i.p.)</td>
<td>Recovered the striatal DA levels and SNc neurons after accepting nicotinamide</td>
</tr>
<tr>
<td>Vitamin C (ascorbic acid)</td>
<td>Khan et al. [117]</td>
<td>PD Drosophila model</td>
<td>L-Ascorbic acid (AA, 11.35 × 10⁻⁵ M, 22.71 × 10⁻⁵ M, 45.42 × 10⁻⁵ M, and 68.13 × 10⁻⁵ M for 21 days)</td>
<td>Except 11.35 × 10⁻⁵ M, other concentrations of AA attenuated the loss of climbing ability of PD model flies in a dose-dependent manner</td>
</tr>
<tr>
<td></td>
<td>Yan et al. [52]</td>
<td>Mesencephalic precursors from the E12 rat</td>
<td>Ascorbic acid (0.1 μM, 1 μM, 10 μM, 100 μM, and 1 mM)</td>
<td>Ascorbic acid promoted the dopaminergic differentiation</td>
</tr>
<tr>
<td></td>
<td>Seitz et al. [49]</td>
<td>Human neuroblastoma cell line SK-N-SH</td>
<td>Short-term incubation (100–500 μM for 2 h) and long-term incubation (200 μM for 5 days)</td>
<td>Ascorbic acid increased the DOPA production and tyrosine hydroxylase gene expression</td>
</tr>
<tr>
<td></td>
<td>Pardo et al. [47]</td>
<td>Human neuroblastoma cell line NB69</td>
<td>10⁻³ M ascorbic acid or 23 and 115 × 10⁻³ M alpha-tocopherol</td>
<td>Ascorbic acid prevents the levodopa toxicity and quinone formation, but alpha-tocopherol did not</td>
</tr>
<tr>
<td></td>
<td>Sershen et al. [48]</td>
<td>MPTP-BALB/cBy mice</td>
<td>Ascorbic acid 100 mg/kg i.p.</td>
<td>Ascorbic acid may protect against the MPTP neurotoxicity</td>
</tr>
<tr>
<td></td>
<td>Nakaso et al. [75]</td>
<td>MPTP-C57BL/6 mice</td>
<td>δ-Tocotrienol (100 μg/kg for 4 days, p.o.)</td>
<td>δ-Tocotrienol administration inhibited the loss of dopaminergic neurons and improved the motor performance</td>
</tr>
<tr>
<td></td>
<td>Sharma and Nehru [70]</td>
<td>Rotenone-Sprague-Dawley rats</td>
<td>Vitamin E (100 IU/kg/day for 35 days i.m.)</td>
<td>Vitamin E administration significantly improved locomotor activity and increased the dopamine level, GSH, and SOD</td>
</tr>
<tr>
<td></td>
<td>Ortiz et al. [118]</td>
<td>MPTP-C57BL/6 mice</td>
<td>Vitamin E (50 mg/kg/day p.o.)</td>
<td>Vitamin E administration has decreased the COX-2 activity, LPO, and nitrite/nitrate level</td>
</tr>
<tr>
<td></td>
<td>Pasbakhsh et al. [119]</td>
<td>6-OHDA-rat</td>
<td>Alpha-tocopherol acid succinate (24 IU/kg, i.m.)</td>
<td>Vitamin E treatment can protect locus coeruleus neurons in the PD model</td>
</tr>
<tr>
<td></td>
<td>Roghani and Behzadi [69]</td>
<td>6-OHDA – Sprague-Dawley rats</td>
<td>δ-α-Tocopheryl acid succinate (24 IU/kg, i.m.)</td>
<td>Vitamin E treatment improved the rotational behaviour and prevented the reduction of tyrosine hydroxylase-immunoreactive cells</td>
</tr>
</tbody>
</table>
7. Conclusion

In summary, vitamins may play a protective role in PD. Among the fat-soluble vitamins, we briefly summarized the effects of vitamin E and vitamin D. At present, although many studies have shown that vitamin E supplementation can reduce the risk of Parkinson’s disease (Table 1), the DATATOP study has showed that vitamin E supplementation is ineffective in Parkinson’s disease (Table 2). Many non-interventional studies found that the high levels of serum vitamin D can reduce the risk of PD (Table 1), and several clinical intervention trials also proposed that vitamin D supplementation can attenuate the deterioration of the Parkinson’s disease and reduce the occurrence of fractures in patients with PD (Table 2). Among the water-soluble vitamins, we elaborated the functions of vitamin B3 and vitamin C. There is still a paucity of clinical evidence for determining the pros and cons of vitamin B3 in PD (Table 2). Vitamin C is vital to the human organism, and it can improve levodopa absorption in elderly PD patients (Table 2); current epidemiological evidence is still insufficient to establish a correlation between the serum level or dietary intakes of vitamin C and the risk of PD (Table 1). Although there have been many researches on the relationship between vitamins and PD (Tables 1–3), there is still lack of a clinical intervention trial explicitly confirming that vitamin supplementation can reduce the incidence of PD and prevent the progression of the disease. Moreover, the individual physical and chemical properties, absorption rate, and bioavailability of vitamins may affect the efficacy. Further studies are still needed to clarify the potentials of vitamins for the treatment of PD.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors’ Contributions

Xiuzhen Zhao and Ming Zhang equally contributed to this study.

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