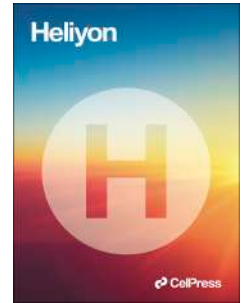


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## **Vitamin D and Neurodegenerative Diseases**

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# 1 **Vitamin D and Neurodegenerative Diseases**

## 2 **Abstract**

3 Neurodegenerative diseases, featured by progressive loss of structure or function of neurons, are considered incurable at present. Movement disorders like  
4 tremor and postural instability, cognitive or behavioral disorders such as memory impairment are the most common symptoms of them and the growing patient  
5 population of neurodegenerative diseases poses a serious threat to public health and a burden on economic development. Hence, it is vital to prevent the  
6 occurrence of the diseases and delay their progress. Vitamin D can be transformed into a hormone *in vivo* with both genomic and non-genomic actions, exerting  
7 diverse physiological effects. Cumulative evidence indicates that vitamin D can ameliorate neurodegeneration by regulating pertinent molecules and signaling  
8 pathways including maintaining  $\text{Ca}^{2+}$  homeostasis, reducing oxidative stress, inhibiting inflammation, suppressing the formation and aggregation of the  
9 pathogenic protein, *etc.* This review updates discoveries of molecular mechanisms underlying biological functions of vitamin D in neurodegenerative diseases  
10 including Alzheimer's disease, Parkinson's disease, multiple sclerosis, and vascular dementia. Clinical trials investigating the influence of vitamin D  
11 supplementation in patients with neurodegenerative diseases are also summarized. The synthesized information will probably provoke an enhanced  
12 understanding of the neuroprotective roles of vitamin D in the nervous system and provide therapeutic options for patients with neurodegenerative diseases in  
13 the future.

## 14 **Keywords**

15 vitamin D; neurodegenerative disease; Alzheimer's disease; Parkinson's disease; multiple sclerosis;

## 16 **1. Introduction**

17 Vitamin D is a kind of fat-soluble steroid vitamin which was discovered in the late 1800s when England was suffering an epidemic of rickets because  
18 ultimately the patients were found to be a result of reduced  $\text{Ca}^{2+}$  levels related to vitamin D deficiency [1]. And now, the problem of vitamin D deficiency still  
19 exists all over the world. It has been reported that half of the people across the world lacked vitamin D to different degrees and more than 1 billion people were  
20 suffering from vitamin D deficiency [2]. More importantly, except for bone-related diseases, subsequent findings suggest that vitamin D deficiency is related to  
21 many other human diseases, including neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS) and  
22 vascular dementia (VaD), as well as cancer, cardiovascular disease, immunity disease, *etc* [3-11].

23 Overlapping pathologies are shared by many neurodegenerative diseases, such as oxidative stress, inflammation, protein aggregation, and demyelination  
24 [12]. In recent years, the effects of vitamin D on the nervous system have been receiving increasing attention. Many vitamin D-related enzymes and vitamin D  
25 receptors (VDRs) are widely presented in the brain, and the metabolites of vitamin D could interact with neuronal and glial cells to exert various effects [13-

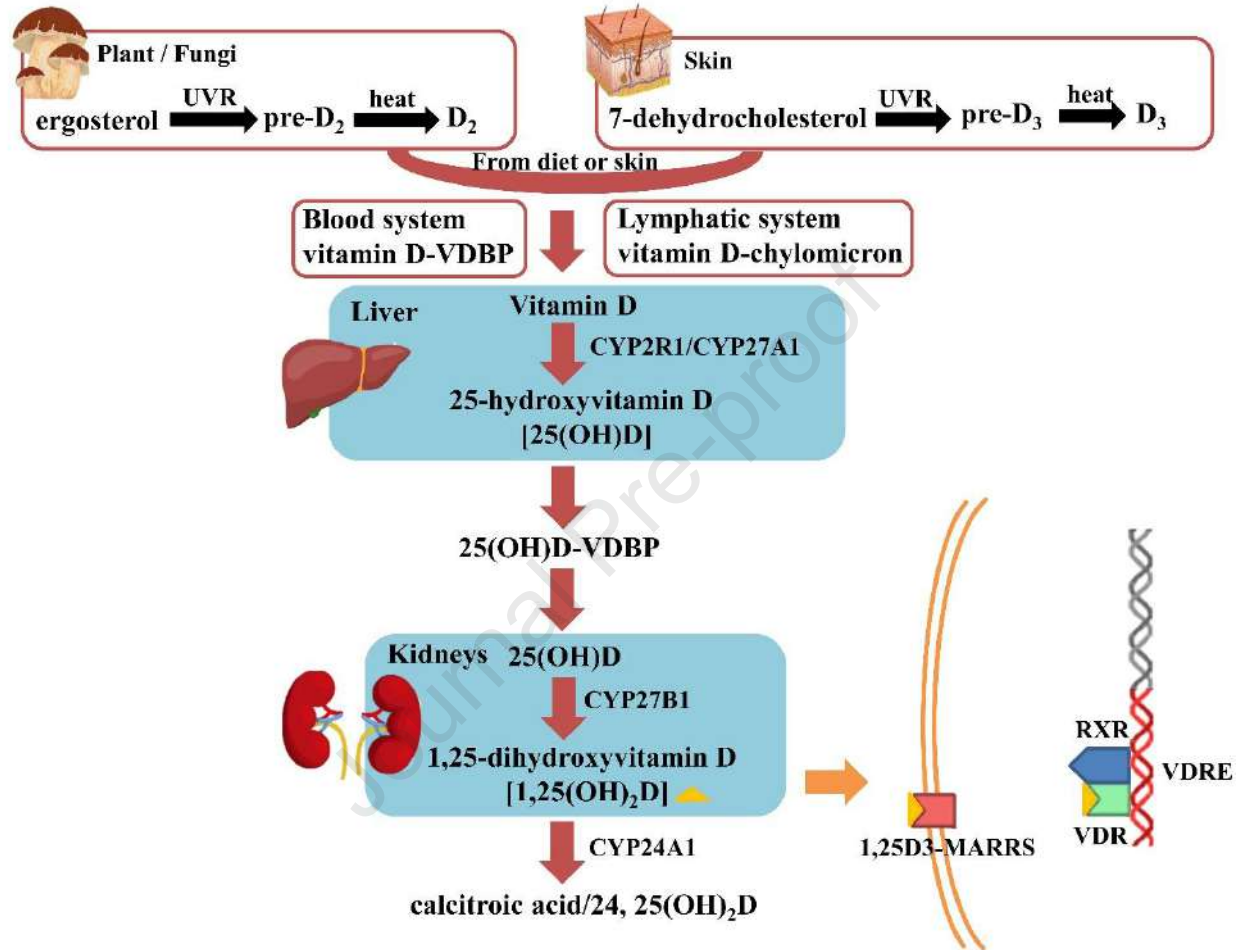
26 15]. Vitamin D has been shown to ameliorate neuropathological features and vitamin D supplementation contributes to a better prognosis [16]. In this review,  
27 we will discuss the relationship between vitamin D and some neurodegenerative diseases and present possible mechanisms through which vitamin D affects the  
28 occurrence and development of these diseases as well as clinical applications of vitamin D in the diseases.

## 29 **2. Biosynthesis and Metabolism of Vitamin D**

30 Vitamin D exists in nature in two major forms, vitamin D<sub>2</sub> (ergocalciferol) and vitamin D<sub>3</sub> (cholecalciferol). Vitamin D<sub>3</sub> is mainly produced in animal  
31 skin from 7-dehydrocholesterol (7-DHC) while vitamin D<sub>2</sub> is synthesized in plants and fungi from ergosterol (E) by ultraviolet rays (UVR) irradiation. The  
32 synthesis of them is similar, containing two processes that are not enzymatic. First, the B ring in E/7-DHC is broken by the UVR (290-315 nm) irradiation, and  
33 E/7-DHC converts to pre-D<sub>2</sub>/D<sub>3</sub>, an isomer of vitamin D<sub>2</sub>/D<sub>3</sub>. Then, through a thermo-sensitive process, pre-D<sub>2</sub>/D<sub>3</sub> finally isomerizes to vitamin D<sub>2</sub>/D<sub>3</sub> (Fig. 1)[1,  
34 17].

35 For humans, most vitamin D is produced in the skin by the irradiation of UVR and only 20% of vitamin D is ingested diet [18]. Most vitamin D enters the  
36 blood circulation and binds to vitamin D binding protein (VDBP) or chylomicron to be transported to tissues and organs. The metabolism of vitamin D includes  
37 three main processes, which are 25-hydroxylation, 1 $\alpha$ -hydroxylation, and 24-hydroxylation [17]. The first conversion of vitamin D is in the liver, where it is  
38 hydroxylated on C-25 by the enzymes cytochrome P450 2R1 (CYP2R1) and cytochrome P450 27 (CYP27A1) forming 25-hydroxyvitamin D [25(OH)D], a  
39 major type of circulating metabolite of vitamin D. 25(OH)D is mainly transported to the kidney by VDBP and starts the second hydroxylation at the C1-position  
40 by the cytochrome P450 [5(OH)D-1 $\alpha$ -hydroxylase; CYP27B1]. This process yields 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D], a biologically active form of  
41 vitamin D, which is also named calcitriol. The third process, 24-hydroxylation catalyzed by 24-hydroxylase (CYP24A1), participates in vitamin D<sub>3</sub> inactivation  
42 (Fig. 1)[1, 19]. Therefore, the functions of vitamin D we synthesize below are actually implemented by calcitriol.

43



44

45 **Fig. 1. The biosynthesis, metabolism, and mechanism of action of vitamin D.** VDBP, vitamin D binding protein; RXR, retinoid X receptor; VDR, vitamin D receptor; 1,25D<sub>3</sub>-MARRS, 1,25D<sub>3</sub>  
 46 membrane-associated rapid-response steroid-binding protein; VDRE, vitamin D-responsive elements.

### 47 3. Mechanism of action and Functions of Vitamin D

48 Vitamin D receptor (VDR) is a DNA-binding transcription factor and a member of the steroid hormone nuclear receptor family, which is expressed and  
49 distributed in almost all tissues and organs in the human body [17, 20-22]. 1,25(OH)<sub>2</sub>D binds to VDR by its ligand-binding domain with the assistance of  
50 vitamin A to induce a change in conformation, forming a heterodimer with retinoid X receptor (RXR), which binds to vitamin D-responsive elements (VDREs)  
51 and starting gene transcription[23-26]. More recently, the 1,25D<sub>3</sub> membrane-associated rapid-response steroid-binding protein (1,25D<sub>3</sub>-MARRS), activated by  
52 calcitriol [1,25(OH)<sub>2</sub>D<sub>3</sub>], was also identified (Fig. 1)[27].

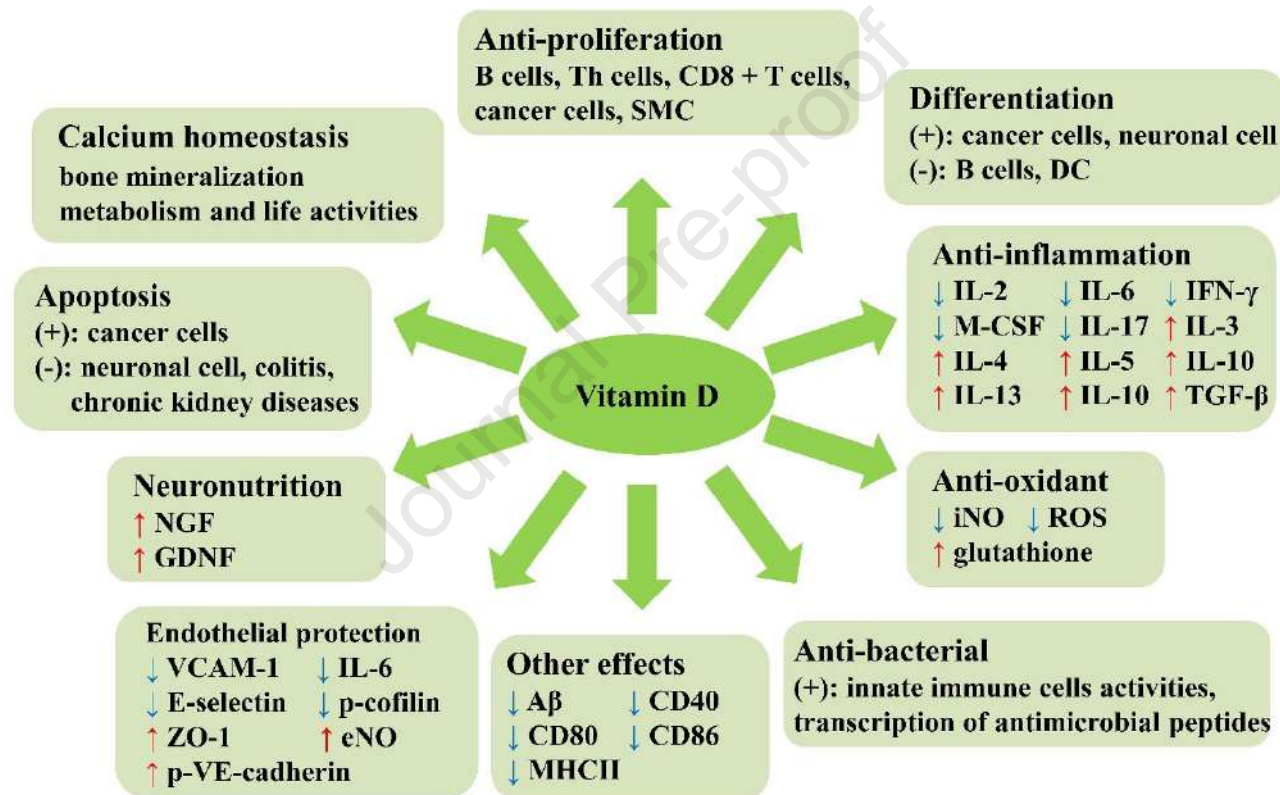
53 The classic effect of vitamin D is associated with bone [28]. Vitamin D can promote the absorption of calcium and phosphorus, maintaining calcium  
54 homeostasis in order for proper mineralization of bone. Several surveys found that vitamin D supplementation could reduce the incidence of hip fractures and  
55 other non-vertebral fractures [29-31]. Besides, vitamin D can also sustain muscle function and enhance postural and dynamic balance. A meta-analysis published  
56 in 2004 found that vitamin D supplementation could reduce the risk of falls by over 20% in ambulatory or institutionalized older individuals with stable health  
57 [32].

58 Vitamin D also plays an important role in the immune system. Calcitriol could strengthen the antimicrobial effects by enhancing the chemotaxis and  
59 phagocytic capabilities of innate immune cells and the transcription of antimicrobial peptides in them [33]. In macrophages or monocytes, vitamin D induces  
60 the production of antibiotic peptides, such as cathelicidin and  $\beta$ -Defensin 2 [34, 35]. Vitamin D increases transcription of the autophagy-associated proteins  
61 Atg-5, and Beclin-1, which promote autophagy through the upregulation of cathelicidin and their downstream factors (p38, ERK, and C/EBP) [36]. Vitamin D  
62 could suppress dendritic cells (DC) to express MHCII, co-stimulatory molecules, and cytokines essential for T cells differentiation and inhibit the activity of T  
63 helper cells (Th) and its production of cytokines like interleukin-17 (IL-17) and IL-21 [33, 37, 38]. Furthermore, vitamin D could either directly repress naïve  
64 B cell differentiation, memory B, and plasma cells maturation or indirectly suppress B cell differentiation, proliferation, and antibody production via Th cells  
65 [39].

66 Vitamin D could also regulate the differentiation, proliferation of neurons and microglia, and dopamine signaling transduction [40, 41]. The effects of  
67 vitamin D, including regulating synaptic plasticity and molecular transport in cell organelles, and maintaining cytoskeleton, are sufficiently proved, which  
68 implies the important roles of vitamin D in brain development and synaptic plasticity [40, 42, 43]. Calcitriol could restore calcium homeostasis and reduce  
69 apoptosis and neuronal death by downregulating the expression of L-type voltage-sensitive calcium channel (LVCC) while upregulating the expression of  
70 plasma membrane Ca<sup>2+</sup>-ATPase (PMCA) and Na<sup>+</sup>/Ca<sup>2+</sup> exchanger (NCX1) that efflux Ca<sup>2+</sup> and Calbindin D-9k, Calbindin D-28k, as well as parvalbumin that  
71 buffer Ca<sup>2+</sup> [16, 44, 45]. Besides, vitamin D sustains normal functions of mitochondria thus reducing the formation of ROS, and controlling the expression of  
72 antioxidants through the vitamin D–Klotho–Nrf2 regulatory network[46]. Vitamin D assists in anti-oxidation by up-regulating the expression of glutathione and  
73 superoxide dismutase and down-regulating the expression of nitric oxide (NO) and inducible nitric oxide synthase (iNOS) [47-49]. Moreover, vitamin D  
74 enhances neuronal survival by regulation of neurotrophins, including neural growth factor (NGF), glial-line derived neurotrophic factors (GDNF), and brain  
75 derived neurotrophic factors (BDNF) [41, 50, 51]. The synthesis of neurotransmitters, including acetylcholine (ACh), dopamine (DA), serotonin (5-HT), and  
76 gamma-aminobutyric (GABA) is also under the control of vitamin D [52-55]. Vitamin D could protect neurons by altering glutamate levels and reducing

77 excitotoxicity caused by long-term increases in extracellular glutamate levels and hyperactivation of N-methyl-D-aspartate receptor (NMDAR) [56].

78 Other functions of vitamin D, including inhibiting inflammation and smooth muscle cells proliferation, may also play roles in cardiovascular diseases  
 79 and neurodegenerative diseases [57-59]. In various cancers, vitamin D has been found to exert its effects through inhibition in proliferation, inflammation,  
 80 angiogenesis, invasion, metastasis, induction of differentiation, and promotion of cell apoptosis [60]. Further, vitamin D plays an anti-apoptosis role through  
 81 Caspase-3, Bcl-2, and other probable mechanisms in many other diseases (Fig. 2)[61-63].





83 **Fig. 2. The functions of vitamin D.** ↑: up-regulate; ↓: down-regulate; +: positive influence in; -: negative influence in. DC, dendritic cells; Th, T helper; iNOS, inducible nitric oxide synthase;  
 84 GDNF, glial-line derived neurotrophic factors; SMC, smooth muscle cells; A $\beta$ , beta-amyloid; P-gp, P-glycoprotein; TNF- $\alpha$ , tumor necrosis factor alpha; eNO, endothelial NO; VCAM-1, vascular  
 85 cell adhesion molecule 1; VE-cadherin, vascular endothelial cadherin; M-CSF, macrophage colony stimulating factor; IL, interleukin; ZO-1, zonula occludin-1.

## 86 4. Effects and Molecular Mechanisms of Vitamin D in Neurodegenerative Diseases

### 87 4.1 Vitamin D and Alzheimer's Disease

88 As a major kind of neurodegenerative disease, Alzheimer's disease (AD) has a growing patient population in the world [64]. AD is the main cause of  
 89 dementia [65]. At present, almost 48 million people are suffering from dementia and this population is increasing at the speed of about 10 million every year  
 90 around the world [64, 66]. Initial symptoms include short-term memory loss, and as the disease advances, other symptoms, such as problems with language,  
 91 disorientation, and mood swings, would ensue [67]. The major neuropathological features of AD include the accumulation of extracellular senile plaques  
 92 consisting of beta-amyloid (A $\beta$ ) protein aggregates, intra-neuronal neurofibrillary tangles made up of tau protein, and loss of cholinergic neurons and synapses  
 93 in the cerebral cortex and certain subcortical regions [68, 69]. Besides, neuroinflammation was also proved to promote AD pathogenesis [70].

94 Vitamin D deficiency could be a risk factor for AD [71]. A meta-analysis conducted in 2019 found that vitamin D deficiency (<10 ng/mL) has a positive  
 95 correlation with the risk of AD and every 10 ng/mL supplement of vitamin D could reduce the risk of AD by 17%, while these associations were not found in  
 96 vitamin D insufficiency (10-20 ng/mL) [72]. It has been found in a mouse experiment that a deficiency of vitamin D in the early stage of AD could increase the  
 97 amyloid load in the hippocampus and the cortex and strongly inhibit cell proliferation, neurogenesis, and neuron differentiation in both wild-type and transgenic  
 98 AD-like mice (5XFAD model) in the late stage [73]. All evidence presented above proves that vitamin D deficiency could enhance the development of AD.

99 Contrarily, supplements of vitamin D may prevent or inhibit the development of AD (Table 1). It has been found that vitamin D supplements could improve  
 100 the cognition of young amyloid- $\beta$  protein precursor (A $\beta$ PP) transgenic mice and maintain memory abilities of old transgenic mice or aging rats [18, 74]. Loads  
 101 of evidence supports the positive effect of vitamin D in reducing A $\beta$  accumulation, but some findings with the opposite conclusion also exist. In an animal  
 102 experiment, vitamin D could decrease the formation of A $\beta$  and increase the degradation of A $\beta$  [75]. However, a recent study showed a contradictory result that  
 103 vitamin D supplementation increased A $\beta$  deposition and aggravated AD. The explanation is that A $\beta$ 42 in the AD brain switched VDR binding target from RXR  
 104 to p53 to transduce the non-genomic vitamin D signal [76]. In humans, vitamin D could increase the level of the  $\beta$  amyloid peptide A $\beta$ 1–40 in serum and decrease  
 105 the level of A $\beta$  in the brain, inhibiting amyloidogenesis [77]. Some researchers put forward probable mechanisms.  $1\alpha,25(\text{OH})_2\text{D}_3$  could stimulate macrophages  
 106 to devour A $\beta$  in AD patients [78]. The activation of VDR could inhibit the phosphorylation of tau probably by decreasing the activity of glycogen synthase  
 107 kinase 3 $\beta$  (GSK3 $\beta$ ) in APP/PS1 transgenic mice [79]. VDR overexpression or vitamin D supplement was found to inhibit the transcription of amyloid precursor  
 108 protein (APP) [80]. Moreover, a vitamin D analog, maxacalcitol, could decrease the level of A $\beta$  and hyperphosphorylated Tau protein by down-regulating the  
 109 level of MAPK-38p and ERK1/2 [81]. In addition, vitamin D can act on calcium channels and upregulate the expression of calcium buffer to maintain calcium



110 homeostasis, breaking the  $A\beta/Ca^{2+}$  positive feedback loop, increasing neuronal excitability, and promoting cell proliferation and neurogenesis [82-85].

111 Anti-inflammation and reducing oxidative stress are also benefits of vitamin D in AD. It was found that  $1,25(OH)_2D_3$  possesses anti-inflammation quality  
 112 in brain pericytes by influencing the transcription process, which means vitamin D could direct protective effect in brain capillaries under the situation of chronic  
 113 inflammation happened in AD [86]. Moreover, vitamin D could prevent the up-regulation of iNOS, NO, and other proinflammatory factors like tumor necrosis  
 114 factor alpha (TNF- $\alpha$ ) and IL-6 in damaged neurons, microglia, and astrocytes [18, 47, 82]. Another study also found that vitamin D could reduce oxidative  
 115 stress through SIRT1/Nrf-2/NF-kB signaling pathway, restore the level of neuronal synapse protein and decrease the formation of  $A\beta$  induced by D-Galactose  
 116 (D-gal) in adult mice [87]. Maxacalcitol could be beneficial to AD via its antioxidant effect by increasing the level of nuclear factor erythroid2-related factor 2  
 117 (Nrf2), heme oxygenase-1 (HO-1), and glutathione (GSH) [81]. The anti-aging effect of vitamin D is also involved in AD, by increasing the expression of an  
 118 anti-aging gene Klotho, as well as decreasing the expression and inhibiting the activity of aging-related protein mTOR, through PI3K/Akt/mTOR pathway [88,  
 119 89]. Besides, calcitriol can also up-regulate the expression of NGF and GDNF to influence neuronal cell differentiation and maturation, promoting learning and  
 120 memory process through the septohippocampal pathway [90-92].

121

**Table 1. Vitamin D and Alzheimer's disease.**

Model (duration of the disease)	Strain and/ or age	Supplement	Dose	Cognition/memory test	Effects	Signaling Pathway or molecule	Reference
Tg2576 and TgCRND8 mouse models of AD(chronic)	C57BL/6 mice; 8-week-old	$1,25(OH)_2D_3$	2.5 $\mu$ g/kg, q2d $\times$ 4 or q3d $\times$ 19	Fear conditioning	Improved memory  Reducing $A\beta$ in the brain	NA  VDR, P-gp	[74]
Vitamin D deficient mice (chronic)	C57BL/6 mice; age not obtained	Calcifediol or its analogues	100 nM	NA	Reducing amyloid plaques	$\alpha$ -secretase/ $\beta$ -secretase/ $\gamma$ -secretase/ BACE1	[75]
APP695 overexpressing human and mice neuroblastoma (NA)	SH-SY5Y; N2a	vitamin $D_3$ / vitamin $D_2$ / vitamin $D_3$ analogues/ vitamin $D_2$ analogues	100 nM	NA	Inhibiting $A\beta$ formation; increasing $A\beta$ degradation		
APP/PS1 tg mice (chronic)	Strain not obtained;6-month old	Paricalcitol	200 ng/kg, q2d, 15 weeks	NA	Inhibiting Tau phosphorylation	GSK3 $\beta$	[79]

Mice neuroblastoma with overexpression of VDR or vitamin D treatment (NA)	N2a	1,25 (OH) <sub>2</sub> D <sub>3</sub>	0.02, 0.2 and 2 μM	NA	Inhibiting Aβ formation	APP	[80]
AD rats induced by LPS (acute)	Female white albino rats ;6 months-1 year old	Maxacalcitol	1 μg/kg, tid, 4 weeks	T-maze test	Inhibiting Aβ formation and Tau phosphorylation	MAPK-38p/ERK1/2	[81]
APP/PS1 tg mice (chronic)	C57BL/6 N mice;4.5 months old	Cholecalciferol	8044 IU/Kg/day, 3 months	Morris water maze test	Worse cognitive function; more severe Aβ deposit	Aβ/BACE1/ Nicastrin	[76]
Human neuroblastoma pretreated with Aβ42 (NA)	SH-SY5Y	Calcitriol	10, 30, or 100 nM	NA	Promoting apoptosis and autophagy	VDR/PARP/LC3-1/LC3-II	[76]
VDR-silenced neurons (NA)	Primary cortical neurons from Sprague-Dawley rat embryos	1,25 (OH) <sub>2</sub> D <sub>3</sub>	10 <sup>-7</sup> /10 <sup>-8</sup> /10 <sup>-9</sup> M	NA	Maintaining calcium homeostasis; inhibiting inflammation and oxidative stress	LVSCC-A1C/NO/ TNF-α/IL-6	[82]
Aged male rats (chronic)	F344 ;3-4 months and 24-25 months	1,25 (OH) <sub>2</sub> D <sub>3</sub>	500 ng/kg, 6 days	NA	Maintaining calcium homeostasis	L-VGCC	[83]
Neurons treated with 1,25 (OH) <sub>2</sub> D <sub>3</sub> (NA)	Hippocampal neurons from Sprague Dawley fetal rat	1,25 (OH) <sub>2</sub> D <sub>3</sub>	1-100 nm	NA	Maintaining calcium homeostasis	L-VSCC	[84]
Human brain pericytes	NA	1,25 (OH) <sub>2</sub> D <sub>3</sub>	10 <sup>-8</sup> M	NA	Inhibiting inflammation	TNF-α/IFN-γ	[86]
Mice exposed to oxidative stress AD pathology induced by D-gal (subacute)	Male adult albino mice; 8 weeks old	Vitamin D	100 μg/kg, 3 times/week, 4 week	Morris water maze and Y-maze tests	Improving memory dysfunction Enhancing pre- and post-synaptic protein expression; reducing inflammation	NA SYP/PSD-95	[87]

					Inhibiting inflammation and oxidative stress	NF-kB/TNF- $\alpha$ /IL-1 $\beta$ /SIRT1/NRF-2/HO-1	
					Inhibiting A $\beta$ formation	BACE-1	
Rats with AD induced by LPS (acute)	Female white albino rats; 6 months-1 year	Maxacalcitol	1 $\mu$ g/kg, tid, 4 weeks	T-maze test	Improvement of the cognitive functions of the brain of Maxacalcitol treated rats	NA	[81]
					Inhibiting oxidative stress	Nrf2/HO-1/GSH	
Human and murine kidney cells treated with 1,25 (OH) $_2$ D $_3$ (NA)	mpkDCT, HEK, IMCD-3, HK-2, COS-7	1,25 (OH) $_2$ D $_3$	10 $^{-8}$ M	NA	Anti-aging	Klotho	[88]
Neurons treated with 1,25 (OH) $_2$ D $_3$ (NA)	Embryonic hippocampal cells	1,25 (OH) $_2$ D $_3$	100 nM	NA	Promoting neurite growth	NGF	[92]

122 P-gp, P-glycoprotein; SYP, Synaptophysin; PSD-95, post synapse density 95; NF-kB, Nuclear Factor kappa B; SIRT1, Silent mating type information regulation 2 homolog 1; NRF-2, Nuclear factor erythroid 2-related  
 123 factor 2; BACE-1, beta-site amyloid precursor protein-cleaving enzyme-1; LVCC, L-type voltage-sensitive calcium channel; PMCA, plasma membrane Ca $^{2+}$ -ATPase; NCX1, Na $^+$ /Ca $^{2+}$  exchanger; iNOS, inducible nitric  
 124 oxide synthase; GDNF, glial-line derived neurotrophic factors; BDNF, brain derived neurotrophic factors; NGF, neural growth factor; AchACh, acetylcholine; DA, dopamine; 5-HT, serotonin; GABA, gamma-  
 125 aminobutyric; NMDAR, N-methyl-D-aspartate receptor; A $\beta$ , beta-amyloid; A $\beta$ PP, amyloid- $\beta$  protein precursor; GSK3 $\beta$ , glycogen synthase kinase 3 $\beta$ ; APP, amyloid precursor protein; TNF- $\alpha$ , tumor necrosis factor alpha;  
 126 D-gal, D-Galactose; Nrf2, erythroid2-related factor 2; HO-1, heme oxygenase-1; GSH, glutathione; Tg, transgenic; LPS, lipopolysaccharide; NA, not applicable.

#### 127 4.2 Vitamin D and Parkinson's Disease

128 Parkinson's disease (PD) is also a common neurodegenerative disease with which patients show motor system problems including rigidity, tremor, postural  
 129 instability, and slow movement, while non-motor symptoms entail sleep disorder, anosmia, constipation, and depression [93, 94]. More than 6 million individuals  
 130 were diagnosed with PD around the world in 2015 [95]. The characteristics of PD are dopamine (DA) neurons loss in the substantia nigra pars compacta (SNc),  
 131 insoluble cytoplasmic protein inclusions accumulation called Lewy bodies, and Lewy neuritis [96]. The specific pathogenesis of PD is not clear yet but it is  
 132 widely recognized that  $\alpha$ -synuclein ( $\alpha$ -Syn) protein is the core of pathogenesis of the disease [96].  $\alpha$ -Syn aggregation is cytotoxic, causing cellular damage and

133 dysfunction [97, 98].

134 Deficiency or insufficiency of vitamin D is common in PD patients and vitamin D insufficiency in serum [25(OH)D <30 ng/ mL] increases the risk of PD  
 135 [99]. On the contrary, vitamin D supplement and sunlight exposure ( $\geq 15$  min/week) was found to be a preventive measure for PD [100]. In the aspect of balance,  
 136 a review showed that a high dose of vitamin D may improve balance and postural equilibrium and reduce the occurrence of falls only in young PD patients  
 137 rather than elderly PD patients [101]. Besides, a high level of serum vitamin D is associated with better cognition in PD patients without dementia. Few studies  
 138 showed that vitamin D was associated with mood and olfactory function in PD [101]. However, some studies obtained contradictory results. A prospective  
 139 cohort study with a 17-year follow-up period proposed that there was no correlation between vitamin D levels and the risk of PD [102]. Another Mendelian  
 140 randomized study, involving 4 single-nucleotide polymorphisms which affect 25-hydroxyvitamin D concentrations, also showed no clear support for the  
 141 relationship between vitamin D and PD onset [103].

142 The effects of vitamin D on PD may be achieved through the following mechanisms (Table 2). In a PD preclinical animal model induced by 1-methyl-4-  
 143 phenyl-1,2,3,6-tetrahydropyridine (MPTP), vitamin D treatment is beneficial in alleviating dopaminergic neurodegeneration and attenuating neuroinflammation  
 144 mediated by microglia through down-regulating the expression of iNOS and toll-like receptor 4 (TLR-4) and up-regulating the expression of anti-inflammatory  
 145 cytokines (IL-10, IL-4, and TGF- $\beta$ ) mRNA, as well as CD163, CD206 and CD204 [104]. The effect of restoring calcium homeostasis could also be beneficial  
 146 in PD since SNc neurons are more prone to be damaged by  $Ca^{2+}$  and oxidative stress which is caused by the repeated rises in  $Ca^{2+}$  occurring every few seconds  
 147 when the dopaminergic neuronal pacemaker mechanism is functioning [85]. Vitamin D also could reduce the cytotoxicity caused by  $\alpha$ -synuclein aggregation in  
 148 the early state by down-regulating the production of ROS. Cell death and apoptosis might result from the inhibition of  $\alpha$ -Syn aggregation for strong affinity  
 149 energy to  $\alpha$ -Syn monomer [97]. What's more, vitamin D could also decrease the exocytotic release of neurotransmitters raised by  $\alpha$ -Syn oligomers, indicating  
 150 the neuroprotective effect of vitamin D in PD [97]. In the 6-OHDA PD mouse model, 1,25(OH) $_2$ D $_3$  pretreatment could prevent neuroinflammation and the loss  
 151 of dopamine cells induced by oxidative stress and increase the transcription of VDR, CYP24, and MDR1a which encodes a membrane transporter P-gp mainly  
 152 expressed in vascular endothelial cells [105]. Besides, vitamin D could directly up-regulate the expression of C-Ret which is a multifunctional receptor vital for  
 153 GDNF signaling in DA neurons, and increase the expression of GDNF which is important for the survival of DA neurons [41]. It has been proved that the  
 154 activation of poly (ADP-ribose) polymerase-1 (PARP1) which contributes to the pathogenesis of PD in MPTP model, can be inhibited by overexpression of  
 155 VDR [106, 107]. Another experiment also found that over-expression of VDR could increase the expression of tyrosine hydroxylase (TH), catechol-o-methyl  
 156 transferase (COMT), monoamine oxidase A (MAO-A), and vesicular monoamine transporter 2 (VMAT2) which can influence the differentiation of DA neurons  
 157 [108].

158

**Table 2. Vitamin D and Parkinson's disease.**

Model/Patients (duration of the	Strain and/ or age	Supplement	Dose	Behavioral test	Effects	Signaling Pathway or	Reference
---------------------------------	-----------------------	------------	------	-----------------	---------	-------------------------	-----------

disease)						molecule	
MPTP induced PD model in mice (acute)	Male C57BL/6 N mice; 8–10 weeks	Vitamin D	1 µg/kg/day, 10 d	NA	Inhibiting neuroinflammation	iNOS/TLR-4/IL-10/IL-4/TGF-β/CD163/CD206/CD204	[104]
Human neuroblastoma cells incubated with α-Syn monomer solution (NA)	SH-SY5Y	Vitamin D	4 µM	NA	Inhibiting α-synuclein aggregation and toxicity	α-Syn monomer	[97]
6-hydroxydopamine -induced PD mouse (acute)	Male C57BL/6N mice; 3 months	1,25 (OH) <sub>2</sub> D <sub>3</sub>	2.56µg/kg, q2d×4	NA	Inhibiting α-synuclein aggregation and toxicity	P-gp	[105]
Developmental vitamin D-deficient rat model (chronic)	Embryonic forebrains of Sprague-Dawley rats at E18	Calcitriol	0 IU/kg	NA	Differentiation and maintenance of dopaminergic neurons	C-Ret	[41, 109]
Neuroblastoma cells transfected with VDR (NA)	SH-SY5Y	Calcitriol	20 nM	NA	Differentiation and maintenance of dopaminergic neurons	C-Ret /GDNF/ GFRα1	[41]
PD cell model induced by MPP <sup>+</sup> (NA)	SH-SY5Y	Calcitriol	25-75 nM	NA	Protecting SH-SY5Y cells from Parthanatos	PARP1/AIF/ phosphor-histone H2A.X	[106]
PD mice model induced by MPTP (subacute)	C57 / BL6 mice; 8 weeks	Calcitriol	2.5 µg/kg/day, i.p, for 21 days	Rotarod Testing; Pole Testing	Alleviated PD-related behavioral damage Alleviating behavioral and dopaminergic neuron damage	NA VDR/PARP1	[106]
Over-expression of VDR in neuroblastoma cells (NA)	SH-SY5Y	1,25 (OH) <sub>2</sub> D <sub>3</sub>	20 nM	NA	Promoting neuronal development and maturation	TH/COMT/MAO-A/VMAT2	[108]
Dopaminergic neurons (NA)	Embryonic	1,25 (OH) <sub>2</sub> D <sub>3</sub>	10 nM	NA	Neuronutrition	GDNF	[91]

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ventral midbrain  
of Sprague-  
Dawley rats at  
E12/E13

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159 A-Syn,  $\alpha$ -synuclein; PARP1, poly (ADP-ribose) polymerase-1; TH, tyrosine hydroxylase; COMT, catechol-o-methyl transferase; MAO-A, Monoamine oxidase A; VMAT2, vesicular monoamine transporter 2; i.p,  
160 intraperitoneal injections; NA, not applicable.

161 *4.3 Vitamin D and Multiple Sclerosis*

162 Multiple sclerosis (MS) is a central nervous system (CNS) disease with chronic inflammation and degenerative process mediated by the immune system  
163 [110]. Approximately 2.3 million people were affected by the disease worldwide in 2015 [111]. MS is regarded as an autoimmune disease because it is initiated  
164 by immune cells passing through the blood-brain barrier (BBB) and abnormal immune responses, causing demyelination and damage to neuroaxonal in the  
165 brain, retina, and spinal cord [112, 113].

166 In general, the prevalence of MS shows latitude-related differences. Notably, MS has a minimal prevalence at the equator, implying the correlation between  
167 vitamin D and MS [114]. It is recognized that vitamin D is a risk factor for MS [115]. In a study with only whites included, it was found that people with the  
168 highest concentrations of vitamin D had a 62% lower risk of developing MS than people with the lowest concentrations [116]. Low levels of serum vitamin D  
169 in the early stage of MS predict a more active disease process [117]. Besides, in animal experiments, high levels of serum vitamin D have effects on preventing,  
170 improving the symptoms, and inhibiting the development of experimental autoimmune encephalomyelitis (EAE) [112]. Moreover, continuous moderate vitamin  
171 D supplements also could reduce the rate of recurrence [115].

172 Since MS is an autoimmune disease, the effects of vitamin D related to the immune system may also influence the disease (Table 3). Vitamin D could  
173 suppress the activity of Th1 and Th17 by down-regulating the level of Jak1/Jak2, Erk/MAPK, Pi3K/Akt/mTOR, Stat1/Stat4, and Stat3, which are important for  
174 the differentiation of Th1 and Th17, decreasing the secretion of many inflammatory cytokines including IL-2, IL-6, IFN- $\gamma$ , macrophage colony stimulating  
175 factor (M-CSF) and IL-17 in EAE model, while enhancing the activity of Th2 and induce the response of regulatory T-cell (Treg), up-regulating the level of  
176 IL-3, IL-4, IL-5, IL-10, IL-13, IL-10 and TGF- $\beta$  [118, 119]. An animal experiment found that calcitriol could suppress neuroinflammation by decreasing the  
177 expression of NLRP3, caspase-1, and IL-1 $\beta$  local mRNA, stabilizing BBB by increasing the mRNA expression of zonula occludin-1 (ZO-1), a junctional adaptor  
178 protein controlling the formation of BBB, and reducing the activation of local macrophage and microglia and mediate autoimmune response by decreasing the  
179 level of MHCII in EAE animal model [120]. Besides, the proliferation of B cells, Th cells, and CD8 + T cells and the differentiation of B cells and DC are  
180 inhibited by vitamin D while the amount of Treg increases [39, 118, 121, 122]. Vitamin D could also down-regulate the expression of co-stimulatory molecules,  
181 such as CD40, CD80, and CD86 causing a VDR-dependent loss of MHCII in monocytes [121, 123]. Furthermore, an animal study found that vitamin D could  
182 up-regulate the level of Bcl-2/Bax and Beclin 1 which reduces LC3-II, leading to inhibited apoptosis and autophagy in EAE mouse model, dampening the

183 progression of EAE [124]. Except for the effects on the immune system, vitamin D could also act in CNS, mediating neuroprotection, neurotrophic effect, and  
 184 remyelination [115].

185

**Table 3. Vitamin D and multiple sclerosis.**

Model/ Patient (duration of the disease)	Strain and/ or age	Supplement	Dose	Clinical assessment	Effects	Signaling Pathway or molecule	Reference
EAE mice model (acute)	Dark Agouti rats; age not obtained	Vitamin D <sub>3</sub>	10 IU/g	0 = no paralysis; 1 = loss of tail tone; 2 = hindlimb weakness; 3 = hindlimb paralysis; 4 = hindlimb and forelimb paralysis; 5 = moribund or dead	Alleviating in clinical symptoms Immunomodulation and anti-inflammation	NA Jak1/Jak2, Erk/Mapk, Pi3K/Akt/mTor, Stat1/Stat4, Stat3	[119]
EAE mice model (acute)	C57BL/6J female mice; 9 weeks old	1,25 (OH) <sub>2</sub> D <sub>3</sub>	5 µg/kg, every 2 days		Alleviating in clinical symptoms and inhibiting progressing Immunomodulation and anti-inflammation	NA NLRP3/caspase-1/IL- 1β/ZO-1/MHCII	[120]
EAE mice model (acute)	C57BL/6J female mice; 8- 10 weeks	1,25 (OH) <sub>2</sub> D <sub>3</sub>	0.1 µg/day, every 3 days		Alleviating in clinical symptoms and inhibiting progressing Reducing inflammation, demyelination, and neuron loss in the spinal cord	NA Bcl-2/Bax/Beclin 1/LC3- II	[124]
EAE mice model (acute)	C57BL/6J female mice; age not obtained	Vitamin D <sub>3</sub>	75 000 IU/kg food		Alleviating in clinical symptoms Triggering MS activity by attenuating phenotype and function of myeloid APC	NA IFN-γ/IL-17/MHC II /CD40/CD80/CD86	[125]



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development of pro-inflammatory T cells and accelerated activation and differentiation of both myeloid APC and T cells

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186 JAK, Janus Kinase; Erk, extracellular regulated protein kinases; Mapk, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NLRP, Nod-like receptors protein; EAE, experimental autoimmune  
187 encephalomyelitis.

#### 188 4.4 Vitamin D and Vascular Dementia

189 Vascular dementia (VaD) is the most common type of dementia second only to AD, caused by infarcts in the brain [126, 127]. Cognitive, motor, and  
190 behavioral dysfunction can be signs of VaD, including cognitive decline, memory impairment, hemiparesis, bradykinesia, hyperreflexia, extensor plantar  
191 reflexes, ataxia, pseudobulbar palsy, gait problems, and dysphagia [128]. The pathology of VaD involves diffuse and focal white matter lesions, lacunar and  
192 microinfarcts, intracerebral microbleeds, cerebral amyloid angiopathies, and familial small vessel diseases [129-133]. For chronic hypoperfusion induced VaD,  
193 oxidative stress, neuroinflammation, and central cholinergic dysfunction are its pathophysiological features [134].

194 In VaD patients, vitamin D deficiency was more common than in normal people [135]. It was found that a low level of vitamin D could increase the risk  
195 of VaD, while a recent study showed that higher level of vitamin D could reduce the risk of VaD [135, 136]. In an animal experiment, vitamin D could reduce  
196 the amount of induced infarction in the cortex *in vivo* [137]. Besides, in a cross-sectional study of 318 elderly adults, vitamin D deficiency may result in a  
197 greater number of large vessel infarcts, which are associated with a higher risk of VaD [138]. In addition, VDR polymorphism is suggested to relate to VaD  
198 which could be caused by small vessel disease (SVD). In an Asian India cohort study, it was found that the presence of "ff" genotype of *FokI* variant increased  
199 the odds of SVD by 2.5 folds in subjects with low serum 25(OH)D and *Apal* polymorphism decreased the risk of cerebral SVD in women [135].

200 The probable effects of vitamin D in VaD mainly include two aspects, vascular and nerves (Table 4). Vitamin D could inhibit the influx of calcium into the  
201 endothelial cells and decrease the release of vasoconstrictor metabolites to induce vasodilatation in the microcirculation [139]. Vitamin D could also directly  
202 up-regulate the expression of the endothelial form of NOS (eNOS) and increase the production of endothelial NO (eNO), inhibiting platelet aggregation and  
203 endothelial dysfunction [140, 141]. Vitamin D attenuates cerebral artery remodeling and vasospasm through the upregulation of osteopontin (OPN) and  
204 phosphorylation of AMPK and eNOS in the cerebral arteries [142]. What's more, vitamin D could decrease the level of vascular cell adhesion molecule 1  
205 (VCAM-1), cytokine IL-6, and E-selectin, reducing the adhesion of endothelial cells [143]. Vitamin D counteracts inflammation in endothelial colony-forming  
206 cells (ECFC) involved in angiogenesis and endothelial repair by increasing endothelial interconnections through vascular endothelial cadherin (VE-cadherin)  
207 junctions and impacting cell dynamics through cofilin and VE-cadherin phosphorylation, contributing to an improvement in endothelial barrier integrity [144].

208 Vitamin D also could prevent hypoxia/reoxygenation-induced BBB disruption by NF- $\kappa$ B pathway and diminish the response of endothelial cells to inflammatory  
 209 cytokines, reducing brain injury [145]. It was also proposed a conjecture that vitamin D could inhibit the proliferation of arterial smooth muscle cells (SMC)  
 210 [146]. The mechanisms mentioned above could prevent the development of atherosclerosis, which is a pathogenic factor of VaD [147]. In the presence of  
 211 vitamin D, NO could activate phospholipase A2 in the astrocytes, triggering the prostaglandin cascade, widening the arteries, and the expression of ACh and  
 212 vasoactive intestinal peptide (VIP) increases, amplifying the process [148]. an animal experiment conducted with *VDR*<sup>-/-</sup> mice showed that without the existence  
 213 of VDR, the progress of atherosclerosis was accelerated and promoted [149]. In terms of neurons, vitamin D could mediate neuroprotection and the improvement  
 214 in neurogenesis, cell proliferation and differentiation, and neurotransmitter metabolism, which are similar to other neurodegenerative diseases [150].

215

**Table 4. Vitamin D and vascular dementia.**

Model/Subject (duration of the disease)	Strain and/or age	Supplements	Dose	Behavioral test	Effects	Signaling pathway	Reference
Vitamin D deficient rat model (chronic)	Male Sprague Dawley; 10 weeks	1,25 (OH) <sub>2</sub> D <sub>3</sub>	0.15 $\mu$ g/kg, 4 weeks	NA	Vitamin D deficiency impaired microvascular vasodilation. Calcitriol supplementation improves endothelium-dependent contraction	eNOS	[140]
Healthy college-aged Africa-Americans (NA)	18-30 years	Oral vitamin D	2000 IU/day, 4 weeks	NA	Promoting microvascular function	eNO	[141]
Endovascular perforation SAH model in Sprague-Dawley rat (acute)	Male Sprague Dawley; 10 weeks	1,25 (OH) <sub>2</sub> D <sub>3</sub>	30 ng/kg, 24 hours	Spontaneous activity, spontaneous movement of all limbs, vibrissae touch, forelimbs outstretching, and climbing wall of cage	Improves neurological deficits  Reducing cerebral artery remodeling and vasospasm	NA  OPN/AMPK/eNOS	[142]
Patients with metabolic syndrome (NA)	30-50 years; (BMI) <40 kg / m <sup>2</sup>	Vitamin D	50,000 IU/week, 16 weeks	NA	Inhibiting atherosclerosis	VCAM-1/IL-6/E-selectin	[143]
Endothelial colony-forming cells (ECFC) pretreated with 1 $\alpha$ ,25-	NA	1,25 (OH) <sub>2</sub> D <sub>3</sub>	0.1/10 nM, 24 hours	NA	Vasoprotective, neovasculogenetic and anti-inflammation effects	VE-cadherin/cofilin	[144]

(OH) <sub>2</sub> vitamin D <sub>3</sub> (NA)							
Immortalized mouse brain endothelial cells exposed to different vitamin D <sub>3</sub> concentrations	bEnd.3	1,25 (OH) <sub>2</sub> D <sub>3</sub>	0/5/20/200 nmol/L	NA	Protection against ischemic injury-induced BBB dysfunction in cerebral endothelial cells	NF-κB	[145]
Atherosclerosis induced by high fat-high cholesterol (HFHC) diet and water containing 2 mM CaCl <sub>2</sub> LDLR <sup>-/-</sup> /VDR <sup>-/-</sup> mice, Rag-1 <sup>-/-</sup> /VDR <sup>-/-</sup> mice	C57BL / 6 mice; 8 weeks	NA	NA	NA	Inhibiting atherosclerosis	MCP-1/IL-1β/IFN-γ/matrix metalloproteinase 9/renin/ICAM-1/E-selectin/VDR	[149]

216 eNO, endothelial NO; OPN, osteopontin; AMPK, Adenosine 5'-monophosphate activated protein kinase; VCAM-1, vascular cell adhesion molecule 1; MCP, monocyte chemoattractant protein; VE-cadherin, vascular  
 217 endothelial cadherin; OPN, osteopontin; NF-κB, Nuclear Factor kappa B; ICAM, intercellular cell adhesion molecule; NA, not applicable; SAH:subarachnoid hemorrhage.

## 218 5. Clinical Application of Vitamin D in Neurodegenerative Diseases

219 The beneficial effects of vitamin D in neurodegenerative diseases have been widely studied in cellular and animal experiments. There are also some clinical  
 220 trials and case reports about the effects of vitamin D in some neurodegenerative diseases. The specific information of them is summarized in Table 5.

221 Whether Vitamin D could improve the clinical symptoms of AD also has been investigated. A trial investigated the influence of vitamin D supplements on  
 222 the cognition of 210 AD patients, showing that oral vitamin D supplements (800 IU/day) for 12 months can significantly improve cognitive function in AD  
 223 patients [151]. But in 2011, a randomized controlled trial including 63 individuals found that vitamin D couldn't improve cognition or disability in mild-  
 224 moderate AD, no matter low dose (1000 IU/day) or high dose (6000 IU/day) [152]. Cognitive impairment is an important feature of AD patients [153]. In a  
 225 study about aged people, medium-chain triglycerides in combination with leucine and vitamin D may benefit cognitive function in frail elderly individuals  
 226 [154]. And a trial by 183 elderly subjects with mild cognitive impairment (MCI) found that vitamin D supplement (800 IU/day) for 12 months showed to have  
 227 an improvement in cognition through reducing oxidative stress regulated by increased TL in elder MCI adults [155]. But more trials showed vitamin D  
 228 supplements couldn't improve the cognition of subjects [156-158]. In summary, no sufficient evidence could prove that vitamin D could improve the symptoms  
 229 in AD patients.

230 Vitamin D supplement was found to have some clinical benefits for PD patients. A trial conducted in 1999 with 86 elderly PD patients found that 1α(OH)D<sub>3</sub>  
 231 supplement (0.1 μg/day) for 18 months could reduce the risk of hip and other non-vertebral fractures by retarding the bone mineral densities loss in osteoporotic

232 elderly PD patients [159]. And Michela *et al.* performed a trial in completely cognitive PD patients for 10 months. The subjects received a standard hospital  
233 diet with or without whey protein-based nutritional supplement enriched with leucine and vitamin D twice daily and underwent a 30-day multidisciplinary  
234 intensive rehabilitation treatment (MIRT). In this trial, a whey protein-based nutritional formula enriched with leucine and vitamin D with MIRT showed benefits  
235 in lower extremity function and maintained muscle mass in PD patients and Class I evidence also showed the diet formula used in this study with intensive  
236 rehabilitation could increase the walking distance of PD patients during a 6-minute walking test (6MWT) [160]. In addition, it was suggested that vitamin D  
237 could have the potential of improving balance in younger PD patients with the intake of high-dose vitamin D (10,000 IU/day) for 16 weeks [161]. Except for  
238 the effect on motor function, the development of PD could also be controlled by vitamin D. A trial appeared that a vitamin D<sub>3</sub> supplement (1200 IU/day) for 12  
239 months probably could prevent the deterioration of PD in a short time in patients with *FokI TT* or *CT* genotypes [162]. However, only a case reported in 1997  
240 presented that regular therapy with 4000 IU D<sub>3</sub>/day and 1 g Ca/day for 3 years couldn't benefit the fifty-year-old PD patient [163]. In general, the benefit of  
241 vitamin D on PD is obvious.

242 In a 10-year case report, a female MS patient ingested vitamin D supplements every day since January 2001 with a dose of 800 IU/day, then increased to  
243 4000 IU/day in September 2004 and 6000 IU/day in December 2005. The supplement reduced muscular pain and improved ambulation in the patient [164].  
244 The clinical effects of vitamin D in MS have been well investigated in many trials. A trial was conducted in 2011 and included 62 MS patients. They received  
245 300,000 IU/month or placebo by intramuscular injection for 6 months. The result showed no significant differences between these two groups in the expanded  
246 disability status scale scores (EDSS) and the number of gadolinium-enhancing lesions [165]. Another study also found that 20000 IU/week supplements of  
247 vitamin D for 96 weeks had limited effects in fully ambulatory MS patients [166]. A trial conducted by Daniel *et al.* about vitamin D and interferon (IFN) - $\beta$  in  
248 45 MS patients showed both 800 IU/day and 4370 IU/day of vitamin D<sub>3</sub> for a year had no significant improvement in ARR, EDSS, Quality of Life (QoL) and  
249 Flu-like symptoms (FLS), which are common side effects of IFN- $\beta$  treatment [167]. They also found that the intake of vitamin D<sub>3</sub> in the same doses for a year  
250 did not affect depression conditions in MS patients [168]. A similar result was also yielded in another study [169].

251 However, a study in 94 relapsing-remitting MS (RRMS) patients appeared that 50,000 IU/5d vitamin D for 3 months significantly improved the mental  
252 health of the patients [170]. A study in 66 MS patients was conducted to find the security and efficiency of the addition of vitamin D<sub>3</sub> to the treatment of IFN  
253  $\beta$ -1b ( IFNB), showing that the combination of 20000 IU/week of vitamin D<sub>3</sub> and IFNB for a year could reduce the activity of the disease without a higher risk  
254 of adverse events [171]. In addition, William *et al.* performed a trial in 2019 involving 189 RRMS patients. The group with the dose of 100,000 IU every week  
255 for 96 weeks had less progress in MS [172]. Another similar finding was also obtained in other studies [173, 174]. In terms of cognition, vitamin D also showed  
256 benefits to MS patients. In a study, the levels of serum vitamin D in the patients were supplemented by diet and sunlight exposure. After 3 months, this form of  
257 vitamin D supplement could improve cognition in MS patients [175]. Another trial also investigated the effect of vitamin D on fatigue, one of the most common  
258 and disabling symptoms of MS. 158 MS patients with significant fatigue were involved in this trial. Randomly divided into two groups, they were given 1  
259 mcg/day of alfacalcidol or placebo for six months and assessed the level of fatigue by the Fatigue Impact Scale (FIS) score. The result appeared that alfacalcidol  
260 could decrease fatigue and improve QoL in MS patients without serious adverse events [176].

261 While the doses of vitamin D supplementation might vary from person to person, it was suggested increasing vitamin D intake and having appropriate  
 262 sunlight exposure to maintain serum 25-hydroxyvitamin D at least 30 ng/mL (75 nmol/L), and preferably at 40–60 ng/mL (100–150 nmol/L) to achieve the  
 263 optimal overall health benefits of vitamin D. However, it is still crucial and essential to determine the doses and duration of vitamin D supplementation since  
 264 vitamin D supplementation can trigger undesirable consequences [177]. A case report of an 88-year-old woman showed that a long-term supplement of vitamin  
 265 D with 0.75 µg eldecalcitol capsules per day could worsen the symptoms of AD and cause hypercalcemia and renal dysfunction, leading to chronic delirium  
 266 [178]. Similarly, some case reports also alarmed that excessive intake of vitamin D could cause hypercalcemia and even threaten patients' lives [179-181]. But  
 267 this toxicity of vitamin D can be alleviated by simultaneous supplements of vitamin K and vitamin A[182].

268

**Table 5. Clinical studies including the effects of vitamin D in AD, PD, and MS patients**

Design	Subjects	Supplement	Dose	Assessment	Results	Reference
R, DB, PC	210 AD patients (age: over 65 years)	Vitamin D <sub>3</sub>	800 IU/day for 12 months	WAIS-RC, ADL, MMSE	Significantly improvement in cognitive function	[151]
R, PC	32 mild-moderate AD patients (median age: 77.5)	Vitamin D	1000 IU/day for 8 weeks, 6000IU/day for 8 weeks	ADAS-cog, Disability Assessment, WMS-R LM	No improvement in cognition, memory, and disability	[152]
R, DB, PC	86 PD patients (average age: 70.6 years)	1α (OH) D <sub>3</sub>	0.1 µg/day for 18 months	Computed radiographic densitometry in the second metacarpals	Significant improvement in bone mineral densities and reduce the risk of hip and other non- vertebral fractures	[159]
R, AB	150 cognitively intact PD patients	Vitamin D	ND	6MWT, 4MWS, TUG, BBS, HS, SPDDS, BW, SMM	Significant improvement in lower extremity function and muscle mass	[160]
R, DB, PC	51 PD patients (average age: 66.57 years)	Vitamin D	10,000 IU/day for 16 weeks	SOT, TUG, SLLE, FF, NHP	Significant improvement in balance in younger patients	[161]

R, DB, PC	114 PD patients (average age: 72 years)	Vitamin D <sub>3</sub>	1200 IU/day for 12 months	HY, UPDRS, NEDL, MEDL, ME, MC, MMSE	Significantly inhibit the development of PD	[162]
CR	1 PD patient (age: 55 years)	Vitamin D	4000 IU/day for 3 years	Neurological examination	No improvement in any symptom	[163]
CR	1 MS patient born in 1950	Vitamin D <sub>3</sub>	800 IU/day, 4000 IU/day, 6000 IU/day	muscular pain, ambulation ability	Improvement in motor function	[164]
R, PC	62 MS patients	Vitamin D <sub>3</sub>	300,000 IU/month for 6 months	EDSS, number of gadolinium- enhancing lesions	No significant improvement in the status of disability	[165]
R, DB, PC	68 fully ambulatory MS patients	Vitamin D <sub>3</sub>	20,000 IU/week for 96 weeks	ARR, EDSS, MSFC, grip strength, fatigue	No significant improvement in any symptoms	[166]
R, DB	45 MS patients (age: over 18 years)	Vitamin D <sub>3</sub>	800 IU/day or 4370 IU/day for a year	ARR, EDSS, QoL, FLS	No significant improvement in any symptoms	[167]
R, DB	40 MS patients (age: over 18 years)	Vitamin D <sub>3</sub>	800 IU/day or 4370 IU/day for a year	FAMS	No significant effect on depression	[168]
R, PC	40 MS patients (age: 18-55 years)	Vitamin D <sub>3</sub>	14,000 IU/d ay for 48 weeks	HADS-D	No significant effect on depression	[169]
R, DB, PC	94 RRMS patients (age: 18-55 years)	Vitamin D <sub>3</sub>	50000 IU/5 days for 3 months	MSQOL-54 Persian version	Significant improvement in mental health	[170]

R, DB, PC	66 MS patients (age: 18-55 years)	Vitamin D <sub>3</sub>	20000 IU/week for a year	ARR, BOD, EDSS, timed 25- foot walk test, and timed 10 foot tandem walk tests	Significant reduction in the activity of the disease	[171]
R, DB, PC	181 RRMS patients (age: 18-65 years)	Vitamin D <sub>3</sub>	100,000 IU/week for 96 weeks	ARR, MRI parameters, EDSS	Significantly less progress	[172]
R, DB, PC	229 RRMS patients (age: 18-55 years)	Vitamin D <sub>3</sub>	6,670 IU/day for 4 weeks; then 14,007 IU/day for 44 weeks	NEDA-3	Significantly less progress	[174]
R	88 MS patients (average age: 36.3 years)	Vitamin D <sub>3</sub>	diet and sunlight expose	MoCA, SDMT, BVMT-R	Significant improvement in cognition	[175]
R, DB, PC	158 MS patients (average age: 41.1 years)	Alfacalcidol	1 mcg/day for 6 months	FIS	Significant decrease in fatigue and improvement in QoL	[176]
CR	1 AD patient (age: 88 years)	Eldecalcitol	0.75µg/day for 5 months	MMSE, IADL, Electrocardiogram , laboratory examination	Cognitive decline, hypercalcemia, and renal dysfunction	[178]
CR	1 MS patient (age: 45 years)	Vitamin D <sub>3</sub>	ND	ND	hypercalcemia	[179]
CR	1 MS patient (age: 58 years)	Vitamin D <sub>3</sub>	5500 IU/day for several years	Electrocardiogram , laboratory examination	Severe hypercalcemia	[181]

269 CR, Case report; R, Randomized; DB, Double-blind; PC, Placebo-controlled; OL, Open-label; AB, assessor-blind; WAIS-RC, Wechsler Adult Intelligence Scale-Revised; ADL, Activity of Daily Living; MMSE, Mini-  
270 Mental State Examination; ADAS-cog, Alzheimer's disease assessment scale-cognitive subscale; WMS-R LM, Wechsler Memory Scale-Revised Logical memory; BPSD, behavioural and psychological symptoms of  
271 dementia; IADL, instrumental activities of daily living; 6MWT, 6-minute walking test; 4MWS, 4-meter walking speed; TUG, Timed Up and Go test; BBS, Berg balance scale; HS, handgrip strength; SPDDS, Self-  
272 assessment Parkinson's Disease Disability Scale; BW, body weight; SMM, skeletal muscle mass; SOT, Sensory Organization Test; SLLE, strength of leg flexion and extension; FF, fall frequency; NHP, Nottingham health  
273 profile; HY, the modified Hoehn and Yahr stage; UPDRS, Unified Parkinson's Disease Rating Stage; NEDL, nonmotor experiences of daily living; MEDL, motor experiences of daily living; ME, motor examination;



274 MC, motor complications; EDSS, expanded disability status scale; ARR, relapse rate; MSFC, multiple sclerosis functional composite; QoL, Quality of Life; FLS, Flu-like symptoms; FAMS, Functional assessment of  
275 MS; HADS-D, Hospital Anxiety Depression Scale depression subscale; BOD, burden of disease; RRMS, relapsing-remitting MS; NEDA-3, no evidence of disease activity; MoCA, Montreal Cognitive Assessment;  
276 SDMT, Symbol Digit Modalities; BVMT-R, Brief Visuospatial Memory Test; FIS, Fatigue Impact Scale; ND, not determined.

## 277 **6. Conclusions**

278 Vitamin D exhibits its functions through binding to its nuclear receptor VDR, membrane receptor 1,25 D3-MARRS, or interfering with molecules in  
279 signaling pathways that are associated with the pathogenesis of neurodegenerative diseases, such as AD, PD, MS, and VaD. Still, more experiments on cell and  
280 animal models are required for further insight into molecular mechanisms of vitamin D to attenuate cognitive and motor dysfunctions caused by  
281 neurodegenerative diseases. In addition, some of the clinical studies that we concluded in this review demonstrated positive effects of vitamin D supplementation  
282 on neurodegenerative diseases while the rest displayed no significant influence. The contradictory results can probably be attributed to diverse doses and  
283 durations of vitamin D treatment. Therefore, intricately designed, large multicenter clinical trials need to be conducted to investigate and analyze the potency  
284 of vitamin D in influencing the clinical symptoms of patients with neurodegenerative disorders whether as clinical nutrition or as a therapy.

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### 286 **Author contribution statement:**

287 All authors listed have significantly contributed to the development and the writing of this article. </p>

288

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294

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296 The authors declare no competing interests.

297

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