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Review

Molecular insights into the pathogenic impact of vitamin D deficiency in neurological disorders

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ABSTRACT

Neurological disorders are the major cause of disability, leading to a decrease in quality of life by impairing cognitive, sensorimotor, and motor functioning. Several factors have been proposed in the pathogenesis of neurobehavioral changes, including nutritional, environmental, and genetic predisposition. Vitamin D (VD) is an environmental and nutritional factor that is widely distributed in the central nervous system's subcortical grey matter, neurons of the substantia nigra, hippocampus, thalamus, and hypothalamus. It is implicated in the regulation of several brain functions by preserving neuronal structures. It is a hormone rather than a nutritional vitamin that exerts a regulatory role in the pathophysiology of several neurological disorders, including Alzheimer's disease, Parkinson's disease, epilepsy, and multiple sclerosis. A growing body of epidemiological evidence suggests that VD is critical in neuronal development and shows neuroprotective effects by influencing the production and release of neurotrophins, antioxidants, immunomodulatory, regulation of intracellular calcium balance, and direct effect on the growth and differentiation of nerve cells. This review provides up-to-date and comprehensive information on vitamin D deficiency, risk factors, and clinical and preclinical evidence on its relationship with neurological disorders. Furthermore, this review provides mechanistic insight into the implications of vitamin D and its deficiency on the pathogenesis of neurological disorders. Thus, an understanding of the crucial role of vitamin D in the neurobiology of neurodegenerative disorders can assist in the better management of vitamin D-deficient individuals.

1. Introduction

Vitamin D (VD) is a fat-soluble vitamin that is either supplied through diet or synthesized in the skin after exposure to sunlight of a wavelength ranging from 280 nm to 320 nm [1]. In nature, VD exists in two isomeric forms; vitamin D_2 (ergocalciferol), the most common dietary form photochemically synthesized in plants, and vitamin D_3 (cholecalciferol), which is synthesized from 7-dehydrocholesterol under the skin following exposure to UV radiation. The maintenance of adequate plasma VD levels has become a universal public health problem, especially in elderly people with limited exposure to sunshine [2]. According to an estimate, approximately 90% of the elderly population in western countries suffer from a mild to moderate range of VD deficiency [3]. Vitamin D insufficiency is a global health concern, afflicting more than 1 billion populations worldwide [4]. Several risk factors have been found to cause VD deficiency, such as modifiable (sunscreen, low dietary intake, and drugs), non-modifiable (age, skin color, seasonal variation, individuals' variability), and patients' independent factors (high and low altitude). Sunshine and its sufficient exposure are considered the most versatile factors for the maintenance of an adequate plasma level and the reduction of dietary dependency [5]. However, there are many variables that impact the exposure dose of UV rays, such as time of exposure, seasonal variation, latitude, altitude, body covering, traditional costumes, sunscreen creams, skin color, age and drug therapy (Table 1) [6].

The UV radiation of sunlight through a non-enzymatic process produces previtamin D_3 from the photolytic cleavage of the B ring of 7-dehydrocholesterol (7-DHC) that further undergoes spontaneous isomerization by heat to form vitamin D_3 in the epidermis. However, both the synthesized and dietary VD are physiologically inactive and require metabolic activation for their cellular activity. The metabolism of VD is tightly regulated and involves complex metabolic pathways in the liver and kidney [40]. The synthesized VD and its metabolites bind to vitamin D binding protein (DBP) which then transports them to different tissues,

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Table 1
Risk factors for reduced serum vitamin D level.

S. No.	Risk Factor	Comments	References
1.	Increased dependence on fortified food	Reduced intake of fortified foods or sometimes inadequacy of fortified foods and also strictly vegetarians are at increased risk.	[7]
2.	Limited dietary source	Fish-liver oil and fatty fish are the only rich sources of vitamin D, which is becoming gradually unreachable to most of the population.	[8]
3.	Limited exposure to the sun		
	a.Pigmentation of skin	Dark skin contains higher melanin content, which efficiently blocks UVB radiation and thus requires about 5 times more exposure than average skin color.	[9]
	b.Season, latitude, and angle of exposure to the sun	People living at 52° degrees north have reduced or almost no VD synthesis by skin from November to March. Furthermore, people living at higher altitudes are deprived of adequate UVB exposure, especially in winter.	[10]
	c.Sunscreen cream uses	Continuous use of sunscreen with greater than factor 8 UVB protection blocks radiation and contributes to VD deficiency. However, low risk has been reported by observational studies and field trials.	[11]
	d.Time and duration of exposure	In general, between 10:00 AM and 2:00 PM, the exposure is maximum and an exposure of 1 erythemal dose produces 10 000 IU of VD.	[12]
	e.Traditional skin coverings	All clothing blocks the exposure to sunlight and impairs VD synthesis, with a 2.3 odds ratio in reduction of bone mineral density.	[13]
	f.Urbanization and reduced exercise opportunities	Increased indoor residence time and prioritization of vehicle use and confinement due to poor urban development results in reduced exposure to the sun and diminished production of VD.	[14]
4.	Age		
	a.Diminished production by the skin	VD production in a 70-year-old person is 25% lower than in an adult. Reduced VD production by skin could be attributed to aged skin's reduced conversion capabilities.	[15–17]
	b.Lactose malabsorption and intolerance	A 74-year-old person has a higher prevalence of lactose malabsorption and thus intolerance, leading to a diminished intake of fortified milk.	[18]
	c.Immobility	Increased housebound time, hospitalization, and other organizational activities reduce sun exposure.	[19]
	d.Reduced kidney function	With advancing age, there is a significant decline in kidney function, leading to reduced activation of VD.	[20]
5.	Altered physiological state		
	a.Pregnancy	The development of a child entirely depends on maternal VD level and if there is inadequacy, leads to VD deficiency, leading to altered fetal bone growth.	[21]
	b.Exclusive breastfeeding	The amount of VD in breast milk is low, so supplementation is needed, and 4000 IU improves both the mother and child's VD status.	[22]
6.	Pharmacogenetic variations	A lack of physiologically active VD is also caused by genetic variation in the VD metabolizing enzyme. In some Indo-Asians, increased activity of 24-hydroxylase results in increased catabolism and thus reduced serum levels of 25-hydroxy-vitamin D.	[23]
7.	Diseased state		
	a.Malabsorption syndrome	Reduced absorption of VD is also reported in some comorbid illnesses, including Crohn's disease, Whipple disease, cystic fibrosis, sprue, and severe hepatic impairment.	[24]
	b.Obesity	Increased body fat results in irreversible sequestration of active vitamin D, leading to reduced physiologically active VD.	[25]
	c.Chronic diseases	Increased indoor confinement due to chronic diseases such as renal diseases, neurological disorders, and musculoskeletal disorders contributes to vitamin D deficiency.	[26]
8.	Drug-induced VD deficiency		
	a.Antiepileptic drugs (Phenytoin, carbamazepine, phenobarbital, and pirimidone)	Activates the pregnane X receptor (PXR), which in turn upregulates 24-hydroxylases, leading to reduced activation of vitamin D and also altering its clearance.	[27-30]
	b.Glucocorticoids	Increased catabolism of vitamin D by upregulation of renal vitamin D-24-hyroxylase.	[31]
	c.Antidepressant	Tricyclic antidepressants increase the metabolism of vitamin D by modulating 1-α-hydroxylase and/or 24-hydroxylase.	[32]
	d.Miscellaneous (rifampin, cimetidine, thiazide)	Impairment of metabolic activation and clearance of vitamin D.	[33–35]
	e.Antimanic drug (Lithium)	Raises the level of parathyroid hormone and thus lowers the levels of active VD (1,25-dihydroxyvitamin D).	[36]
	f.Laxatives/Mineral oil	Continued use of stimulant laxatives reduces the absorption of vitamin D.	[37]
	g.Antihyperlipidemic agents (Orlistat, Cholestyramine, Colestipol)	They reduce the absorption of fat-soluble vitamins (Vitamin D)	[38,39]

including liver and kidney. VD is activated by hepatic microsomal (CYP2R1) and mitochondrial (CYP27A1) enzymes into 25OHD, the main circulating form, which is further metabolized by renal proximal tubular enzyme CYP27B1 into 1,25-dihydroxyvitamin D (1,25(OH)2D), a steroidal ring metabolite [27,41]. The latter mediates several genomic actions by acting as a ligand for the vitamin D receptor (VDR), which in turn regulates the transcription of several responsive genes by modulating Vitamin D Responsive Elements (VDREs) present in the promoter region of the target genes. Further, the polymorphism of vitamin D metabolizing enzyme has been recognized as an important risk factor for reduced metabolically active vitamin D levels and has been reported to produce a variance of up to 65% in serum VD level [42]. Polymorphisms in the VD-metabolizing genes CYP2R1 and CYP27A1 are known genetic risk factors for decreased serum VD levels. Furthermore, evidence for the polymorphism of CYP2R1 and reduced VD level has been provided by a genome-wide association study showing different variants with variable enzymatic activity [43]. It is believed that the cytochrome P450 enzymes CYP2D6 and CYP27 primarily function as 25-hydroxylases and are involved in several metabolic reactions of vitamins, steroids, and xenobiotics [44]. The CYP2D6 gene codes for the metabolizing enzyme and it has been reported that patients with Parkinson's disease (PD) express a genotype frequency of the CYP2D6*4 variant resulting in unpredictable enzyme activity and increased risk of PD pathogenesis [45]. Nonetheless, not only the polymorphism of VD metabolizing enzymes but also that of the VD receptor (VDR) has been demonstrated to be a risk factor for diminished vitamin D activity and the pathogenesis of neurological diseases [46,47].

In addition to the regulation of calcium and phosphate homeostasis, the genomic and nongenomic actions of vitamin D exhibited pleiotropic effects, including regulation of the immune system, cellular inflammation, oxidative stress, differentiation, proliferation, and also apoptosis [48]. Vitamin D regulates the mucosal barrier function of the intestine by modulating the immune system, and its deficiency could result in intestinal diseases by favoring endotoxin translocation and disturbing microbiota [49]. Further, adequate vitamin D supplementation and maintenance of an acceptable plasma level along with vitamin B restored the disturbed gut microbiome [50]. Furthermore, numerous clinical and preclinical studies have linked altered gut microbiota to neurological diseases [51]. There have been multiple reports of neurological diseases associated with a weakened immune system as a result of alterations in the gastrointestinal microbiota and microbial metabolite synthesis. The communication between the microbiota and brain is bidirectional and occurs through the microbial metabolites and neurotransmitters of the host cell [52]. In addition to metabolite-dependent communication, several other mechanisms, such as endocrine, neurochemical, and toll-like receptors, have been proposed for their implication in the gut-brain axis. Furthermore, it has been shown that there is a constant relationship between VD, gut microbiota, and the precise balance of immune function, which is regulated by both innate and adaptive immune responses [53]. The impaired gut-brain connection is frequently related to neuronal degeneration secondary to immune dysfunction [54]. VDR is expressed on several immune cells, and the action of VD intricately regulates immune function, and its deficiency may result in a disbalance of pro-inflammatory and anti-inflammatory activities [55]. The alteration of neuroimmune function has been recognized as an important mediator in neurodegenerative diseases [56]. It has also been observed that the IL-33/IL-31 axis is crucial in immune-mediated allergy disorders [57]. The regulatory role of VD and the gut microbiome on the immune system is mediated by modulation of the IL-33/IL-31 axis. Intriguingly, it has been observed that patients with allergy conditions have lower plasma VD levels and higher IL-33 and IL-31 levels [58].

The presence of vitamin D metabolizing enzymes and vitamin D receptors (VDR) in various nervous tissue and brain areas suggests that VD may play a role in neurological disorders.

This review focuses mainly on the links between vitamin D deficiency and neurological disorders such as Alzheimer's, Parkinson's, epilepsy, and multiple sclerosis. In this review, we discuss recent advances in our understanding of the numerous molecular mechanisms implicated in vitamin D's modulation of neuronal function. In addition, the recognition of vitamin D deficiency risk factors and their interaction with several neurological illnesses highlights the necessity for routine monitoring of blood levels and clear recommendations for diet and supplementation in individuals at elevated risk for insufficiency.

2. Vitamin D and Alzheimer's disease

Alzheimer's disease (AD) is a complex progressive neurodegenerative disease characterized by dementia with progressive loss of intellect, language, and social performance, as well as an increased degree of reliance on others for daily living activities. AD is a multifactorial disease with complex underlying mechanisms, including amyloid β plaque and neurofibrillary tangles as hallmark histopathologic changes [59]. In addition, increased oxidative stress, altered processing of amyloid precursor protein, neurotrophic factor insufficiency, poor mitochondrial functioning and energy metabolism, and genetic anomalies have been postulated to have a role in the etiology of Alzheimer's disease (AD) [60]. The clinical diagnosis is mainly reliant on the degree of dementia, which is diagnosed using a cognitive score. Although, the definitive diagnosis for AD is the histopathological examination of brain specimens for accumulation of β-amyloid plaques in the cerebral cortex and the appearance of neurofibrillary tangles [61,62]. However, expanding evidence supports the clinical use of cerebrospinal fluid (CSF) biomarkers as they can reflect changes in the brain because of their direct connection through extracellular space. It has been shown that amyloid β of 42 residue long (Aβ42), total-tau (T-tau), and phosphorylated tau (P-tau) have the greatest potential for the diagnosis of AD [63] and may help in the prediction of the transition from preclinical to clinical AD [64]. In addition to CSF biomarkers, neuroimaging such as magnetic resonance imaging (MRI), and positron emission tomography (PET) techniques allow for early diagnosis, disease-related pathophysiological changes, and the detection of beta-amyloid deposition in the brain [65]. Modulators of cholinergic transmission such as tacrine, galantamine, donepezil, and rivastigmine are used for the management of AD, which provide symptomatic relief and have a modest effect on disease progression [66]. Memantine, an antagonist for N-Methyl-D-aspartate (NMDA) receptors, has been approved for the treatment of moderate to severe Alzheimer's disease [67]. Several therapies that target the amyloid beta ($A\beta_{13-28}$), including monoclonal antibodies (solanezumab, gantenerumab, crenezumab, and aducanumab) and BACE inhibitors (verubecestat, lanabecestat, and atabecestat), are in various stages of development for the treatment of AD [68]. Current research is also focusing on other potential therapeutic targets, such as tau protein, anti-inflammatory medicines, and neuroprotective compounds. Recently, the FDA approved lecanemab [69] and aducanumab [70] for the treatment of people with early AD, and they have been demonstrated to slow the disease progression by reducing beta-amyloid plaque [71]. Due to the significant increase in the number of AD cases and the rising health burden, there is an ongoing need to search for disease-modifying agents that prevent or delay the onset of disease, reduce neurodegeneration, and enhance the quality of life. There are no effective treatments to prevent neurodegeneration from deteriorating, and the majority of currently available drugs for Alzheimer's disease (AD) are limited to treating dementia [72]. Furthermore, there is compelling evidence suggesting the damage to additional brain areas following the disease progression that is not mainly linked to memory function warrants the search for novel therapeutic agents to prevent neuronal damage.

Despite several hypotheses attempting to explain the pathobiology of the disease, the exact cause of AD is still not precisely known. There is growing evidence for dietary nutritional deficiencies such as antioxidant nutrients, dietary fats, and vitamins in the pathophysiology of AD. Thus,

the probable role of nutrition in the pathogenesis of AD is of considerable interest as there is an urgent need for the search for novel and effective strategies that are of preventative and therapeutic potential. Moreover, adequate dietary intake of nutrients especially by introducing a Mediterranean diet and/or ketogenic diet, proffers essential requirements for brain functioning and exerts neuroprotective effects [73]. However, vitamin D (VD) is considered both a dietary factor and a hormone and is well known for its significant role in bone and calcium metabolism. In addition to bone and calcium metabolism, VD exerts a regulatory role in protein homeostasis and slows age-related pathobiologic processes, especially in neurodegenerative processes such as AD, Parkinson's disease, multiple sclerosis, and vascular dementia [74]. VD deficiency is also thought to be a genetic risk factor for neurodegenerative diseases [75]. Moreover, the expression of vitamin D receptors (VDR) and the presence of enzymes that convert vitamin D into an active form in various brain areas provide evidence for its central action [76].

2.1. Clinical evidence linking vitamin D deficiency and the AD

There is a large body of literature reporting vitamin D deficiency in Alzheimer's disease patients, with 70–90% of patients having a low vitamin D level [77,75,78,79], with female patients having a higher incidence [80,81]. The reduced physiological vitamin D level may result in the deterioration of cognitive function in older Mexican adults with dementia and serves as a risk factor for cognitive decline [82]. After 5.6 years of monitoring vitamin D status in 1658 elderly individuals, a prospective study showed that hypovitaminosis D (<25 nmol/L) was associated with a significantly elevated risk of dementia and Alzheimer's disease pathogenesis in later life [83]. A decrease in plasma vitamin D was associated with an increased risk of Alzheimer's disease (AD) and vascular dementia, as shown by the fact that 418 participants developed AD and 92 persons had vascular dementia in a prospective cohort research involving 10186 adults from Denmark [84]. The InCHIANTI study, which included 858 adults over the age of 65, indicated that lower blood VD levels (<25 nmol/L) were associated with an elevated risk of neurocognitive loss, with a relative risk of cognitive function decline of 1.6 [85]. A meta-analysis of 12 prospective cohort studies and four cross-sectional studies revealed that a low VD is associated with both the progression of dementia and the pathogenesis of Alzheimer's disease [86]. Annweiler et al. proposed that high-dose supplementation of VD (100,000 IU) with memantine in patients with moderate AD for one month produced improvement in cognition and memory function [77]. Furthermore, vitamin D supplementation with memantine in moderate Alzheimer's patients exhibited a potentiating effect on cognitive performance and memory ability by preventing neuronal damage [87]. Further evidence for the involvement of vitamin D in memory function was provided by a study on 146 patients, consisting of 78 women and 68 men, wherein it was reported that the individuals with lower minimal-mental state examination (MMSE) scores had characteristically lower serum vitamin D levels. These findings were also supported by magnetic resonance imaging (MRI) of the brains of the study participants [88]. Moreover, a study of 230 participants, comprising 61 healthy subjects, 61 individuals with mild cognitive decline, and 108 Alzheimer's patients with varying degrees (41, mild; 35, moderate; and 32, severe) of cognitive impairment, reported that MMSE and serum vitamin D level well correlate with cognitive function in both genders and are thus considered as useful biomarkers for prediction and diagnosis of dementia and stages of AD [89]. Recently, the 'Nutrition the Unrecognized Determinant for Alzheimer's Disease (NUDAD)' study explores several biomarkers to demonstrate a link between cognitive decline and 28 nutritional components in serum and 5 in cerebrospinal fluid (CSF). Reduced levels of S-adenosylmethionine in the cerebral spinal fluid (CSF) and elevated levels of high-density lipoprotein (HDL), cholesterol, iron, and 1,25(OH)2 D were found to be related to memory impairment [90]. However, the authors believed that the contradictory findings on the association between high iron and $1,25(OH)_2$ vitamin D with a decline in memory function might be biased in their study as they show diurnal variation in plasma levels, which is usually short-lived [91,92]. In addition, a cohort study on 1182 Swedish men reported that there was no correlation between plasma VD level, dietary VD intake, vitamin D–synthesis genetic risk score (GRS) at baseline with cognitive decline following 18 years of follow-up in community living old men [93]. A randomized, double-blinded, placebo-controlled study reported that there was no improvement in cognitive function following supplementation with vitamin D3 (400 IU) with calcium (1000 mg) in 2044 participants [94]. Moreover, it has been reported by another randomized double blind placebo controlled trial on 210 adults with AD that daily supplementation of VD (800 IU/day orally) for 12 months results in significant improvement in cognitive performance and also reduces the amyloid β related plasma markers such as Aβ42, amyloid precursor protein (APP), Beta-Secretase-1 (BACE1), APPmRNA, and BACE1mRNA following repeated measure analysis [95]. The supplementation of VD in AD patients not only prevents the synthesis of amyloid β but also stimulates the clearance of Aβ peptides from the extracellular site of brain [96]. Moreover, it has been reported that VD was safe and produced a normal serum level of 25 (OH) D following supplementation at a dose of 50,000 IU (3 times/week) for 4 weeks in AD patients [97].

2.2. Preclinical evidence linking vitamin D deficiency and the AD

Besides the clinical findings, several preclinical studies demonstrated that there is a reciprocal relationship between vitamin D and AD. Ample evidence suggests the cognitive function of vitamin D and its deficiency may accelerate the aging-related decrease in learning and memory [98]. A study demonstrated the causal relationship between vitamin D status and memory in middle-aged F344 rats, wherein VD-deficient rats exhibited impairment of memory function. Vitamin D3 supplementation at low, medium, and high doses (100, 1000, or 10,000 IU/kg of diet) improved memory performance on the Morris Water Maze by upregulating G protein function, cellular communication, and synaptic transmission in hippocampal neurons [99]. Impaired neurogenesis has been recognized as one of the early pathological changes caused by the deposition of Aβ plaque in patients with AD and vascular dementia [100]. Early vitamin D deficiency in transgenic AD-like mice resulted in increased amyloid plaque, whereas late deficiency causes impairment of neurogenesis in both wild-type and AD-like mice. Furthermore, the preventive and curative treatment with a high dose of vitamin D resulted in improvement in cognition evidenced by a significant increase in percentage alteration and also improved neurogenesis in the hippocampus of both wild and AD-like mice [101]. In addition, pre- and post-treatment with vitamin D3 (42 IU/kg/day subcutaneously) demonstrated a neuroprotective effect against colchicine (15 μg/rat icv injection)-induced Alzheimer's disease (AD) in rats. This effect was evidenced by a significant reversal of the increase in latency time and amyloid beta (Aβ) peptide and decrease of brain-derived neurotrophic factor (BDNF), glutathione reductase (GR), and glutathione peroxidase (GPX) in hippocampal tissues [102]. Recent research has shown that VD treatment (5 μg/kg/day) ameliorates Aβ-induced memory impairment in rats, as measured by the passive avoidance test and Morris water maze test. In addition, it was reported that the VD reversed the Aβ-induced decrease in total antioxidant capacity (TAC), total thiol group (TTG), increased malondialdehyde (MDA) level, and DNA damage in both hippocampal tissues and serum after 2 weeks of treatment [103]. Furthermore, pretreatment with VD (100, 1000, and 10,000 IU/kg) restored biochemical markers of oxidative stress and interleukin (IL-6) in the hippocampus of rats, resulting in a significant improvement in memory following lipopolysaccharide-induced memory impairment [104]. However, contrary to these reports, Byrne et al. conducted a behavioral assessment on adult rats with vitamin D deficiency and observed no behavioral changes, including the absence of an active avoidance response test [105].

2.3. Pathophysiologic mechanisms of vitamin D deficiency and AD

Multifactorial mechanisms have been proposed for pathogenesis and involve both genetic as well as non-genetic mechanisms in the pathophysiology (Fig. 1) of AD. The antioxidant and anti-inflammatory actions of vitamin D in addition to modulatory effects on the growth, development, and proliferation of neurites have been extensively investigated for the involvement of vitamin D deficiency (VDD) in AD pathogenesis [106]. VD also exerts neuroprotective action by multifaceted actions, including alteration of neurotransmission, anti-inflammatory, antioxidant, the plasticity of synapses, and modulation of calcium homeostasis. The neuronal effects of VD are caused by genomic actions mediated by transcriptional activities through the vitamin D receptors (VDR) located in the nucleus of the neuron and non-genomic actions mediated by the induction of fast signaling through the VDR located on the neuronal membrane and/or cytosol. The neuronal effects of VD in AD via the non-genomic mechanism are further supported by a report showing the expression of VDRs on the neuronal cell membrane and their co-localization with amyloid precursor protein (APP) [107].

It is generally accepted that the formation of extracellular amyloid plaque and intracellular neurofibrillary tangles (NFTs) are the primary causes of the severe neuronal loss observed in Alzheimer's disease. The familial form of AD typically manifests at an earlier age than the sporadic form, which is mostly caused by mutations in amyloid precursor protein (APP) and/or presenilin 1 and 2 (APP processing enzymes), leading to aberrant extracellular deposition of amyloid-β protein and the formation of neuritic plaques [108]. Nevertheless, the sporadic form is typically late-onset AD with multiple etiopathogeneses, including genetic, environmental, and lifestyle factors. In sporadic AD the failure of the mechanism that mediates the clearance of Aβ plays a key role in the pathogenesis. Previously, the ε4 allele of the Apolipoprotein E (APOEε4) gene was reported as the only risk factor for sporadic AD [109]. A recent study suggested that the risk of AD may be caused by less than 100 common factors [110]. Some uncommon variants of genes, including TREM2, SORL1, ABCA7, ABCA1, PLC2, and ADAM10, with extremely low frequency, have been identified as risk factors for the pathogenesis of sporadic AD [111]. In addition to hereditary factors, various other etiologies, including middle-aged hypertension, ischemic heart disease, high serum cholesterol, diabetes, inflammatory processes, and viral infection, have been implicated in the etiology of late-onset Alzheimer's disease [112].

Tau is a microtubule-associated protein that is crucial for the preservation of normal cellular structure, axonal transport, and synaptic plasticity. The excessive and abnormal phosphorylation of tau, especially by glycogen synthase kinase 3β (GSK3β), results in the formation of paired helical filaments of tau and intracellular deposition of neurofibrillary tangles (NFTs) [113]. Nonetheless, it is worth mentioning that VD exerted neuroprotective action by regulating the APP and amyloid β (Aβ) processes in AD. VD and its analogs such as D2 and D3 suppress the production of Aβ in the VD-deficient mouse brain and also in neuroblastoma cells by modulating the production of BACE2 and γ-secretase [114]. Further, VD has been shown to decrease the accumulation of Aβ by promoting phagocytosis and also through an efflux mechanism

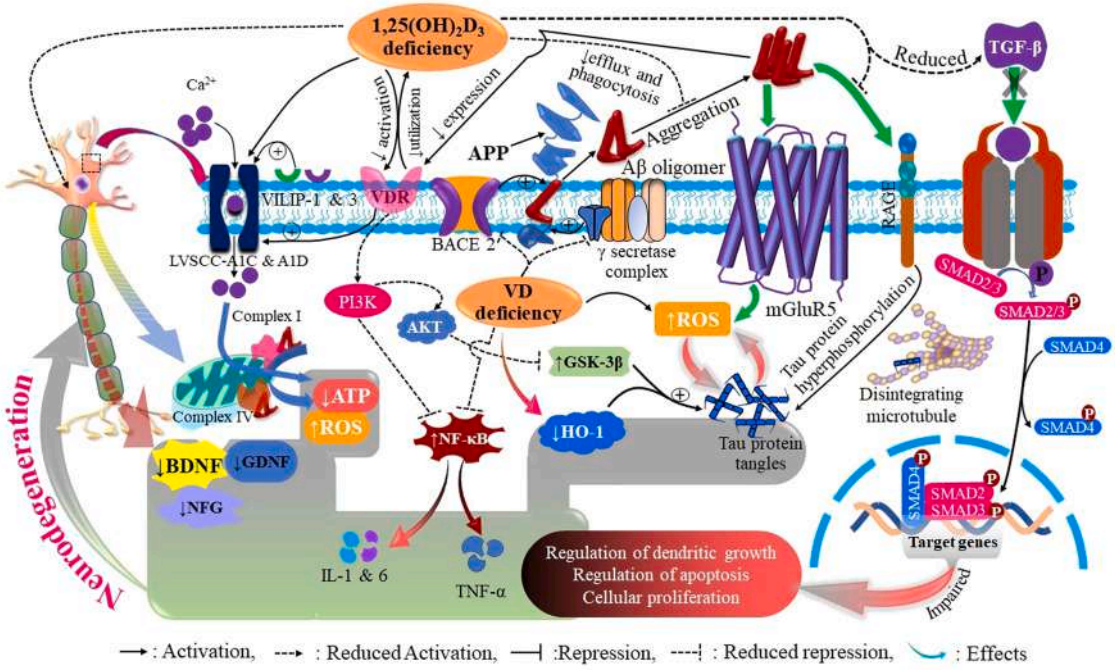

Fig. 1. Pathophysiologic mechanism of vitamin D deficiency-induced Alzheimer's disease. VD deficiency (VDD) directly and indirectly dysregulates neuronal Ca^{2+} homeostasis by modulating LVSCC-A1C and LVSCC-A1D expression, allowing unrestricted Ca^{2+} entry, which alters mitochondrial ATP production and increases reactive oxygen species (ROS). VDD results in decreased activation of neuronal cell membrane VDR, resulting in increased production of GSK-3β and NF-κB via PI3K/AKT pathway. VDD represses inhibitory control over BACE2 and the γ-secretase complex, which alters APP processing and the formation of Aβ polymers and their extracellular polymerization due to a lack of VD-mediated efflux and phagocytosis, resulting in elevated ROS and reducing heme-oxygenase-1 (HO-1) expression and triggering tau protein tangles through mGluR5 and RAGE activation. VDD reduces TGFβ receptor activation as a result of latent TGFβ activation, affecting the expression of some target genes via SMAD pathways, which in turn impairs the regulation of dendritic growth, apoptosis, and cellular proliferation. The resultant increase in ROS, intracellular tau tangles, TNF-α, IL-1, and IL-6, decreased production of HO-1, ATP, BDNF, GDNF, and NGF, and impairment of expression of genes involved in cellular differentiation and repair all contribute to neurodegeneration. AKT: Protein Kinase B (PKB), APP: Amyloid precursor protein, ATP: Adenosine triphosphate, Aβ: Amyloid beta, BACE2: β-site Aβ precursor protein cleaving enzyme 2, BDNF: Brain-derived neurotrophic factor, GDNF: Glial cell line-derived neurotrophic factor, GSK3β: Glycogen synthase kinase-3 beta, HO-1: Heme Oxygenase-1, IL-1: Internleukin-1, IL-6: Internleukin-6, LVSCC-A1C: L-type voltage-sensitive calcium channels A1C, LVSCC-A1D: L-type voltage-sensitive calcium channels A1D, NGF: Nerve growth factor, PI3K: Phosphoinositide-3-kinase, RAGE: Receptor for advanced glycation end-products, ROS: Reactive oxygen species, SAMD: Suppressor of mothers against decapentaplegic, TGF-β: Transforming growth factor-β, TNF-α: Tumor necrosis factor-α.

between the brain and blood across the blood-brain barrier (BBB) [115]. Furthermore, 1,25(OH)2D has been shown to promote the phagocytosis of soluble Aβ proteins by improving the recovery ability of macrophages [116]. Regardless of Aβ-peptide being toxic to cultured neuron cells and a major component of amyloid plaques, it has been reported that the formation of Aβ deposits in transgenic mice overexpressing APP failed to cause sufficient neurodegeneration [117] suggesting the implication of some additional mechanisms in the pathogenesis of AD.

Transforming growth factor- β (TGF-β) exists in three isomeric forms such as TGF-β1, -β2, and -β3, which is a multifunctional polypeptide cytokine mainly secreted as a latent form that regulates cellular proliferation, growth, and development, migration, and differentiation [27]. In the brain, TGFβ1 has been shown to interfere with the Aβ-induced cellular death cascade in addition to its neuroprotective action against excitatory neurotoxins, hypoxia, and ischemic tissue injury [118]. The secretion of TGFβ1 has been found to stimulate microglial recruitment, a crucial cellular response for the removal of toxic insults at the site of injury. The increased secretion and activation of TGFβ1 have been observed following lipopolysaccharide (LPS) and interferon-gamma (IFNγ) mediated stimulation of cultured hippocampal neuron cells [119]. Further, TGFβ1 has been reported to increase neuronal viability [120] and decrease the release of inflammatory mediators, including reactive species and nitric oxide (NO) from microglia [121,122]. TGF-β1 was overexpressed in astrocytes of transgenic mice for human amyloid precursor protein (hAPP) [123], and TGF-β has been shown to increase Aβ phagocytosis in rats and cultured neuron cells [124,125]. Furthermore, the Smad 3 pathway intricately regulates neuronal TGFβ1 action, and age-related decline in Smad activation has a significant impact on microglial TGFβ regulation [126]. Nerve growth factor (NGF) and their extracellular signals are important for neuronal growth, maintenance, and survival and have been implicated in the neuromodulation of the septohippocampal pathway. In addition, the neuroprotective effect of TGF- βs could also be due to its synergistic action with neurotrophins, including NGF, brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), neurotropin 3 (NT-3) and NT-4 against neurotoxic insults [127]. Several lines of evidence suggest that vitamin D plays a role in neuronal differentiation and maturation by modulating the synthesis of neurotrophins, GDNF, and NGF [128]. VD has been reported to decrease hippocampal inflammation and alleviate amyloid-β accumulation. Further, increased synthesis of NGF in mouse fibroblast has been reported following treatment with VD and calcitriol, which could be attributed to increased activator protein-1 (AP-1) binding with the NGF promoter [129]. Furthermore, enhanced APP clearance by VD is mediated by VDR interaction with SMAD3, which modulates APP processing via TGF-beta signaling [130,131].

It is well known that both aging and Alzheimer's brains exhibit fluctuations in neuronal calcium (Ca^{2+}) concentration, which affects fundamental neuronal processes such as neuronal excitability, signal integration, synaptic plasticity, gene expression, mitochondrial dysfunction, and apoptosis [132]. Mitochondria play a crucial role in neuronal homeostasis by acting as a sink for Ca^{2+} overload, which is normally returned to the cytosol through the mitochondrial Na^{+}/Ca^{2+} exchanger (NCLX). Further, the extracellular deposition of Aβ peptide as well as the aging process leads to an exceptionally large influx of Ca^{2+}, resulting in a failure of the mitochondrial exchange mechanism that leads to induction of mitochondrial permeability membrane transition pore opening [133] and cytosolic release of cytochrome c and other pro-apoptotic proteins. These released pro-apoptotic proteins cause irreversible activation of apoptosomes, leading to neuronal cell death [134]. Also, neuronal Ca^{2+} dysregulation and altered expression of calcium-sensing receptor (CaSR) both contribute to neurodegeneration. Immunostaining for vicinin-like protein 1 and − 3 (VILIP-1 and −3), a calcium sensor protein, revealed reduced expression in the neocortical brain region of Alzheimer's disease (AD) patients [135]. Vitamin D stabilizes neuronal calcium homeostasis by lowering the expression of L-type voltage-sensitive calcium channels (LVSCC-A1C and LVSCC-A1D) in cortical neurons [136]. Moreover, VDR silencing results in a prompt elevation in the expression of LVSCC-A1C, indicating inefficient VD utilization by neurons leading to neuronal degeneration [137]. The beneficial effects of VD could also be attributed to its regulatory effect on the expression of calcium-sensing receptors.

The cellular antioxidant defense system intricately regulates the neuronal function and exerts neuroprotection against reactive oxygen species (ROS). Age-related decline in cognitive function well correlates with increased oxidation of cellular proteins, products of lipid peroxidation, proteasome activities, and modification in both nuclear and mitochondrial DNA of the rat brain [138,139]. Vitamin D is reported to exert neuroprotective action by lowering lipid peroxidation as a result of the maintenance of normal Ca^{2+} homeostasis through the induction of parvalbumin (Ca^{2+} binding protein) [140]. In addition, it reduces tissue MDA levels by enhancing the expression of calbindin-D28K and calbindin-d9K in neurons [141]. Several lines of evidence point to cellular glutathione depletion and heat shock inducing an antioxidant enzyme, heme oxygenase-1 (HO-1) in neurodegenerative diseases such as Alzheimer's [142]. Furthermore, hippocampal and cortical neurons, as well as astrocytes, showed increased expression of HO-1 immunoreactive protein, which co-distributed with senile plaques and neurofibrillary tangles [143]. Interestingly, increased aggregation of tau proteins has been demonstrated in the mouse brain following prolonged overexpression of HO-1 [144]. Recent research has demonstrated that lowering oxidative stress by administering 100 μg/kg of VD to mice improves neuronal synapse function as well as memory function. This is accomplished through the upregulation of Nuclear factor erythroid 2-related factor 2 (Nrf2) and HO-1, as well as the downregulation of Nuclear Factor kappa B (NF-kB), Tumor Necrosis Factor alpha (TNF-α), and Interleukin 1 beta (IL-1β) [145].

However, not only oxidative stress but also inflammatory processes are implicated in the pathogenesis of a decline in cognitive function. It has been observed that aging processes result in the accumulation of end glycation products (AGEs) and the level is 1.7 times higher in AD patients as compared to matched group [146]. The modification of advanced glycation end products due to aging, which in turn leads to the deposition of cross-linking protein, has been reported in both plaques and tangles. Vitamin D exerts protective action against the deleterious effects of brain AGEs induced due to aging processes. Interestingly, VD supplementation decreases the amount of mRNA for the receptor for advanced glycation end product (RAGE) as well as TNF-α when compared to the matched group. Calcitriol treatment reduced the LPS-induced increased expression of adhesion molecules, RAGE, secretion of IL-6, and NF-κB p65 binding in human umbilical vein cord endothelial cells [147].

3. Vitamin D and Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder that ranks second only to Alzheimer's. It affects 1–2 out of every 1000 people and is characterized by rigidity, tremor, hypermyotonia, disturbed gait, and bradykinesia. The incidence of PD increases with age, affecting about 1% of the population over the age of 60 [148]. As per an estimate of a systematic review, the yearly incidence of PD in the general population is 14 per 100000, which increases to 160 per 100,000 in the aged population over 65 years or more [149]. In patients with Parkinson's disease, rigidity, hypokinesia, and postural instability lead to increased indoor confinement, which in turn reduces exposure to sunlight, resulting in diminished vitamin D synthesis in the skin. It is widely acknowledged that adequate vitamin D levels are necessary for the maintenance of physiological functions such as muscular strength, balance, and innate immunity [150].

3.1. Clinical evidence linking vitamin D deficiency and the PD

A meta-analysis of single interventional, 14 observational, and 5

preclinical studies reported an inverse correlation between serum vitamin D and the developmental risk of PD. Sufficient exposure to sunlight has been associated with a reduced risk of PD in outdoor workers in their old age. A population-based case-controlled study on Danish men reported a reduced risk of development of PD in outdoor workers as compared to indoor workers [151]. Furthermore, PD patients have significantly lower biologically active vitamin D levels when compared to healthy individuals [152], and this decreases as the severity of rigidity and tremor increases as the disease progresses [153]. The higher plasma vitamin D level in patients with PD correlates with improved motor function [154] and also shows improvement in cognitive function and mood [155].

Patients with PD were stabilized following supplementation with Vitamin D3 (1200 IU/d), though this effect is only for a brief period, especially in those patients with *Fok*I TT or CT genotypes as compared to the placebo-controlled group [156]. A cohort study investigated the effect of vitamin D supplementation (≥400 IU/day) on the clinical outcomes of early PD wherein they reported no improvement in the early 3rd year of disease progression following VD supplementation [157]. Recently, a randomized, double-blind controlled pilot study reported that high-dose vitamin D (10,000 IU/day) supplementation failed to produce improvement in balance and motor function in PD. However, the post hoc analysis from the same study showed improvement in balance in PD, especially in the younger population [158]. However, contrary to these findings, a case-controlled study compared the intake of calcium and vitamin D in 249 patients with PD with 368 patients without neurodegenerative diseases, wherein no correlation was reported between dietary intake and PD [159].

3.2. Preclinical evidence linking vitamin D deficiency and the PD

The impact of VD supplementation on dopamine containing neurons in the substantia nigra (SN) of 6-hydroxydopamine (6-OHDA)- and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated animals has been studied in a number of in vivo experiments [160–164]. Pre-treatment with VD3 in rats for 8 days restored the 6-OHDA-induced decrease in locomotor activity and depletion of dopamine (DA) and its metabolites in the neurons of the SN. Moreover, VD3 pre-treatment protected dopaminergic (DA) neurons of ventral mesencephalic (VM) region against 6-OHDA-induced neuronal toxicity [161]. The neurotoxicity of 6-OHDA is primarily the result of the production of extremely reactive free radicals and cellular oxidative stress, which impede mitochondrial enzyme complexes. In addition to its antioxidant properties, vitamin D has also been demonstrated in both in vitro and in vivo experiments to increase the expression of glial cell-derived neurotrophic factor (GDNF), and the exogenous administration of GDNF has been reported to show protective effects against 6-OHDA-induced dopaminergic neuron damage in the ventral mesencephalic region in rats [165]. A study demonstrated that VD3 therapy protected dopaminergic neuron tissues in the SN of rats against a zinc-infusion-induced increase in oxidative degradation of neuronal membrane lipids and cytoplasmic cytochrome c complex [162]. In accordance with this finding, low dosages of 1,25-(OH)2D3 are able to protect the dopamine-containing neurons of the mesencephalic locomotor region against neuronal damage induced by a mixture of L-buthionine sulfoximine (BSO) and 1-methyl-4-phenylpyridium ions (MPP+) [160]. In contrast, high levels of 1,25 (OH)2D increased neurotoxicity, a phenomenon previously observed in Klotho-deficient mice, which mimic aging humans and display abnormal levels of blood 1,25-(OH)2D due to unusually high vitamin D metabolism in the kidney [166]. In addition, Dean et al. (2012) observed that vitamin D deficiency was not related to heightened sensitivity to MPTP and that there was no significant difference between control and VD-deficient animals [164].

The expression of VDR in multiple locations of the brain, including the substantia nigra, cortical, subcortical, hippocampal, thalamic, and hypothalamic areas, suggested the potential role of VD in neurodegeneration [167,168]. Kaluef et al. demonstrated that mice lacking the vitamin D receptor had markedly reduced motor function [169]. The impairment of motor function in VDR knockout mice provides further credence for the function of vitamin D in the pathogenesis and progression of Parkinson's disease, and polymorphisms in the VDR gene have been identified that are linked with specific PD symptoms [170,171]. VD pre-treatment for 8 days had no influence on the decrease in evoked dopamine (DA) outflow or the fall in nigrostriatal DA levels in rats injected intravenously with 6-OHDA. In contrast, long-term administration of calcitriol significantly raised both the evoked overflow of DA and the striatal neuron DA level in comparison with saline-treated rats [172].

3.3. Pathophysiologic mechanisms of vitamin D deficiency and PD

The formation of lewy bodies due to the inclusion of abnormal neuronal proteins, consisting of mainly α-synuclein, is the hallmark of PD. These eosinophilic inclusion bodies are the major contributor of neuronal cell death leading to progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) of the midbrain [173,174]. However, the exact pathophysiology of PD is not fully understood and a multifactorial mechanism has been proposed for the loss of dopaminergic neurons, including genetics, overexposure to environmental toxins, mitochondrial dysfunction, and oxidative stress. In addition, the nutritional changes due to microbial imbalance increased intestinal permeability, and altered lifestyle habits are also considered contributing factors in the pathogenesis of PD [175].

The correlation between vitamin D status and Parkinson's disease has been attributed to both genomic and non-genomic factors. Nonetheless, it remains unclear whether vitamin D is a cause or marker of Parkinson's disease (Fig. 2). The presence of vitamin D receptors (VDR) and the abundance of 25-hydroxyvitamin D-1-alpha-hydroxylase (1α-hydroxylase) in substantia nigra neurons demonstrates the role of vitamin D in Parkinson's disease [176]. The vitamin D activating enzyme, 1α-hydroxylase, encoded by the CYP2D6 gene, showed polymorphic expression. The Parkinson's disease patient was found to have a CYP2D6*4 allele with a poor metabolizing variant, which may contribute to the diminished vitamin D activity in the substantia nigra [177]. The striatum of MPTP-induced Parkinson's disease phenotype in mice showed expression of CYP2D22, an ortholog of human CYP2D6, and nicotine exerts the neuroprotective effect by modulating the expression of this gene [178]. Furthermore, impaired motor function and decreased muscular activity in VDR knockout mice support the link between vitamin D and PD [170]. Calcitriol suppresses the expression of major histocompatibility complex (MHC) antigen and therefore enhances the phagocytotic processes. Phagocytic cells collected from the cerebrospinal fluid of PD patients were reported to have significantly increased expression of MHC class II [15]. In addition, the presence of human leukocyte antigen-DR isotype (HLA-DR)-positive microglia in the substantia nigra and nigrostriatal pathways of Parkinson's disease (PD) patients demonstrates the involvement of the HLA gene in the pathogenesis of PD [16].

Dopaminergic neurons in the SN of Parkinson's disease patients express ploy (ADP-ribose) polymerase-I (PARP-1), a nuclear enzyme that regulates neuronal growth under oxidative stress. It has been reported that overexpression of PARP-1 in PD patients causes degeneration of dopaminergic neurons by depletion of neuronal nicotinamide adenine dinucleotide (NAD+) and adenosine triphosphate (ATP) [17]. This is also evident from the preclinical study wherein mice demonstrated signs of neurotoxicity following MPTP treatment [179], whereas the PARP gene knockout mouse didn't show the neurotoxicity of MPTP [180]. Vitamin D downregulates the expression of PARP-1 and also the NB4 cells showed reduced expression following treatment with calcitriol [181]. Furthermore, vitamin D reduces oxidative stress via receptor-mediated changes in hydrogen peroxide secretion and the restoration of stimulated monocyte superoxide production [182].

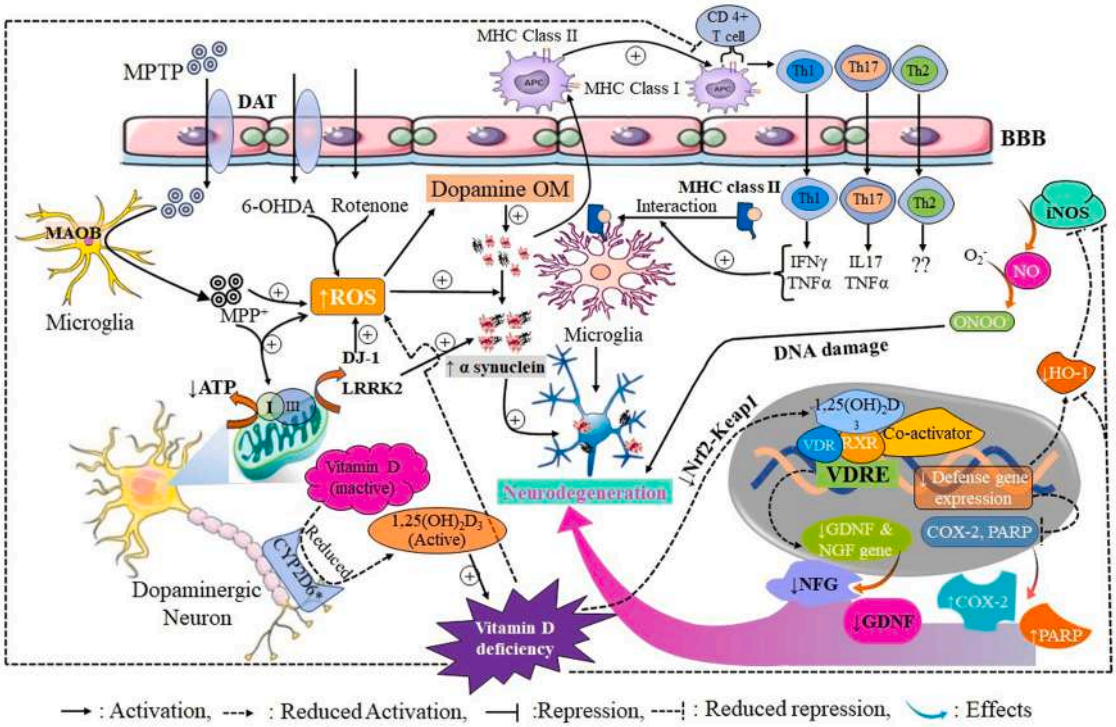

Fig. 2. Pathophysiologic mechanism of vitamin D deficiency-induced Parkinson's disease. Glial cell MAO-B converts MPTP into MPP+ after its passage into the brain through the BBB. MPP+ , rotenone, and 6-OHDA result in dysfunction of the mitochondrial enzyme complex, leading to reduced ATP production and LRRK2 and DJ-1 functioning, which in turn enhance oxidative stress and dopamine oxidation, promoting neurodegeneration due to the aggregation of α-synuclein. VDD impedes antioxidant activities, thereby subjecting dopaminergic neurons to oxidative injury. The genetic polymorphism of CYP2D6 also contributes to VDD by reducing VD activation. The α-synuclein in the bloodstream increases MHCII expression, which supports CD4 + T cell presentation by MHCI and Th1, Th17, and Th2 differentiation. These cells migrate to the brain and produce inflammatory mediators like TNFα, IFN, and IL-17, favoring MHCII-microglia interactions and neurodegeneration. VDD results in the repression of inhibitory control on the differentiation of these immune mediators. VDD through the Nrf2-keap1 pathway reduces VDR-RXR complex activation and VDRE activation, which reduces GDNF, NGF, and defense gene expression and dopaminergic neurotoxicity. The diminution of inhibitory control over COX-2 and PARP gene expression due to reduced defensive gene expression causes neurodegeneration by increasing COX-2 and PARP generation. Reduced defensive gene expression and VDD-mediated repression of inhibitory control over the decline in HO-1 production and iNOS activity cause DNA damage by producing NO and highly reactive peroxynitrite. 6-OHDA: 6-hydroxydopamine, APC: Antigen-presenting cell, ATP: Adenosine triphosphate, BBB: Blood brain barrier, COX-2: Cyclooxygenase-2, DAT: Dopamine transporter, DJ-1: Protein deglycase DJ-1, GDNF: Glial cell line-derived neurotrophic factor, HO-1: Heme Oxygenase-1, IFN-γ: Interferon gamma, IL17: Interleukin-17, iNOS: Inducible nitric oxide synthase, Keap1: Kelch-like ECH-associated protein 1, LRRK2: Leucine rich repeat kinase 2, MAO-B: Monoamine oxidase B, MHC-II: Major histocompatibility complex class II molecules, MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, NGF: Nerve growth factor, NO: Nitric oxide, Nrf2: Nuclear factor erythroid 2–related factor 2, PARP: poly adenosine diphosphate-ribose polymerase, ROS: Reactive oxygen species, RXR: Retinoid X receptor, TNF-α: Tumor necrosis factor-α, VDR: Vitamin D receptor, VDRE: Vitamin D response element.

Animal studies demonstrated that 6-OHDA and MPTP treatment enhances the inducible and neuronal nitric oxide (NO) which in turn reacts with oxygen free radical (O_2^-) to form a highly reactive peroxynitrite ($ONOO^-$) resulting in DNA damage, and lipid peroxidation [183]. Calcitriol inhibits the expression of inducible nitric oxide synthase (iNOS) in lipopolysaccharide (LPS) stimulated macrophages leading to a decrease in NO levels and thus alleviating NO-induced oxidative stress and cellular damage [184]. However, in response to oxidative stress, cells can express a stress protein, heme oxygenase-1 (HO-1), which helps to counter the oxidative stress by converting pro-oxidant heme into bilirubin, biliverdin, and free iron, having free radical scavenging properties. The expression of HO-1 is significantly increased in neurodegenerative disorders, including Alzheimer and Parkinson disease [185]. Calcitriol has been shown to reduce the reactivity of glial HO-1 in focal cerebral ischemia [186]. Pretreatment of human umbilical epithelial cells with 1,25(OH)2D3 reversed leptin-induced increases in oxidative mRNA expression, including HO-1 [187]. In addition, vitamin D protects against acetaminophen-induced hepatotoxicity and acute renal toxicity by modulating the antioxidant pathway via HO-1, BACH1, and Nrf2 [188].

Dopaminergic neurons of the brain, function in an autonomous manner, unlike other neurons and their autonomic pace, making signals rely on the L-type voltage-sensitive calcium channel (L-VSCC). The D2 receptors of freshly isolated medium spiny neurons from 6-OHDA-treated rats and protein deglycase DJ-1 and PINK1 (PTEN induced kinase 1) knockout mice showed increased activity of L-VSCC, leading to increased sensitivity to mitochondrial toxins and downregulation of vitamin D receptors (VDR) [189]. The implication of L-VSCC in neurotoxicity is further demonstrated by the prevention of MPTP-induced neurotoxicity by pretreatment with nimodipine [190]. The neuroprotective effect of vitamin D is probably due to the upregulation of VDR and the downregulation of L-VSCC [191]. In addition to oxidative stress, neuronal insult with MPTP results in recruitment of inflammatory cells, leading to production of IL-1β, TNF α, and interferon-gamma (IFN-γ) through increased expression of proinflammatory cytokine genes in SN and striatum [192]. The release of these proinflammatory cytokines, including prostaglandin E2 (PGE_2), and a number of reactive oxygen species, such as hydrogen peroxide, nitric oxide, and O_2^-, causes neurotoxicity and the death of dopaminergic neurons. The expression of PGE_2 receptors in SN further provides evidence for their involvement in selective toxicity to dopaminergic neurons in PD. In addition, MPTP-treated animals showed overexpression of cyclooxygenase-2 (COX-2), which is also evident in PD [193]. Vitamin D selectively prevents inflammation mediated neurotoxicity by inhibition of COX-2 through targeting of the thioesterase super family member 4 (THEM4) gene [194]. In neurodegenerative disorders, neurotrophic factors (NTFs)

represent one of the key mediators involved in neuroprotective mechanisms after toxic neuronal insults. The SN of patients with PD showed reduced expression of NTF and vitamin D has been reported to regulate the low-affinity neurotrophic receptor expression [195] and also acts as a potent inducer of glial-derived neurotrophic factor (GDNF) in rats [196]. Nerve growth factor (NGF) exert protective action against MPTP, rotenone, and 6-OHDA-induced toxicity to dopaminergic neurons [197–199]. VD and its analogs boost the induction of NGF via enhancing AP-1 binding to its promoter site [200]. Interestingly, VD has been reported to regulate the release of NGF from hippocampal and cortical neurons [201].

The involvement of vitamin D deficiency in the loss of dopaminergic neurons in Parkinson's disease suggests that correcting vitamin D deficiency may help to manage the disease. A meta-analysis found that patients with Parkinson's disease had lower vitamin D levels than healthy controls [202]. However, not only vitamin D but also polymorphism of VDR has been proposed by several researchers. The decline in cognitive function in PD patients with VDR polymorphism has been reported and the FokI polymorph of VDR was found to be associated with memory impairment [203]. The polymorphism of VDR *Apa*I, in addition to FokI polymorphism, has also been associated with PD [204].

4. Vitamin D and epilepsy

Epilepsy is one of the most common multifaceted neurological diseases, affecting approximately 65 million people globally, and is prevalent in all age groups [205]. However, the incidence was higher in children and the elderly population [206]. In addition to uncontrollable seizure episodes, epilepsy is characterized by neurological, cognitive, and psychosocial impairment [207]. Regardless of the multifactorial underlying pathogenic mechanisms that can lead to the development of epilepsy, the precise cause and mechanism in approximately half of all global epileptic cases remain unknown [208]. Therefore, treatment of epileptic seizures continues to remain challenging despite significant progress in diagnosis and pharmacologic management. Firstly, because of the development of drug-resistant epilepsy in about 22–30% of the epileptic population [209], and secondly because of poor therapeutic adherence to combination therapy with relatively more adverse effects, drug interactions, and drug intolerance.

The goal of therapy is often to attain seizure-free life with minimal impairment of quality of life. However, even in patients with controlled seizure episodes with antiepileptic drugs (AEDs) or their combination, neurotoxic side effects as well as idiosyncratic adverse effects such as rashes, thrombocytopenia, hepatotoxicity, and loss of bone density are frequently documented [28,210]. The potential toxicities and limitations of existing AEDs result in an increased interest in the search for alternatives to conventional therapeutic agents. Further, a growing body of reports suggests that brain function and development are intricately regulated by vitamin D, which is also evident from a finding showing vitamin D directly influences brain development in mice born from pregnancy with transient vitamin D3 deficiency [211]. Therefore, Vitamin D3 has been advocated as a promising candidate as an alternative to conventional treatment. Christiansen et al. (1974) proposed that VD supplementation might result in a reduction in hyperexcitability in epileptic patients by improving calcium and magnesium levels [212]. Furthermore, it has been reported by numerous studies that both adult and young epileptic patients [213–215] suffered from hypovitaminosis D, proffering a rationale for vitamin D supplementation in epilepsy [216]. In addition to this, an increased risk of vitamin D deficiency has been reported by a cross-sectional study on 244 ambulatory epileptic children following long-term AED therapy for more than 1 year [217]. A recent study on 104 children aged 6–60 months, with or without a febrile seizure, found no significant reduction in serum VD in patients with seizure, indicating the need for further research into VD in febrile patients [218]. More recently, a cohort study on 92 Portuguese epileptic patients reported vitamin D deficiency in half of the study population receiving enzyme-inducing AEDs (EIAEDs) [219]. A meta-analysis of published literature reported a reduced serum vitamin D level in epileptic children following long-term treatment with valproate [220]. However, not just AEDs therapy but also the frequency, duration, and earlier age of onset of generalized epilepsy due to a genetic etiology have been linked to vitamin D insufficiency in treatment-naive children [221].

4.1. Clinical evidence linking vitamin D deficiency and epilepsy

Until recently, four clinical studies investigated the possible effect of vitamin D supplementation on the control of seizure activity. First, a placebo-controlled study involving 23 epileptic patients in which the treatment group received 4000 IU/day of vitamin D3 for 28 days, followed by 16,000 IU/day for the following 28 days, while the placebo group received placebo for the first 28 days, followed by 8000 IU/day of vitamin D3 for the following 28 days. The results of this study demonstrated the anticonvulsant effect of vitamin D3 supplementation, as indicated by a significant decrease in mean seizure frequency (67–71%) compared to baseline seizure frequency [212]. Hallo et al. (2012) investigated the effect of normalization of serum vitamin D levels by administration of vitamin D_3 by a single oral dose of 40,000–200,000 IU bolus followed by a daily maintenance dose of 2000–2600 IU for 90 days in 13 patients with pharmacoresistant epilepsy and reported a 40% reduction in median seizure frequency compared to the baseline [222]. These findings of the antiepileptic potential of vitamin D supplementation were also corroborated by a relatively recent study wherein there was a significant reduction in median seizure frequency from 5.18 seizures/month to 3.64 seizures/month at the 6th week and 4.2 seizures/month at the 12th week of oral VD_3 supplementation (5000 IU/day) in adults with focal epilepsy [223]. A cross-sectional cohort study of 160 epileptic patients reported VD insufficiency in 41.9% and VD deficiency in 33.1% of patients following AEDs treatment; however, polytherapy and EIAEDs had a more detrimental effect. Further, the effect of correcting VD levels with cholecalciferol at doses of 100,000 IU/week for 12 weeks and 100,000 IU biweekly for 3 months in VD-deficient and VD-sufficient patients, respectively, on seizure frequency was investigated. The findings of this study showed that VD administration failed to reduce the seizure frequency in drug-resistant epileptic patients compared to 42 matched controls [224], which is contrary to previous reports of antiepileptic effects of VD and warrants further investigation for possible effect in larger sample size studies.

4.2. Preclinical evidence linking vitamin D deficiency and epilepsy

Furthermore, in addition to clinical evidence, the effectiveness of vitamin D in epilepsy has also been demonstrated in several animal models. It has been reported that stereotaxic injection of 1,25- dihydroxyvitamin D3 (100 μg or 50 μg in 2 μL of propylene glycol) into the electrically stimulated dorsal hippocampal area of the rat brain resulted in a significant increase in seizure threshold that persisted for at least 120–180 min, although intravenous injection produced a short-lived increase in seizure threshold [225]. In another study, Kalueff et al. (2005) investigated the anticonvulsant effect of subcutaneous injection of 1,25-dihydroxyvitamin-D (33 μg/20 μl) against pentylenetetrazole (PTZ)-induced seizure in NMRI mice, which persists till 3 h after administration [226]. Further, evidence for the anticonvulsant effect of VD and involvement of the vitamin D receptor (VDR) was extended by the report of increased severity of PTZ-induced seizure in VDR knockout mice compared to wild-type (WT) 129S1 mice [227]. Despite the lack of an appropriate animal model to mimic clinically epileptic conditions, maximal electroshock (MES)-induced seizure in rodents is the most useful tool for screening anticonvulsant compounds. There was a significant increase in seizure threshold following intraperitoneal injection of vitamin D3 at doses of 37.5 and 75 μg/kg against MES induced seizure in mice. Furthermore, administration of cholecalciferol at a

subthreshold dose (18.75 μg) potentiated the anticonvulsant action of conventional AEDs (valproate, carbamazepine, phenytoin, and phenobarbital) against MES-induced seizure [228]. In agreement with this finding, VD has been reported to exert potentiation of the anticonvulsant and nootropic effect of lamotrigine in PTZ-kindled rats [229]. Interestingly, a relatively recent study demonstrated the acute and chronic intraperitoneal injection of VD (5.000 and 60.000 IU/kg) and paricalcitol (0.5, 5, and 10 μg/kg) significantly reduced the number and duration of spike-wave discharge and also exhibited anxiolytic and antidepressant effect in WAG/Rij rats[230].

4.3. Pathophysiologic mechanisms of vitamin D deficiency and epilepsy

There is a great deal of complexity involved in the pathophysiologic mechanisms that underlie epilepsy and seizure activity (Fig. 3). However, the most extensively studied and widely recognized mechanism is the imbalance between GABAergic inhibitory signals and glutamatergic excitatory signals at the synapse, which leads to the development of epileptic seizures. In addition, voltage-gated calcium channels (VGCCs) are ubiquitously expressed in the mammalian central nervous system, and activation of these channels is essential for fundamental neuronal processes such as neurotransmitter release, neuronal excitation, and nerve impulse transmission at synapses [231]. Similarly to several conventional AEDs, vitamin D3 demonstrated anticonvulsant activity by offsetting neuronal calcium (Ca^{2+}) overload via decreased expression of voltage-gated calcium channels on neurons [232,233]. Furthermore, increased neuronal Ca^{2+} load results in the generation of nitric oxide (NO) through activation of Ca^{2+}-dependent neuronal nitric oxide synthase (nNOS) [234], which possibly regulates the development and maintenance of epileptic seizure. The contribution of nNOS to oxidative stress-induced injury to the endoplasmic reticulum of hippocampal neurons in PTZ-induced mice provides additional evidence for neurotoxicity [235]. VD also exerts neuroprotection by mitigating cellular oxidative damage by inhibiting the formation of NO via inducible nitric oxide synthase [236].

Oxidative neuronal damage plays a vital role in epileptogenesis and the decline in neurocognitive function through neurodegeneration. In addition to this, increased activity of proinflammatory mediators such as COX-2, IL-1β, IL-6, TNF-α, IFN-γ and TGF-β at epileptogenic foci in experimentally induced epilepsy in animals provide further evidence for neuroinflammation mediated neuronal damage [237,238]. The released inflammatory cytokines alter the neuronal physiology, such as neuronal excitation by blockade of glutamate uptake [239], increased activity of N-methyl-D-aspartate (NMDA) receptors [240], alteration of GABAergic neurotransmission [241], and increased activity of caspase-1 [242]. It has been reported that VD pretreatment produced a significant increase in GABA and a decrease in glutamate in the brain against lithium-pilocarpine-induced status epilepticus in rats [243]. The neuroprotective action of VD could be attributed to its immunomodulatory action through its suppressive action of various inflammatory cytokines such as IFN-γ, IL-2, TNF-α, and IL-6 [244,245]. Furthermore, it has been reported that there was a marked decrease in the concentration of proinflammatory cytokines including IL-1β, IL-6, IL-8 [246], macrophage inflammatory protein 1β (CCL4), monocyte chemoattractant protein-1 (MCP-1) [247], and IFN-inducible protein 10 [248] following treatment with VD, which provides further evidence for neuroprotective

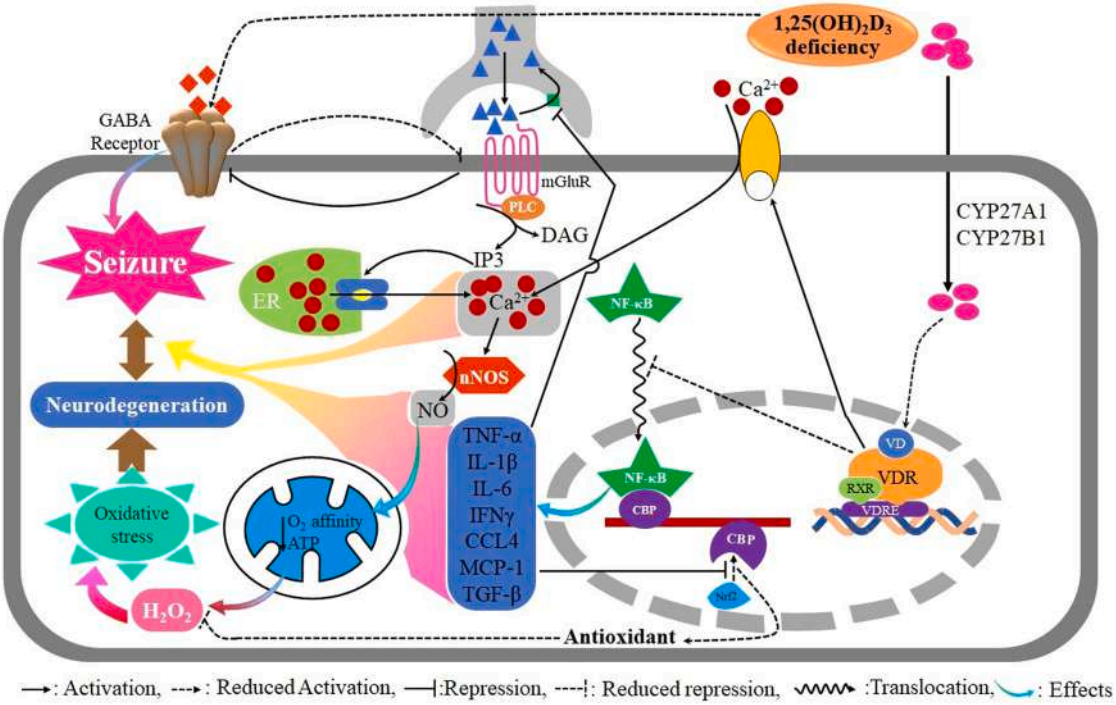

Fig. 3. Pathophysiologic mechanism of vitamin D deficiency-induced epilepsy. Vitamin D deficiency (VDD) reduces VDR-RXR activation and expression of the vitamin D response element. This, in turn, represses the inhibitory control over NF-κB binding to CBP, leading to increased production of TNF-α, IL-1β, IL-6, IFNγ, CCL4, MCP-1 and TGF-β. The released cytokines induce cellular oxidative stress by inhibiting Nrf2 binding with CBP and increasing glutamate activity by inhibiting glutamate reuptake in presynaptic neurons, generating IP3 via phospholipase C activation, and thus increasing Ca2 + release from the endoplasmic reticulum. VDD increases Ca^{2+} influx due to the repression of inhibitory control over L-type CaV1.2 channel expression. VDD also decreases GABA-mediated effects, which in turn activate NMDA receptors and increase neuronal Ca^{2+} overload. Ca^{2+} overload causes decreased GABA receptor activation, increased glutamate activity, inflammatory cytokines, and neuronal oxidative stress, which eventually results in neurotoxicity and epileptogenesis. CBP: CREB-binding protein, CCL-4: Macrophage inflammatory protein 1β, DAG: Diacylglycerol, ER: Endoplasmic reticulum, GABA: Gamma-aminobutyric acid, IFN-γ: Interferon gamma, IL-1β: Interleukin-1β, IL-6: Interleukin-6, IP3: Inositol trisphosphate, MCP-1: Monocyte chemoattractant protein-1, mGluR: Metabotropic glutamate receptor, NF-κB: Nuclear factor kappa B, nNOS: Neuronal nitric oxide synthase, NO: Nitric oxide, Nrf2: Nuclear factor erythroid 2–related factor 2, PLC: Phospholipase C, RXR: Retinoid X receptor, TGF-β: Transforming growth factor-β, TNF-α: Tumor necrosis factor-α, VD: Vitamin D, VDR: Vitamin D receptor, VDRE: Vitamin D response element.

effects.

Leifke et al. demonstrated that a relatively high concentration of prostaglandins in several brain areas such as the cerebral cortex, striatum, and hippocampus of gerbil following seizure activity indicating the induction of COX-2 enzyme [249] which is further supported by the reports of seizure-induced activation of phospholipase A_2 in the cytosol [250]. The enduring upsurge of COX-2 activity augments the inflammatory processes in neurons and further contributes to epileptogenesis, which is also evident from the reports of increased COX-2 expression in the brains of mice following kainic acid-induced convulsions [251]. 1,25 (OH)2 D, the active form of vitamin D, produced dose-dependent inhibitory action on both basal and LPS-induced upregulated COX-2 protein expression in murine macrophages [194]. This further confirmed the anti-inflammatory action that probably also contributed to neuroprotection. Ergosterol, an active constituent of *Hericium erinaceus* (edible mushroom) that can be converted in vivo into vitamin D [252], exhibited protection of hippocampal neurons by suppressing the glial cell expression of COX-2 against pilocarpine-induced status epilepticus in mice [253].

Transforming growth factor β (TGF β) is a pleiotropic polypeptide that exists in three isoforms, TGF-β1, -β2, and -β3, each with distinct effects on cellular growth and differentiation. All isoforms are widely distributed, but TGF-β1 is predominantly expressed in lymphoid tissue, whereas β2 and β3 are predominant in mesenchymal tissues and bone cells [27]. Astrocytes of the injured spinal cord showed more reactivity and a neurotoxic (A1) phenotype, leading to neuronal death. However, the culture of naïve and activated astrocytes on poly-L-lactic acid microfibers in the presence of transforming growth factor β3 (TGFβ3) exhibited a significant reduction in the expression of neurotoxic phenotype (A1), leading to increased neuronal survival in culture [254]. The expression of TGFβ3 in the rat hippocampus was significantly reduced after 3 h of kainic acid (KA) administration. Further, intracerebroventricular injection of TGF-β3 (5 or 10 ng) produced dose-dependent attenuation of KA-induced seizure and neurodegeneration [255]. Intriguingly, preventive and therapeutic treatment with calcium and VD reversed phenytoin and sodium valproate-induced decreases in bone TGF-3 levels [29]. These findings suggest the neuroprotective effect of VD could be due to the upregulation of TGF-β3 which needs to be further investigated. However, contrary to this, TGF-β1 is upregulated following seizure activity, demonstrating its role in neurotoxic insults. Furthermore, the receptors of TGF β facilitate the uptake of albumin and therefore stimulate altered astrocyte plasticity through NMDA receptors [256]. To make sense of these seemingly contradictory findings about epilepsy, more research needs to be done on how VD protects neurons and how it acts differently on different isoforms.

5. Vitamin D and multiple sclerosis

Multiple sclerosis (MS) is a chronic immune-mediated inflammatory neurodegenerative disease of the central nervous system (CNS), most common in western countries, affecting about 2.5 million people globally. It is among the leading causes of disability and early retirement among younger generations [257]. It is characterized by recurrent subacute episodes of dysfunction of central motor neurons, leading to incoordination, cognition decline, imbalance, sensory disturbance, and optic neuritis [258]. The exact etiology of MS is not fully understood and it is considered a complex disease with multifaceted pathophysiologic mechanisms. Several etiologic factors, such as genetics, altered immune function, and environmental factors, have been reported in the pathogenesis of MS. The orchestration of encephalitogenic T cells in concert with B cells and other immune cells that showed reactivity against CNS structures resulted in neuronal demyelination and axonal damage of neurons in the brain, spinal cord, and retina [259,260].

In addition to the immunogenic pathophysiologic mechanism, environmental etiological factors, such as infection by the latent human herpes virus or retroviruses, have been proposed as etiological factors for MS pathophysiology. However, no evidence of such viral infection has been found in MS patients [261]. The higher prevalence of multiple sclerosis in temperate regions suggests the active participation of additional environmental factors such as latitude. Intriguingly, the prevalence of multiple sclerosis showed a latitudinal gradient in age-standardized subjects, with a significant increase with increasing latitude and a peak at 55° latitude [262]. One of the risk factors for low vitamin D levels is latitude, and this is especially true for people who live at higher altitudes (Table 1). In addition, a Caucasian population study revealed a strong correlation between latitude and serum vitamin D levels [263]. According to estimates, approximately 15% of the world's population resides at higher altitudes and receives relatively low exposure to sunlight, which is a recognized risk factor for vitamin D deficiency [262]. It was reported that people living at higher altitudes experienced the onset of multiple sclerosis two years earlier than those living at lower altitudes [264]. However, there are some contrary reports to this higher altitude and the increased incidence of early MS, which enlightened the possibility of the implication of genetic factors and/or nutritional variations [265].

A sufficiently large volume of literature on nutritional deficiencies associated with increased incidence and susceptibility to MS etiology suggests a positive correlation with the intake of meat, fat, milk, and cereals rich in phytic acid [266–268]. However, an inverse correlation has been reported between the intake of fish, oil, skimmed milk, vegetables, fruits, and rice and the incidence of MS [269–271]. Interestingly, phytic acid and fats have been reported to impair vitamin D absorption and bioavailability of metabolites of vitamin D [272]. Regardless of several dietary sources, it has also been recognized as one of the environmental factors as ultraviolet radiation from sunlight mediates the conversion of endogenous substances into vitamin D in the skin. These reports demonstrated that vitamin D deficiency is often associated with MS and has been reported by several studies and is recognized as a risk factor for MS. In addition, a case-controlled study on the Australian population examined the effect of serum 25(OH) D level and sun exposure on the onset of demyelination. The results indicated that sun exposure, skin type, and 25(OH) D levels were all associated with a reduced risk of demyelination [273].

5.1. Clinical evidence linking vitamin D deficiency and multiple sclerosis

Several epidemiological studies have found a link between low vitamin D levels and an increased risk of MS. A study on the Norwegian population demonstrated that people with a relatively high intake of fish oil and sufficient exposure to the sun have a relatively reduced risk of MS [266,270,274]. In addition, the results of two cohort studies conducted on women by Nurses Health, study I and study II, on 92,253 and 95,310 women, respectively, revealed an inverse relationship between dietary VD intake and the risk of MS. The results of the study showed that there was a reduction in the relative risk of developing MS by 40% in female participants who took $\geq$ 400 IU of vitamin D per day in comparison to female participants who did not take any vitamin D supplements [275]. Furthermore, a prospective case-control study on stored serum samples of US army personnel who developed MS later in life discovered a 41% reduction in relative risk of MS with every 50 nmol/L increase in serum 25(OH) D3 level, with no discernible effect of sex [276]. A low serum 25 (OH) D3 level, on the other hand, was not only associated with an increased risk of developing MS but also significantly contributed to disease severity and progression rate in clinically isolated syndrome (CIS) and early MS patients. Furthermore, numerous clinical studies show the effects of vitamin D supplementation on the incidence rate, disease severity, and progression of MS [277–281]. In the Betaferon Efficacy Yielding Outcomes of a New Dose (BEYOND) study, the effect of serum vitamin D on the rate of MS activity was examined in a large, multicentric, phase 3, prospective, randomized clinical trial involving 1482 patients receiving randomized treatment with 250 μg and 500 μg of interferon-1β. The annual MRI scan of patients receiving interferon-1β

showed a reduced rate of disease activity in those with higher serum vitamin D levels [282]. Moreover, a sufficient number of controlled trials have demonstrated the positive effects of vitamin D supplementation on MS patient outcomes [283–290].

In another randomized double-blind trial, 25(OH) D supplementation led to an increase in serum IL-17, but there was no change in flu-like symptoms, rate of relapse, expanded disability status scale (EDSS), quality of life (QoL), or inflammatory cytokines like IL-10 and IFN-γ [291]. Recently, a multicenter, double-blind randomized trial on 53 MS patients reported inconclusive outcomes on relapse rate and disease progression following VD supplementation for 18 months [292]. On the other hand, a phase 2, randomized, double-blind, placebo-controlled trial on Relapsing-Remitting Multiple Sclerosis (RRMS) patients on subcutaneous interferon-β-1a (44 μg) 3 times weekly treatment showed that high dose VD3 supplementation did not affect disease activity. However, the results suggest that it may protect against the development of new MRI lesions [289].

5.2. Preclinical evidence linking vitamin D deficiency and multiple sclerosis

In addition to clinical findings, many preclinical studies have reported the modulatory effect of VD supplementation on the pathogenesis of MS. Despite the lack of exact animal models that mimic clinical MS, experimental autoimmune encephalomyelitis (EAE) is widely used as a human MS animal model [293]. Administration of myelin or myelin components results in the generation of autoreactive myelin-specific T lymphocytes, leading to demyelination of neurons in the brain and spinal cord, manifested as paralysis of the tail and limbs in rats. Administration of myelin or myelin components results in the generation of autoreactive myelin-specific T lymphocytes, leading to demyelination of neurons in the brain and spinal cord, manifested as paralysis of the tail and limbs in rats [294]. The first preclinical evidence for vitamin D's protective effect in EAE was reported by Lemire and Archer (1991), who demonstrated that concurrent administration of 1,25-(OH) 2D with an immunizing agent produced significant protection against the onset and pathogenesis of EAE in mice [295]. Further pretreatment with 1,25-(OH)2D completely vanquished immunization-induced EAE pathogenesis in mice [296] and rats [297], whereas post-treatment after the onset of clinical symptoms reduced disease severity and progression. Further, increased susceptibility to EAE pathogenesis and early onset of clinical symptoms have been reported after feeding on a vitamin D deficient diet, and also the withdrawal of vitamin D supplementation following induction of EAE resulted in the resumption of signs of tail and limb paralysis in mice [296]. In addition, Garcion et al. (2003) reported an increase in early signs of EAE in rats on VD-deficient diets [298]. Interestingly, in a cuprizone model in mice, supplementation with high or very high doses of vitamin D3 (VD3) resulted in a significant reduction in demyelination of white matter, attenuation of microglial activation, and infiltration of macrophages. In addition, the study demonstrated remyelination of white matter in groups receiving a low dose of VD3 following cessation of cuprizone administration [299]. VD has long been associated with calcium homeostasis, and restoring calcium levels has been shown to prevent disease progression as well as reduce 1,25-(OH)2D doses in experimentally induced EAE in mice [300]. It has been demonstrated that calcium and phosphate can modulate the expression of the VDR gene on target tissue [301], which is crucial for the immunosuppressive action of VD in experimental EAE [302]. In addition, immunosuppressants such as cyclosporine and sirolimus have been shown to enhance the protective effect of 1,25-(OH)2D in EAE [300,303,304]. The effect of VD is not uniform throughout the developmental stages rather it shows stage-dependent efficiency in EAE wherein it has been reported that VD produced marked attenuation of EAE in juvenile/adolescent rats manifested by a less severe upsurge in IFN-γ producing T cells and demyelination [305]. Besides this, vitamin D supplementation showed a gender disparity in that it inhibited EAE pathogenesis in female mice but not in male mice. It has also been concluded that the protective effect of VD is lost in ovariectomized animals [306]. The differential central action of VD could be due to altered gender specific vitamin D3 metabolism, resulting in reduced susceptibility to EAE in female mice on VD3 supplementation.

5.3. Pathophysiologic mechanisms of vitamin D deficiency and multiple sclerosis

There is a growing body of research available on the potentially harmful effects of vitamin D deficiency (VDD) in MS. Several lines of evidence suggest the modulatory action of VD on immune cells, dendritic cells, macrophages, cytokines, nitric oxide expression, and alteration in the blood-brain barrier in addition to genetic modulatory action (Fig. 4). The dissociated VD from Vitamin D binding protein (VBP) diffuses into cells from the circulation and binds to cytoplasmic vitamin D binding receptors (VDR), which form heterodimers with nuclear retinoid X-receptors (PXR) [307]. The VDR-RXR complex, activated by VD, regulates the expression of several genes by modulating vitamin D response elements (VDRE) at the promotor site of VD target genes. The polymorphism of the vitamin D receptor gene (VDRG) has also been reported as one of the determinants of MS susceptibility in VD-deficient individuals. Fukazawa et al. (1999) reported a linkage disequilibrium of VDRG with the loci of other pathogenic genes in Japanese women [308]. A meta-analysis of 30 case-controlled studies has reported a significant association of MS susceptibility with VDR Taql (rs731236) polymorphism and also the Bsml (rs1544410) polymorphism in the Asian population [309]. Vitamin D deficiency reduced the inhibition of antigen-specific T- lymphocyte proliferation [310], resulting in increased Th1 cell proliferation and the production of IFN-γ and macrophage activation. The significant downregulation of Tbx21 and RORc mRNA expression, which encode for Th1 and Th17 lymphocytes, respectively, by 1,25-VitD3 treatment, provides evidence for T lymphocyte involvement in the immunopathogenesis of EAE and MS [311]. VD deficiency blunts the VDR-mediated intrinsic tolerogenic capacity of dendritic cells (DC) [312], resulting in loss of inhibitory control on differentiation, maturation, and the modulatory action of DC through the production of IL-12. Furthermore, VD deficiency results in loss of inhibitory control on the expression of inflammasome components NLRP3, caspase-1, and IL-1β and also the expression of MHCII in microglia and macrophages [313]. Interestingly, 1,25-VitD3 (VD_3) has been shown to downregulate the expression of *Tbx21* and *RORc* mRNA and reduce their expression products *Th1* and *Th17*, respectively [313]. Th1 cell reduction results in attenuation of the inflammatory response mediated by interaction with microglia and astrocytes; however, Th17 cell reduction results in downregulation of chemokine expression [314]. It reduces the expression of MHCII in macrophages and microglia, in addition to the antioxidant effect and reduced mRNA expression of several chemokine cells.

The induction of an efficient Th1 response requires mature dendritic cells (DC), and several studies have shown that 1,25-(OH)2D treatment reduces dendritic cell maturation [315,316]. The failure of DC maturation in VDR-deficient mice provides further evidence for this statement [317]. 1,25(OH)2D offsets the production of IL-12 from mature DC and thus inhibits the proliferation of *Th1* cells. The disparity in VDR and vitamin D activating enzyme expression during immune response suggests that VD plays a role in the differentiation of precursor monocytes to macrophages [318,319]. In both in vitro and in vivo studies, 1,25 (OH)2D treatment reduced the production of inflammatory cytokines such as IL-2, TNF-α, and INF-γ [320,321]. Contrary to these pro-inflammatory effects, it promotes the production of TGF-β1 in the periphery but not in the CNS, which explains the favorable effects of VD in EAE and MS [322,323]. The damaging effects of these inflammatory cells are plausible only when they enter the brain following passage through the blood-brain barrier. It is possible that 1,25-(OH)2D3 has a direct protective effect on the blood-brain barrier and prevents its

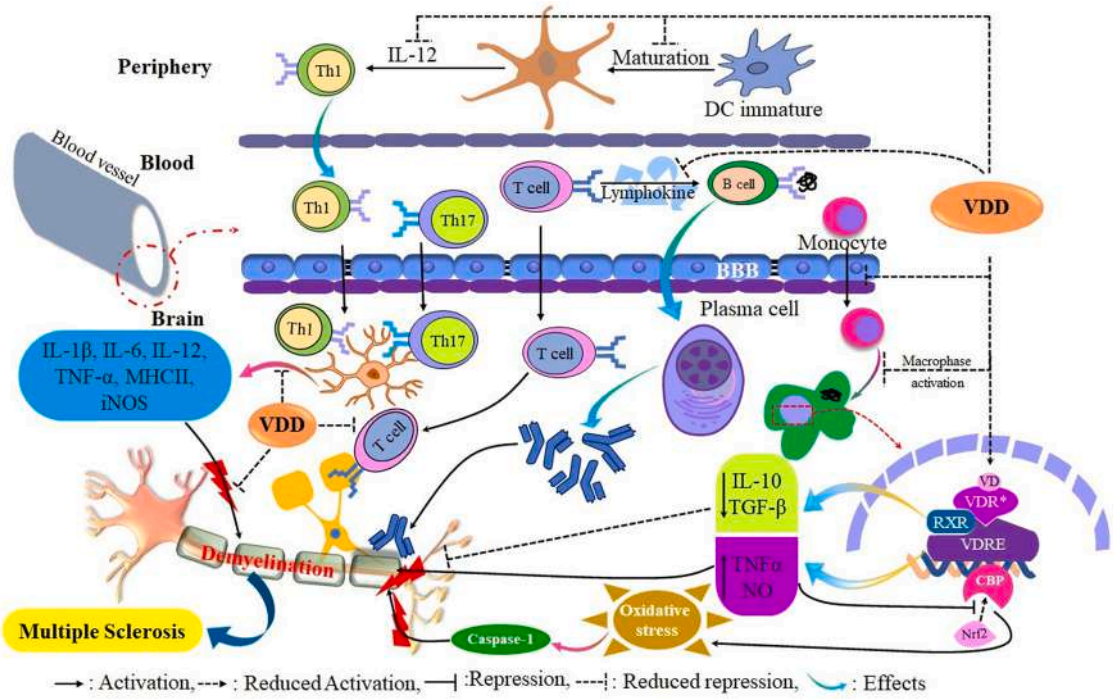

Fig. 4. Pathophysiologic mechanism of vitamin D deficiency-induced Multiple sclerosis. Vitamin D exhibits multitargeted effects, including peripheral, circulatory, and cerebral effects. In the periphery, VDD results in maturation and differentiation of dendritic cells due to loss of inhibitory control over the actions of IL-12 leading to production of Th1 cell which then enter the circulation. Th1 and Th17 cells cross the BBB and trigger microglia to produce IL-1β, IL-6, IL-12, TNF-α, iNOS, and MHC-II expression, which results in neuronal demyelination. VDD causes repression of inhibitory control on BBB permeability, allowing T cells, B cells, and monocytes to enter the brain. In circulation, VDD cause repression of inhibitory control over lymphokine-mediated T-cell and B-cell differentiation. T cells directly attack oligodendrocytes in the brain, while B cells differentiate into plasma cells, which generate antibodies that demyelinate neurons. The evidence from EAE demonstrates that VD inhibits cellular infiltration, and consequently VD deficiency results in brain macrophage activation. The expression of the polymorphic form of VDR* in addition to VDD results in altered expression of VDRE in the macrophage, leading to a loss of inhibitory control on neuronal demyelination due to reduced production of IL-10 and TGF-β, and enhanced damage to neuronal myelin through increased production of TNF-α and NO. The latter also inhibits Nrf2 interaction with CBP, resulting in oxidative stress, which facilitates demyelination through caspase-1 activation. B cell: B lymphocytes, BB: Blood brain barrier, CBP: CREB-binding protein, DC: Dendritic cell, IL-10: Interleukin-10, IL-12: Interleukin-12, IL-12: Interleukin-12, IL-1β: Interleukin-1β, IL-6: Interleukin-6, iNOS: Inducible nitric oxide synthase, MHCII: Major histocompatibility complex class II molecules, NO: Nitric oxide, Nrf2: Nuclear factor erythroid 2–related factor 2, RXR: Retinoid X receptor, T cell: T lymphocytes, TGFβ: Transforming growth factor-β, Th1: T helper type 1, Th17: T helper 17, TNF-α: Tumor necrosis factor-α, VD: Vitamin D, VDD: Vitamin D deficiency, VDR: Vitamin D receptor, VDRE: Vitamin D response element.

disruption in patients with relapsing-remitting MS [324]. In addition, VD3 treatment has been shown to reduce macrophage infiltration into the CNS of EAE mice [325]. These findings suggest the disruption of the BBB in a VD3 deficient state leads to infiltration of inflammatory cells and neurodegeneration.

6. Concluding remarks and future perspectives

A growing body of literature indicates that vitamin D functions as a neurosteroid and its adequate level is essential for the optimal development and functioning of the brain. Further, data from both in vitro and in vivo experiments supported the hypothesis that low levels of physiologically active VD are associated with a broad range of neurological illnesses, including Alzheimer's disease, Parkinson's disease, epilepsy, and multiple sclerosis. Unfortunately, till date most of the have not investigated the opposite causality, the reduced VD level which may be due to indoor confinement, exercise restriction and sunshine escaping behavior. In spite of plenty of evidence for the association of reduced vitamin D and neurodegenerative diseases there is dearth of literature regarding the molecular mechanism implicated in the pathogenesis in individuals at associated risk factors. Therefore, this article intends to review the existing literature on the diverse molecular mechanisms of neurodegeneration in vitamin D deficiency. This review mainly volunteered to provide extensive insights into the vitamin D deficiency related neurodegenerative pathophysiology and implication of associated risk factors. However, randomized clinical trials on treatment with vitamin D in individuals at risk for neurological diseases are therefore needed to develop the knowledge and accuracy regarding the efficacy, appropriate dosing, and appropriate biochemical and clinical monitoring of vitamin D. Thus, in view of the given fact that supplementation with vitamin D is affordable and readily available necessitates more research in this area.

There are conflicting studies regarding whether vitamin D supplementation can be utilized as a supplemental therapy for individuals with neurological illnesses or patients at high risk of developing the disease. Nonetheless, one of the most plausible explanations is that the vitamin D dosages used in the clinical studies were insufficient to achieve significant results. Therefore, the determination of the appropriate VD is extremely important because, while low dosages may be ineffective, large doses of vitamin D may have harmful consequences by disrupting intracellular calcium signaling. This objective may benefit from the selection of pertinent outcomes, such as fracture risks, cognitive deterioration, and hospitalization rates. Further research should look into aspects including ethnicity, latitude, age, BMI, dietary intake, physical activity, and sunshine exposure, which may influence the optimal dose of vitamin D.

CRediT authorship contribution statement

Md Jamir Anwar: Conceptualization, design, collection of literature, drafting the manuscript. **Sattam Khulaif Alenezi:** Revision of the manuscript critically for important intellectual content. **Ahmad Hamad**

Alhowail: Review and approval of the final version of the manuscript to be published.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work presented in this review.

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Authors contribution

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