Mechanism of Vitamin D for Protection of Alzheimer Disease, Parkinsonism and Multiple Sclerosis[1]

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ABSTRACT

Vitamin D is a fundamental fat-soluble key vitamin that is obtained either from de novo synthesized by the human body during exposure to sunlight or from other external sources. In the body, vitamin D undergoes two hydroxylase-depended metabolic pathways into its biologically active form "1,25dihydroxycalciferol (1,25(OH)2 vitamin D3), or calcitriol". "1,25(OH)2 vitamin D3 maintain "calcium and phosphate homeostasis" and supports "bone health "through binding with its nuclear receptors, "Vitamin D Receptor (VDR)". VDR and vitamin D metabolic enzymes are distributed throughout the body explain the pleiotropic effects of vitamin D3 in our body. one of these effects showed in "Central Nervous System (CNS)" where calcitriol exerts "neuroprotective effects". This review shed light on the mechanism of neuroprotective induced -calcitriol in some of "neurodegenerative disorders".

Keywords: *Neurodegeneration, vitamin D, Alzheimer, Parkinson, Multiple Sclerosis.*

INTRODUCTION:

Vitamin D is a lipid-dissolvable vitamin which has a vital role in bone health through its regulation of phosphate and calcium levels in the body. The human body acquires vitamin D either orally by taking vitamin D- rich food or food supplements or by direct exposure of the skin to sun lights.

Following direct exposure of skin to sunlight, 7-dehydrocholesterol (provitamin D3) was activated to form cholecalciferol (vitamin D3). After that vitamin D3 metabolizes in the liver to 25-hydroxycholecalciferol by the action of 25-hydroxylase. 25-hydroxy cholecalciferol then undergoes further metabolism in the kidney to yield the biologically active form, "calcitriol (1,25-dihydroxyvitamin D3)(1,25-(OH)2D3)" by the action of "cytochrome P27B1" (CYP27B1) enzyme (Figure 1)[1].

Calcitriol has genomic and non-genomic biological actions. Mainly, Calcitriol exerts genomic biological activities through binding with the "vitamin D receptor (VDR)" which is a nuclear receptor. The receptor of vitamin D is considered a transcription factor, after activation by its ligand, VDR regulates a gene expression through binding with sequences of DNA in target genes termed "vitamin D response elements (VDREs)". Finally, this process results in the production of a specific protein involved in the biological activities of vitamin D3[2].

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The presence of VDR with vitamin D-activating enzyme (CYP27B1) in different tissues in the body explains the various biological effects of vitamin D3 that include immune function, cardiovascular effects, regulation of proliferation and differentiation of various cells like keratinocytes [3].

The present review will focus on the existence of "VDR" and the expression of "1-α hydroxylase enzyme (CYP27B1)"in neurons and glial cells that explained the beneficial effects of calcitriol in the treatment of some nervous system diseases[4]. Such effects involve the biosynthesis of neurotrophic factors and enzyme-induced neurotransmitter synthesis, suppression of the generation of "inducible nitric oxide synthase(iNOS)" and rises in the levels of glutathione that described the potential value of "vitamin D3" in "neurodegenerative diseases"[5].

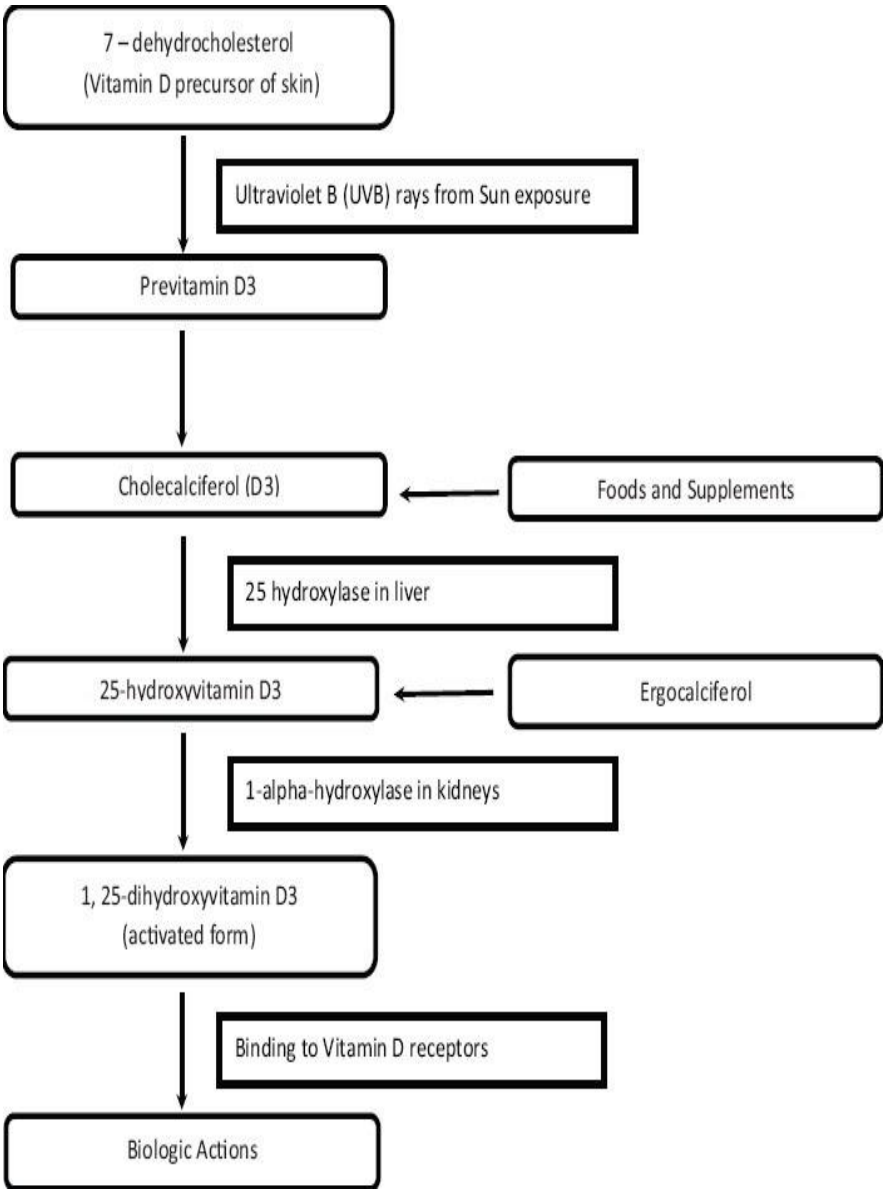

Figure 1. Activation of vitamin D inside the body [1].

VITAMIN D AND NEURODEGENERATIVE DISEASES

"Alzheimer's disease (AD)": is one of the most popular types of degenerative nerve diseases in the world, it is characterized by memory loss and change in personality. Alzheimer's disease results from amyloid-beta peptides (Aβ) with Neurofibrillary Tangles; hyperphosphorylated Tau protein accumulations in the brain, atrophy occurs as a result of neuronal and synaptic loss, neuroinflammation, oxidative stress and loss of cholinergic neurons (Figure 2)[6].

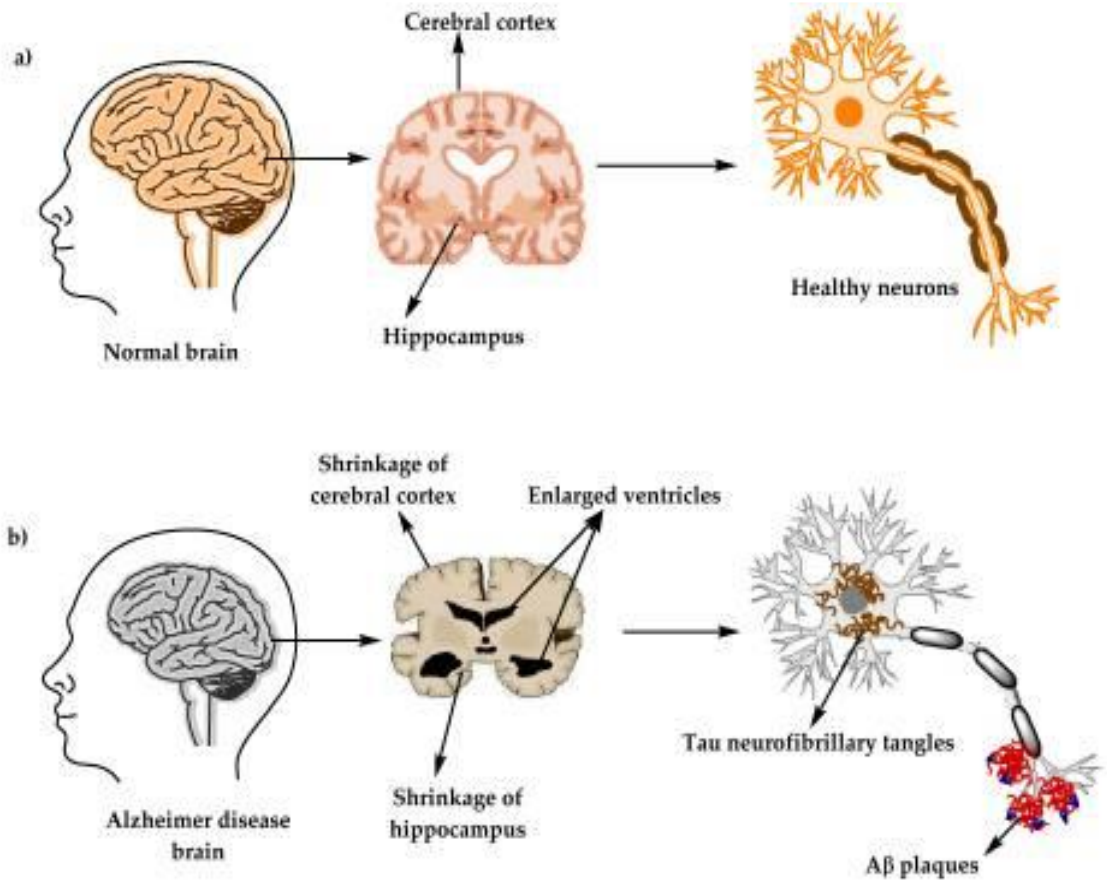

Figure 2. (A) Normal brain (B) Brain with Alzheimer's disease(6)

Effects of calcitriol in Alzheimer's disease:

Effects of calcitriol on Aβ aggregation

Many studies appeared to the valuable role of calcitriol in reducing the accumulation of amyloid plaque in the frontal cortex, neocortex, and hippocampus cortex by impairment the process of amyloidogenesis. Furthermore, "vitamin D-binding protein (VDBP)"; which increased in cerebrospinal fluid of AD patients, binds with (Aβ) and thus reduces Aβ aggregation. In addition, calcitriol activates its receptors to increase the production and transport activity of "P-glycoprotein" in the capillaries of the brain leading to alteration of "blood-brain barrier (BBB)" permeability and decreasing "Aβ" accumulation as revealed by cell line study. as a result vitamin D3 and its binding protein prevent β-induced neurotoxicity lead to improve cognition and reduce memory loss[7].

Effect of calcitriol on synaptic transmission and calcium homeostasis

Brain in AD-patient characterized partly by impairment of synaptic transmission and changes in calcium homeostasis. calcitriol has a direct regulatory effect on gene expression of many proteins involved in calcium homeostasis, synaptic vesicles trafficking and neurotransmitters. At the presynaptic level, calcitriol upregulates synaptojanin 1 and synaptotagmin 2. Synaptojanin 1 helps the synaptic vesicle recycling by its phosphatase property, while Synaptotagmin 2 starts docking of vesicle and coalescence to the "presynaptic membrane" via its calcium-dependent action, eventually, the neurotransmitter liberation takes place[8,9].In addition, calcitriol regulates the transcription of "vesicular glutamate transporter 2" that package "glutamate" into vesicles in "presynaptic neurons" for release at the synapse.

At the postsynaptic level, calcitriol regulates several protein productions like "calcium/calmodulin-dependent protein kinase IIδ (CaMKIIδ)" and receptors for many neurotransmitters such as serotonin, "glutamate" as well as dopamine. "CaMKIIδ" occurs in the nucleus and enhances the expression of "BDNF" which is a CNS growth factor that stimulates synaptic plasticity and neurogenesis, through phosphorylates a "transcription factor; cAMP response element-binding protein (CREB)"[10]. Furthermore, It activates the transcription of nuclear receptor 4A2 (Nr4a2), which enhances cognition because it has the effect of strengthening long-term memories(Figure 3)[11].

Moreover, in a study of cultured neurons, vitamin D3 treatment showed decreasing in L-type voltage-gated calcium channel (LVSCC), which is present in the ageing neuron of the hippocampus resulting in neuroprotection from calcium excitotoxicity. Together, these impacts of calcitriol on calcium controlling and synaptic function counteract cognitive decline and memory loss associated with (AD)[12, 13].

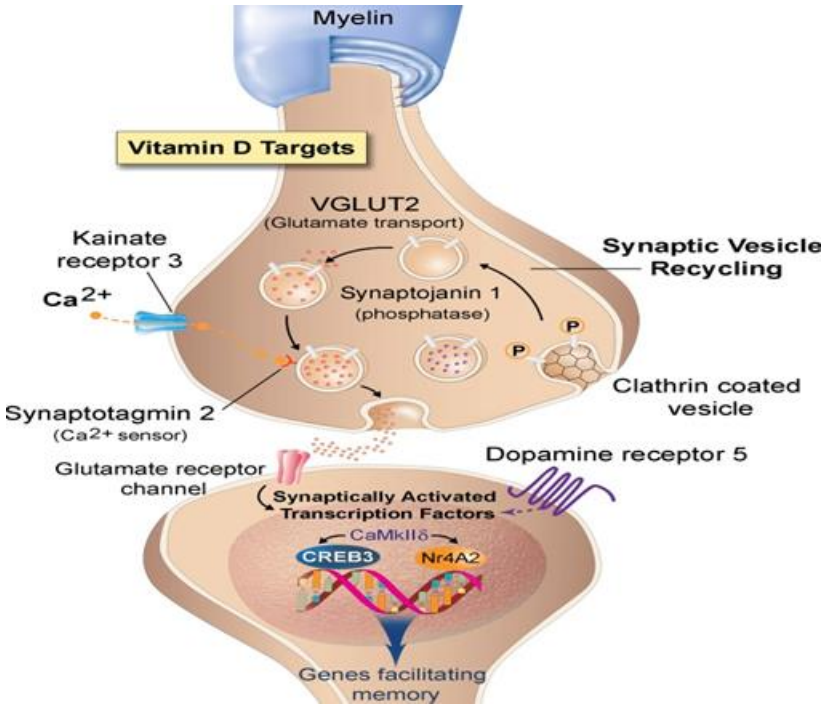

Figure 3. Effect of vitamin D3 on synaptic transmission[7].

Effect of calcitriol on neuroinflammation in AD

VitD3 inhibits the expression of proinflammatory cytokines like "macrophage colony-stimulating factor (M-CSF) and tumour necrosis factor α (TNF-α)" according to cell-cultured studies.in addition, it regulates prostaglandin production and selectively inhibits the activity of the cyclooxygenase2 enzyme (cox-2 enzyme)[13].

Effect of calcitriol on oxidative stress in AD

Various studies show that vitamin D3 exerts neuroprotective effects due to its antioxidant property. Calcitriol inhibits the generation of "reactive oxygen and nitrogen species", blocks the production of iNOS and stimulates the action of "the Gamma Glutamyl Transpeptidase", which is a critical "enzyme" of glutathione "metabolism"[14,15]. "1,25$(OH)_2$D" also maintains cerebral endothelial normal function via its inhibiting reactive oxygen species production and NF-κB activation[16].

In addition, Vitamin D3 supplementation enhances energy homeostasis of the brain and Protein Phosphatase 2A (PP2A) activity thus diminishing age-associated Tau hyperphosphorylation and cognitive weakness[17].

Parkinson's disease (PD) is the second "neurodegenerative" disorder that is most commonly affects elderly people through the word. it characterized by movement slowness, postural imbalance, rigidity and tremors[18].

Pathologically, PD involves loss of "dopaminergic nerve cells" in "the substantia nigra pars compacta", as a result of intracellular aggregation of "α-synuclein" in the form of "Lewy bodies", neuroinflammation, defect in protein clearance systems, and mitochondrial dysfunction[19].

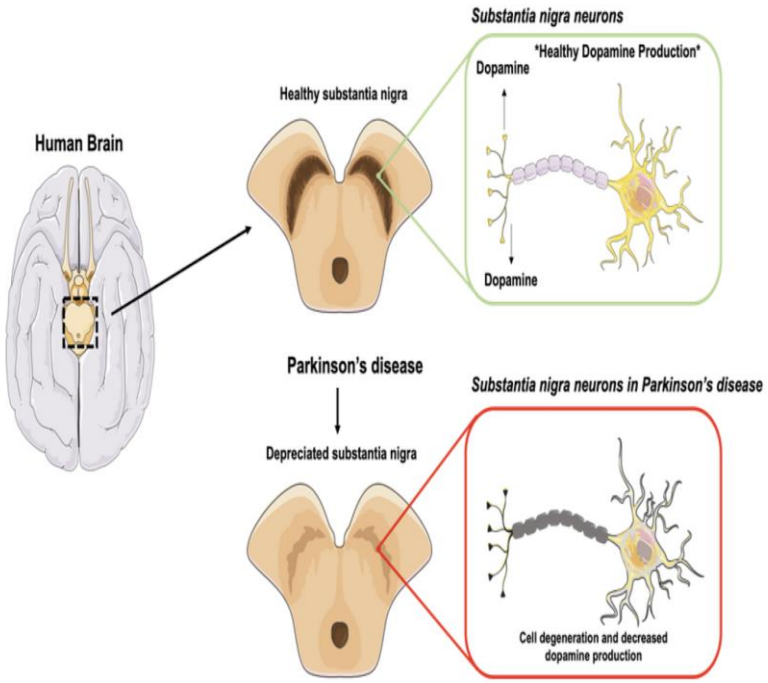

Figure 4. Pathology of parkinsonism[20].

Effects of calcitriol in Parkinson's disease

"1-alfa hydroxylase and VDR" are expressed highly in "substantia nigra" which explains the effect of vitamin D in PD. vitamin D enhances "dopamine" synthesis by activation of "tyrosine hydroxylase gene expression".

Vitamin D has a role in neuronal plasticity and axogenesis due to its stimulating effect on the synthesis of "neurotrophic factors" and enhancement of detoxification mechanisms that protect the neuronal structure and integrity[21].calcitriol regulates the synthesis of "Glial cell-derived neurotrophic factors (GDNF)" which in turn enhances regrowth of neuron. "Glial cell-derived neurotrophic factors" bind with "GDNF Family Receptor alpha 1 (GFRa1)" then binds to the "proto-oncogene tyrosine-protein kinase receptor Ret (C-Ret)". This complex results in the stimulation of signalling inside "DA neurons" that activate the existence and differentiation of "midbrain DA neurons"(Figure 5)[22].

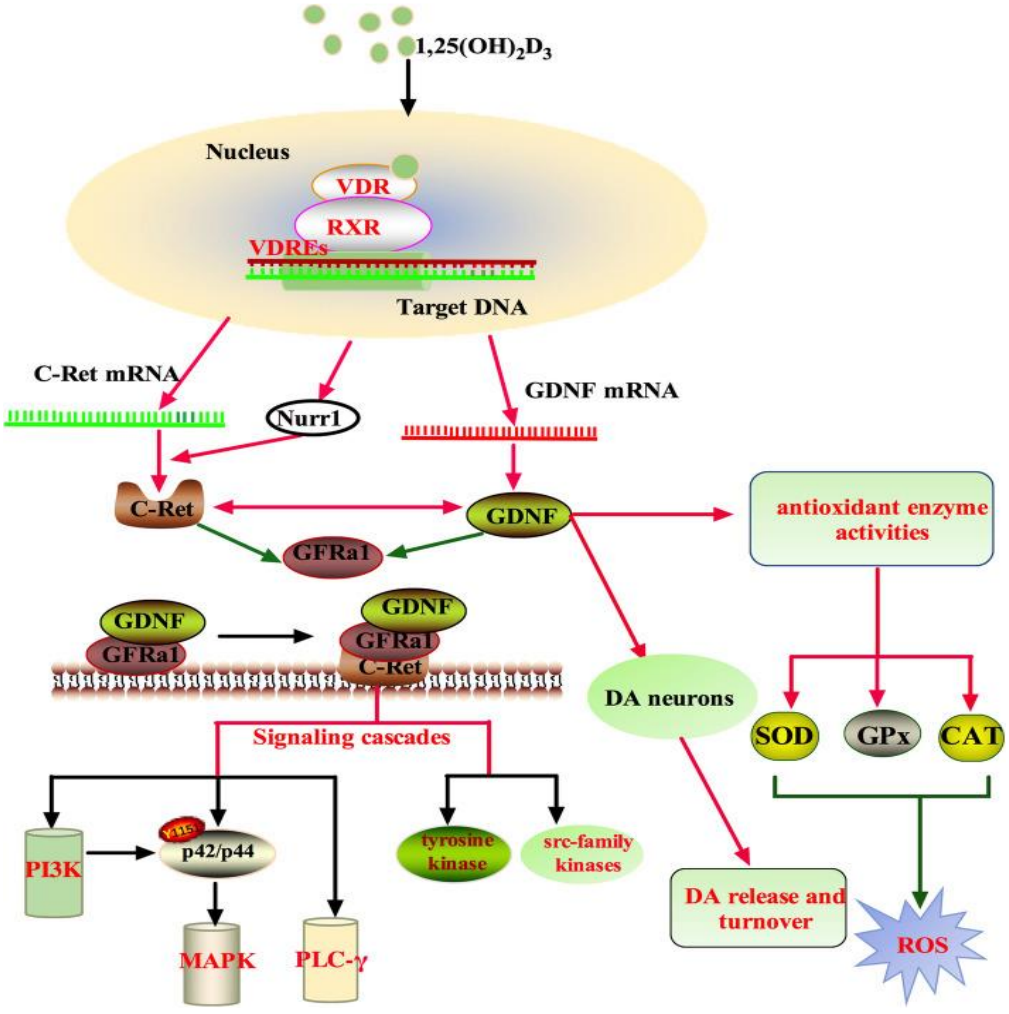

Figure 5. Neuroprotective effect of calcitriol through its effect on GDNF synthesis [23].

GDNF also reduces "reactive oxygen species (ROS)" and remarkably elevates the levels of antioxidant enzymes such as "glutathione peroxidase, superoxide dismutase", and "catalase in the striatum"[24]. furthermore, during inflammation, microglia produce $1,25(OH)_2D_3$ which enhances "gamma-glutamyl transferase (γ-GT)" expression. 'Gamma-glutamyl transferase" facilitates the influx of glutathione GSH into the cells. which diminishes the synthesis of "reactive nitrogen

species (RNS)" and "hydrogen peroxide(H2O2)"[25]. Moreover, "calcitriol" increases the expression of the" nuclear factor erythroid 2-related factor 2 (Nrf2)".that enhance the expression of both "VDR and RXR" (retinoid x receptor) (Figure 6)[26].

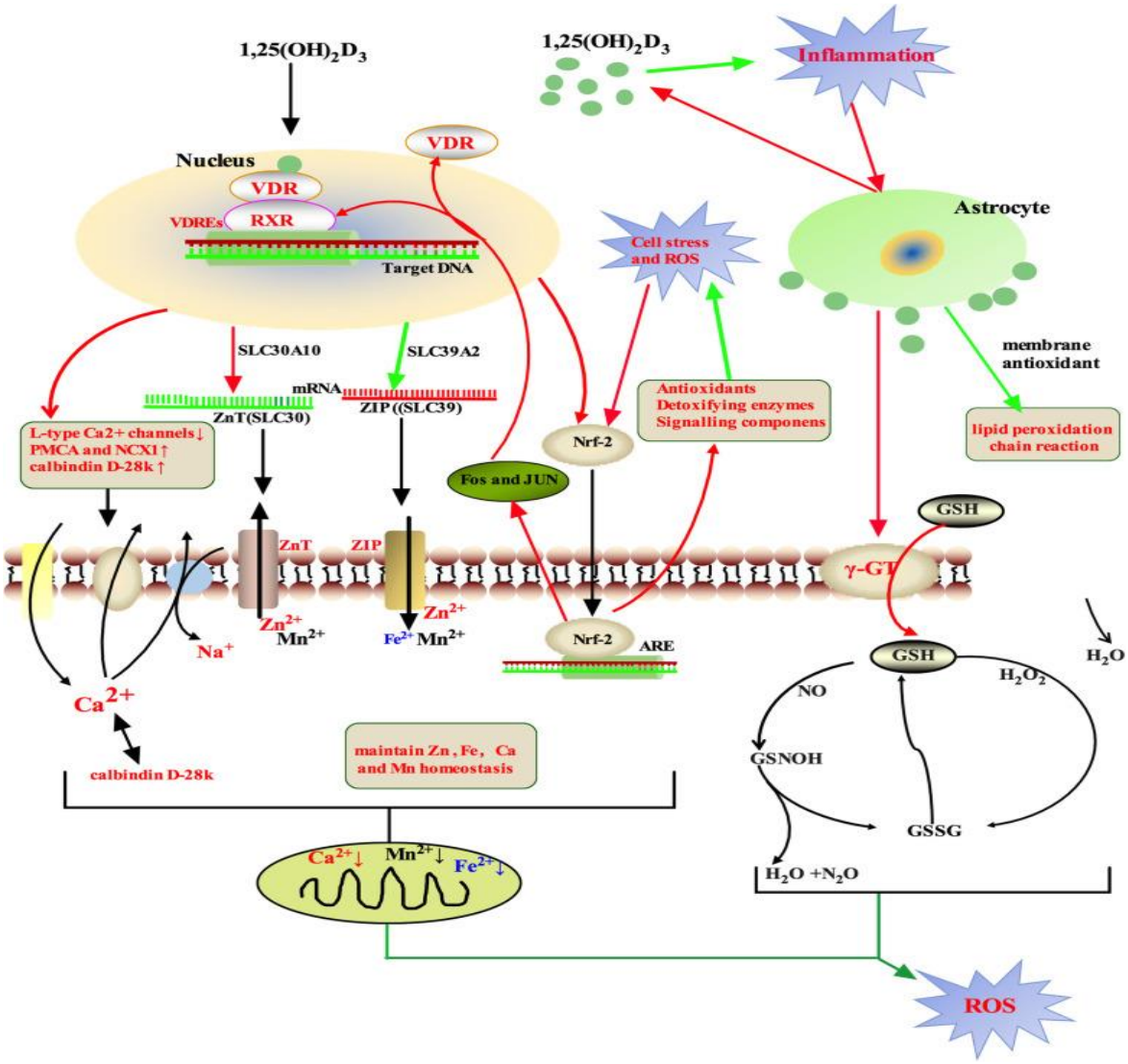

Figure 6. Neuroprotective effect of calcitriol through its effect Effects on Nrf2,γGT, Ca^{2+} ATPase, NCX1, calbindin D28k and *L*-type Ca^{2+} channels [27].

In addition to an inhibitory effect of calcitriol on" L-type Ca^{2+} channels, it increases the expression of the plasma membrane Ca^{2+} ATPase, anti-apoptotic factor Bcl-2 sodium-calcium exchanger (NCX1), and buffering protein calbindin D28k". collectively, these effects make calcitriol conserve the low concentrations of Ca^{2+} intracellularly and thus protect against Calcium-induced oxidative damage and aggregation of α-synuclein in dopaminergic neurons in substantia nigra.

The anti-inflammatory properties of "$1,25(OH)_2D_3$ "include attenuation of pro-inflammatory and upregulation of anti-inflammatory processes. As a result, these effects explain the enhancement of motor activity, cognition and mood in PD patients after the elevation of their serum vitamin D level[23]**.**

MULTIPLE SCLEROSIS (MS):

is one of the long-standing neurodegenerative diseases, which affect males, and young people; aged 20-40 old; more than females. "Multiple sclerosis" is an "autoimmune disease" of the "central nervous system (CNS)" which is mediated mainly by "CD8+T- lymphocytes". "Autoreactive T lymphocytes" cross the "blood-brain barrier " and enter the central nervous system. Together, T lymphocytes, activated macrophages and microglia locally initiate inflammation through the release of proinflammatory cytokines like TNF-α and interferon-gamma (IFN-γ), reactive oxygen or nitric oxide species causing plaques of demyelination of the axon, gliotic scarring and axonal loss. It is noteworthy that these plaques are distributed in different areas in CNS including white and grey matters. Multiple sclerosis is characterized by a relapsing-remitting phase followed by secondary progressive, irreversible neurological deterioration. Patients with MS suffer from sensory disturbance, cognitive deficits, fatigue, ataxia, limb weakness bladder dysfunction, bowel troubles, and unilateral painless loss of vision and double vision (Figure 7)[27].

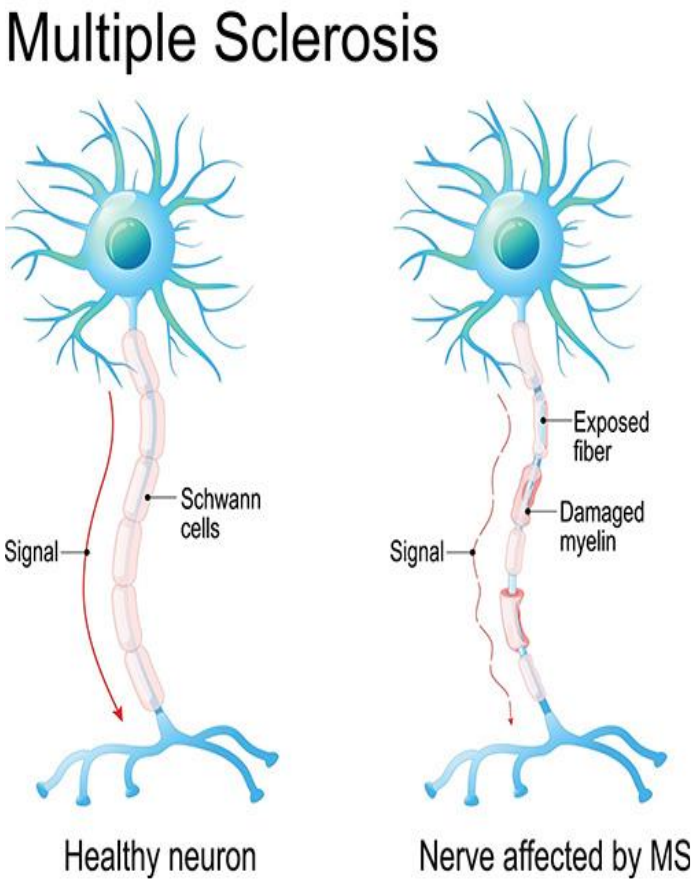

Figure 7. Difference between healthy neurons and neurons with multiple sclerosis[28].

Mechanism of calcitriol in multiple sclerosis:

As an immunomodulator, calcitriol affects (MS) and other autoimmune diseases. Both VDR and CYP27B1 are expressed in "innate and adaptive immune cells". "$1,25(OH)_2D_3$ " enhances glucocorticoid-stimulated monocytes to produce "mitogen-activated kinase phosphatase 1 ", which decreases the pro-inflammatory activity of "mitogen-activated protein kinases". "$1,25(OH)_2D_3$ "inhibits differentiation of monocytes into a dendritic cell, "maturation" and function of dendritic cells and induces dendritic cells apoptosis. Several studies appear that "$1,25(OH)_2D_3$ inhibits the proliferation of CD4 +

T cells (Th1, Th2, Th17, regulatory T cells Treg cells), their secretion of pro-inflammatory cytokines (IL-2, IL-17, IFN-γ) and stimulates their secretion of anti-inflammatory cytokines (IL-4, IL-10)".

In addition, $1,25(OH)_2D_3$ induces differentiation of Treg cells; which are immunosuppressant and prevent autoimmune response, by (indoleamine 2,3-dioxygenase) IDO-mediated mechanism and inhibits the differentiation of Th1, Th2, and Th17 cells. Therefore, $1,25(OH)_2D_3$ inhibits cytotoxic T cells(CD8+T cells) by its action on CD4+Tcells [29]. Furthermore**,** Calcitriol induces "remyelination" by enhancing the generation of "myelin-producing oligodendrocyte precursor cells (OPC)" and "neuronal stem cells (NSC)" [30].

CONCLUSION

Vitamin D is one of the most important lipid-soluble micronutrients, its active form has pleiotropic effects in the human body in addition to calcium and phosphate homeostasis and bone health. several studies show a neuroprotective effect of calcitriol in several commonly spread "neurodegenerative diseases like Alzheimer's disease Parkinson's disease and Multiple Sclerosis". Calcitriol-induced neuroprotection mediated by reduction of calcium toxicity and generation of reactive oxygen and nitrogen free radicals, alteration of cytokine release, enhanced production of antioxidant molecules, induction of "neurotrophin, and neuritogenesis", as well as the protection of neurons against cell death so that Vitamin D supplement may be considered as an effective neuroprotective agent.

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Conflict of Interest: None

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