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Review Article

Vitamin D: Sources, Metabolism, Mechanism of Action, and Its Role in Health and Disease

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Abstract *- Vitamin D(VD), which is accepted widely to function as both a hormone and a vitamin, plays a crucial role in maintaining normal physiological processes. Its potential to mitigate disease severity has garnered significant scientific interest. Studies across various cell lines, animal models, and human populations have highlighted its extensive protective effects on multiple systems, including brain function, cardiac health, muscle and bone metabolism, immune response, mitochondrial integrity, and cellular interactions. Additionally, vitamin D has become a potent activator in human reproduction, pregnancy, and cancer regulation, underscoring its broad biological significance. This review compiles the multifaceted roles of vitamin D and its therapeutic potential in health and disease.*

Keywords *- Immunity, Inflammation, Mitochondria, Reproduction, VD/VDR.*

1. Introduction

With its pleiotropic activities, VD is found in practically all types of life.[1] It is essential for the healthy operation of the cardiovascular, neurological, musculoskeletal, immunological, and the regeneration of epithelial barriers. [1],[2] VD/VDR signaling overall contributes to the mammalian hair cycle, healthy aging, antimicrobial defense, cardiovascular protection, anti-inflammatory, anti-cancer, and xenobiotic detoxification.[3]

Still, its deficiency is a worldwide problem affecting 69% of adults worldwide,[1] and is because of the unawareness and less experimental evidence. Vitamin D level is known to be influenced by both environmental and personal factors, including dark skin, high latitude or low sunshine conditions, sunscreen use, ethnic background, specific clothes, and cultural customs.[5] Different studies report the likeliness of VDD (vitamin D deficiency) in individuals with deep skin tone and high body fat.[6] The status of VD declines in people aged 70 or older is considered a result of decreased sunlight exposure and cutaneous synthesis.[7]

Risk and severity of systemic autoimmune diseases, cancer progression, obesity, type 2 diabetes, insulin insensitivity, dermatitis, cardiovascular disorders, hypertension, venous thromboembolism, pregnancy-related complications, osteoporosis, and many age-related diseases are reported to exacerbate in VDD.[8],[9],[10] In the treatment of cancer, neurodegenerative disorders, autoimmune diseases, hypertension, psoriasis, and preeclampsia, high doses of vitamin D were promising.[1],[2] Beyond that, Vitamin D was reported to indirectly control different ion channels and play a key role in mineral homeostasis.[11]

Vitamin D thus demands more and more research attention. Earlier studies tried to focus on one or a few areas, but this review highlights the overall mechanism, protective role, and deficiency consequences of VD in different physiological states.

2. Source and requirement of Vitamin D

In humans, VD originates from its non-enzymatic photochemical reaction in the skin's basal layer of the epidermis in UVB radiation (280–320 nm).[1] Almost 80-90 % of daily vitamin D3 comes from this photolysis of 7-dehydrocholesterol (7-DHC) and little from the diet, only ~10 % of the body’s demand.[12],[5] Vit-D-containing foods include fatty fish, fish oil, cod oil, dairy products, mushrooms and dietary supplements.[1],[9] Daily UVB exposure of 7–30 min is considered to fulfill the amount of VD supplement, and interestingly, prolonged exposure to UVB does not accumulate excess Vit D.[13]

Endocrine Society’s daily vitamin D recommendations are- 400 IU for less than one year, 600 IU for one to eighteen years, and 1500-2000 IU for both men and women over 18 years old.[9] Being the stable circulating form of VD, 25(OH)D[11] serum concentration is considered as VD status; when it is <30 nmol/L or 12 ng/ml, it is deficiency state, while the range is between 30 and 50 nmol/L or 12–20 ng/ml is insufficiency.[6],[14] In general, VDD runs in obese individuals.[7] A recent study in northern Taiwan shows that VDD predominates in women than men [15].

3. Metabolism of Vitamin D

Pre-vitamin D, tachysterol, and lumisterol are three initial iso-products resulting from the photodegradation of 7-Dehydrocholesterol, and in the next step, VD forms in time-dependent thermal conversion.[1] A 58 KD vitamin-D-binding protein with nearly 120 isoforms (primarily Gc1f, Gc1s, and Gc2) transports into all organs and maintains the VD metabolite pool.[1],[13],[9],[16] Two successive hydroxylation reactions in the liver mediated by CYP2R1 or CYP27A1 result in 25-hydroxylation product- 25-hydroxyvitamin D3, which then undergoes 1α-hydroxylation by CYP27B1 in the proximal tube of kidney and turns into active calcitriol-1,25(OH)2D3.[17],[1],[13],[6] Organs, that can express CYP27B1, including skin, are capable of forming active Vitamin D3.[1] The skin has all the elements for the synthesis, activation, catabolism, and response towards vitamin D.[17]

In another pathway, CYP11A1 or cytochrome P450scc activate vitamin D metabolism, where initially C-22 and C-20 of 7- DHC are hydroxylated, followed by side chain cleavage to convert into 7-dehydropregnenolone (7-DHP) then it further modified in 5,7- diene-analogues, which are convertible to equivalent vitamin D analogues.[17] According to circannual rhythm, VD levels get altered, and so do the VDR mRNA expression, concentrations of inflammatory cells, and their biomarkers.[13]

4. Mechanism of action of Vitamin D

4.1. The Genomic Pathway

Vitamin D receptors (VDR) are widely distributed across various human tissues, with particularly high expression in the pituitary and parathyroid glands, the small intestine, the colon, the kidneys, the skin, and a majority of immune system cells.[13]

Upon binding with vit-D, VDR triggers its homodimerization VDR: VDR or heterodimerization with retinoid X receptor (RXR) VDR: RXR[18] to translocate into the nucleus.[1] Activated VDR: RXR complex then binds to the vitamin D-responsive elements (VDREs) of VD-regulated genes,[1],[6],[19],[20],[21] and in humans, the number is almost 3000.[17] The outcome manifests as changes in the suppression of cell proliferation, promotion of cell differentiation, modulation of the immune response, regulation of reactive oxygen species (ROS), and shifts in mitochondrial function.[1]

4.2. In the Non-Genomic Pathway

The rapid response of Vitamin D can act like a steroid hormone and work through binding with membrane receptor proteins[22], which are described as 1,25D3-MARR, PDIA3, GRP58, ERp57, P58, ER60, ERp60, ERp61, GRP57, GRP58.[1],[23] Being present on each side of the ER and cytoplasm, PDIA3 mediates signaling cascades.[1],[23]

In ER, PDIA3 plays a crucial role in protein folding, exporting rapid uptake of calcium and phosphate, attenuating PKA or PKC signaling by interacting with calreticulin and calnexin, and SERCA2b-mediated calcium uptake.[1] PDIA3 interacts with the main scaffolding caveolae protein- caveolin-1, resulting in downstream signaling of IP3, DAG, and cAMP production.[1] Thus, by modulating calcium influx and the generation of secondary messengers, PDIA3 takes part in the rapid activation of WNT5A.[1] In Figure 1, the overall metabolism and mechanism of action are depicted.

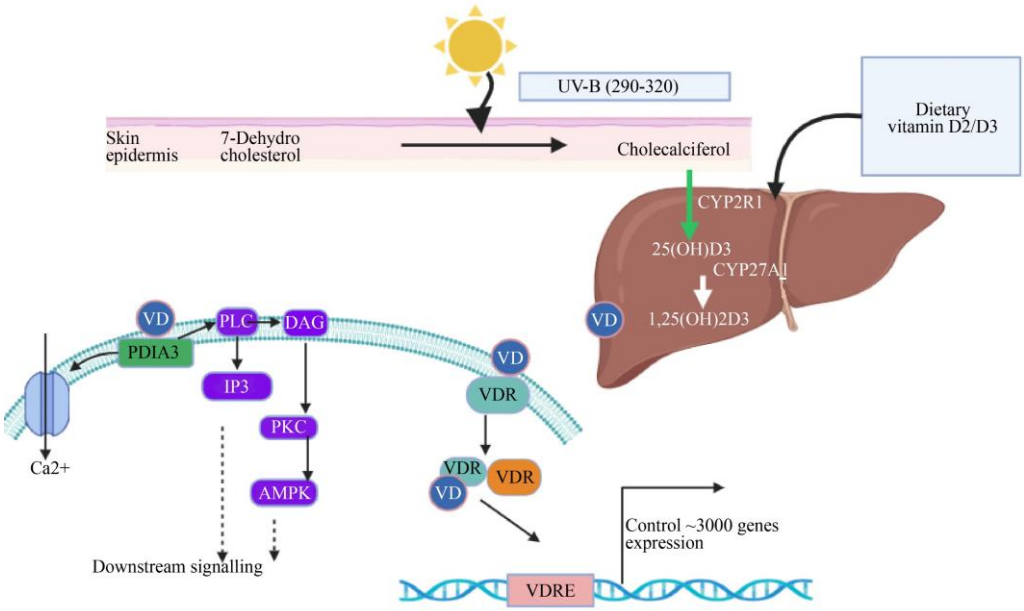

Fig. 1 Overall metabolism and mechanism of action of Vitamin D.

5. Literature Review

Haeri et al. reported vitamin D's involvement in improving bone microenvironment and mobility performance in women aged 65 and up, considering- Spine Bone Texture Score, Grip Strength, and Gait speed.[24] Yang et al. showed its regulatory effect on fatty acid metabolism and cardiac function in in-vivo mice mode.[25] Moreover, they proved that SIRT3 overexpression along with respiratory complexes in mice.[25] Inadequacy of VD was shown to induce obesity, intramuscular fat deposition, and tissue damage in C2C12 muscle cells.[26] Besides that, Eugene Chang showed a significant reduction of the tertiary butyl-hydrogen peroxide-induced ROS in C2C12 muscle cells.[27] In human skeletal muscle myoblasts, Ryan et al. showed a protective effect of calcitriol in mitochondrial dysfunction and fragmentation.[28] Vanhevel et al. proved that Vitamin D analogues have a synergistic antiproliferative effect in the palbociclib treatment MCF7 (ER+) cell line.[29] VDR was shown as a self-protective receptor that auto-upregulates both mRNA and protein levels in ischemia/reperfusion-induced myocardial injury in mouse cardiomyocytes.[30] In BALB/c mice, the different expression pattern of Brain-derived neurotrophic factor (Bdnf) as well as transforming growth factor-β1(TGFβ1) was found in VDD fetuses both are crucial for neuronal development [31]; along with that Hawes et al. showed both tyrosine hydroxylase (TH) and Forkhead box protein P2 (Foxp2) reduced expression (in humans, Foxp2 is important in speech and language).[31] Depending on the cell and tissue types, VDR can inhibit or promote apoptosis.[30] Recently, VD/VDR signaling was reported to work against apoptosis in an LPS-induced AKI model.[32] Also, VDR activation reduced the lipid peroxidation level, restored GPX4 expression, and decreased necrosis in tuberculosis-infected lung tissue of mice.[32] Oral VD supplementation is protective against asthmatic inflammation.[33]

5.1. Vitamin D in Muscle & Bone

VD contributes to the maintenance of skeletal muscle health.[14] It regulates intestinal uptake and urinary excretion of calcium[9], along with PTH level, thus contributing to the modulation of Calcium and Phosphate homeostasis.[13],[2],[29] Lack of vitamin D causes osteopenia, osteoporosis, fractures, muscle weakness, and decreased bone density.[6] Softening and weakening of the bones in children-rickets and adults-osteomalacia results from its severe deficiency. [6] Moreover, VDR deletion results in impaired bone formation.[1]

$1,25(OH)_2D$ promotes the growth, differentiation, proliferation, and regeneration of muscle cells.[14],[27],[26] It activates the expression of myoblast determination protein 1 (MyoD1) and subsequently suppresses myostatin in a time-dependent fashion. Additionally, vitamin D influences the forkhead box O (FOXO)3 and Notch signaling pathways, supporting myoblast self-renewal and maintaining the satellite stem cell population.[14]

VDD results in an improvement in muscle performance and strength, which was reported with Vitamin D supplementation in aged people[1],[6],[9]. It was found preventive in sarcopenia and sarcopenic obesity in vit-D deficient subjects.[7] In animals with vitamin D deficiency, supplementation helped restore the balance between muscle protein synthesis and degradation.[6] 1α,25(OH)2 D3 was found to be promising in treating low back pain.[14] Human myoblasts showed increased cellular Oxygen Consumption Rate (OCR), mitochondrial volume, and expression of mitochondrial pro-fusion and pro-fission protein changes upon 1α,25-dihydroxy vitamin D3 administration.[28]

Poor VD status is linked with dysfunction of mitochondria, ATP depletion, increased Reactive Oxygen Species (ROS) and oxidative damage, contributing to muscle atrophy and impaired muscle function.[14],[8] Besides this, VDD significantly inhibited muscle AMPK/SIRT1 activation[26]. Muscle injury models revealed that VD enhances mitochondrial oxidative phosphorylation, eventually antagonising muscle damage and promoting muscle regeneration.[6],[14] Muscular atrophy and faintness were proved to be connected with insufficient Vitamin D levels of 50 nmol/L in various clinical investigations.[9]

5.2. Vitamin D in the Brain

VD has enormous neuroprotective roles as a developmental Neurosteroid.[34] In the brain, its effects are mediated by regulating essential survival pathways, including the stimulation of neurotrophic factors like glial cell line-derived neurotrophic factor (GDNF), nerve growth factor (NGF), and neurotrophin-3 (NTF3)[35], regulation of inflammation, mineral homeostasis, and thrombosis.[36],[23] Animal models have underscored vitamin D as a fundamental factor for CNS proper functioning.[37]

From cell culture studies, it was found that vitamin D administration prevented Aβ toxicity by mitigating amyloid-β (Aβ) production, deposition [38] and increased neuronal survival.[23] CSF, with high 25(OH)D, had reduced tau levels.[23] Different earlier work suggest high VD consumption to prevent neurodegeneration.[23] Also, calcitriol ameliorates neuropathic pain by preventing the loss of GABAergic interneurons in the spinal cord by PKCα/NOX4 signaling mediated inhibition of mitochondria-associated ferroptosis.[39] Additionally, VDR-activated ERK1/2 activation contributes to the attenuation of neuronal apoptosis.[34]

It has been observed that 25-(OH)D3 inhibits the generation of nitric oxide (NO) in primary microglia and BV-2 cells; VDR knockdown reversed this effect.[37] Another study reports that 1,25(OH)2D3 downregulates microglial activation by eliminating the age-related rise in microglial expression of MHC-II, stress-activated protein kinase, and c-Jun N-terminal kinase in the rat hippocampal region.[13]

phagocytic activity of microglia is also affected by VD3. [37] There is proof that VD3 is connected to Parkinson's disease, Alzheimer's disease, autism spectrum disorder, sleep difficulties,[37] and multiple sclerosis (MS),[40],[41] where microglia are involved in all.[37] In MS, VD sufficiency is fundamental in combatting axonal degeneration and glial and neuronal loss [41]. Cholinergic, dopaminergic, and noradrenergic neurotransmitter systems in the central nervous system can all be altered by VD [23] and are essential in the brain for serotonin production. [10]

Lack of VD can alter one's brain development by triggering premature aging, non-aligned enlargement of the lateral ventricles, and decreased nerve growth factor. Decreased expression of neuronal structure-related genes [23] and is a potent contributor to dementia, seasonal affective disorder, depression, schizophrenia, Parkinson's disease, modest cognitive impairment, Alzheimer's disease, and cognitive decline in humans.[23],[10],[37],[42] research has found that VDD is linked with hyper intensive volume of white matter, suggesting increased dementia risk.[36] Beyond that, long-term vitamin D deficiency is suspected of making neurons vulnerable to aging and neurodegeneration.[23]

5.3. Vitamin D in Cardiovascular Biology

Hypovitaminosis D is associated with cardiovascular dis eases that are primary factors driving disease burden and fatality, including conditions like heart failure, aortic aneurysmal disease, peripheral vascular disease, high blood pressure, atherosclerosis, coronary artery disease, heart attacks, cardiac hypertrophy, cardiomyopathy, and fibrosis of the heart.[9],[25]

In a mouse model, Vitamin D3 was shown to inhibit oxidative burden and regulate the activity of mitochondria to abate hypoxia/reoxygenation (H/R)-driven cell death and revert H/R-induced mitophagy and mitochondrial fragmentation and by means of mitochondrial fission proteins such as Drp1 and Mff downregulation.[9] Besides, by inducing eNOS expression and nitric oxide (NO) generation, VD is capable of boosting endothelial cell proliferation.[9]

VDR has gained its acquaintance as a newly identified natural receptor that plays a self-protective and heart-protective role against myocardial ischemia/reperfusion (MI/R) injury[30]. Without altering caspase-8 activity, VDR agonists markedly suppressed the activities of caspase-12 and caspase-9 triggered by myocardial ischemia/reperfusion (MI/R).[30] It also suppressed CHOP overexpression, prevented mitochondrial swelling, and reduced cytochrome c (Cyto-C) release, thereby alleviating Endoplasmic Reticulum (ER) stress and improving mitochondrial function.[30] SIRT3 and mitochondrial respiratory chain complexes are upregulated by VD/VDR while limiting the hyperlipidemia-induced oxidative damage.[25] Vitamin D supplementation in humans promotes mitochondrial integrity and helps regulate the progression of cardiovascular diseases.[9]

5.4. Vitamin D in Inflammation & Immunity

Vitamin D metabolites affect the immune cell fate and cytokine production both in type and amount to control the systemic inflammatory condition and the aging process.[9] Vitamin D supplementation alleviated cellular inflammation and stress in humans and rodents.[27]

1,25(OH)2D3 have paracrine and autocrine to inflammatory and immune cells where calcitriol promptly enhances response by tuning cytokine profile. For instance, VD3-induced cathelicidin expression induces chemotaxis of neutrophils, monocytes, macrophages, and T cells to the infection site and promotes pathogen clearance promoting clearance.[13] Again, VD-induced NOD2 expression causes stimulation of NF-κB, then it enhances the defensin β4A that recognizes peptidoglycan of bacteria and attracts immune cells of innate response synergistically.[13] Also, VD is capable of reducing insulin insensitivity.[9] It suppresses cholesterol absorption by macrophages, which otherwise would promote atherosclerosis by cholesterol uptake and deposition into endothelial spaces.[9]

Moreover, 1,25(OH)2D3 shows anti-inflammatory action by blocking NF-κB translocation.[13] VD–VDR complex can impede ROS-mediated apoptosis.[10] In BEAS-2B cells, VD has shown its capacity to restore mitochondrial morphology and reduce the expression of cleaved caspase-3, Bcl-2, Bax and cytokines like- IL-1β, IL-6, TNF-α, and IFN-γ.[43],[2],[13] VD can suppress expression of CD40, CD80–CD86, HLA-DR, MHC-II, and selected cytokines of DC and macrophages for maintaining tolerance.[13] Reports show that 1,25(OH)2D3 and dexamethasone together drive T cell differentiation towards a more anti-inflammatory profile in vitro by enhancing IL-10 production along with suppressing IgE.[13] 1,25(OH)2D3 treated DCs produce huge CD4+CD25+ Treg cells.[44]Endoplasmic reticulum (ER) stress was reported to be inhibited by VDR activation.[30] Beyond that, VD maintains the M1- M2 macrophage profile.[13]

Age-related NAFLD was reported to be rescued by Vitamin D treatment.[45] VDR gene deletion in the intestinal epithelium in mice exacerbated the fibrosis condition.[18] Suppressing IL-12 production of 1,25(OH)2D3 favors the shift from TH1–TH17 to a TH2-Treg cell profile with increased IL-4, IL-5,IL-13 and decreased IFN-γ, TNF-α, IL-1, IL-2, IL-12, IL-17, IL-21,IL-23.[13],[35] 1,25(OH)2D3 is considered protective in diabetic nephropathy, chronic kidney inflammation, proteinuria, and renal fibrosis.[32]

Vitamin D insufficiency significantly deteriorated the obesity-associated intramuscular fat deposition, Lipid Peroxidation, Tissue Damage, and suppressed AMPK/SIRT1

activities.[26] High VD levels promote a reduction in weight and fat gain.[2] Vitamin D3 was found to overcome poor glucocorticoid sensitivity[13] and is also involved in reversing UVB-mediated skin impairment.[19],[17] VDD is usual in skin cancer and psoriasis patients.[17]

5.5. Vitamin D in Mitochondria and Cellular Oxidation

Mitochondria play a crucial role in vitamin D metabolism, handling its activation, modification, and inactivation through cytochrome P450 enzymes (CYP27A1, CYP27B1, CYP24A1, and CYP11A1) located in the inner mitochondrial membrane.[1],[11] Therefore, all steps of Vitamin D activation can be conducted within mitochondria.[1]

Vitamin D plays a pivotal role in controlling various cellular processes, including the clearance of damaged mitochondria, maintenance of mitochondrial integrity, regulation of inflammatory responses, reduction of oxidative stress, modulation of epigenetic mechanisms, preservation of DNA stability, and the fine-tuning of calcium and Reactive Oxygen Species (ROS) signaling pathways.[1],[9] The respiration of mitochondria drastically reduces upon VDR silencing.[46],[10],[7] VDR can be considered as respiratory gatekeeper of the mitochondria.[47] To maintain optimal mitochondrial respiration and protect cells against excess breathing and ROS production, VDR is required.[9] In response to ROS, VD was found to activate selected genes by NRF2 in response to ROS exposure, which eventually binds to Antioxidant Response Elements (AREs) and initiates transcription of oxidative stress protective genes.[1]

Mitochondrial density and function are reported to improve with vitamin D supplementation.[6]In C2C12 myotubes, TEM observation revealed that VD treatment increases mitochondrial volume and significantly increases mtDNA and mRNA, for instance, the RNA of NRF1, PGC-1α, CPT1, PPARα, VLCAD, LCAD, MCAD, UCP2, UCP3, CYP24, CYP27, and Tfam.[26],[2] 1α,25(OH)2D3 also reported to suppress PDK4 expression and reduce inactive phospho- PDH (pyruvate dehydrogenase) [28].

5.6. Vitamin D in Reproduction & Pregnancy

Beginning from the initiation of menarche in females, adolescence, the reproductive period, throughout the childbearing and nursing stages, to menopause, and finally in male fertility, the role of VD is well defined.[9]

In ovarian cells, vitamin D promotes the secretion of progesterone, estrogen, estrone, and estradiol, acting independently or in synergy with insulin; also, it might promote human follicular development.[9] Proper supplementation of vitamin D can remove Menstrual irregularity.[9] On the other hand, inadequate levels of vitamin D are directly or indirectly associated with subfertility, endometriosis, polycystic ovary syndrome (PCOS), preeclampsia, preterm birth, gestational diabetes, and bacterial vaginosis.[48],[9] Pregnant women with 25(OH)D3 level <37.5 nmol/l delivered by cesarean section are almost four times more likely than women with 37.5 nmol/l or more.[9] Maternal VD also controls the fetal epigenome that later determines disease onset and progression[40]. Its deficiency during pregnancy precedes the onset of chronic illnesses in later childhood, such as respiratory issues like wheezing and asthma, as well as neurological and metabolic disorders, including schizophrenia, multiple sclerosis, type 1 diabetes, and insulin resistance.

[9] Human neonates with <20.4 nmol/L serum 25(OH)D3 are at high risk of schizophrenia.[40] In female rats, a deficiency in vitamin D leads to a 75% decrease in fertility, which in turn can cause complications during pregnancy and is occasionally linked to uterine hypoplasia and impaired follicular development.[9] VD3 inhibits placental cytochrome P450scc competitively, reducing the formation of lipid peroxides and excess progesterone, both of which may contribute to the onset of preeclampsia.[12]

Working as a modulator of calcium metabolism, through the induced CaBP28k expression, VD takes part in semen quality and spermatogenesis.[9] Severe hypo-spermatogenesis or idiopathic Sertoli cell-only syndrome (SCOS) in males directly correlates with reduced plasma levels of 25(OH)D.[9] Literature suggests that a total of 50% of girls aged 9–13 years and 32% of those aged 14–18 years are fulfilling the recommended vitamin D intake[9]. This deficiency varies between 8% to 100% worldwide in pregnant women.[40]

5.7. Vitamin D in Cancer

VD executes anticancer properties by modulating the whole process from tumorigenesis to metastasis, including autophagy, cell proliferation, differentiation, angiogenesis, and epithelial-mesenchymal transition.[50]

Different studies support that higher 25(OH)D3 levels in serum suggest reduced incidence of breast, colon, lung, prostate, gastric, and skin cancer.[17],[1],[50],[51] In vitro studies reveal that 1,25(OH)2D can reduce the viability of highly metabolic cancer cells by inhibiting glucose, fatty acid, and glutamine metabolism along with decreased production of NADPH.[20] Downregulating the NFκB and COX-2, calcitriol can attenuate the secretion of prostaglandins and cytokines secretion in the tumor stroma, which eventually interrupts tumor progression.[49]

By impeding the G1/S gate, VD3 and its analogs can control the overall cell-cycle progression.[29] Studies show that VD3 inhibits BC cell proliferation by interfering in G0/G1 to S transition phase by inducing cyclin-dependent kinase inhibitors (CDKIs).[29],[4] Cisplatin, doxorubicin, cyclophosphamide, and a few more anticancer drugs have been reported to enhance the effectiveness upon VD combination therapy [17].

6. Conclusion and Future Direction

Vitamin D, as a multifunctional molecule, plays a pivotal role in maintaining overall health and preventing a wide range of pathological conditions. This review covers all its protective effects and extends beyond bone health to encompass cardiovascular diseases, venous thromboembolism, insulin resistance, pregnancy complications, cognitive decline, and systemic inflammatory disorders. While its therapeutic potential is well-established, the precise mechanisms and optimal dosage remain areas of ongoing research, whether as a standalone treatment or in synergy with other factors. Future studies in both in vitro and in vivo models are essential to unravel its full potential, paving the way for targeted clinical applications and personalized supplementation strategies.

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