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REVIEW ARTICLE

Role of vitamin D in targeting cancer and cancer stem cell populations and its therapeutic implications

Jyoti Bharamgoud Marigoudar[1] · Diptendu Sarkar[2] · Yakubu Magaji Yuguda[3] · Reem Fawaz Abutayeh[4] · Avneet Kaur[5] · Ankita Pati[6] · Disha Mitra[7] · Animikha Ghosh[8] · Debashis Banerjee[9] · Sudarshana Borah[10] · Kamallochan Barman[10] · Bhanita Das[10] · Shubham Jagdish Khairnar[11] · Emir Šeherčehajić[12] · Shivam Kumar[13]

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Abstract

Cancer is recognized globally as the second-most dominating and leading cause of morbidities. Fighting the global health epidemic threat posed by cancer requires progress and improvements in imaging techniques, surgical techniques, radiotherapy, and chemotherapy. The existence of a small subpopulation of undifferentiated cells known as cancer stem cells has been supported by accumulating evidence and ongoing research. According to clinical data, cancer recurrence, tumor development, and metastasis are thought to be caused by CSCs. Nutritional or dietary supplements can help you to fight against cancer and cope with the treatment side effects. Vitamin D, sometimes known as the sunshine vitamin, is produced in the skin in reaction to sunlight. Vitamin D deficiency is hazardous to any degree, increasing the risk of diseases such as cancer and disorders like osteoporosis. Bioactive vitamin D, or calcitriol, regulates several biological pathways. Many modes of action of Vitamin D might be helpful in protecting somatic stem cells (e.g., DNA damage repair and oxidative stress protection) or restricting cancer stem cell growth (e.g., cell cycle arrest, cell apoptosis). Researchers have recently begun to investigate the inhibitory effects of dietary vitamin D on cancer stem cells. In this review, we investigated the therapeutic impact of vitamin D and its molecular processes to target cancer and cancer stem cells as well.

Jyoti Bharamgoud Marigoudar, Yakubu Magaji Yuguda, and Reem Fawaz Abutayeh have contributed equally and should be considered as first authors.

✉ Shivam Kumar
commonn007@gmail.com

[1] MES College of Arts, Commerce, and Science, Bengaluru, Karnataka 560003, India

[2] Department of Microbiology, Ramakrishna Mission Vidyamandira, Belur Math, Haora, West Bengal 711202, India

[3] Department of Science Laboratory Technology, Faculty of Sciences, Federal Polytechnic, Kaltungo, Gombe State, Nigeria

[4] Department of Pharmaceutical Chemistry and Pharmacognosy, Faculty of Pharmacy, Applied Science Private University, Amman 11931, Jordan

[5] SGT College of Pharmacy SGT University, Gurgaon, Haryana 122505, India

[6] Department of Immunology and Rheumatology (IMS & SUM HOSPITAL), Siksha 'O' Anusandhan Deemed to be University, Jagamara, Bhubaneswar, Odisha 751030, India

[7] Department of Biophysics, Molecular Biology and Bioinformatics, University of Calcutta, Calcutta 700073, India

[8] Department of Biotechnology School of Life Science and Biotechnology, Adamas University Barasat, Calcutta 700126, India

[9] Department of Biotechnology, Faculty of Science, Atmiya University, "Yogidham Gurukul", Kalawad Road, Rajkot, Gujarat 360005, India

[10] School of Pharmaceutical Sciences, University of Science and Technology, Baridua, Meghalaya 793101, India

[11] MET's Institute of Pharmacy, Bhujbal Knowledge City, Nashik, Maharashtra 422003, India

[12] Faculty of Health Studies, University of Sarajevo, 71000 Sarajevo, Bosnia and Herzegovina

[13] School of Biological Science, University of Portsmouth, Portsmouth PO1 2DY, England

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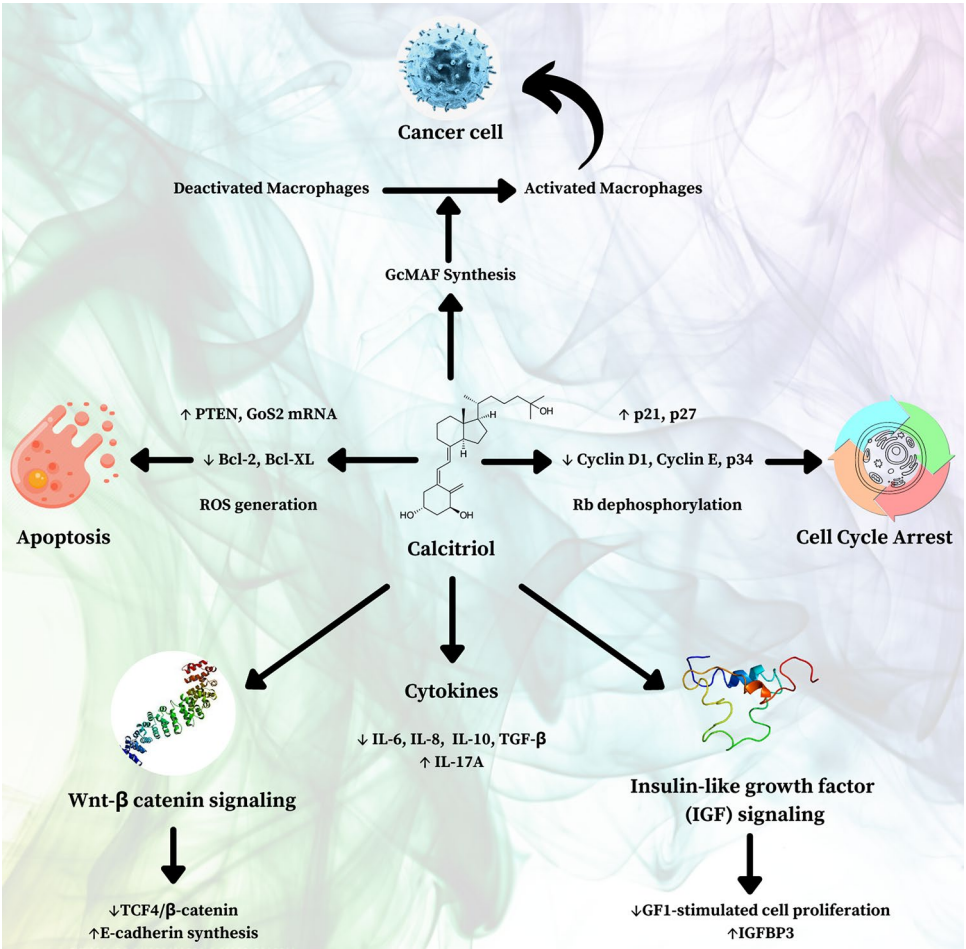
Graphical abstract



Keywords Cancer · Cancer stem cell · Dietary supplements · Therapeutics · Vitamin D

Introduction

Vitamin D is a fat-soluble vitamin required for various metabolic activities in the body, including maintaining homeostasis and bone metabolism [1]. Vitamin D deficiency is the most prevalent risk factor that contributes to tumor development and invasion of new tissues. People are spending more time indoors these days, while children are spending less time playing outside. Several studies have shown that vitamin D insufficiency is one of the most serious dietary issues affecting public health [2]. In individuals, vitamin D deficiency has been related to an increased risk of chronic diseases, including cancer and autoimmune disorders [3, 4]. Furthermore, people are heavily dependent on medications, many of which may impair vitamin D's ability to convert to a bio-available form (calcitriol) [5].

Somatic stem cells (or adult stem cells) have become a popular target for the accumulation of mutations that lead to carcinogenesis. Cancer stem cells are a tiny subset of cancer cells that give rise to new malignancies or survive cancer therapies and induce tumor recurrence and metastasis. Cancer stem cells were discovered to be a viable target for cancer prevention and treatment in pioneering investigations of their characteristics [6]. Such a small subpopulation of cancer cells has been called "cancer stem cells" and are cancer cells that give rise to primary cancers or that survive cancer treatments and cause recurrence of tumors and metastasis. Work published by Fedirko et al. observed that hTERT (human telomerase reverse transcriptase) labeling in the upper portion of the colon crypt is reduced when patients take vitamin D3 and calcium supplementation. hTERT is a catalytic element of the telomerase enzyme that labels a population of multipotent adult stem cells that rotates slowly [7], therefore allowing vitamin D supplementation to restrict cell growth and lower the chance of cancer-causing gene mutations. Vitamin D and its active analogs encourage the

expression of a cancer stem cell marker, such as a cluster of differentiation 44 (CD44) [8]. The overall findings of vitamin D research targeting cancer (or cancer prevention) and cancer stem cells need to be investigated further.

Preventing cancer with vitamin D supplements

Recent research suggests that daily vitamin D3 intake (20,000 IU) may be safer and more effective in decreasing systemic inflammation and cancer development [9]. GcMAF (Gc protein-derived macrophage activating factor) is a potent protein that enhances immune response. The routine intake and maintenance of a good dose of vitamin D facilitate GcMAF synthesis. GcMAF activity can also aid in tumor cell killing. This is an efficacious therapeutic option to inhibit cancer cell proliferation and metastasis [10]. There is increasing evidence that GcMAF inhibits the pro-cancer receptor, which implies the inhibition of cancerous activity [11].

These findings paved the path for more research, demonstrating that GcMAF might lower nagalase (α-*N*-acetylgalactosaminidase) levels [12]. GcMAF has excellent biological action since it stimulates the immune system's natural defensive mechanisms, inhibits the formation of nagalase, and therefore increases macrophage activation [10, 11]. Macrophages are beneficial to blood cells that kill foreign invaders as an immune response to foreign bacteria or viruses and cancer in the body. To activate macrophages, our bodies make the protein GcMAF (Gc-Macrophage Activating Factor). However, viruses and cancer cells have found a way to interfere with macrophages by producing an enzyme called Nagalase (alpha-*N*-acetylgalactosaminidase) that disrupts GcMAF. So, without GcMAF, macrophages are not signaled to kill and remove the virus or cancer cells [11, 13]. Furthermore, individuals with melanoma, prostate, breast, colorectal, and pancreatic cancer had increased serum nagalase in their blood plasma [9]. The vitamin D supplementation axis improves macrophage production, dramatically increases lymphocyte levels to normal, increases blood platelet count and red blood cell counts, and induces apoptosis of cancer cells, all of which indicate anti-cancer action (programmed cell death) (Fig. 1).

Vitamin D to target cancer and cancer stem cells

According to preliminary research, Vitamin D supplement development might be a combination of cancer prevention and cancer stem cell targeting [14]. The use of vitamin D in conjunction with other nutrients to suppress tumor cells and improve cancer prevention benefits is a promising strategy [15, 16]. Treatment of cancer cells and tumors in mice with vitamin D revealed that vitamin D has several activities that may delay or prevent tumor formation, including promoting cell differentiation, suppressing cancer cell growth, inducing cell death (apoptosis), and the formation of tumor blood vessels (angiogenesis) [13]. Calcitriol (the active form of vitamin D) regulates cancer stem cell signaling pathways. As a result, vitamin D may be able to impact cancer development and proliferation [17]. Recent research data indicate that calcitriol is able to

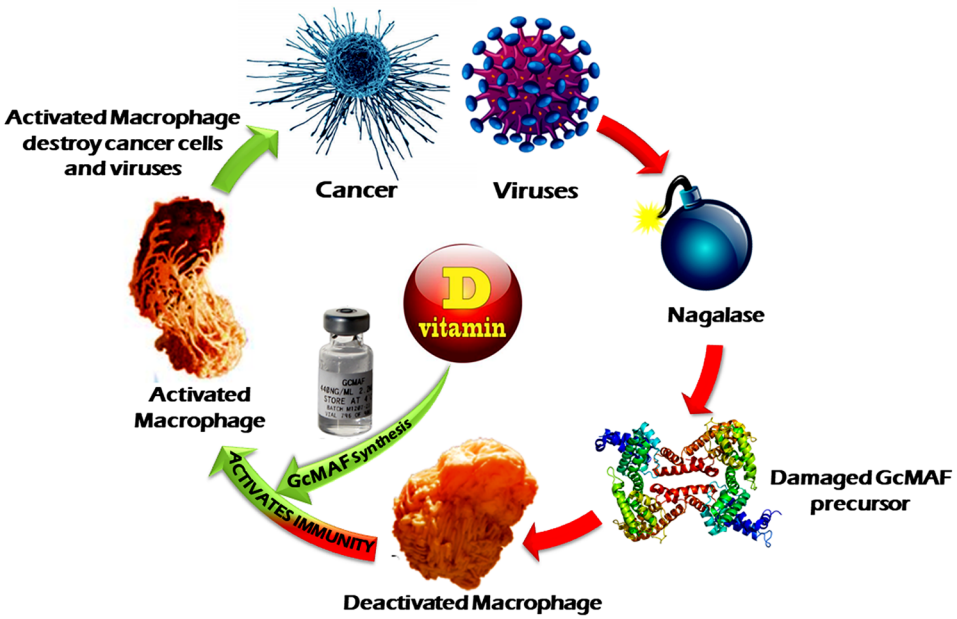


Fig. 1 Anti-cancer and antiviral effects of vitamin D

deplete the ovarian CSC population by inhibiting the Wnt signaling pathway, consequently impeding the growth of xenograft tumors [18]. Recent research indicates that calcitriol controls micro-RNA (miRNAs) production and can modulate CSC initiation and stemness features by regulating multiple pathways and targeting stemness-related factors [19]. Non-coding miRNAs regulate the protein expression responsible for cell growth and proliferation. miRNAs also play a role in cancer cells' response to drug treatment. A recent study investigated the role of miRNA to analyze the correlation between the miRNAs and the regulated proteins in response to vitamin D. The studies indicate that the antitumor activity of the level of vitamin D in human leukemia and lymphoma from the interaction of several miRNA molecules and the level of the targeted protein [20]. Calcitriol may have inhibitory effects on the normal PSC (adult prostate stem cell) population, and these cells, when transformed into CSCs through mutations, may be the cause of prostate cancer [21]. Furthermore, in vitro and xenograft experiments revealed that a calcitriol analog (BXL0124) inhibits tumor development and lowers the expression of a stem cell marker CD44 in breast cancer [22].

In a study including 1,000,000 people, researchers discovered an association between high vitamin D3 levels and a lower risk of colorectal cancer [23]. The main kinds of cancer treatment are radiation, chemotherapy, and targeted therapy, and some tumors do not respond to this traditional and novel treatment. For potential preventive measures, vitamin D supplementation exerted anti-proliferative effects in glands like the prostate glands. Vitamin D3 inhibitory action has been demonstrated in numerous studies to limit prostate cancer cell progression and cell proliferation [21]. It inhibits cancer cell growth, promotes apoptosis, and inhibits anti-apoptotic pathways (Fig. 2) that contribute to the proliferation and expression of prostate cancer cells [24]. The in vitro study has shown that vitamin D3 allows GcMAF to target and destroy human breast cancer cells in a variety of preclinical tests [25]. Numerous studies have found a link between amino acids and the ability of GcMAF receptors to bind efficiently and increase macrophage invasion surrounding cancer cells [12]. These macrophages will then "feed," resulting in the death of breast cancer cells. Other evidence of alternative cancer treatment suggests that vitamin D3 and GcMAF can work together to remove an oncogene known as HER-2, a breast cancer activator [12, 25].

According to research, severe vitamin D deficiency or the deletion of the vitamin D receptor gene (VDR) increases the risk of invasive malignancies [5]. On the other hand, Vitamin D supplementation has opposing effects on stem cell signaling in normal and malignant cells. Similarly, some studies indicate that Vitamin D and its analogs can block cancer stem cell signaling pathways [15, 18]. Vitamin D's varied impacts on the signaling pathways involved with stem cells suggest that it can control and target CSCs.

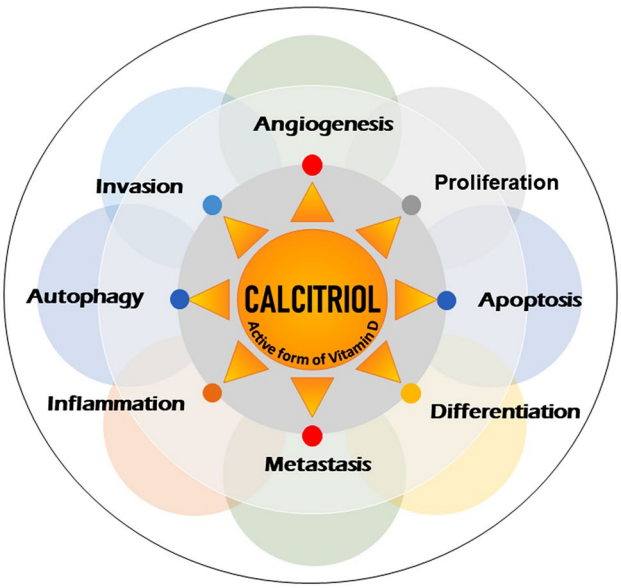


Fig. 2 Role of vitamin D to target cancer and cancer stem cells

Role of vitamin D on cell proliferation and apoptosis

Cell cycle regulators

Several researchers have been looking for the direct impacts of vitamin D on gene expression, which controls cell development. For example, in the myelomonocytic line U937, vitamin D-mediated transcriptional control of the gene produces the cyclin-dependent kinase inhibitor p21 [26]. Due to growth arrest, cyclin-dependent kinase inhibitors such as p21 or p27 were up-regulated, while the cell cycle level of regulatory proteins such as cyclins was downregulated. In prostate cancer cell lines, antisense RNA or siRNA against p21 can prevent vitamin D-mediated growth arrest [26, 27]. In contrast, vitamin D has only a minor effect on the levels of p21 mRNA in MCF-7 cells [28]. Microarray study has discovered many potential therapeutic targets for the vitamin D gene associated with cell cycle control. Vitamin D has an indirect effect on a variety of transcripts that code for proteins involved in cell cycle control [26, 29].

Insulin-like growth factor (IGF) signaling

Vitamin D can also indirectly impact cell development by interfering with the function of growth hormones that promote cell proliferation or by hastening cell differentiation. In

MCF-7 cells, vitamin D analogs reduced insulin-like growth factor 1 (IGF1)-stimulated cell proliferation, which was associated with the increased release of IGF binding protein 3 (IGFBP3) [30]. IGFBP3 binds to IGF1 and IGF2 and prevents them from binding to cell surface receptors, reducing their proliferative and anti-apoptotic activities. Furthermore, they have induced the accumulation of IGFBP3 in prostate cancer cells and primary prostate epithelial cells, which inhibits IGF2-action [30]. Microarray analyses of vitamin D-treated SW480-ADH cells (a subline of the SW480 colon cancer cell line) indicate elevations of insulin-like growth factor binding proteins (IGFBP2 and IGFBP6) [31]. However, the functional significance of IGFBP2 and IGFBP6 regulation has not been explored.

Transforming growth factor-beta (TGF-β) signaling pathway

Transforming growth factor-2 (TGF2) is necessary for tissue homeostasis in normal epithelial cells and early carcinogenesis stages and operates as an anti-proliferative agent [32]. After 12-h treatment with vitamin D and its analogs, enhanced expression of TGF2 mRNA was identified in breast cancer cells and primary prostate cancer cells [33]. Two Vitamin D response elements (VDREs) in the TGF2 promoter were discovered and described by Wu et al. [34] in a deletion/mutation study in reporter gene experiments using EMSA in accordance with this induction. In MCF-7 cells and immortalized 185A1 cells, vitamin D and its analog EB1089 stimulate the expression of TGF receptors and are activated by a mechanism that appears to entail SMAD family member 3 as a co-activator [33]. Furthermore, vitamin D therapy significantly reduced negative TGF-β availability regulators, latent TGF binding protein 1 (LTBP1) and latent TGF-β binding protein 2 (LTBP2), in ovarian adenocarcinoma cells (OVCAR-3) [35] and primary prostate cancer cells [36]. The initial response of these genes to vitamin D shows that certain genes whose protein products influence TGF signaling might be vitamin D/VDR's direct targets.

Wnt-β catenin signaling

β-Catenin is found in the cytoplasm along with antigen-presenting cells adenomatous polyposis coli (APC) [37]. When Wnt signaling is activated, β-catenin accumulates and is released from the APCs. This free β-catenin enters the nucleus, attaches to DNA with the transcription factor TCF4, and activates the transcription of genes that control proliferation [38]. In colon cancer, mutations in the APC gene that alter the interactions between APC and catenin are frequent [37]. By promoting VDR binding to β-catenin [8], vitamin D lowers the formation of the complex transcriptional TCF4/β-catenin. As a result, it inhibits catenin-mediated gene transcription in SW480-ADH, Caco-2, and HT-29 colon cancer cells [39]. Another study found that giving Apc(Min/+) mice thrice-weekly injections of vitamin D and its analogs for 12 weeks decreased the frequency and load of polyps and that this was linked to lower expression of β-catenin target genes in the small intestine and colon [40]. In HEK293 kidney cells, VDR's AF-2 domain interacts with catenin's C-terminus; this contact may be aided by lysine 671/672 acetylation on β-catenin [41]. Vitamin D-mediated events can indirectly impact β-catenin activity by increasing the synthesis of a membrane protein, E-cadherin, that can bind β-catenin and prevent it from accumulating in the nucleus. Even in SkBr3, a human breast cancer cell line that lacks the E-cadherin gene, vitamin D therapy can suppress transcription of the β-catenin-mediated gene [41]. As a result, findings suggest that E-cadherin upregulation is not the main mechanism underlying vitamin D-mediated β-catenin signaling suppression. Although it is unclear if vitamin D and VDR have the same effect on β-catenin binding to these different sites or not (Fig. 3).

Apoptosis

According to preliminary research, vitamin D promotes apoptosis in breast cancer cells MCF-7 [42] and a number of colon cancer cell lines [16]. Treatment with vitamin D induced apoptosis in HGC-27 cells via a mechanism involving VDR-mediated upregulation of a tumor suppressor gene, phosphatase, and tensin homolog (PTEN) [8, 43]. Furthermore, vitamin D administration enhanced basal and chemotherapy-induced cell death in the colorectal cancer cell line MIP101 through a molecular mechanism [31]. Blutt et al. discovered that 6 days of vitamin D administration caused apoptosis in human prostate cancer cell lines (LNCaP cells), followed by downregulation of the anti-apoptotic proteins Bcl-2 and Bcl-XL [44, 45]. Following the influence of vitamin D on the regulation of pro-and anti-apoptotic proteins, several investigations have found that vitamin D therapy regulates transcripts for genes encoding proteins that govern apoptosis. GoS2 is a pro-apoptotic protein whose gene expression is repressed or downregulated in malignancies in humans [17]. After vitamin D therapy, expression of GoS2 mRNA was increased in colon cancer cells, SW480-ADH, and squamous carcinoma cells SCC25 [31].

Vitamin D mediated novel molecular mechanisms

Autophagy

The regulatory mechanism used by cells in lysosomes to remove membrane-bound organelles is known as autophagy.

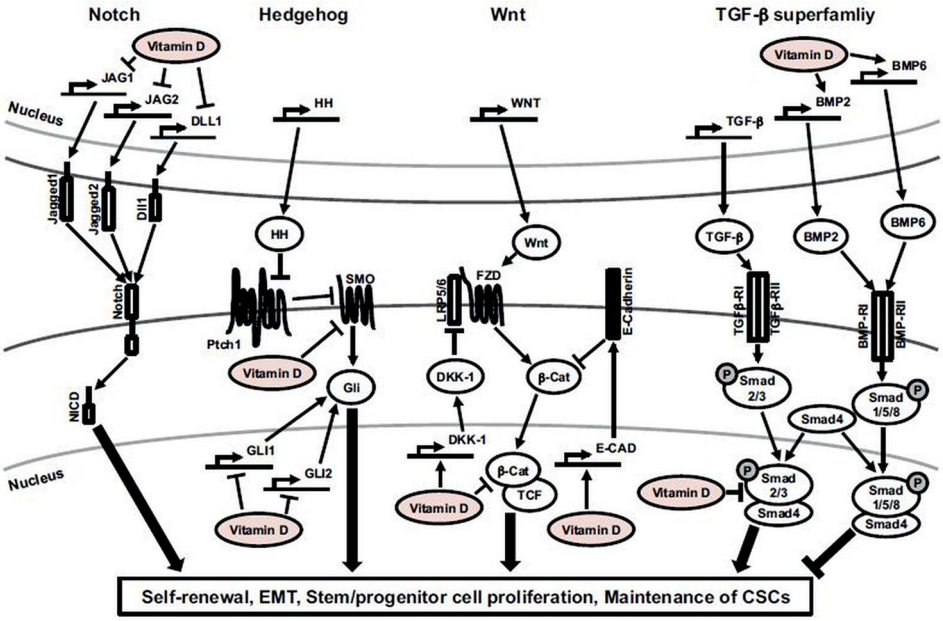


Fig. 3 A schematic diagram depicting actions of vitamin D on the Notch, Hedgehog, Wnt, and TGF-β superfamily signaling pathways (adapted with permission from [15] Copyright 2016 Elsevier). The main components of the Notch, Hedgehog, Wnt, and TGF-β superfamily and their regulation by vitamin D are presented. Full names of the abbreviations shown in the diagram are listed; *JAG1* Jagged1; *JAG2* Jagged2; *DLL1* Delta-like protein 1; *NICD* Intracellular domain of Notch; *HH* Hedgehog; *Ptch1* Patched1; *SMO* Smoothened; *LRP5/6* Low-density lipoprotein receptor-related protein 5/6; *FZD* Frizzled; *β-Cat* β-Catenin; *DKK-1* Dickkopf-related protein 1; *TCF* T cell factor; *E-cad* E-cadherin; *BMP2* Bone morphogenetic protein 2; *BMP6* Bone morphogenetic protein 6; *TGFβ-RI* TGF-β receptor 1; *TGFβ-RII* TGF-β receptor 2; *BMP-RI* BMP receptor 1; *BMP-RII* BMP receptor 2.gr1

However, autophagy is widely regarded as a viable stress-resistance mechanism in cells. (Examples include hunger and pro-oxidative circumstances). Furthermore, this technique can be used to induce cancer cell death and inhibit tumor development [46]. Mathiasen et al. discovered that vitamin D inhibits cell growth and death via an independent caspase and p53 pathway that the anti-apoptotic Bcl-2 protein may trigger. It is suggested that the vitamin D analog EB1089 is primarily responsible for autophagy in breast cancer cells [47], which may be exacerbated by the beclin-1 protein Atg. In HL-60 leukemia cells, vitamin D treatment inhibits the anti-autophagic mTOR protein and activity while increasing the expression of the pro-autophagic protein beclin-1. This therapy also enhances the interaction of beclin-1 with PI3K (a pro-autophagic event) or Bcl-XL (the anti-apoptotic protein), which contributes to narrowing down the cell death activity. In p19-deficient SCC25 cells, autophagy triggered by vitamin D would entail a complex interaction with cyclin-dependent kinase inhibitors.

Antioxidant defense and DNA repair

Carcinogenesis is facilitated by oxidative stress, DNA damage, and the lack of DNA repair systems. The activation of antioxidant defense mechanisms that decrease reactive oxygen species can avoid this sort of carcinogenic impact. According to a new study, vitamin D deficiency promotes tumor onset and development by causing oxidative stress and DNA damage, whereas vitamin D treatment reduces instinctive tumor advancement [48]. Vitamin D administration of 800 IU daily inflates oxidative DNA damage in the distal colonic epithelium of VDR knockout mice and decreases it in the colon epithelium of humans [49, 50]. Vitamin D increases the expression of numerous antioxidant defense enzymes responsible for antioxidant defense O-induced apoptosis. Because of the overexpression of NFE2L2 (nuclear factor erythroid-derived 2-like 2), vitamin D-mediated protection against pro-oxidant stress is indirect [36, 51]. NFE2L2 regulates the expression of numerous antioxidant enzyme genes [52]. The number of NFE2L2 target genes, such as GPX3, HMOX1, AKR1C2, and TXNRD1, surged after vitamin D therapy in RWPE1 cells [53]. Vitamin D clearly controls genes for genome-protecting proteins. The vitamin D derivative EB 1089 was shown to up-regulate the growth arrest and DNA damage-inducible 45 (GADD45) mRNA and protein levels in SSC cells [31]. GADD45 is a p53 target gene that plays a role in DNA repair. The GADD45 gene, which possesses an exonic enhancer element that interacts with the vitamin D receptor (VDR), overexpresses GADD45 mRNA levels in ovarian cancer cells after

vitamin D treatment [31, 54]. Taken together, vitamin D may control the expression of a variety of genes involved in DNA damage repair and apoptosis, therefore protecting against carcinogenesis.

Prostaglandin metabolism and action

Prostaglandin signaling is well known to promote cancer cell proliferation and development [55]. The rate-limiting enzymes in prostaglandin production are cyclooxygenases 1 and 2 (COX1 and COX2). COX-2 is a promising therapeutic target for cancer therapy since it is overexpressed by a number of mitogens, cytokines, and tumor promoters [56]. Prostaglandin synthesis and signaling are negatively regulated by vitamin D [57, 58]. Vitamin D therapy suppressed COX2 expression, lowered the prostaglandin receptors EP2 and FP expression, and promoted the production of 15-Hydroxyprostaglandin dehydrogenase (15-PGDH), the enzyme that inactivates prostaglandins, in advanced prostate cancer cell lines LNCaP and PC-3 [36, 58]. More significantly, vitamin D reduced prostaglandin E2 levels and prevented c-Fos mRNA activation mediated by prostaglandins [58]. These results indicate that vitamin D has a direct role in the regulation of prostaglandin metabolism and signaling.

Non-epithelial cells targets of vitamin D

Inhibition of angiogenesis

Angiogenesis is required for tumor development and cell metastasis. Angiogenesis is aided by a number of pro-angiogenic factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and platelet-derived growth factor-BB homodimer (PDGF BB) [59]. Vitamin D has been shown to prevent the growth of tumor blood vessels, which are crucial for solid tumor progression and metastasis [60]. Vitamin D inhibits the production of VEGF family members, which is a key pro-angiogenic cytokine in normal prostate epithelial cells [61]. It decreases VEGF mRNA and elevates mRNA levels for the anti-angiogenic protein thrombospondin-1 in colon cancer cells, according to another study [31]. The effect of vitamin D on the VEGF gene, on the other hand, has not always been clear. Treatments with the vitamin D derivative EB1089 decreased pancreatic ductal adenocarcinoma cell proliferation, self-renewal, and metastasis via inhibiting FOXM1. FOXM1 is an oncogene that controls cell cycle progression and has a role in cancer [62]. Dickkopf WNT signaling pathway inhibitor 4 (DKK4) is a known vitamin D downstream target and inhibitory Wnt ligand. In colon cancer cells, DKK4 has been found to reduce tumor angiogenesis, migration, and invasion. Vitamin D also inhibited the epithelial-mesenchymal transition (EMT) in SKOV-3 ovarian cancer cells by lowering Slug and Snail levels and increasing E-cadherin expression [63].

Regulation of immune cell function

In the context of cancer, several studies have confirmed the function of vitamin D in regulating both the innate and adaptive immune systems [31, 64]. However, non-cancer studies of vitamin D regulation immune systems give us a better understanding of its impact on inflammation and immunity in carcinogenesis. Vitamin D has the potential to direct a variety of genes in innate immune cells that are required for autophagy and antimicrobial activity [65]. Many cytokines, including IFN and TNF, can control vitamin D metabolism [65, 66]. Inflammatory cytokines and toll-like receptor agonists have been reported to increase the expression of CYP27B1 and VDR in dendritic cells. In monocytes, IL-4 increases CYP24 expression, resulting in the generation of the vitamin D inactive metabolite [66]. This can impact local vitamin D metabolite levels, which can then influence the function of other cells in the microenvironment. In the tumor microenvironment, interactions between cancer cells and host immune cells can form an immunosuppressive network that promotes tumor growth and protects it from immune attack, whereas vitamin D could influence stromal cells to limit tumor angiogenesis and spread. Immune system cells may be key targets for cancer prevention as a result of these activities. These findings show that vitamin D may be able to reduce cancer-promoting immunological and inflammatory disorders.

Clinical significance of vitamin D and its analogs

Clinical studies show that a lack of vitamin D increases the chance of developing severe cancer. According to randomized trial statistics, vitamin D may have a greater impact on cancer survival and mortality than cancer incidence [67, 68]. In a trial, the Vitamin D and Omega-3 Trial compared the active treatment to placebo [16], the hazard ratio for the vitamin D arm was 0.96 (95% CI 0.88–1.06) for incident total invasive cancer, but for total cancer mortality was 0.83 (0.67–1.02), indicating a potential function of vitamin D in lowering metastatic or lethal cancers. Additionally, incident cancers were decreased in people with normal body mass index but not in people who were overweight or obese, indicating that characteristics related to obesity may dampen the efficacy of vitamin D supplementation. Similarly, another randomized clinical trial found that taking high doses of vitamin D daily for 5 years decreased the overall adult cohort's incidence of advanced (metastatic or fatal) cancer

Table 1 Vitamin D analogs that have been investigated for potential anti-cancer activity

S. No.	Name	Chemical name	Investigated/undergoing in clinical trial*	Cancer type	Molecular target
1	EB1089	22,24-Diene-24,26,27-trishomo-1α,25(OH)2D3	Yes [74, 75]	Breast [76], head and neck squamous cancers [77], hepatocellular cancer [78], ovarian cancer [79], pancreatic cancer [80], non-small cell lung cancer [81]	By regulating concentrations of cell cycle inhibitors, inducing apoptosis, miR498- mediated downregulation of hTERT, decreased expression of the nuclear transcription protein (FOXM1)
2	BXL0124	1α,25-Dihydroxy-20R-21(3-hydroxy-3-deuteromethyl-4,4,4-trideuterobutyl)-23- yne-26,27-hexafluoro-cholecalciferol	No	Breast cancer [82], ductal carcinoma [83]	Decreased CD44 protein level, suppressed STAT3 signaling, and inhibited invasion and proliferation of cancer cells
3	Inecalcitol	19-nor-14-epi-23-yne-1,25-$(OH)_2D_3$)	Yes [84, 85]	Breast cancer [86], prostate cancer [87], squamous cell cancer [88]	By mediating caspase 3 and 8/10-induced apoptosis, up-regulated levels of p21 and p27, reduce expression of the Ets variant 1 and the serine/threonine kinase, Pim-1
4	Calcipotriol	22-ene-26,27-dehydro-1α,25(OH)2D3	No	Pancreatic cancer [89]	Decreased Wnt/catenin signaling
5	Alfacalcidol	1α(OH)D3	No	Colorectal cancer [90] and breast cancer [90]	Inhibit cell proliferation, promote cell differentiation, induce apoptosis
6	EM1	Diethyl [(5Z,7E)-(1S,3R)- 1,3-dihydroxy-9,10-secochola-5,7,10(19)-trien23-in-24-yl]	No	Several cancer cell lines [91], breast Cancer [92]	Reduced the formation of metastasis
7	Paricalcitol	19-nor-1α,25(OH)2D2	Yes [93–95]	Breast, prostate, rectal, pancreatic [96]	Inhibit cell proliferation, block angiogenesis, inhibit invasion and metastasis

[69]. A multicenter randomized, placebo-controlled, double-blind trial in Sweden was performed [70]. In this trial study, it has been found that the correction of vitamin D deficiency may have positive effects on opioid use and fatigue in palliative cancer patients, but only in those with a survival time of more than 12 weeks. Vitamin D exerts a wide range of biological functions, including pro-apoptotic, anti-angiogenic, anti-inflammatory, anti-proliferative, anti-invasion, and anti-metastatic actions on cancer cells, which are firmly supported by preclinical investigations [71]. Supplementing with vitamin D was observed to increase disease-free survival in patients with early breast cancer receiving neoadjuvant chemotherapy and trastuzumab. Supplementing with vitamin D was observed to increase disease-free survival in patients with early breast cancer receiving neoadjuvant chemotherapy and trastuzumab (HR 0.36) [72]. After a median follow-up of 29.5 months in this observational analysis, patients who got vitamin D supplements had significantly higher median disease-free survival rates than those who did not (32.6 vs. 25.5 months, $p=0.022$). The median overall survival for the group receiving supplements was 43.8% after a median follow-up of 40.2 months, compared to 32.8% for those getting no supplementation ($p=0.07$) [72]. In phase III randomized prospective trial, metastatic colorectal cancer patients with high concentrations of 25-(OH) D3 had improved survival compared to those with low concentrations when treated with combined chemotherapy and targeted therapy [73]. In this study, it has been found that patients in the highest quintile of 25-(OH)D3 levels had significantly improved overall survival compared with those in the lowest quintile (median 32.6 months vs. 24.5 months; HR: 0.65; 95% CI 0.51, 0.83; $p=0.001$), i.e., patients with the highest levels of 25-(OD)D3 showed a 35% improvement in overall survival versus those with the lowest levels. Improved progression-free survival was also significantly associated with the higher plasma of 25-(OD)D3 ($p=0.01$). Apart from vitamin D supplementation, several analogs of vitamin D also used for the cancer therapeutics. A list of vitamin D analogs investigated for potential anticancer therapy is shown in Table 1.

Conclusion

Cancer Stem cells (CSCs), small tumor residing sub-population, having differentiation potential and self-renewal capacity, play a pivotal role in tumor relapse metastasis, heterogeneity, multidrug resistance, and radiotherapy resistance. Natural compounds, drugs, vaccines, etc., to target the key molecular pathways of tumorigenesis have also been developed to target CSCs. However, it has been very difficult to eliminate CSCs that need to be solved effectively. We now have population-based research that shows that having a greater vitamin D level can protect you from a number of malignancies. Nonetheless, molecular explanations and research regarding vitamin D and its anti-cancer function are becoming more widely available. There are still many unknowns about vitamin D's role in cancer prevention and therapeutic strategies. Several studies based on the potential molecular pathways for vitamin D and cancer prevention have only been investigated in the context of one tissue or one kind of cancer, suggesting that considerable research is warranted. Furthermore, while numerous studies have shown that vitamin D can affect different transcript levels, it is unclear whether VDR directly regulates genes. Despite these gaps in our knowledge, vitamin D targeted treatment might be a potential way to eradicate cancer and CSCs, and it has to be investigated further.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by JBM, DS, YMY, RFA, AK, AP, DM, AG, DB, SB, KB, BD, SJK, and EŠ. The first draft of the manuscript was written by SK and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

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