

Review

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Anti-aging and anti-carcinogenic effects of $1\alpha, 25$ -dihydroxyvitamin D_3 on skin

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Abstract

Photoaging and carcinogenesis are facilitated by oxidative stress, inflammation, angiogenesis, and extracellular matrix (ECM) remodeling. Oxidative effects include DNA damage, membrane oxidation, lipid peroxidation, and alterations in the expression of p53 and antioxidant enzymes. The inflammatory and angiogenesis mediators include interleukin-1, tumor necrosis factor- α , interleukin-8, transforming growth factor- β , and vascular endothelial growth factor. ECM remodeling includes alterations in the expression and organization of collagen, elastin, matrix metalloproteinases, and elastase. $1\alpha, 25$ -dihydroxy-vitamin D_3 has antioxidant, anti-inflammatory, and ECM regulatory properties, and can counteract the processes that facilitate photoaging and carcinogenesis. This review provides an overview of the beneficial effects of vitamin D supplementation at a molecular level, followed by a brief discussion regarding its use as a supplement.

Keywords: Ultraviolet radiation, superoxide dismutase, p53, interleukins, tumor necrosis factor- , transforming growth factor- , vascular endothelial growth factor, collagen, elastin, matrix metalloproteinases



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INTRODUCTION

Vitamin D (VD) is a prohormone involved in a broad range of functions in the organism that has been shown to exert protective effects against several types of cancer^[1] and skin aging^[2], among others. In the human epidermis, exposure to sunlight - ultraviolet B radiation (UVB, 280-315 nm) - promotes the transformation of 7-dehydrocholesterol to previtamin D₃, which undergoes thermal isomerization into cholecalciferol, also known as vitamin D₃ [Figure 1]. Cholecalciferol is then hydroxylated in the liver to 25-hydroxycholecalciferol or calcidiol, and further hydroxylated in the kidney into 1,25-dihydroxyvitamin D₃ or calcitriol, which is the biologically active form of VD^[3]. Calcitriol, therefore, acts through an intracellular receptor, vitamin D receptor (VDR), which is ubiquitously expressed in most nucleated cells^[4]. Calcitriol exerts antiproliferative, antiangiogenic, pro-differentiating, and antiapoptotic effects^[5].

Recent research has identified an alternative vitamin D activation pathway through CYP11A1^[6-8]. CYP11A1-mediated metabolism of vitamin D results in the production of 20-hydroxyvitamin D and its hydroxymetabolites. These byproducts have antiproliferative, differentiative, and anti-inflammatory effects in skin cells, comparable or greater than those of calcitriol^[9]. Additionally, these metabolites improve different defense mechanisms against UVB-induced DNA damage and oxidative stress^[9,10]. Alternative nuclear receptors for vitamin D hydroxyderivatives have also been identified, such as retinoid-related orphan receptor (ROR) alpha and ROR gamma^[11-13].

Both skin aging and cancer have been associated with increased cellular oxidative stress, the release of inflammatory and angiogenic mediators, and abnormal extracellular matrix (ECM) remodeling, among others^[14-17]. Other non-classic effects of VD include cell growth suppression, apoptosis regulation, modulation of immune responses, control of differentiation, or antioxidant effect, among others^[18], suggesting that VD might be of potential relevance in skin aging and cancer.

OXIDATIVE DAMAGE

Cellular oxidative stress arises when the levels of reactive oxygen species (ROS), including hydroxyl radicals, superoxide, or hydrogen peroxide, exceed the ability of endogenous antioxidants or antioxidant enzymes to quench them^[19]. These antioxidant systems include glutathione, glutathione peroxidase, superoxide dismutase, and catalase^[20,21]. Oxidative damage occurs during the intrinsic cutaneous aging phenomenon, and it is exacerbated by exposure of the skin to damaging physical or environmental pollutants such as ultraviolet (UV) radiation, heavy metals, or benzene derivatives^[22-26]. UVA radiation (315-400 nm) reaches the dermis, causing DNA damage mainly through oxidative stress, whereas UVB (280-315 nm) reaches the epidermis and causes direct DNA damage as well as oxidative stress-related DNA damage^[20,21,23,24,27]. In addition, exposure to pollutants also results in detrimental alterations through direct oxidative stress^[25,26]. Intrinsic skin aging is also associated with diminished levels of steroidal hormones, among others, thus, resulting in the thinning and fine wrinkling of the skin^[22]. Additionally, ROS produced by extrinsic damaging factors correlates with coarse wrinkling.

In relation to carcinogenesis, numerous studies have demonstrated that ROS are able to induce mutagenesis through diverse mechanisms. In fact, nucleotides are highly susceptible to free radical damage, and their oxidation promotes base mispairing, leading to mutagenesis^[28]. One of the best-characterized mutations caused by ROS is the conversion of guanine into thymine, as a result of guanine oxidation at the eighth position, resulting in 8-hydroxy-2'-deoxyguanine (8-OHdG) production^[29]. This last nucleotide base tends to pair with adenine instead of cytosine, leading to mispairing and mutagenesis. These mutations have been extensively found in different types of skin tumors^[30]. Furthermore, exposure to UV radiation has mutagenic effects beyond the time of exposure due to ROS production, leading to the so-called dark-

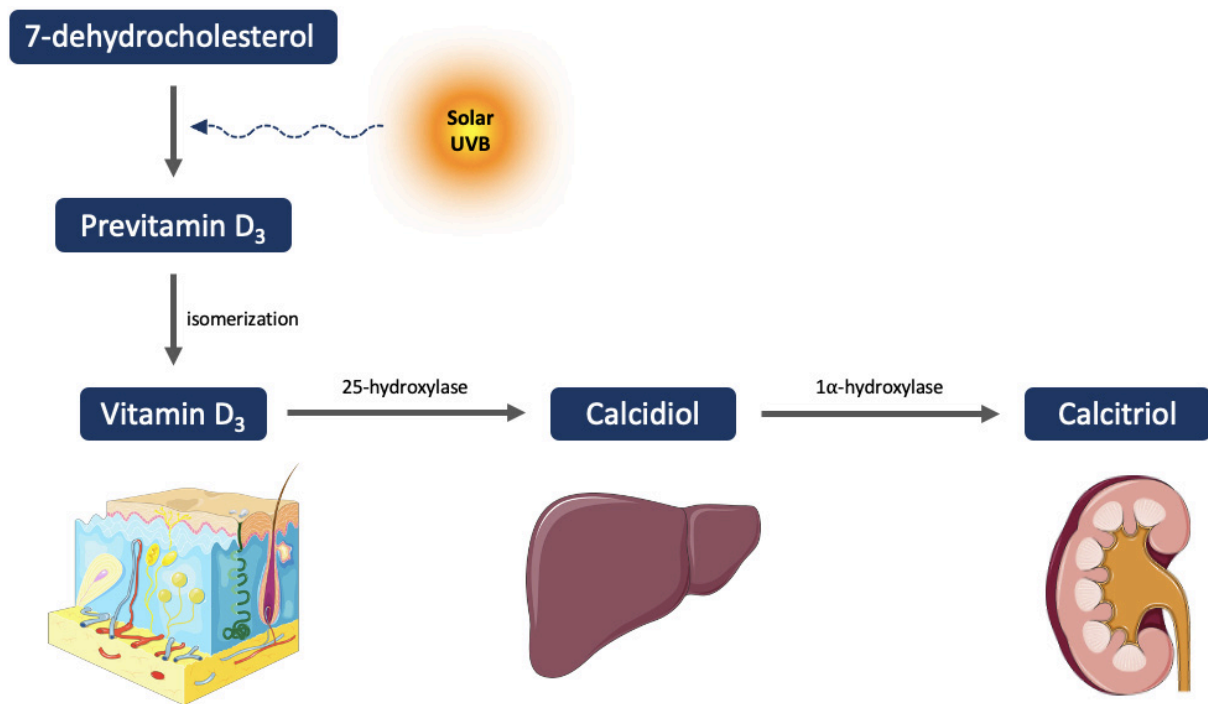


Figure 1. Biosynthesis of active vitamin D.

cyclobutane pyrimidine dimers (CPD)^[31]. ROS generated through UV radiation, superoxide and nitric oxide, undergo a series of reactions involving melanin fragments resulting from its photochemical degradation. Excited-state triplet carbonyls are formed, which transfer their energy to DNA bases leading to the formation of CPDs^[32]. Additionally, oxidative DNA damage has been seen to be accentuated by the depletion of glutathione in fibroblasts and melanoma cells^[33]. Moreover, oxidative stress can also induce lipid peroxidation and cell membrane damage that leads to the leakage of intracellular proteins to the exterior^[34,35]. Active substances with antioxidant properties such as VD, lutein, *P. leucotomos* extract and *H. lupulus* extract beneficially regulate oxidative stress in dermal fibroblasts and melanoma cells^[31,34-39].

VD is photoprotective as it inhibits UV radiation-mediated oxidative DNA damage^[34,35], and induction of cellular skin defenses^[40,41]. VD inhibits oxidative stress and tissue damage induced by exhaustive exercise and 2,2'-azino-di-(3-ethylbenzthiazoline sulphonate) oxidation in the presence of hydrogen peroxide and met-myoglobin^[34,42]. It also inhibits oxidative DNA damage in non-irradiated or UV-radiated fibroblasts and melanoma cells; prevents membrane damage in UV-radiated fibroblasts and melanoma cells; decreases lipid peroxidation in non-irradiated and UVA-radiated fibroblasts; stimulates expression of superoxide dismutase in melanoma cells^[34,35] [Figure 2]. These data emerged from *in vitro* experiments in which different treatment conditions were evaluated: non-irradiated, UVA-irradiated, or UVB-irradiated human dermal fibroblasts, and melanoma cells (American Type Culture Collection, ATCC) were incubated for 24 h in the presence of different doses of VD (0, 0.02, 0.2, or 2 μM). Cells were analyzed for products of oxidative damage and for membrane damage and lipid peroxidation. A competitive DNA/RNA oxidative damage ELISA kit (Cayman Chemical) revealed lower levels of 8-OHdG and 8-hydroxy-2'-guanine in VD-treated cells. The supernatants of VD-treated cells also displayed lower levels of lactate dehydrogenase, which is an indicator of membrane damage. Finally, a kit that enables hydroperoxide to oxidize ferrous to ferric ion, forming a colored adduct with xylenol orange {“3,3'-bis[N,N-bis(carboxymethyl)aminomethyl]o-cresolsulfonephthalein, sodium salt”} revealed that VD decreased cellular lipid peroxidation. In summary,

		Vitamin D			
		Oxidative Damage	Inflammatory Mediators	Cell Viability Mediators	ECM proteins
Anti-Photoaging	<ul style="list-style-type: none"> ✗ 8-OHdG / 8-OHG ✗ Lipid peroxidation 	<ul style="list-style-type: none"> ✗ IL-1 ✗ IL-8 	<ul style="list-style-type: none"> ↑ Cell viability 	<ul style="list-style-type: none"> ↑ Collagen I ✗ Elastase 	
	Anti-Carcinogenic	<ul style="list-style-type: none"> ✗ 8-OHdG / 8-OHG ✗ Membrane damage ↑ Superoxide dismutase 	<ul style="list-style-type: none"> ✗ IL-1 ✗ TNF-α ✗ TGF-β ✗ VEGF 	<ul style="list-style-type: none"> ↑ p53 promoter activity 	<ul style="list-style-type: none"> ✗ MMP-1 ✗ MMP-2

Figure 2. Table summarizing the anti-photoaging and anti-photocarcinogenic effects of vitamin D. Green plus sign means upregulation; Red X denotes inhibition. IL-1: Interleukin-1; TNF- α : tumor necrosis factor- α ; IL-8: interleukin-8; TGF- β : transforming growth factor- β ; VEGF: vascular endothelial growth factor; MMP: matrix metalloproteinases; 8-OHdG: 8-hydroxy-2'-deoxyguanine; ECM: extracellular matrix.

these results showed that VD reduced the formation of 8-OHdG and CPDs caused by oxidative stress through the reduction of ROS in UV-irradiated skin explants, as well as other mutagenic alterations such as thymine dimers or 8-nitroguanosine^[43].

INFLAMMATION

Exposure of the skin to UV radiation or environmental pollutants initially causes localized inflammatory response involving innate immunity, and later adaptive immunity involving the T- and B-lymphocytes^[44-48]. The initial inflammation results in the release of cytokines, such as interleukins (IL) and tumor necrosis factor (TNF)^[45]. These cytokines activate I- κ B kinase, which activates the NF- κ B transcriptional factor, amplifying the expression of inflammatory mediators^[44]. The activation of adaptive immunity causes the release of Th2 cytokines, such as IL-4, which drives the activation of Janus tyrosine kinases, induces dimerization of signal transducers of transcription, and increased expression of additional inflammatory mediators, such as Immunoglobulin E (IgE)^[44-48]. IgE antibodies cause the release of histamine and other inflammatory mediators from basophils and mast cells^[48].

Cellular inflammation is also associated with increased production of angiogenic factors, such as vascular endothelial growth factor (VEGF), transforming growth factor- β (TGF- β), and IL-8^[20,21]. VEGF binds to receptor tyrosine kinase to activate the mitogen-activated protein kinase (MAPK) pathway and thereby the activation of several transcription factors such as c-fos^[34]. TGF- β binds to its receptors to activate SMADs that regulate the expression of cell cycle and the ECM^[34]. Finally, IL-8 binds to its chemokine receptors and mediates its effects through several means, including the increase in intracellular calcium levels^[44,45].

Both innate and adaptive immunity are regulated by VD^[49]. VD deficiency, as well as that of its receptor, is associated with inflammation, increased serum levels of inflammatory factors, and inflammatory diseases^[50,51]. VD supplementation inhibits the activity of NF- κ B in peritoneal macrophages^[52]. VD inhibits angiogenesis *in vivo* and *in vitro* by decreasing IL-8 expression in human fibroblasts^[53,54]. It also decreases the levels of IL-1 and IL-8 in UVA-irradiated fibroblasts, but not in UVB-irradiated or non-irradiated fibroblasts, suggesting that VD specifically curbs inflammatory reactions to UVA exposure^[34]. Additionally, VD inhibits the expression of the inflammatory mediators IL-1 and TNF- α , and the angiogenesis factors TGF- β and VEGF at protein and mRNA levels in melanoma cells, implicating transcriptional regulation^[35]. The stated conclusions on the effects of VD on the inflammatory factors have been determined through *in vitro* experiments, in which non-irradiated, UVA-irradiated, or UVB-irradiated human dermal fibroblasts, and melanoma cells were incubated with different concentrations of VD^[34,35]. The culture media were examined by ELISA for protein levels of the inflammatory and angiogenic factors IL-1, IL-8, TNF- α , TGF- β , and VEGF. mRNA levels of these inflammatory and angiogenic factors were measured by reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR).

Cell viability

Cellular oxidative damage causes cell death through the intrinsic apoptosis pathway^[55], whereas inflammatory players cause cell death via extrinsic apoptosis^[56]. Conversely, oxidative effects and inflammatory mediators facilitate resistance to cell death through mutations in protooncogenes or tumor suppressor genes, or through the activation of the protein kinase B (PKB) pathway.

DNA damage activates ATM (ataxia telangiectasia mutated) and ATR (ataxia telangiectasia and Rad3-related protein), leading to p53 activation^[44,57,58]. Then p53 activates the pro-apoptotic factor Bax, allowing the release of cytochrome C into the cytoplasm and the subsequent activation of caspases^[35,44]. Also, the increase in p53 activity activates p21 triggering its binding to cyclin-dependent kinases to cause cell cycle arrest^[44]. Conversely, mutations in p53, due to oxidative damage, facilitate carcinogenesis^[59].

Inflammatory cytokines are implicated in the extrinsic apoptotic pathway by activating Fas-associated death domain and TNF receptor-associated death domain. These cause the release of Bax from Bcl-2 (antiapoptotic protein) in the mitochondrial membrane and, therefore, the activation of the caspases^[44,60]. Conversely, activation of the PKB pathway retains the binding of Bcl-2 to Bax in the resistance to apoptosis^[44,60].

VD increases the viability of UVB radiated fibroblasts and the p53 promoter activity in melanoma cells, suggesting cell-specific protective effects [Figure 2]^[34,35]. VDR knock-out mice display reduced expression of p53 and premature aging^[61]. The supplementation of VD results in an increase of p53 expression and photoprotection^[62]. p53 promoter activity has been assessed by co-transfecting cells with p53 promoter cDNA linked to firefly luciferase and thymidine kinase (TK) promoter linked to renilla luciferase (to normalize transfection efficiency) and measuring luciferase activity following supplementation with VD^[35].

EXTRACELLULAR MATRIX REMODELING

Oxidative damage and inflammation are associated with increased ECM remodeling, promoting skin wrinkling and cancer progression^[63]. There is a coordinated regulation between inflammatory mediators and the ECM proteins^[63,64]. The primary structural ECM proteins are collagen and elastin, and the primary ECM remodeling or degrading enzymes are matrix metalloproteinases (MMP) and elastase. A loss of collagen and an increase in MMPs/elastases is associated with skin aging and cancer. Intrinsic aging is associated with loss of elastin, whereas photoaging is associated with solar elastosis^[65,66]. The action of MMPs is based on substrate specificity or the elements in its promoters. Therefore, different MMPs can be found. Based on substrate specificity, MMPs can be classified as: interstitial collagenases that cleave the fibrillar collagens (predominantly MMP-1), the gelatinases (MMP-2 and MMP-9), and stromelysins (MMP-3 and MMP-10) that cleave primarily the basement membrane, the membrane-type MMPs that cleave pro-MMPs, and the other MMPs such as metalloelastase (MMP-12) that cleaves the basement membrane and elastin^[65]. MMPs are alternatively also classified according to their regulatory promoter elements: group I that contain TATA box and activator protein-1 (AP-1 site); group II, which bears no AP-1 site; and group III, which display no TATA box or AP-1 sites^[66]. The transcription factor AP-1 is stimulated by the MAPK pathway, which is activated by cellular inflammation and angiogenesis^[44]. MMP activity is inhibited by the tissue inhibitors of matrix metalloproteinases (TIMP). The four TIMPs (TIMP-1, -2, -3, -4) bind to all of the MMPs, though TIMP-1 has a preference for MMP-1 and TIMP-2 to MMP-2^[67]. The TIMP-1 and TIMP-3 are inducible, TIMP-2 is constitutive, and TIMP-4 exhibits tissue specificity^[67]. ECM remodeling is associated with increased expression of MMPs and elastase, and reduced expression of TIMPs and collagen^[67].

VD improves ECM proteins regulation in fibroblasts and melanoma cells^[34,35] [Figure 2]. VD promotes the expression of collagen, whereas it inhibits the expression of elastin^[68,69]. VD stimulates the expression of collagen by transcriptional mechanism, in non-irradiated and UVA-irradiated fibroblasts, though not in UVB-irradiated fibroblasts^[35]. In UVA-irradiated fibroblasts, VD also stimulates heat shock protein-47 (HSP-47), a chaperone involved in the formation of collagen fibers, but again not in non-irradiated and UVB-irradiated fibroblasts^[35]. VD also inhibits elastin promoter activity in non-irradiated and UV-irradiated fibroblasts^[35]. It has also been described that VD inhibits elastase activity directly and its expression in non-irradiated, and UVA-irradiated fibroblasts, though not in UVB-irradiated fibroblasts^[35]. Elastase activity can be measured by incubating the enzyme with VD followed by the addition of its substrate, whose degradation to a colored product can be followed by spectrophotometrically (Elastin Products Co)^[35]. VD also inhibits MMP-1 and MMP-2 protein levels in melanoma cells^[33].

The stated conclusions on the effects of VD on the extracellular matrix remodeling were determined through *in vitro* experiments, in which non-irradiated, UVA-irradiated, or UVB-irradiated human dermal fibroblasts, and melanoma cells were incubated for 24 h with different concentrations of VD, and expression of different proteins was measured by RT-qPCR and/or ELISA. Protein levels of type I collagen, elastin, MMP-1, and MMP-2 were measured in the media, and protein levels of HSP-47 were measured in cells using ELISA. The RT-qPCR was used to measure mRNA levels of MMP-1 and MMP-2. Fibroblasts were co-transfected with COL1 α 1 promoter-firefly luciferase or elastin promoter-firefly luciferase and TK promoter-Renilla luciferase plasmids for 24 h, prior to the dosing with UV radiation and/or VD; and firefly and renilla luciferase activities were measured sequentially to determine the normalized type I collagen or elastin promoter activities. Melanoma cells were co-transfected with the MMP-1 promoter-chloramphenicol acetyltransferase (CAT) plasmid and RSV2- β Galactosidase (β -GAL) prior to incubation with or without VD, and the cells were examined for CAT expression and β -GAL activity to determine the normalized MMP-1 promoter activity. Collectively, VD strengthens the ECM and is beneficial to the

prevention of photoaging and carcinogenesis.

CONCLUSION

VD facilitates skin health through its action on dermal fibroblasts and/or melanoma cells by preventing oxidative DNA damage, membrane damage, and lipid peroxidation, and by stimulating superoxide dismutase expression ameliorating the effects of oxidative stress^[34,35]. In addition, VD reduced the expression of IL-1, TNF- α , IL-8, TGF- β , and VEGF, decreasing inflammation^[35,53,54] and also preventing cell death in UVB-irradiated fibroblasts, increasing p53 promoter activity^[34,35]. At the extracellular level, VD stimulated the expression of type I collagen and inhibited elastase, elastin, and MMPs, particularly MMP-1 and MMP-2, with beneficial ECM effects^[68,69].

In summary, the data reviewed here suggested that VD supported the maintenance of skin health with anti-aging^[70] and anti-carcinogenic effects. The currently recommended doses of VD (as cholecalciferol, D₃) are 400 units (1 unit = 0.025 μ g VD) for children until one year of age, 600 units for people ranging from 1 year through 70 years of age, and 800 for people over 70 years of age^[28,71,72]. The physiological dose of VD is 2.5-10 μ g (1 μ g = 40 units), and the pharmacological dose of VD (as cholecalciferol, D₃, or ergocalciferol, D₂) is 0.625-5 mg for 1-3 months to treat VD deficiency^[73]. The other commonly used VD metabolites or analogs, paricalcitol, doxercalciferol, and calcitriol, are used to treat secondary hyperparathyroidism^[47]. The current research on VD effects strongly advocates for dietary supplementation with VD. Further, the anti-photoaging and anti-carcinogenic effects of VD could be potentiated by non-steroidal anti-inflammatory drugs (NSAIDs). The cyclooxygenase-2/prostaglandin E₂ pathway, which is inhibited by NSAIDs, has been implicated in the etiology of cancer, along with the inflammatory cytokines. Piroxicam and Diclofenac (NSAIDs) inhibit MMP-2 activity in a fibrosarcoma cell line. Both NSAIDs are suitable for field cancerization treatment of actinic keratosis. It is inferred that the combination of Diclofenac, or other NSAIDs, with VD, would provide added benefit.

DECLARATIONS

Authors' contributions

Conceptualization: Philips N

Writing - original draft preparation: Philips N, Portillo-Esnaola M

Writing - review and editing: Philips N, Portillo-Esnaola M

Figures: Portillo-Esnaola M, Samuel P, Gallego-Rentero M

Initial bibliographic research: Keller T, Franco J

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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