



## The regulatory and pleiotropic role of vitamin D

S. Tsekhmistrenko\*, V. Bityutskyy\*, O. Tsekhmistrenko\*, T. Tokarchuk\*\*,  
L. Savchuk\*\*, V. Harkavenko\*\*\*, L. P. Horalskyj\*\*\*\*, S. Oliynyk\*\*\*\*\*

\*Bila Tserkva National Agrarian University, Bila Tserkva, Ukraine

\*\*Podillia State University, Kamianets-Podilskyi, Ukraine

\*\*\*Vinnytsia National Agrarian University, Vinnytsia, Ukraine

\*\*\*\*Zhytomyr Ivan Franko State University, Zhytomyr, Ukraine

\*\*\*\*\*Ewha Womans University, Seoul, Republic of Korea

### Article info

Received 04.01.2026

Received in revised form

03.02.2026

Accepted 19.02.2026

Bila Tserkva National Agrarian  
University, Soborna Square, 8/1,  
Bila Tserkva, 09117, Ukraine.  
Tel.: +38-068-034-48-48, E-mail:  
svetlana.tsehmistrenko@gmail.com

Higher Educational Institution  
"Podillia State University", Odien-  
ka st., 61, Kamianets-Podilskyi,  
32316, Ukraine.

Vinnytsia National Agrarian  
University, Sonyachna st., 3,  
Vinnytsia, 21008, Ukraine.

Zhytomyr Ivan Franko State  
University, Velyka Berdychivska  
st., 40, Zhytomyr, 10008, Ukraine.

Ewha Womans University, Seoul,  
Republic of Korea. E-mail:  
sergiyoliynyk622@gmail.com

Tsekhmistrenko, S., Bityutskyy, V., Tsekhmistrenko, O., Tokarchuk, T., Savchuk, L., Harkavenko, V., Horalskyj, L. P., & Oliynyk, S. (2026). The regulatory and pleiotropic role of vitamin D. *Regulatory Mechanisms in Biosystems*, 17(2), e26035. doi:10.15421/0226035

Vitamin D is a multifunctional secosteroid compound that plays a key role in maintaining systemic homeostasis in humans and animals. Its active form, 1,25-dihydroxyvitamin D<sub>3</sub> (calcitriol), acts as an endocrine and autocrine modulator, influencing the expression of hundreds of genes that regulate metabolism, immune response, cell proliferation, and antioxidant protection. In recent years, a significant amount of evidence has been accumulated indicating the pleiotropic nature of vitamin D: it is involved not only in phosphorus-calcium metabolism, but also in the regulation of the NF-κB, PI3K/Akt/mTOR, and Wnt/β-catenin signaling cascades, which control cell survival, apoptosis, inflammatory response, and aging processes. It has been proven that adequate levels of 25(OH)D in blood plasma reduce the risk of developing autoimmune, metabolic, cardiovascular, and oncological diseases. Calcitriol inhibits excessive NF-κB activation, reducing the production of pro-inflammatory cytokines IL-6, TNF-α, and IL-17; at the same time, it activates AMPK and PTEN, inhibiting the PI3K/Akt/mTOR pathway and promoting autophagy. By inhibiting β-catenin, vitamin D blocks the transcription of proto-oncogenes, preventing excessive proliferation. Due to its effect on these signaling systems, vitamin D acts as a universal integrator of cellular responses to stress, oxidative disturbances, and inflammatory stimuli. Particular attention is paid to its effect on the antioxidant and excretory systems, where vitamin D enhances the expression of antioxidant enzymes, reduces lipoperoxidation, and promotes the normalization of renal tubule function. In addition, epidemiological and clinical studies confirm the inverse relationship between vitamin D deficiency and the incidence of cancer, especially breast, prostate, and colon cancer. Vitamin D should be considered as a systemic regulator that integrates immune-endocrine, antioxidant, and metabolic processes, ensuring the stability of the body's functional systems. Its pleiotropic effect opens up new opportunities for the development of personalized approaches to the prevention and treatment of chronic diseases.

**Keywords:** signaling pathways; immune regulation; antioxidant system; cellular homeostasis; pleiotropic effect.

### Introduction

Vitamin D (calciferols) is considered in modern biology to be a multifunctional secosteroid that goes beyond the classical paradigm of an "anti-rachitic factor" and regulator of calcium-phosphorus metabolism. The presence of the vitamin D receptor (VDR) in most cell types, as well as the discovery of extra-renal activation of 25(OH)D to 1,25(OH)<sub>2</sub>D (calcitriol) have led to a revision of traditional ideas about its physiological role and emphasized its hormone-like action (Bouillon et al., 2019; Wimalawansa, 2023). In this concept, vitamin D appears as an endocrine, paracrine, and autocrine module capable of controlling the expression of a significant array of genes associated with metabolism, immune response, cell proliferation/differentiation, and antioxidant protection.

At the level of systems biology, vitamin D acts as a coordinator of interconnected regulatory circuits in biosystems, from cellular signaling cascades to integrative axes of body homeostasis. In particular, the interaction of the "calcium-phosphorus-PTH-FGF23" axis with the "immune response–inflammation–oxidative stress axis" creates a basis for interpreting pleiotropic effects as a result of cross-talk between key molecular regulatory pathways (Fenercioglu et al., 2024). In clinical and population studies, 25(OH)D deficiency is associated with metabolic disorders and an increased risk of cardiovascular, autoimmune, neurodegenerative, and mental disorders. However, the degree of causality and modifying factors (baseline level, dose, duration, population differences) require careful interpretation (Malihi et al., 2017; Aslam et al., 2019).

It is worth noting that review articles on vitamin D often have an overly broad scope, resulting in the mechanistic line being lost in a list of phenotypes and associations. However, it is fundamentally important to consider the pleiotropy of vitamin D as a consequence of specific regulatory nodes (VDR-dependent and VDR-independent effects) and signaling pathway interactions, rather than as a collection of disparate clinical observations. Therefore, this review focuses on a mechanistic approach: from the metabolism and availability of D-metabolites to molecular targets, biomarkers, and phenotypic consequences in humans and animals.

The aim of the review is to systematize current understanding of vitamin D as a regulatory factor in biosystems, focusing on the molecular nodes of the VDR-mediated transcriptional response and cross-talk between key signaling axes that shape pleiotropic effects. The novelty of the review lies in the comparison of mechanistic data (*in vitro/in vivo*), observational population results, and evidence from randomized clinical trials in a single logic: "signaling axis → targets / biomarkers → functional consequences → level of evidence".

The scope of the review covers: vitamin D metabolism and transport and key regulators of active forms; VDR-dependent mechanisms of gene expression regulation; vitamin D involvement in the regulation of inflammation, oxidative stress, energy metabolism, and cell fate through universal signaling cascades. The review does not aim to formulate clinical recommendations on dosing for specific nosologies; issues of therapeutic doses and protocols are considered only within the limits of evidence and biosafety. The review is presented in a narrative format with transparent elements of search and source selec-

tion. The literature search was conducted in leading scientometric databases (e.g., PubMed/Medline, Scopus, Web of Science, Google Scholar) using the following key terms: “vitamin D,” “VDR,” “calcitriol,” “25(OH)D,” “CYP27B1,” “CYP24A1,” “DBP,” “FGF23,” “PTH,” “NF- $\kappa$ B,” “PI3K / Akt / mTOR,” “Wnt/ $\beta$ -catenin,” “oxidative stress,” and “immune regulation.” The main focus is on publications from the last 10–12 years, including classic works that defined conceptual approaches and terminology (Bouillon et al., 2019; Wimalawansa, 2023).

Criteria for inclusion of sources: peer-reviewed articles, systematic reviews, and meta-analyses; randomized controlled trials; high-quality *in vivo* and *in vitro* experimental studies that reveal the mechanisms of VDR-mediated regulation. Exclusion criteria: non-peer-reviewed materials without a clear editorial policy, duplicates, studies without defined methods for measuring 25(OH)D or without the possibility of verifying bibliographic data. To minimize bias, priority was given to sources with clearly described methodologies and reproducible endpoints, and in cases of conflicting results, both positions were presented with an explanation of the possible causes of heterogeneity (Malihi et al., 2017; Aslam et al., 2019).

### Structure of vitamin D

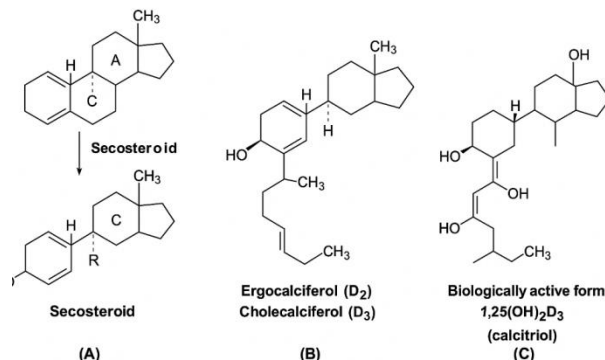
Vitamin D is a member of a group of fat-soluble secosteroid compounds that are structurally derived from steroids but differ in the presence of a cleaved B-ring (from Latin *secare* – to cut). This feature gives the molecule conformational flexibility and the ability to bind to the vitamin D receptor (VDR), providing a wide range of biological effects (Christakos et al., 2011; Bishop et al., 2021).

The main natural forms of vitamin D are ergocalciferol (D<sub>2</sub>) and cholecalciferol (D<sub>3</sub>). Ergocalciferol (D<sub>2</sub>) is formed by ultraviolet (UV-B) irradiation of ergosterol, which is synthesized by fungi and some invertebrates. Cholecalciferol (D<sub>3</sub>), the main form in humans and animals, is formed by the action of UV-B on 7-dehydrocholesterol in the skin and provides up to 90% of the body's vitamin D requirement (Holick, 2007).

After entering the body, vitamin D is metabolized in two successive hydroxylating stages: first, 25-hydroxyvitamin D (25(OH)D) is formed in the liver, and then the active hormonal form 1,25(OH)<sub>2</sub>D,

or calcitriol, is formed in the kidneys. The latter interacts with the vitamin D receptor (VDR) in the cell nucleus, forming a complex with the retinoid X receptor (RXR), which acts as a transcription factor that regulates the expression of genes associated with calcium homeostasis, immune response, cell proliferation, and differentiation (Norman, 2008; Fleet, 2017; Wimalawansa, 2018).

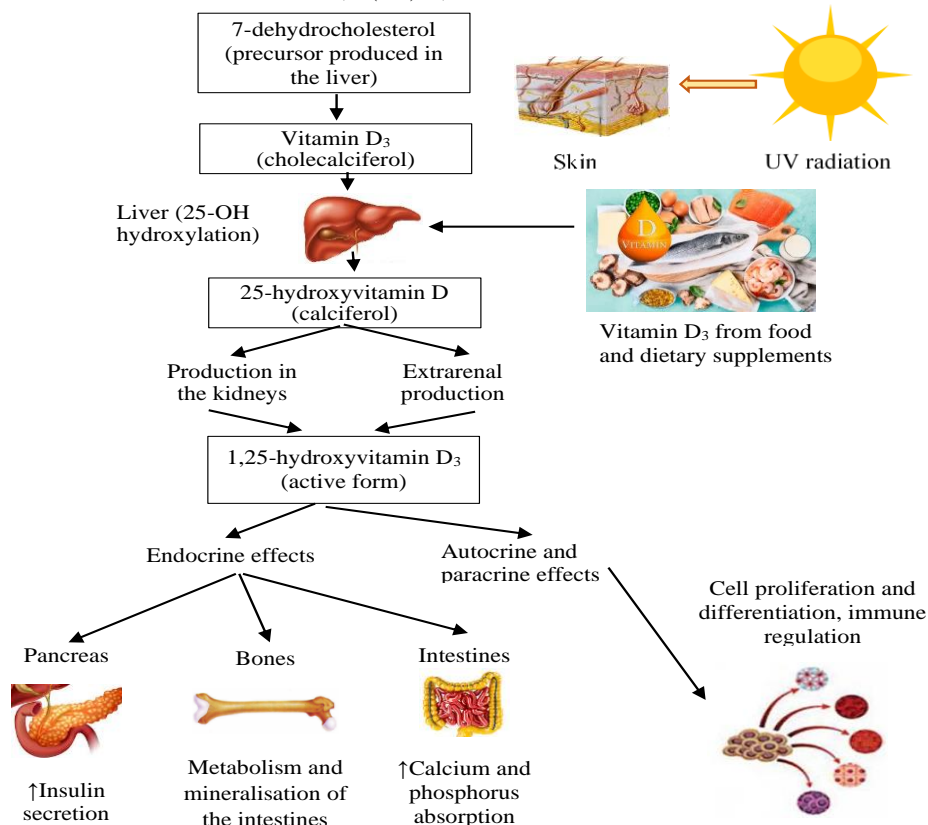
Vitamins D<sub>2</sub> and D<sub>3</sub> differ only in the structure of their side chains, but their biological activity is not identical: D<sub>3</sub> has a higher affinity for VDR and provides more stable maintenance of serum 25(OH)D levels (Jäpelt & Jakobsen, 2013) (Fig. 1).



**Fig. 1.** General structure of secosteroids compared to traditional steroids (A) and structure of vitamin D secosteroids (B) and calcitriol (C)

### Biochemical pathways and metabolism of vitamin D

D<sub>3</sub> is synthesized in the skin from 7-dehydrocholesterol (7-DHC) under the action of UV-B ( $\approx$ 290–315 nm) through the previtamin D<sub>3</sub> stage with subsequent thermoisomerization (Fig. 2). D<sub>2</sub> comes mainly from mushrooms/yeast or fortified foods (both forms are also possible in a fortified diet) (Sun et al., 2024). The proportion of endogenous synthesis in real populations is currently declining due to “indoorization” of lifestyles, sun protection habits, and latitudinal/seasonal factors, making 25(OH)D deficiency common in many countries (Battistini et al., 2020).



**Fig. 2.** Vitamin D metabolism

After being formed in the skin or ingested with food, vitamin D is transported in the blood in a complex with vitamin D-binding protein (DBP) (Chen et al., 2022). In the liver, with the participation of the enzyme 25-hydroxylase (CYP2R1), it is converted to 25(OH)D (Elkhwanky et al., 2020). The next step occurs mainly in the kidneys, where 25(OH)D is hydroxylated by  $1\alpha$ -hydroxylase (CYP27B1) to 1,25(OH)<sub>2</sub>D (calcitriol) – the main biologically active form (Khan et al., 2020). Excess 1,25(OH)<sub>2</sub>D and 25(OH)D are inactivated by 24-hydroxylase (CYP24A1) to form water-soluble metabolites for excretion (Wimalawansa, 2018; Bikle, 2020).

The discovery of alternative pathways for vitamin D metabolism (via the CYP11A1 enzyme to form a series of hydroxy derivatives) has broadened our understanding of its functions. These metabolites exhibit their own biological activities and may be involved in the regulation of cellular processes (Milan et al., 2024; Slominski et al., 2024). In addition, local production of 1,25(OH)<sub>2</sub>D outside the kidneys (e.g., in immune cells) plays an important role in autocrine and paracrine regulation (van Meegen et al., 2021).

### Vitamin D in the regulation of calcium homeostasis and bone health

Optimal D status is an important condition for maintaining bone mineral density (BMD) and preventing disorders such as rickets, osteomalacia, and osteoporosis (Fig. 3). Studies show that maintaining 25(OH)D levels above 30 ng/mL significantly reduces the risk of hip fractures and vertebral compression fractures (Bischoff-Ferrari et al., 2020). In children, deficiency leads to rickets with impaired mineralization of growth plates, while in adults it leads to osteomalacia and osteoporotic changes (Chowdhury et al., 2023; Thacher & Bishop, 2023).

Vitamin D stimulates calcium absorption in the intestine (Christakos et al., 2021) and ensures mineralization of the bone matrix (Hausler et al., 2022). At the same time, excessive levels of 1,25(OH)<sub>2</sub>D (calcitriol) can cause hypercalcemia and accelerated bone resorption. However, vitamin D toxicity is rare and is usually associated with extremely high doses (Marcinowska-Suchowierska et al., 2018). It is important to adhere to the recommended doses and regularly monitor 25(OH)D during long-term supplementation.

VDR receptors are present in muscle tissue, and vitamin D affects myogenesis and the maintenance of muscle strength. Calcitriol affects the expression of calcium transport channels (L-type Ca<sup>2+</sup> channels, RyR) and buffer proteins that maintain intracellular Ca<sup>2+</sup> homeostasis (Holick et al., 2020; Girgis et al., 2022). Vitamin D deficiency causes a decrease in calcium sensitivity and neuromuscular synapse conduction, which manifests itself in muscle weakness, tremors, or tetany (Bislev et al., 2021; Visser et al., 2021). Restoring 25(OH)D levels above 30 ng/mL improves walking speed, balance, and muscle strength-effects associated with increased calcium signaling in myofibrils (Veuglers et al., 2015; Visser et al., 2021; Girgis & Brennan-Speranza, 2022). Calciferol supplementation in this group can improve muscle function and coordination (Girgis & Brennan-Speranza, 2022).

The physiological action of calcitriol is to maintain adequate concentrations of ionized calcium in the blood plasma, which is necessary for the depolarization of cell membranes, the release of neurotransmitters, and the contraction of skeletal and cardiac muscles (Fig. 3).

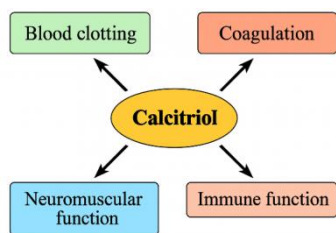


Fig. 3. Calcium-dependent processes regulated by calcitriol

Calcitriol also regulates calcium-dependent stages of the blood coagulation cascade. Ca<sup>2+</sup> ions are necessary for the activation of prothrombin (factor II), factors VII, IX, and X, which bind to the phospholipid surface via  $\gamma$ -carboxylated glutamic acid residues. By activa-

ting the expression of  $\gamma$ -glutamyl carboxylase in hepatocytes, calcitriol promotes the biosynthesis of functionally active coagulation proteins (Matsunuma & Hattori, 2020).

At the same time, calcitriol regulates the balance between coagulation and fibrinolysis by inhibiting PAI-1 expression and increasing tPA activity, which prevents excessive thrombus formation (Wu et al., 2021). Calcitriol affects calcium-dependent signaling pathways in immune cells, primarily through NFAT (Nuclear Factor of Activated T-cells) and Ca<sup>2+</sup>/CaM-dependent kinase II. Activation of VDR in T-lymphocytes suppresses the Th1/Th17 response and increases T<sub>reg</sub> activity, which promotes immune homeostasis and suppression of autoimmune reactions (Mousa et al., 2022).

Calcitriol stimulates macrophages to produce antimicrobial peptides – cathelicidin (LL-37) and  $\beta$ -defensins, enhancing phagocytosis and protection against bacterial pathogens (Adams & Hewison, 2021). Since Ca<sup>2+</sup> plays a central role in macrophage and lymphocyte signaling, vitamin D indirectly regulates their activation and cytokine secretion through calcium channels (ORAI1, STIM1).

Thus, the relationship between calcitriol and calcium is fundamental to the neuromuscular, hemostatic, and immune balance of the body. Maintaining adequate D status is necessary for the normal functioning of Ca<sup>2+</sup>-dependent pathways in all systems.

### Vitamin D and key signaling pathways

Vitamin D is one of the most important systemic regulators of cellular homeostasis, coordinating signaling cascades related to proliferation, apoptosis, immune response, metabolism, and antioxidant protection. The active form, 1,25(OH)<sub>2</sub>D<sub>3</sub>, interacts with the VDR receptor to regulate the expression of hundreds of genes that maintain cellular stability and reduce inflammatory stress (Tkach et al., 2022; Jaroslawska & Carlberg, 2023). This effect is pleiotropic in nature and manifests itself in the influence on several universal signaling systems, including NF- $\kappa$ B, PI3K/Akt/mTOR, and Wnt/ $\beta$ -catenin (Fig. 4).

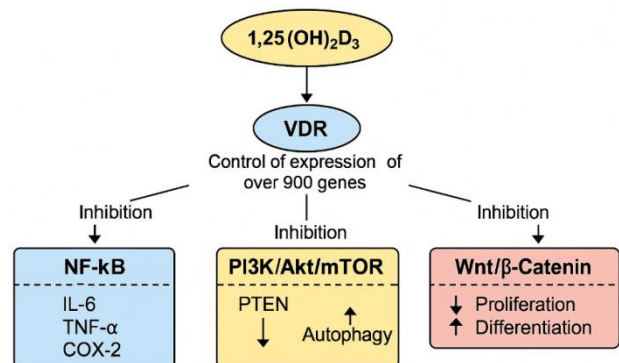


Fig. 4. Mechanisms of cellular signaling pathway regulation by vitamin D

NF- $\kappa$ B is a key mediator of the inflammatory response that activates the transcription of cytokines IL-6, TNF- $\alpha$ , IL-1 $\beta$ , and enzymes COX-2 and iNOS (Bityutsky et al., 2020). Excessive activation of this cascade underlies chronic inflammation and tumor growth. Vitamin D inhibits I $\kappa$ B kinase phosphorylation, stabilizes the I $\kappa$ B inhibitor, and prevents the translocation of the p65/p50 complex into the nucleus (Sartika & Gayatri, 2022). This mechanism limits the synthesis of pro-inflammatory cytokines, reduces oxidative stress, and maintains cellular balance (Deepika et al., 2025). Thus, vitamin D acts as a natural antagonist of NF- $\kappa$ B-dependent hyperactivation and may be a protective factor in autoimmune and metabolic diseases.

Another important pathway, PI3K/Akt/mTOR, coordinates cell growth, metabolism, and autophagy. Its hyperactivation is observed in many neoplasms and neurodegenerative processes (Jiang et al., 2025). Vitamin D inhibits Akt phosphorylation, reducing mTORC1 activity, activates AMPK, and promotes autophagy. Through the induction of PTEN expression, it blocks PI3K and inhibits cell proliferation. Such regulation contributes to the antitumor potential of the D-hormone (Al-Hendy et al., 2016; Singh et al., 2025).

The Wnt/ $\beta$ -catenin pathway is key in regulating epithelial cell growth. Its activation stimulates the transcription of proto-oncogenes (c-Myc, Cyclin D1), leading to increased proliferation. The active form of vitamin D interacts with  $\beta$ -catenin via VDR, preventing its translocation to the nucleus, which limits the expression of proliferative genes and inhibits carcinogenesis (Al-Hendy et al., 2016). In addition, the D-hormone stimulates the formation of Wnt pathway inhibitors (DKK1, SFRP), which reduces the activity of the cascade (Deepika et al., 2025).

Thus, vitamin D functions as a universal regulator of signaling networks that provide adaptive, anti-inflammatory, and antiproliferative responses of the cell. Its effect on NF- $\kappa$ B, PI3K/Akt/mTOR, and Wnt/ $\beta$ -catenin explains the multifaceted biological action of D-hormone – from maintaining cellular homeostasis to preventing pathological tissue transformation (Jaroslawska & Carlberg, 2023; Giustina et al., 2024).

### Vitamin D and the metabolic system

Vitamin D plays an important endocrine-metabolic role, affecting insulin sensitivity, pancreatic  $\beta$ -cell function, and systemic glucose metabolism. The active form 1,25(OH) $_2$ D binds to receptors in  $\beta$ -cells, enhancing insulin expression, regulating intracellular calcium homeostasis, and preventing apoptosis of these cells. In peripheral tissues (muscle and fat), vitamin D stimulates the expression of insulin receptors, increases the activity of the glucose transporter GLUT4, and reduces the level of inflammatory cytokines that impair insulin signaling (Khamseh et al., 2022; Sun et al., 2024). Epidemiological and interventional studies show that low 25(OH)D levels are associated with an increased risk of type 2 diabetes (T2D) and metabolic syndrome. Optimizing 25(OH)D levels reduces HOMA-IR (insulin resistance index), increases insulin secretion, and improves HbA1c in patients with prediabetes (Pittas et al., 2023; Probosari et al., 2025). Randomized clinical trials show that vitamin D supplementation (>2000 IU/day) in deficient individuals can reduce the risk of progression from prediabetes to diabetes by 15–30 % (Pittas et al., 2023; Mitri et al., 2024). Calcitriol modulates the expression of genes responsible for lipid metabolism, including LPL (lipoprotein lipase) and ApoA-I, leading to a decrease in triglyceride levels and an increase in HDL cholesterol concentration (Kuryłowicz et al., 2021). Metabolic studies in animal and human models show that vitamin D deficiency correlates with higher LDL levels, increased HMG-CoA reductase activity, and accelerated lipogenesis in the liver (Khosravi et al., 2023). Obesity is associated with reduced vitamin D bioavailability due to its sequestration in adipose tissue. At the same time, low vitamin D status impairs energy metabolism, exacerbates inflammatory responses, and increases insulin resistance (Khamseh et al., 2022; Wimalawansa, 2023). Optimizing vitamin D levels improves adipocyte function, reduces leptin and TNF- $\alpha$  levels, and regulates adiponectin secretion, which increases insulin sensitivity (Rafiq et al., 2024). 0

### Vitamin D and the cardiovascular system

Vitamin D deficiency (low serum 25(OH)D levels) is consistently associated with elevated blood pressure, hypertension, ischemic heart disease, heart failure, and overall cardiovascular risk (Forman et al., 2010; Zhang et al., 2020; Kose et al., 2022; Verdoia et al., 2022; Ahmadieh & Arabi, 2023). Mechanistically, vitamin D affects the regulation of the renin-angiotensin system (suppresses renin gene expression) and reduces vascular inflammation, which contributes to improved endothelial function (Pascale et al., 2018; Kose et al., 2022). One of the key pathways is the inhibition of the renin-angiotensin-aldosterone system (RAAS) through a VDR-dependent mechanism (Yuan et al., 2007). Lower levels of 25(OH)D are associated with higher RAAS activity, greater arterial stiffness, and higher blood pressure (Forman et al., 2010; Zhang et al., 2020; Jia et al., 2022).

Low 25(OH)D levels are associated with arterial stiffness, endothelial dysfunction, and progression of atherosclerosis (Tomson et al., 2017; Zhang et al., 2020); mechanistically, this is associated with de-

creased eNOS signaling, increased oxidative stress, and proinflammatory response (Michos & Cainzos-Achirica, 2021).

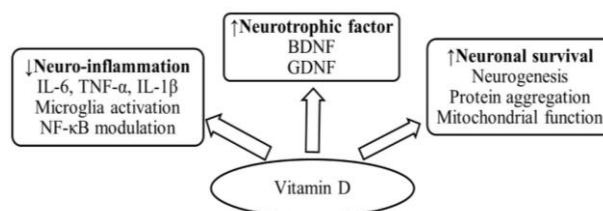
Large RCTs in mixed populations have largely failed to show a significant reduction in “hard” CV events (heart attack/stroke/CV death) with routine vitamin D supplementation (Thompson et al., 2023; Fadini et al., 2024). At the same time, stratified analysis in individual studies indicates a moderate reduction in risk in people with lower predicted 25(OH)D or on concomitant cardiac therapy (Song et al., 2022).

Elevated PTH is an independent predictor of CV risks; optimization of D status reduces PTH and may improve hemodynamics and inflammatory response. Vitamin D deficiency stimulates PTH secretion, which is associated with vascular calcification (Pascale et al., 2018).

Thus, vitamin D is a multi-targeted cardiometabolic modifier: it affects RAAS, endothelium, and oxidative stress and likely reduces pressure in “deficient” or high-risk subgroups (Thompson et al., 2023).

### Vitamin D and the nervous system

Low 25(OH)D status is associated with an increased risk of dementia, Alzheimer's disease, and other neurodegenerative diseases. Mechanisms include dysregulation of calcium homeostasis in neurons, increased neuroinflammation, and oxidative stress (Fig. 5). Studies show that vitamin D promotes neurogenesis, reduces the production of pro-inflammatory mediators, and supports the production of neurotrophic factors (Garcion et al., 2021; Burne et al., 2022; Wang et al., 2023; Fenercioglu et al., 2024; Zhao et al., 2024). Correction of D deficiency in older adults is associated with improved cognitive test scores and a slower rate of cognitive decline (Annweiler et al., 2023; Fu et al., 2023).



**Fig. 5.** Schematic representation of the neuroprotective mechanisms of vitamin D

Vitamin D deficiency is associated with an increased risk of depression, seasonal affective disorder, and sleep disorders (Li et al., 2023). Vitamin D, through VDR receptors in the hypothalamus, can influence the synthesis of neurotransmitters and hormones, including melatonin. Studies have found that people with low 25(OH)D levels are more likely to complain of chronic fatigue, depressive symptoms, and sleep disturbances (Cheng et al., 2022; Smith et al., 2023). The loss of daily fluctuations in melatonin secretion in D deficiency may explain circadian rhythm disturbances. Maintaining adequate D status is considered an adjunctive therapy for affective disorders and insomnia.

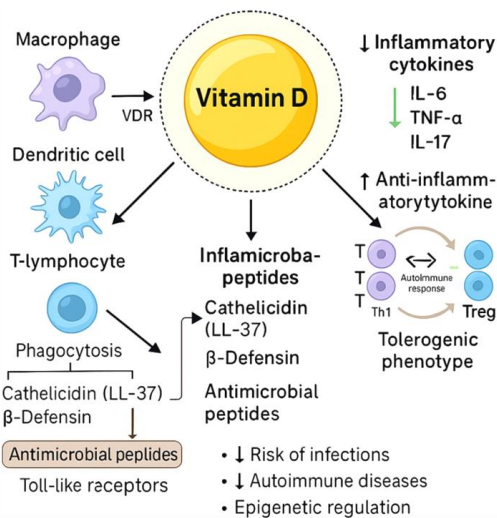
### Vitamin D and the immune system

Vitamin D plays a central role in regulating the immune system, acting as an endocrine and paracrine modulator of inflammation and protection against infections (Fig. 6). Through the VDR receptor, expressed in macrophages, dendritic cells, and T lymphocytes, the active form 1,25(OH) $_2$ D $_3$  regulates the expression of more than 200 genes associated with innate and adaptive immunity (Adams & Hewison, 2021). It enhances phagocytosis and the production of antimicrobial peptides (cathelicidin (LL-37) and  $\beta$ -defensin) by activating Toll-like receptors, providing an effective antiviral and antibacterial response (Martens et al., 2020; Sanlier & Guney-Coskun, 2022).

This promotes the transition of the immune response from a Th1/Th17-dominant to a regulatory (Treg) orientation, which is important for preventing autoimmune reactions. This promotes a shift in the immune response from Th1/Th17-dominant to regulatory (Treg) orientation, which is important for preventing autoimmune reactions (Bui et al., 2021; Daryabor & Shiri, 2023). In particular, vitamin D

has been found to suppress the maturation of dendritic cells by reducing the expression of HLA-DR and CD80/86 molecules, leading to the formation of a tolerant phenotype (Guo et al., 2024).

Low levels of 25(OH)D are associated with an increased incidence of respiratory tract infections, an increased risk of autoimmune disorders, and a more severe course of COVID-19, while its correction improves immune resistance indicators (Rebelos et al., 2023; Srivastava, 2025). Vitamin D supplementation has been shown to reduce the risk of acute respiratory infections and reduce the exacerbation of autoimmune diseases, although the optimal doses and duration of therapy need to be clarified (van Meegen et al., 2021; Milan et al., 2024).



**Fig. 6.** Mechanism of action of vitamin D (1,25(OH)<sub>2</sub>D<sub>3</sub>) in regulating the immune system

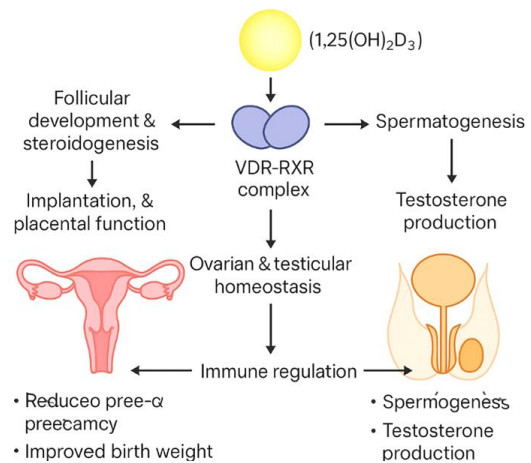
In addition, the D-hormone has an epigenetic effect: it influences DNA methylation and alters the profile of microRNAs that regulate the expression of pro-inflammatory genes and NF-κB signaling pathways (Mavar et al., 2024). The combination of these effects indicates that vitamin D is a universal regulator of immune tolerance, simultaneously enhancing natural antimicrobial defense and preventing the development of chronic inflammation.

### Vitamin D and the reproductive system

Vitamin D plays a key role in maintaining the functional activity of the reproductive system in both females and males (Fig. 7). Its receptors (VDR) are expressed in the ovaries, uterus, placenta, testes, and Sertoli cells, indicating the universal regulatory influence of calcitriol on gametogenesis and hormonal balance (Grzesiak et al., 2022; Hrabia et al., 2023). The active form 1,25(OH)<sub>2</sub>D<sub>3</sub>, interacting with RXR receptors, regulates the transcription of genes associated with steroidogenesis, follicular maturation, granulosa cell function, and spermatogenesis (Reddy et al., 2022).

In females, vitamin D deficiency is associated with impaired folliculogenesis, decreased estrogen and progesterone secretion, hyperprolactinemia, and the development of endometriosis (Farhangnia et al., 2024). D deficiency is associated with fertility disorders, endometriosis, preeclampsia, and gestational diabetes. Adequate maternal D status is associated with better perinatal outcomes (newborn weight, reduced risk of preeclampsia). The mechanisms include effects on steroidogenesis, inflammation, and immune tolerance during pregnancy (Fernando et al., 2020; Kuryłowicz et al., 2021). Experimental studies in chickens have demonstrated local expression of CYP2R1 and CYP27B1 enzymes in reproductive tissues, confirming the autocrine-paracrine action of calcitriol (Hrabia et al., 2023). Additionally, it has been proven that the simultaneous presence of vitamin D and calcium is a prerequisite for normal follicular development and ovulation (Safari et al., 2022). In men, vitamin D regulates spermatogenesis, supports testicular morphogenesis, and normalizes testosterone levels (Calagna et al., 2022; Kumar et al., 2025). Studies in animal models have shown that vitamin D supplements stimulate

germ cell proliferation, reduce oxidative stress, and prevent drug-induced testicular dysfunction (Toloupe et al., 2025). Recent reviews highlight the link between metabolic disorders, gut microbiota, and fertility, where vitamin D acts as an important mediator of the “gut microbiome-reproductive organs” axis. Vitamin D plays a role in the functioning of the gonads and placenta.



**Fig. 7.** Vitamin D and the reproductive system

Thus, vitamin D exerts a multivector regulatory function in the reproductive system, integrating hormonal, metabolic, and immune signaling pathways that ensure fertility, normal embryogenesis, and sex hormone homeostasis in humans and animals.

### Vitamin D in the regulation of gene expression

The vitamin D receptor (VDR) belongs to the family of nuclear transcription factor receptors. The binding of 1,25(OH)<sub>2</sub>D to VDR leads to the formation of a heterodimer with RXR and binding to specific DNA sequences (vitamin D response elements (VDREs)) in the promoters of target genes. Through this mechanism, vitamin D directly regulates the expression of over a thousand genes involved in various processes (Adams & Hewison, 2021; Voltan et al., 2023). In particular, genes associated with the immune response (e.g., CAMP, which encodes cathelicidin), cell cycle (p21, p27), differentiation (osteocalcin gene), etc. are regulated.

Vitamin D can also influence gene expression through epigenetic pathways. 1,25(OH)<sub>2</sub>D modifies the activity of histone acetylases and deacetylases, methyltransferases, and microRNAs, leading to changes in chromatin accessibility and mRNA levels of target genes (Mousa et al., 2022). Such epigenetic effects of vitamin D are important in the long-term regulation of cell phenotype and may explain some of the long-lasting effects of early D status on health.

Polymorphisms in VDR genes and vitamin D metabolism enzymes (CYP2R1, CYP27B1, CYP24A1) determine individual differences in response to vitamin D and susceptibility to deficiency (Elkhwanky et al., 2020). Some VDR variants (e.g., FokI, BsmI, TaqI) are associated with the risk of osteoporosis, autoimmune diseases, and certain types of cancer (Lee et al., 2023; Ma et al., 2024). Identifying the genetic determinants of vitamin D sensitivity may contribute to the personalization of approaches to its supplementation.

### Vitamin D and the excretory system

The kidneys are a key organ in vitamin D metabolism, as this is where it is activated to 1,25(OH)<sub>2</sub>D<sub>3</sub> under the action of the enzyme 1α-hydroxylase (Voiculescu et al., 2025). This form of vitamin acts as a hormone that regulates the expression of genes associated with calcium and phosphate transport, as well as anti-inflammatory mechanisms in nephrocytes (Jørgensen & Demirel, 2025; Magagnoli et al., 2025). Vitamin D deficiency causes hyperparathyroidism and mineral metabolism disorders, which accelerate the progression of chronic kidney disease (Kamal & Allwsh, 2024). In patients with diabetic nephropathy, low levels of 25(OH)D are associated with microalbumin-

uria, oxidative stress, and tubular inflammation (Chackochan et al., 2025). Meta-analyses show that D3 supplementation reduces albuminuria and improves nephroprotection (Zomorodian et al., 2022). At the same time, active D metabolites regulate the DKK-3 protein, which reduces renal tissue fibrosis (Kamal & Allwsh, 2024). New data confirm that in patients with CKD, the pharmacokinetics of calcitriol are altered, therefore individual strategies for correcting D status are needed (Tuey et al., 2024). Thus, maintaining optimal 25(OH)D levels is an important prerequisite for the prevention of nephropathies and normal functioning of the excretory system.

### Vitamin D and the antioxidant system

Vitamin D acts as a powerful modulator of antioxidant defense, influencing the balance between the formation and neutralization of reactive oxygen species (Dentino et al., 2025). Through VDR activation, it stimulates the expression of SOD, GPx, catalase, and paraoxonase-1 enzymes, increasing the overall antioxidant capacity of cells (Honarvar & Zamani, 2022; Vázquez-Lorente et al., 2024). Vitamin D improves mitochondrial function, reduces lipid peroxidation, and helps maintain redox homeostasis (Miao & Goltzman, 2023; Voiculescu et al., 2025). Its metabolites, formed with the participation of CYP11A1, exhibit independent antioxidant activity, reducing the expression of pro-inflammatory cytokines (Vázquez-Lorente et al., 2024). Vitamin D deficiency is associated with increased oxidative stress, which underlies aging, atherosclerosis, and metabolic disorders (Dentino et al., 2025). Clinical studies show that vitamin D supplementation increases glutathione levels, reduces MDA, and enhances the body's antioxidant reserve, especially in patients with inflammatory conditions or COVID-19 (Moslemi et al., 2022). Therefore, vitamin D should be considered a hormone with dual action—metabolic and antioxidant—that supports cellular resistance to stress.

### Vitamin D and cancer

Vitamin D has significant potential as a preventive factor and supportive therapy for malignant tumors. Epidemiological studies indicate that people with higher levels of 25-hydroxyvitamin D (25(OH)D) have a lower risk of developing certain forms of cancer, including colorectal, breast, and lymphoma (Wimalawansa, 2025). Meta-analyses of randomized and observational studies have shown that adequate vitamin D status correlates with lower overall mortality from cancer (Afonso et al., 2025). Patients with D-hormone deficiency are more likely to have aggressive clinical forms of tumors and a poorer response to treatment (Zębalski et al., 2025).

At the molecular level, vitamin D exerts its antitumor effects by binding to the VDR receptor, activating the transcription of target genes (CYP24A1, p21, p53), inhibition of Wnt/β-catenin and NF-κB signaling pathways, as well as stimulation of apoptosis and inhibition of angiogenesis (Bettada et al., 2025; Naji et al., 2025). These mechanisms also include modulation of the tumor immune microenvironment: D-hormone increases the sensitivity of tumor cells to immunotherapy and chemotherapy by reducing the number of pro-inflammatory cytokines and activating killer T lymphocytes (Gupta et al., 2024).

The clinical evidence base is most compelling for colorectal and breast cancer, where maintaining 25(OH)D > 75 nmol/L is associated with a lower risk of recurrence and improved prognosis (Wimalawansa, 2025). In addition, the combined use of vitamin D with standard cancer therapy shows promising results in reducing treatment side effects and improving patients' quality of life. However, the widespread use of active forms of calcitriol is limited by the risk of hypercalcemia, which stimulates the development of analogues with reduced calcium activity (Artusa & White, 2024).

In conclusion, vitamin D should be considered not only as a nutrient but also as a multifunctional regulator in the carcinogenesis system – it affects both tumor initiation and progression and the body's response to therapy. However, to definitively establish its role in clinical oncology, large-scale randomized studies with clear patient stratification and standardized dosing are needed.

### Conclusion

Vitamin D is a multifunctional steroid vitamin with hormonal activity that exerts its effects through interaction with the VDR receptor and influence on the expression of hundreds of genes involved in immune, antioxidant, endocrine, and metabolic regulation. Its role extends far beyond the control of calcium and phosphorus metabolism. It functions as a universal coordinator of cellular homeostasis, modulating the key signaling cascades NF-κB, PI3K/Akt/mTOR, and Wnt/β-catenin. These pathways underlie the anti-inflammatory, anti-proliferative, antioxidant, and cytoprotective effects of vitamin D.

In animals and humans, 25(OH)D deficiency is associated with an increased risk of chronic inflammatory, metabolic, nephrological, and oncological pathologies. Adequate vitamin D levels help maintain redox balance, reduce the production of pro-inflammatory cytokines, enhance autophagy, and protect against oxidative stress. Through the regulation of CYP gene expression and VDR proteins, it influences apoptosis, proliferation, and cell differentiation, which determines its potential in the prevention of neoplasms and maintenance of the functional activity of the kidneys, heart, immune, and nervous systems.

Therefore, vitamin D should be considered not only as a nutrient, but also as an endogenous signaling modulator that integrates the body's immune-endocrine, metabolic, and stress responses. Further research should focus on determining the optimal plasma concentrations of 25(OH)D, the molecular targets of calcitriol, and its potential use in personalized prevention and treatment of diseases associated with impaired cellular regulation.

### References

- Adams, J. S., & Hewison, M. (2021). Vitamin D and the immune system: New perspectives on calcium signaling and innate defense. *Nature Reviews Immunology*, 21(3), 189–200.
- Afonso, M. L., Capelas, M. L., Pimenta, N. M., Santos, T., Mäkitie, A., Ganhão-Arranhado, S., ... & Ravasco, P. (2025). A systematic review of vitamin D supplementation in oncology: Chance of science or effectiveness? *Nutrients*, 17(4), 634.
- Ahmadi, H., & Arabi, A. (2023). Association between vitamin D and cardiovascular health: Myth or fact? A narrative review of the evidence. *Women's Health*, 19, 17455057231158222.
- Al-Hendy, A., Diamond, M. P., Boyer, T. G., & Halder, S. K. (2016). Vitamin D<sub>3</sub> inhibits Wnt/β-catenin and mTOR signaling pathways in human uterine fibroid cells. *The Journal of Clinical Endocrinology and Metabolism*, 101(4), 1542–1551.
- Anweiler, C., Beauchet, O., & Blain, H. (2023). Vitamin D and cognitive decline: A systematic review and meta-analysis. *Frontiers in Aging Neuroscience*, 15, 1173264.
- Artusa, P., & White, J. H. (2024). Vitamin D and its analogues in immune system regulation. *Pharmacological Reviews*, 2024, 100032.
- Aslam, M. M., John, P., Bhatti, A., Jahangir, S., & Kamboh, M. I. (2019). Vitamin D as a principal factor in mediating rheumatoid arthritis-derived immune response. *BioMed Research International*, 2019, 3494937.
- Battistini, C., Ballan, R., Herkenhoff, M. E., Saad, S. M. I., & Sun, J. (2020). Vitamin D modulates intestinal microbiota in inflammatory Bowel diseases. *International Journal of Molecular Sciences*, 22(1), 362.
- Bikle, D. D. (2020). Vitamin D: Newer concepts of its metabolism and function at the basic and clinical level. *Journal of the Endocrine Society*, 4(2), bvz038.
- Bischoff-Ferrari, H. A., Orav, E. J., & Dawson-Hughes, B. (2020). Vitamin D supplementation and fracture prevention: Updated meta-analysis. *New England Journal of Medicine*, 383(1), 173–182.
- Bishop, E. L., Ismailova, A., Dimeloe, S., Hewison, M., & White, J. H. (2021). Vitamin D and immune regulation: Antibacterial, antiviral, anti-inflammatory. *JBMR Plus*, 5(1), e10405.
- Bislev, L. S., Langagergaard Rødbro, L., & Rejnmark, L. (2021). Effects of vitamin D on muscle function and balance in older adults: Systematic review and meta-analysis. *Osteoporosis International*, 32(1), 13–27.
- Bitvutsky, V. S., Tsekhmistrenko, S. I., Tsekhmistrenko, O. S., Tymoshok, N. O., & Spivak, M. Y. (2020). Regulation of redox processes in biological systems with the participation of the Keap1/Nrf2/ARE signaling pathway, biogenic selenium nanoparticles as Nrf2 activators. *Regulatory Mechanisms in Biosystems*, 11(4), 483–493.
- Bouillon, R., Marcocci, C., Carmeliet, G., Bikle, D., White, J. H., Dawson-Hughes, B., ... Bilezikian, J. (2019). Skeletal and extraskeletal actions of vitamin D: Current evidence and outstanding questions. *Endocrine Reviews*, 40(4), 1109–1151.

- Bui, L., Zhu, Z., Hawkins, S., & Cortez-Resendiz, A. (2021). Vitamin D regulation of the immune system and its implications for COVID-19: A mini review. *Frontiers in Physiology*, 12, 746202.
- Burne, T. H., McGrath, J. J., & Eyles, D. W. (2022). Vitamin D deficiency and brain function: A focus on neuroinflammation and oxidative stress. *Neurobiology of Disease*, 167, 105674.
- Calagna, G., Catinella, V., Polito, S., Schiattarella, A., De Franciscis, P., D'Antonio, F., ... & Cucinella, G. (2022). Vitamin D and male reproduction: Updated evidence based on literature review. *Nutrients*, 14(16), 3278.
- Chackochan, A., Kuttan, N., & Thomas, T. (2025). Role of vitamin D in the development and progression of diabetic kidney disease: A review of meta-analyses. *World Journal of Clinical Cases*, 13(8), 1074–1085.
- Charoengngam, N., Shirvani, A., & Holick, M. F. (2019). Vitamin D for skeletal and non-skeletal health: What we should know. *Journal of Clinical Orthopaedics and Trauma*, 10(6), 1082–1093.
- Chen, X., Zhou, M., Yan, H., Chen, J., Wang, Y., & Mo, X. (2022). Association of serum total 25-hydroxy-vitamin D concentration and risk of all-cause, cardiovascular and malignancy-specific mortality in patients with hyperlipidemia in the United States. *Frontiers in Nutrition*, 9, 971720.
- Cheng, S. Y., Liu, J. Y., & Ho, C. C. (2022). Vitamin D, melatonin, and mood disorders: Molecular and clinical evidence. *Nutrients*, 14(18), 3816.
- Chowdhury, R., Khan, H., & Kaur, P. (2023). Vitamin D deficiency and osteomalacia: Current perspectives. *Nutrients*, 15(4), 821.
- Christakos, S., Dhawan, P., & Porta, A. (2021). New insights into the vitamin D-regulated calcium transport system in the intestine. *Endocrine Reviews*, 42(3), 295–319.
- Christakos, S., Dhawan, P., Porta, A., Mady, L. J., & Seth, T. (2011). Vitamin D and intestinal calcium absorption. *Molecular and Cellular Endocrinology*, 347(1–2), 25–29.
- Daryabor, G., & Shiri, H. (2023). A review of the critical role of vitamin D axis on the immune response. *Comparative Biochemistry and Physiology Part A*, 275, 111422.
- Deepika, Kumari, A., Singh, S., Ahmad, M. F., Chaki, D., Poria, V., Kumar, S., Saini, N., Yadav, N., Sangwan, N., BinMowyna, M. N., Alsharari, Z. D., Kambal, N., Min, J. H., & Raposo, A. (2025). Vitamin D: recent advances, associated factors, and its role in combating non-communicable diseases. *NPI Science of Food*, 9, 100.
- Dentino, P., Mora, J., & Zuo, L. (2025). Vitamin D deficiency and its role in pathologies of oxidative stress: A literature review. *Cureus*, 17(8), e90042.
- Elkhwanky, M. S., Kummoo, O., Piltonen, T. T., Laru, J., Morin Papunen, L., Mutikainen, M., ... & Hakkola, J. (2020). Obesity represses CYP2R1, the vitamin D<sub>25</sub> hydroxylase, in the liver and extrahepatic tissues. *Journal of Bone and Mineral Research Plus*, 4(11), e10397.
- Farhangnia, P., Noormohammadi, M., & Delbandi, A. A. (2024). Vitamin D and reproductive disorders: A comprehensive review with a focus on endometriosis. *Reproductive Health*, 21(1), 61.
- Fenercioglu, A. K., Yilmaz, O., Gokalp, D., & Kocabas, F. (2024). The anti-inflammatory roles of vitamin D for improving health outcomes. *Nutrients*, 16(13), 2293.
- Fernando, M., Ellery, S. J., Marquina, C., Lim, S., Naderpoor, N., & Mousa, A. (2020). Vitamin D-binding protein in pregnancy and reproductive health. *Nutrients*, 12(5), 1489.
- Fleet, J. C. (2017). The role of vitamin D in the endocrinology controlling calcium homeostasis. *Molecular and Cellular Endocrinology*, 453, 36–45.
- Forman, J. P., Williams, J. S., & Fisher, N. D. (2010). Plasma 25-hydroxyvitamin D and regulation of the renin-angiotensin system in humans. *Hypertension*, 55(5), 1283–1288.
- Fu, L., Zhou, Y., & Zhang, T. (2023). Effects of vitamin D supplementation on cognitive performance in older adults: A randomized controlled trial. *Nutrients*, 15(3), 655.
- Garcion, E., Darcy, F., Gasnier, C., & Nataf, S. (2021). Neuroprotective functions of vitamin D in the central nervous system. *Molecular Neurobiology*, 58(12), 5937–5954.
- Girgis, C. M., & Brennan-Speranza, T. C. (2022). Physiological role of vitamin D in skeletal muscle function: Mechanisms and clinical implications. *Endocrine Reviews*, 43(5), 678–707.
- Giustina, A., Bilezikian, J. P., Adler, R. A., Banfi, G., Bikle, D. D., Binkley, N. C., ... & Virtanen, J. K. (2024). Consensus statement on vitamin D status assessment and supplementation: Whys, whens, and hows. *Endocrine Reviews*, 45(5), 625–654.
- Grzesiak, M., Tchurzyk, M., Socha, M., Sechman, A., & Hrabia, A. (2022). An overview of the current known and unknown roles of vitamin D<sub>3</sub> in the female reproductive system: Lessons from farm animals, birds, and fish. *International Journal of Molecular Sciences*, 23(22), 14137.
- Guo, D., Ning, Y., Bai, J., Tan, Y., Zhou, X., & Li, H. (2024). Interaction between vitamin D homeostasis, gut microbiota, and metabolic health: A review. *Frontiers in Endocrinology*, 15, 1449033.
- Hausler, M. R., Whitfield, G. K., & Hausler, C. A. (2022). Vitamin D signaling and bone metabolism revisited. *Bone*, 155, 116278.
- Holick, M. F. (2007). Vitamin D deficiency. *New England Journal of Medicine*, 357(3), 266–281.
- Holick, M. F., Binkley, N., Bischoff-Ferrari, H. A., Gordon, C. M., Hanley, D. A., & Heaney, R. P. (2020). Evaluation, treatment, and prevention of vitamin D deficiency: updated guidelines. *Journal of Clinical Endocrinology and Metabolism*, 105(3), e469–e485.
- Honarvar, N. M., & Zamani, N. (2022). Effect of vitamin D on paroxonase-1, total antioxidant capacity and biochemical indices in adults: A randomized clinical trial. *Biological Trace Element Research*, 200(1), 185–192.
- Hrabia, A., Kamińska, K., Socha, M., & Grzesiak, M. (2023). Vitamin D<sub>3</sub> receptors and metabolic enzymes in hen reproductive tissues. *International Journal of Molecular Sciences*, 24(23), 17074.
- Jäpelt, R. B., & Jakobsen, J. (2013). Vitamin D in plants: A review of occurrence, analysis, and biosynthesis. *Frontiers in Plant Science*, 4, 50324.
- Jaroslawska, J., & Carlberg, C. (2023). *In vivo* regulation of signal transduction pathways by vitamin D stabilizes homeostasis of human immune cells and counteracts molecular stress. *International Journal of Molecular Sciences*, 24(19), 14632.
- Jia, J., Tao, X., Tian, Z., Zhan, Y., & Liu, Y. (2022). Vitamin D receptor deficiency increases systolic blood pressure by activating the renin-angiotensin system and sympathetic activation. *Experimental and Therapeutic Medicine*, 23(3), 314.
- Jiang, M., Zhang, K., Zhang, Z., Zeng, X., Huang, Z., Qin, P., Xie, Z., Cai, X., Ashrafizadeh, M., Tian, Y., & Wei, R. (2025). PI3K/AKT/mTOR axis in cancer: From pathogenesis to treatment. *MedComm*, 6(8), e70295.
- Jørgensen, H. S., & Demirel, S. (2025). The role of nutritional vitamin D in chronic kidney disease: Current clinical practice guidelines. *Nephrology Dialysis Transplantation*, 40(1), 64–71.
- Kamal, H. R., & Allwsh, T. A. (2024). Evaluating the effect of vitamin D<sub>3</sub> supplementation on DKK-3 serum for third-stage chronic kidney patients. *Pharmacia*, 71, e127441.
- Khamseh, M. E., Jafari, F., Malek, M., & Aghili, R. (2022). Effects of vitamin D supplementation on insulin resistance and adipokines: A systematic review and meta-analysis. *Hormone and Metabolic Research*, 54(4), 239–248.
- Khan, S. S., Petkovich, M., Holden, R. M., & Adams, M. A. (2022). Megalin and vitamin D metabolism – implications in non-renal tissues and kidney disease. *Nutrients*, 14(18), 3690.
- Khosravi, M., Gholami, F., & Ghasemi, A. (2023). The impact of vitamin D deficiency on hepatic lipid metabolism: A review of molecular mechanisms. *Biomedicine and Pharmacotherapy*, 162, 114643.
- Kose, M., Senkal, N., Tukek, T., Cebeci, T., Atalar, S. C., Altinkaynak, M., Arici, H., Genc, S., Catma, Y., Kocaaga, M., Medetalibeyoglu, A., & Ernet, S. (2022). Severe vitamin D deficiency is associated with endothelial inflammation in healthy individuals even in the absence of subclinical atherosclerosis. *European Review for Medical and Pharmacological Sciences*, 26(19), 7046–7052.
- Kumar, R., Annie, L., Gurusubramanian, G., Singh, A., & Roy, V. K. (2025). Vitamin D supplementation stimulates germ cell proliferation in a restraint-stressed mouse. *Reproductive Toxicology*, 138, 109077.
- Kuryłowicz, A., Wicik, Z., & Bednarczuk, T. (2021). Vitamin D and lipid profile: A review of molecular evidence. *International Journal of Molecular Sciences*, 22(17), 9434.
- Lee, S. J., Kim, K. H., & Choi, S. Y. (2023). Involvement of CYP3A4 and MDR1 in altered metabolism and transport regulated by the vitamin D receptor. *Journal of Chromatography B*, 1214, 123566.
- Li, B., Xiong, Y., Guo, D., Deng, G., & Wu, H. (2025). The gut-reproductive axis: Bridging microbiota balances to reproductive health and fetal development. *International Immunopharmacology*, 144, 113627.
- Li, J., Xie, X., & Wang, Y. (2023). Calcitriol prevents neurodegeneration via mitochondrial protection in Parkinson's disease models. *Brain Research Bulletin*, 201, 113258.
- Li, Y. C., Kong, J., Wei, M., Chen, Z. F., Liu, S. Q., & Cao, L. P. (2002). 1,25-Dihydroxyvitamin D<sub>3</sub> is a negative endocrine regulator of the renin-angiotensin system. *The Journal of Clinical Investigation*, 110(2), 229–238.
- Ma, S., Wang, X., Liu, Y., Li, J., & Chen, L. (2024). Cellular metabolism regulates the differentiation and function of T cells. *Signal Transduction and Targeted Therapy*, 9, 298.
- Magagnoli, L., Cassia, M., Galassi, A., Ciceri, P., Massó, E., Gelpi, R., ... & Cozzolino, M. (2025). Vitamin D: Are all compounds equal? *Clinical Kidney Journal*, 18(S1), i61–i96.
- Malih, Z., Wu, Z., Lawes, C. M., & Scragg, R. (2017). Non-calcemic adverse effects and withdrawals in randomized controlled trials of long-term vitamin D<sub>2</sub> and D<sub>3</sub> supplementation: Systematic review and meta-analysis. *Nutrition Reviews*, 75, 1007–1034.
- Marcinowska-Suchowierska, E., Kupisz-Urbańska, M., Łukasziewicz, J., Płudowski, P., & Jones, G. (2018). Vitamin D toxicity – A clinical perspective. *Frontiers in Endocrinology*, 9, 550.
- Martens, P. J., Gysemans, C., Verstuyf, A., & Mathieu, C. (2020). Vitamin D's effect on immune function. *Nutrients*, 12(5), 1248.

- Matsunuma, A., & Hattori, S. (2020). Calcitriol and vitamin K-dependent proteins in bone and coagulation pathways. *Journal of Steroid Biochemistry and Molecular Biology*, 199, 105604.
- Mavar, M., Sorić, T., Bagarić, E., Sarić, A., & Matek Sarić, M. (2024). The power of vitamin D: Is the future in precision nutrition through personalized supplementation plans? *Nutrients*, 16(8), 1176.
- Miao, D., & Goltzman, D. (2023). Mechanisms of action of vitamin D in delaying aging and preventing disease by inhibiting oxidative stress. *Vitamins and Hormones*, 121, 293–318.
- Milan, K. L., & Ramkumar, K. M. (2024). Regulatory mechanisms and pathological implications of CYP24A1 in vitamin D metabolism. *Pathology-Research and Practice*, 264, 155684.
- Mitri, J., White, M. F., Pittas, A. G., & Dawson-Hughes, B. (2024). Vitamin D and progression from prediabetes to diabetes: A randomized clinical trial update. *Diabetes Care*, 47(1), 45–54.
- Moslemi, E., Musazadeh, V., Kavyani, Z., Naghsh, N., Shoura, S. M. S., & Dehghan, P. (2022). Efficacy of vitamin D supplementation as an adjunct therapy for improving inflammatory and oxidative stress biomarkers: An umbrella meta-analysis. *Pharmacological Research*, 186, 106484.
- Mousa, A., Naderpoor, N., & de Courten, B. (2022). Vitamin D modulation of T-cell activation and calcium signaling pathways. *Frontiers in Immunology*, 13, 961124.
- Norman, A. W. (2008). From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. *American Journal of Clinical Nutrition*, 88(S2), 491S–499S.
- Pascale, A. V., Finelli, R., Giannotti, R., et al. (2018). Vitamin D, parathyroid hormone and cardiovascular risk: The good, the bad and the ugly. *Journal of Cardiovascular Medicine*, 19(2), 62–66.
- Probosari, E., Subagio, H. W., Rachmawati, B., Muis, S. F., Tjandra, K. C., Adiningsih, D., & Winarni, T. I. (2025). The impact of vitamin D supplementation on fasting plasma glucose, insulin sensitivity, and inflammation in type 2 diabetes mellitus: A systematic review and meta-analysis. *Nutrients*, 17(15), 2489.
- Rafiq, S., Jafri, L., & Qureshi, M. A. (2024). Vitamin D and adipokines in obesity: Interplay and clinical significance. *Nutrients*, 16(4), 712.
- Rebelos, E., Tentolouris, N., & Jude, E. (2023). The role of vitamin D in health and disease: A narrative review on the mechanisms linking vitamin D with disease and the effects of supplementation. *Drugs*, 83(8), 665–685.
- Reddy, A. M., Iqbal, M., Chopra, H., Urmi, S., Junapudi, S., Bibi, S., ... & Abdel-Daim, M. M. (2022). Pivotal role of vitamin D in mitochondrial health, cardiac function, and human reproduction. *EXCLI Journal*, 21, 967.
- Safari, H., Hajian, M., Nasr-Esfahani, M. H., Forouzanfar, M., & Drevet, J. R. (2022). Vitamin D and calcium, together and separately, play roles in female reproductive performance. *Scientific Reports*, 12(1), 10470.
- Sanlier, N., & Guney-Coskun, M. (2022). Vitamin D, the immune system, and its relationship with diseases. *Egyptian Pediatric Association Gazette*, 70(1), 39.
- Sartika, K. D., & Gayatri, A. A. Y. (2022). Signaling pathway of vitamin D, vitamin D receptor and autophagy in infection: A systematic review. *International Journal of Advances in Medicine*, 9(10), 1046–1052.
- Singh, S., Meena, R. K., Maharshi, V., Sinha, N., Agarwal, N., Payra, S., & Harsha, D. (2025). Vitamin D supplementation trials: Navigating the maze of unpredictable results. *Perspectives in Clinical Research*, 16(2), 69–74.
- Slominski, A. T., Kim, T. K., Janjetovic, Z., Slominski, R. M., Li, W., Jetten, A. M., ... & Tuckey, R. C. (2024). Biological effects of CYP11A1-derived vitamin D and lumisterol metabolites in the skin. *Journal of Investigative Dermatology*, 144(10), 2145–2161.
- Smith, C. L., Zhao, L., & Tan, D. X. (2023). Vitamin D and sleep regulation: From molecular pathways to clinical outcomes. *Sleep Medicine Reviews*, 68, 101801.
- Song, S., Yuan, Y., Wu, X., Zhang, D., Qi, Q., Wang, H., & Feng, L. (2022). Additive effects of obesity and vitamin D insufficiency on all-cause and cause-specific mortality. *Frontiers in Nutrition*, 9, 999489.
- Srivastava, V. K. (2025). Role of vitamin D<sub>3</sub> in immune system regulation: A systematic review. *Healthcare Bulletin*, 13(3), 188–199.
- Sun, L., Zhao, Q., & Liu, T. (2024). The effects of vitamin D on insulin resistance through AMPK/PI3K pathways: Mechanistic insights. *Frontiers in Nutrition*, 11, 1432891.
- Sun, Y., Alessandrini, L., Angeloni, S., Del Bianco, E., & Sagratini, G. (2024). From 7-dehydrocholesterol to vitamin D<sub>3</sub>: Optimization of UV conversion procedures toward the valorization of fish waste matrices. *Food Chemistry*, X, 22, 101373.
- Szymczak-Pajor, I., Miazek, K., Selmi, A., Balcerczyk, A., & Śliwińska, A. (2022). The action of vitamin D in adipose tissue: is there the link between vitamin D deficiency and adipose tissue-related metabolic disorders? *International Journal of Molecular Sciences*, 23(2), 956.
- Thacher, T. D., & Bishop, N. J. (2023). Rickets and osteomalacia revisited: The role of vitamin D across the lifespan. *Lancet Diabetes & Endocrinology*, 11(4), 267–281.
- Thompson, B., Waterhouse, M., English, D. R., McLeod, D. S., Armstrong, B. K., Baxter, C., Duarte Romero, B., Ebeling, P. R., Hartel, G., Kimlin, M. G., Rahman, S. T., van der Pols, J. C., Venn, A. J., Webb, P. M., Whiteman, D. C., & Neale, R. E. (2023). Vitamin D supplementation and major cardiovascular events: D-health randomised controlled trial. *BMJ*, 381, e075230.
- Tkach, S., Pankiv, V., & Pankiv, I. (2022). Modern views on the metabolism and biological effects of vitamin D. *International Journal of Endocrinology*, 18(2), 109–117.
- Tolulope, O. D., Ochuwa, Y. A., Samuel, E. O., Oluwatoyin, A. L., & Folorunsho, A. A. (2025). The effect of vitamin D<sub>3</sub> supplementation on Flunitrazepam-induced testicular dysfunction in Wistar rats. *Steroids*, 2025, 109650.
- Tomson, J., Hin, H., Emberson, J., et al. (2017). Effects of vitamin D on blood pressure, arterial stiffness, and cardiac function in older people after 1 year: BEST-D trial. *Journal of the American Heart Association*, 6(10), e005707.
- Tuey, S. M., Ghimire, A., Guzy, S., Prebehalla, L., Roque, A. A., Roda, G., ... & Joy, M. S. (2024). Population pharmacokinetic model of vitamin D<sub>3</sub> and metabolites in chronic kidney disease patients with vitamin D insufficiency and deficiency. *International Journal of Molecular Sciences*, 25(22), 12279.
- van Megen, K. M., Chen, Z., Joosten, A. M., Laban, S., Zwaginga, J. J., Natarajan, R., ... & Roep, B. O. (2021). 1, 25-dihydroxyvitamin D<sub>3</sub> induces stable and reproducible therapeutic tolerogenic dendritic cells with specific epigenetic modifications. *Cytotherapy*, 23(3), 242–255.
- Vázquez-Lorente, H., Herrera-Quintana, L., Jiménez-Sánchez, L., Fernández-Perea, B., & Plaza-Díaz, J. (2024). Antioxidant functions of vitamin D and CYP11A1-derived vitamin D, Tachysterol, and Lumisterol metabolites: mechanisms, clinical implications, and future directions. *Antioxidants*, 13(8), 996.
- Verdoia, M., Gioscia, R., Nardin, M., Rognoni, A., & De Luca, G. (2022). Low levels of vitamin D and coronary artery disease: Is it time for therapy? *Kardiologia Polska*, 80(4), 409–416.
- Veugelaers, P. J., Pham, T.-M., & Ekwaru, J. P. (2015). Optimal vitamin D supplementation dosages that minimize the risk for both low and high serum 25-hydroxyvitamin D concentrations in the general population. *Nutrients*, 7, 10189–10208.
- Visser, M., van Schoor, N. M., & Lips, P. (2021). Vitamin D and muscle function in aging. *Journal of Steroid Biochemistry and Molecular Biology*, 213, 105953.
- Voiculescu, V. M., Nelson Twakor, A., Jerpelea, N., & Pantea Stoian, A. (2025). Vitamin D: Beyond traditional roles – insights into its biochemical pathways and physiological impacts. *Nutrients*, 17(5), 803.
- Voltan, G., Cannito, M., Ferrarese, M., Ceccato, F., & Camozzi, V. (2023). Vitamin D: An overview of gene regulation, ranging from metabolism to genomic effects. *Genes*, 14(9), 1691.
- Wang, Q., Zhu, J., & Xu, J. (2023). Vitamin D suppresses neuroinflammation through NF-κB and Nr1f2 signaling. *Frontiers in Immunology*, 14, 1129783.
- Wimalawansa, S. J. (2018). Non-musculoskeletal benefits of vitamin D. *Journal of Steroid Biochemistry and Molecular Biology*, 175, 60–81.
- Wimalawansa, S. J. (2023). Physiological basis for using vitamin D to improve health. *Biomedicines*, 11(6), 1542.
- Wimalawansa, S. J. (2025). Vitamin D's impact on cancer incidence and mortality: A systematic review. *Nutrients*, 17(14), 2333.
- Wu, H., Li, Y., & Zhang, Q. (2021). Vitamin D regulation of fibrinolytic balance and thrombosis risk in metabolic diseases. *Thrombosis Research*, 205, 112–119.
- Zhang, D., Pan, Y., Zhang, X., Wu, J., & Ye, F. (2020). Effect of vitamin D on blood pressure and hypertension in the general population: An updated meta-analysis of randomized controlled trials and cohort studies. *Preventing Chronic Disease*, 17, e03.
- Zhao, H., Li, X., & Liu, R. (2024). Vitamin D promotes neurogenesis via upregulation of BDNF and NGF pathways. *Neuroscience Letters*, 822, 137646.
- Zomorodian, S. A., Shafiee, M., Karimi, Z., Masjedi, F., & Roshanshad, A. (2022). Assessment of the relationship between 25-hydroxyvitamin D and albuminuria in type 2 diabetes mellitus. *BMC Endocrine Disorders*, 22(1), 171.