BRAZILIAN JOURNAL BJHBS OF HEALTH AND BIOMEDICAL SCIENCES

Review article

Relationship between vitamin D and cancer: A narrative review

Luciana L. Alves,[1] Luiza Torres-Nunes,[2]* Marcella de Lucena-Machado,[3] Yanca Maiara A. de Azevedo,[4] Danúbia da C. de Sá-Caputo,[2,5,6] Mario Bernardo-Filho[2]

Abstract

Introduction: Vitamin D is involved in several human metabolism pathways, both in classic pathway, which involves the calcium and phosphorus metabolism, and in non-classic pathways, which are related to several types of diseases, including diseases related to muscles; kidneys; cardiovascular system; immune system; some types of cancer; diabetes; and pregnancy. Objectives: As cancer is one of the main health problems in the world and knowing that it is one of the non-classic effects related to vitamin D, the current narrative review aimed to verify the relevance of vitamin D has on the types of cancer. Methods: The bibliographic research was performed in databases Pubmed, Scopus and PEDro on June 16, 2020, using the keywords "vitamin D", "cancer" and "non-classic". Only articles since the year 2000 were included. Thirty-one articles were analyzed relating vitamin D to colon/rectum cancer, breast cancer, prostate cancer, lung cancer, ovarian cancer, melanoma and other types of skin cancer, and gastric cancer. Results: All studies have shown a relationship between vitamin D and the incidence of cancer in the human body, however, there are peculiarities regarding the concentration levels in each organ. Even with conflicting results, in general, vitamin D has shown to be promise in the prevention of several types of cancer.

Keywords: Vitamin D; Cancer; narrative review; cancer prevention; health problems.

1. Laboratório de Ultraestrutura e Biologia Tecidual, Departamento de Histologia e Embriologia, Instituto de Biologia Roberto Alcântara Gomes, Universidade do Estado do Rio de Janeiro. Rio de Janeiro, RJ, Brasil.
2. Laboratório de Vibrações Mecânicas e Práticas Integrativas, Departamento de Biofísica e Biometria, Instituto de Biologia Roberto Alcântara Gomes and Policlínica Piquet Carneiro, Universidade do Estado do Rio de Janeiro. Rio de Janeiro, RJ, Brasil.
3. Laboratório de Farmacologia Cardiovascular e Plantas Medicinais, Departamento de Histologia e Embriologia, Instituto de Biologia Roberto Alcântara Gomes, Universidade do Estado do Rio de Janeiro. Rio de Janeiro, RJ, Brasil.
4. Laboratório de Pesquisa em Células-Tronco, Departamento de Histologia e Embriologia, Instituto de Biologia Roberto Alcântara Gomes, Universidade do Estado do Rio de Janeiro. Rio de Janeiro, RJ, Brasil.
5. Programa de Pós-Graduação em Ciências Médicas, Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro. Rio de Janeiro, RJ, Brasil.
6. Faculdade Bezerra de Araújo. Rio de Janeiro, RJ, Brasil.

* **Address of Correspondence:**
LAVAMPI, PPC, UERJ
Avenida Marechal Rondon, 381
Rio de Janeiro, RJ
CEP: 20950-003, Brasil.
E-mail: ltnmamae@gmail.com
ORCID: https://orcid.org/0000-0002-6038-4419

BJHBS, Rio de Janeiro, 2021;20(2):161-166
DOI: 10.12957/bjhbs.2021.63969
Received on 11/09/2020. Approved on 05/28/2021.

Introduction

An important function of vitamin D is the maintenance of the balance of calcium and phosphorus metabolism in the human body.[1] There are two main forms of vitamin D: vitamin D3 (or cholecalciferol) that forms on the skin through sun exposure or ultraviolet light, and vitamin D2 (or ergocalciferol) obtained by irradiating plants or vegetable food.[1] They may be obtained through sun exposure, food intake or supplementation.[2] The first observation that uses the natural vitamin D originates from the 19th century in which rickets patients were successfully treated and cured with fish oil rich in vitamin D. In 1890 there was the first demonstration that exposure to sunlight could be effective in the treatment of rickets. But it was only in 1922 the first time that these anti-rickety properties derived from fish oil were linked with a fat-soluble factor first identified as vitamin D, and from then more studies involving this newly discovered hormone emerged.[3] To be biologically activated and have effects on metabolism and physiological functions, such as inhibiting the growth of cancer cells and protecting against certain immune mediated disorders, vitamin D must be converted into its active form.[4]

The sun emanates electromagnetic radiations that can be classified according to their frequencies and wavelengths, and some of them are infrared rays, visible light and ultraviolet radiation (UVR). UVR is found in the electromagnetic spectrum between wavelengths of 100 nm and 400 nm and is subdivided into ultraviolet A (UVA), ultraviolet B (UVB) and ultraviolet C (UVC)[5] Exposure to UVR has physiological and physical benefits, as the participation in synthesis of active vitamin D. The UVB is responsible for the formation of pre-cholecalciferol (pre-vitamin D3) which will later be isomerized in cholecalciferol (vitamin D3).[6]

Both vitamin D2 and vitamin D3 circulate in the bloodstream to bind with a specific protein, the vitamin D binding protein (DBP). To become active, vitamin D is transformed twice; first a hydroxylation occurs forming 25-hydroxyvitamin D (25(OH)D) in the liver, this hepatic hydroxylation is not tightly regulated, so if the production of vitamin D is high, either by ingestion or exposure to the sun, the liver will produce more 25(OH)D, this pre-hormone will also bind to BPD with a half-life of 3 weeks. This pre-hormone can be hydroxylated in the kidney within the cells of the proximal tubule to form 1,25-dihydroxyvitamin D (1,25(OH)2D3), also known as calcitriol, which is the active metabolite of vitamin D; this hydroxylation is strongly regulated and is stimulated mainly by parathyroid hormone (PTH), low serum calcium and phosphate concentrations, and inhibited by fibroblast growth factor 23 and calcitriol itself. When released into the bloodstream, calcitriol is also able to bind to DBP, however with a lower affinity that 25(OH)D, being able to bind to various tissues that have the vitamin D receptor (VDR), which can activate or inhibit the transcription of several genes.[7]

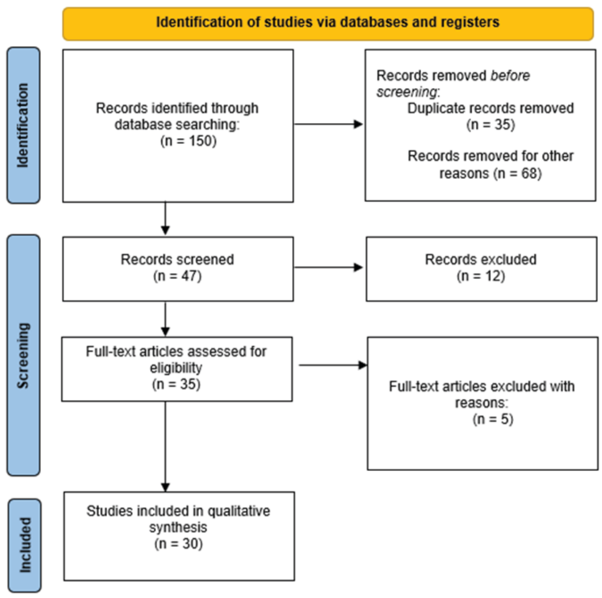
Several tissues have VDR and the mechanism capable of activating and deactivating vitamin D, even though they are not involved with bone and/or calcium and phosphate metabolism. 25(OH)D enters these tissues and it is transformed locally into calcitriol, which will bind to the cell's VDR generating several genomic effects (not "calcemic"), thus not participating in the metabolism of calcium and phosphate. This pathway does not appear to be regulated by PTH or by the fibroblast growth factor 23, but by the extracellular concentration of 25(OH)D shrouded these tissues. Thus, one can understand the non-classic effects of vitamin D, which are considered "intracranial", when compared to the classic effects which are endocrine. The non-classic effects, most common in the body, are related to the muscles; cardiovascular system; kidneys; immune system; some types of cancer; diabetes; and pregnancy.[8]

Cancer is a health problem that affects developed and underdeveloped countries, including the main causes of morbidity and mortality worldwide, with 18.1 million new cases and 9.6 million deaths in 2018, causing damage to patients, families, community and the health system. Knowing that one of the non-classic effects of vitamin D is related to some types of cancer and that this disease is the second leading cause of global death,[9] the current study aimed to conduct a narrative review to verify effects of vitamin D on types of cancer.

Methodology

For this narrative review, the bibliographic research was carried out on Pubmed, Scopus and PEDro on June 16, 2020. The keywords selected for the searches were "vitamin D", "cancer" and "non-classic". Only articles published since the year 2000 were used. The PRISMA[10] was used to guide the development and organization through a diagram flow (Figure 1).

Figure 1. Flow diagram according the findings in the databases



Inclusion criteria

In this narrative review were included nineteen Pubmed articles, twelve Scopus articles and no PEDro articles. The inclusion criteria randomized studies from the year 2000.

Exclusion criteria

Non-randomized and non-meta-analysis studies, articles published prior to 2000, animal clinical trials, studies with vitamin D concomitant with another substance, studies with vitamin D and classical effects and studies with vitamin D and other non-classical effects were excluded.

Results and discussion

A total of thirty articles were analyzed, of which seven related vitamin D with colon/rectum cancer, three with breast cancer, three articles with prostate cancer, three with lung cancer, two with cancer in the ovaries, one related to melanoma and other types of skin cancer, three related to gastric cancer and eight with anticarcinogenic properties of vitamin D.

The relationship between vitamin D and cancer risk

Colorectal Cancer

Four meta-analyzes published in 2011 that demonstrated the inverse association between vitamin D levels and the risk of getting colorectal cancer, in other words a high level of 25(OH)D would be associated with low risk of developing this type of cancer.[11-13] Another study corroborated this information and also found that increased serum levels of vitamin D plays a key role in decreasing the risk of colorectal adenoma.[14] High levels of circulating vitamin D also decreased the methylation of SFRP2 (a not-invasive biomarker for diagnosis of colorectal cancer) in the tumor area and these results suggests that vitamin D has an epigenetic effect on DNA methylation, contributing to a positive response as a neoadjuvant treatment.[15]

A randomized clinical trial also demonstrated that high doses of vitamin D were able to slow the growth rate of colorectal cancer in patients with chemotherapy started.[16] Messaritakis et al.[17] conducted a study that was able to demonstrate that therapies which activate the vitamin D receptor, including the modulation of this pathway, may be a new approach for the treatment of colorectal cancer, according to the thought that vitamin D would be beneficial in the treatment of this type of disease.

Breast Cancer

The investigation involving breast cancer and vitamin D are much less consistent than those related to colorectal cancer, however a work by Shao et al.[18] concluded that a high concentration of circulating 25(OH)D is associated with a low risk of developing this type of cancer. Bauer et al.[19] also conducted a dose-response meta-analysis and found a non-linear inverse association, only in a more restricted group composed by women in the post-menopausal period.

Zhou et al.[20] did not identify in their meta-analysis any protective effect of vitamin D supplementation in reducing the risk of breast cancer, and this may be related to several factors such as an inadequate dosage when compared to the control group, short-term follow-up, patient selection and even unknown factors. This study suggests the complexity surrounding the relationship between vitamin D and breast cancer risk, and this may differ with menopausal status and possibly between races as well.

Prostate Cancer

Studies concluded that men with elevated serum levels of 25(OH)D had a higher risk of developing prostate cancer, compared to men with low levels of the vitamin.[21] Nair-Shalliker et al.[22] suggested that the elevated level of 1,25(OH)2D on plasma after prostate cancer diagnosis and treatment could decrease all specific causes of mortality from this disease, especially in men with aggressive prostate cancer, and also suggested that circulating vitamin D levels post-diagnosis can be used as a prognosis for survival from aggressive prostate cancer.

Torkko et al.[23] did not find a clear or consistent association with the vitamin D pathway and its interactions with 25(OH)D present in the blood, in relation to the risk of prostate cancer. However, they identified that patients with low amounts of 25(OH)D in the serum have a greater chance of developing prostate cancer with a risk of being fatal.

Lung Cancer

Two researches with slightly different criteria have been published reporting the relationship between vitamin D levels and the risk of lung cancer. Zhang et al.[24] included only prospective studies and observed a statistically lower risk of lung cancer, comparing high and low categories of circulating vitamin D. Chen et al.[25] also concluded that there was a 5% reduction in the risk of lung cancer with administration of 10 nmol/L of 25(OH)D.

Kong et al.[26] evaluated the relationship between the single nucleotide polymorphism related to the vitamin D pathway and the prognosis of non-small cell lung cancer (NSCLC). It was noted that some of the genetic polymorphisms related to the vitamin D pathway can influence the prognosis of lung cancer and may be linked to tumor progression, which may indicate vitamin D as a potential therapeutic possibility.

Ovarian Cancer

Despite not having significant statistical relevance, some prospective studies of circulating vitamin D and ovarian cancer suggested a reduced risk of developing the disease associated with a high level of 25(OH)D.[27] Circulating vitamin D levels are significantly lower in patients with ovarian cancer, so vitamin D deficiency is closely related to the pathogenesis of ovarian cancer. Vitamin D treatment reduces the migration and proliferation of ovarian cancer cells and its use should be considered as a potential new therapy for ovarian cancer.[28]

Melanoma and other types of skin cancer

There is a high complexity involving vitamin D and skin cancer, considering that exposure to ultraviolet radiation is both a source of vitamin D and a risk factor for this type of cancer. No association was found between skin cancer and increased vitamin D through food or supplementation, not confirming that a high in vitamin D is associated with cutaneous melanoma. Although vitamin D inhibits the development and spread of the tumor in the early stages of the disease, it is still unclear whether it has an effect in later stages and whether it can increase the survival of patients with melanoma.[29]

Stomach Cancer

Vitamin D is related to the risk of gastric cancer[30] and metabolites or analogues of vitamin D can suppress *Helicobacter pylori*[31] infection and H. pylori-related gastric cancer. The protective role of vitamin D has been identified against this type of human cancer through several studies[30] and has shown that vitamin D suppresses proliferation and stimulates cell cycle arrest in gastric cancer cells.[32]

Anticarcinogenic properties of vitamin D

It is suggested that vitamin D can regulate the process of tumor formation, from the beginning to interactions with the cell.[33] This mechanism includes the cell regulation, such as proliferation, differentiation, apoptosis, autophagy and even the interaction of the cell with the environment in which it is inserted (angiogenesis, inflammation, among others).

The process of tumoral formation is capable of changing irreversible genetic mutations in cells, leading to several transformations mainly related to cell function, and vitamin D in turn participates in key points in the prevention of this whole process, playing an important role of antioxidant, anti-inflammatory defense and without DNA repair process. One of the greatest contributors to the onset of tumor formation is inflammation and works suggest that vitamin D can exert at least four different anti-inflammatory mechanisms:[34] Vitamin D in its active form, that is calcitriol, can inhibit the prostaglandin (PG) pathway, which in turn is involved in the process of repairing tissue damage and infection. Calcitriol inhibits the pathway by inhibiting the expression of cyclooxygenase-2 (COX-2) and PG receptors, and is also involved in the degradation of prostaglandin itself.[35] Vitamin D can also suppress the MAPK p38-mediated proinflammatory signaling pathway by inducing MAPK phosphatase-5 expression, which prevents MAPK p38 phosphorylation and activation, inhibiting the production of proinflammatory cytokines such as interleukin-6 (IL-6).[36] Calcitriol can also inhibit the nuclear factor kappa B (NFkB) signaling pathway that performs functions as a transcription factor. It suppresses protein kinase B (AKT) phosphorylation and its target in macrophages, by the positive regulation of member 4 of the superfamily thioesterase (THEM4), an AKT modulator. This leads to inhibition of NFkB and COX-2 expression.[37] Vitamin D is also able to regulate the interaction between immune cells and tumor cells to suppress the production of pro-inflammatory cytokines.[38]

In addition to inflammation, reactive oxygen species (ROS) are important points in various stages of tumor formation, which can promote DNA mutation, cell proliferation and death, all of which provoke pro-inflammatory responses. So, maintaining a good antioxidant defense system is a critical point in preventing the development of tumors. Studies suggest that vitamin D is able to protect the cell against oxidation induced by DNA damage by promoting antioxidant defenses.[39,40]

The vitamin D-mediated protection from DNA damage that is induced by ROS can be attributed to the process of inducing the expression of several enzymes involved in the body's antioxidant barrier, such as SOD1, SOD2, GSH, NRF2, among others. In addition to the increase in antioxidant capacity, vitamin D is also able to directly regulate the DNA repair process,[40] increasing the expression of genes involved in this process.

The current narrative review has some limitations and therefore its results should be interpreted with caution. Only cohort studies that were published from the year 2000 on were included, the searches were performed only in three databases and in the English language.

The strength of this work is related to the presentation of a relationship between vitamin D and the presence of cancer in various organs.

Conclusion

Vitamin D insufficiency is frequently shown to be related to the incidence of cancer in the human body. It is possible to observe the existence of peculiarities regarding the difference in levels of concentration of vitamin D in each organ. Even with conflicting results, in general, vitamin D has shown promise in the prevention of several types of cancer.

Conflict of interest

The authors have no potential conflicts of interest in publication of this study.

Acknowledgments

The authors would like to recognize and thank the *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (*CNPq*), *Fundação Carlos Chagas filho de Amparo à Pesquisa do Estado do Rio de Janeiro* (*FAPERJ*) and *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (*CAPES*), for the support.

References

1. Chang SW, Lee HC. Vitamin D and health - The missing vitamin in humans. Pediatr. Neonatol. 2019;60(3):237-244. doi:10/1016/j.pedneo.2019.04.007.
2. Schalka S, Reis VMS. Sun protection factor: meaning and controversies. An Bras Dermatol. 2011;86(3):507-515. doi:10.1590/s0365059620110003000013.
3. Ureña-Torres P, Souberbielle JC. Pharmacologic role of vitamin D natural products. Curr Vasc Pharmacol. 2014;12(2):278-285.
4. Prosser DE, Jones G. Enzymes involved in the activation and inactivation of vitamin D. Trends Biochem Sci. 2004;29(12):664-673. doi:10.1016/j.tibs.2004.10.005.
5. Sliney DH. Radiometric quantities and units used in photobiology and photochemistry: recommendations of the commission internationale de l'Eclairage. Photochem Photobiol. 2007;83(2):425-432. doi:10.1562/2006-11-14-ra-1081.
6. Castro LCG. The Vitamin D endocrine system. Arq Bras Endocrinol Metab. 2011;55(8):566-575. doi:10.1590/s0004-27302011000800010.
7. Schlingmann KP, Kaufmann M, Weber S, et al. Mutations in CYP24A1 and idiopathic infantile hypercalcemia. N Engl J Med. 2011;365(5):410-421. doi:10.1056/nejmoa1103864.
8. Dusso A, Lopez-Hilker S, Rapp N, et al. Extra-renal production of calcitriol in chronic renal failure. Kidney Int. 1988;34(3):368-375. doi:10.1038/ki.1988.190.
9. World Health Organization. 2018. WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents. World Health Organization. https://apps.who.int/iris/handle/10665/279700. License: CC BY-NC-SA 3.0 IGO. Access in: 16/06/2020.
10. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372(71). doi:10.1136/bmj.n71.
11. Gandini S, Boniol M, Haukka J, et al. Meta-analysis of observational studies of sérum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma. Int J Cancer. 2011;128(6):1414-1424. doi:10.1002/ijc.25439.
12. Lee JE, Li H, Chan AT, et al. Circulating levels of vitamin D and colon and rectal cancer: the Physicians' Health Study and a meta-analysis of prospective studies. Cancer Prev Res. 2011;4(5):735-743. doi:10.1158/1940-6207.CAPR-10-0289.
13. Touvier M, Chan DS, Lau R, et al. Meta-analyses of vitamin D intake, 25-hydroxyvitamin D status, vitamin D receptor polymorphisms, and colorectal cancer risk. Cancer Epidem Biomar Prev. 2011;20(5):1003-1016. doi:10.1158/1055-9965.EPI-10-1141.
14. Uitterlinden AG, Fang Y, Van-Meurs JB, et al. Genetics and biology of vitaminD receptor polymorphisms. Gene. 2004;338(2):143-156. doi:10.1016/j.gene.2004.05.014.
15. Boughanem H, Cabrera-Mulero A, Hernández-Alonso P, et al. Association between variation of circulating 25-OH vitamin D and methylation of secreted frizzled-related protein 2 in colorectal cancer. Clin Epigenetics. 2020;12(1):83-94. doi:10.1186/s13148-020-00875-9.
16. Kimmie NG, Nimeiri HS, McCleary NJ, et al. Effect of high-dose vs standard-dose vitamin D_3 supplementation on progression-free survival among patients with advanced or metastatic colorectal cancer: the sunshine randomized clinical trial. JAMA. 2019;321(14):1370-1379. doi:10.1001/jama.2019.2402.
17. Messaritakis I, Koulouridi A, Sfakianaki M, et al. The Role of Vitamin D Receptor Gene Polymorphisms in Colorectal Cancer Risk. Cancers. 2020;12(6):1379-1395. doi:10.3390/cancers12061379.
18. Shao T, Klein P, Grossbard ML. Vitamin D and breast câncer. Oncologist. 2012;17(1):36-45. doi:10.1634/theoncologist.2011-0278.
19. Bauer SR, Hankinson SE, Bertone-Johnson ER, et al. Plasma vitamin D levels, menopause, and risk of breast câncer: dose-response meta-analysis of prospective studies. Medicine. 2013;92(3):123-131. doi:10.1097/MD.0b013e3182943bc2.
20. Zhou L, Chen B, Sheng L, et al. The effect of vitamin D supplementation on the risk of breast cancer: a trial sequential meta-analysis. Breast Cancer Res Treat. 2020;182(1):1-8. doi:10.1007/s10549-020-05669-4.
21. Xu Y, Shao X, Yao Y, et al. Positive association between circulating 25-hydroxyvitamin D levels and prostate cancer risk: new findings from and updated meta-analysis. J Cancer Res Clin Oncol. 2014;140(9):1465-1477. doi:10.1007/s00432-014-1706-3.
22. Nair-Shalliker V, Bang A, Egger S, et al. Post-treatment levels of plasma 25- and 1,25-dihydroxy vitamin D and mortality in men with aggressive prostate cancer. Sci Rep. 2020;10(1):7736-7747. doi:10.1038/s41598-020-62182-w.
23. Torkko K, Till C, Tangen CM, et al. Vitamin D Pathway and Other Related Polymorphisms and Risk of Prostate Cancer: Results from the Prostate Cancer Prevention Trial. Cancer Prev

Res. 2020;13(6):521-530. doi:10.1158/1940-6207.capr-19-0413.
24. Zhang L, Wang S, Che X, et al. Vitamin D and lung cancer risk: a comprehensive review and meta-analysis. Cell Physiol Biochem. 2015;36(1):299-305. doi:10.1159/000374072.
25. Chen GC, Zhang ZL, Wan Z, et al. Circulating 25-hydroxyvitamin D and risk of lung cancer: a dose-response meta-analysis. Cancer Causes Control. 2015;26(12):1719-1728. doi:10.1007/s10552-015-0665-6.
26. Kong J, Chen X, Wang J, et al. Genetic Polymorphisms in the Vitamin D Pathway and Non-small Cell Lung Cancer Survival. Path Oncol Res. 2020;26(3):1709-1715. doi:10.1007/s12253-019-00702-4.
27. Yin L, Grandi N, Raum E, et al. Meta-analysis: circulating vitamin D and ovarian cancer risk. Gynecol Oncol. 2011;121(2):369-375. doi:10.1016/j.ygyno.2011.01.023.
28. Ji J, Cheng X, Wang W, et al. Vitamin D regulates cell viability, migration and proliferation by suppressing galectin-3 (Gal-3) gene in ovarian cancer cells. J Biosci. 2020;45(1):69-79. doi:10.1007/s12038-020-00038-1.
29. Caini S, Boniol M, Tosti G, et al. Vitamin D and melanoma and non-melanoma skin cancer and prognosis: A comprehensive review and meta-analysis. Eur J Cancer. 2014;50(15):2649-2658. doi:10.1016/j.ejca.2014.06.024.
30. Du C, Yang S, Zhao X, et al. Pathogenic roles of alterations in vitamin D and vitamin D receptor in gastric tumorigenesis. Oncotarget. 2017;8(17),29474-29486. doi:10.18632/oncotarget.15298.
31. Nasri H, Baradaran A. The influence of serum 25-hydroxy vitamin D levels on Helicobacter Pylori infections in patients with end-stage renal failure on regular hemodialysis. Saudi J of Kidney Dis and Transpl. 2007;18(2):215-219.
32. Li M, Li I, Zhang L, et al. 1,25-Dihydroxyvitamin D3 suppresses gastric cancer cell growth through VDR and mutant p53-mediated induction of p21. Life Sci. 2017;179:88-97. doi:10.1016/j.lfs.2017.04.021.
33. Jeon S, Shin E. Exploring vitamin D metabolism and function in cancer. Exp Mol Med. 2018;50(4):20-34. doi:10.1038/s12276-018-0038-9.
34. Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. Nature. 2008;454(7203):436-444. doi:10.1038/nature07205.
35. Krishnan AV, Feldman D. Molecular pathways mediating the anti-inflammatory effects of calcitriol: implications for prostate cancer chemo-prevention and treatment. Endocr Relat Cancer. 2010;17(1):R19-R38. doi:10.1677/ERC-09-0139.
36. Nonn L, Peng L, Feldman D, et al. Inhibition of p38 by vitamin D reduces interleukin-6 production in normal prostate cells via mitogen-activated protein kinase phosphatase 5: implications for prostate cancer prevention by vitamin D. Cancer Res. 2006;66(8):4516-4524. doi:10.1158/0008-5472.CAN-05-3796.
37. Wang Q, He Y, Shen Y et al. Vitamin D inhibits COX-2 expression and inflammatory response by targeting thioesterase superfamily member 4. The J Biol Chem. 2014;289(17):11681-11694. doi:10.1074/jbc.M113.517581.
38. Bessler H, Djaldetti M. 1alpha,25-Dihydroxyvitamin D3 modulates the interaction between immune and colon cancer cells. Biomed Pharmacother. 2012;66(6):428-432. doi:10.1016/j.biopha.2012.06.005.
39. Uberti F, Morsanuto V, Molinari C. Vitamin D in oxidative stress and diseases. A critical evaluation of vitamin D - basic overview. InTech Rijeka. 2017;2:47-73. doi:10.5772/64506.
40. Nair-Shalliker V, Armstrong BK, Fenech M. Does vitamin D protect against DNA damage? Mutat Res. 2012;733(1-2):50-57. doi:10.1016/j.mrfmmm.2012.02.005.