Balkan Med J 2025;42:276-8

Harnessing the Power of Vitexin as a Vitamin D Receptor Agonist in Colorectal Cancer: A New Frontier

Manahil Mubeen[1], Hafsa Ali[2], Syeda Sabika Zehra[1], Aman Khan[1]

[1]Department of Cardiology, Dow Medical College, Dow University of Health Sciences, Karachi, Pakistan
[2]Department of Medicine, Jinnah Sindh Medical University, Karachi, Pakistan

Colorectal cancer (CRC) presents an enormous burden on cancer-related deaths and ranks third in cancer-associated mortality in both men and women worldwide.[1] CRC develops when stem cells at the base of the colon's crypts experience genetic and epigenetic alterations. Normal stem cells become cancerous because of these changes, which disrupts the delicate balance between oncogenes and tumor suppressor genes.[1] Surgery, chemotherapy, radiation, immunotherapy, and targeted therapy are the routine therapies for CRC. Nonetheless, depending on the CRC subtype, the prognosis following chemotherapy varies considerably.[2] More than 20% of incidences of CRC linked to long-term inflammation are often observed in patients with inflammatory bowel disease (IBD). This type of CRC, called colitis-associated colorectal cancer (CAC), is common in patients with IBD.[3]

A remarkable relationship exists between vitamin D receptor (VDR) and the pathogenicity of CRC and colitis. In the advanced stages of cancer, its activity becomes impaired. Patients with IBD and CRC often exhibit vitamin D or VDR deficiency, and premature suppression of VDR is common in patients with colitis. CAC attributed to VDR deficiency results in more aggressive as well as increased tumors.[3]

VDR is an intracellular ligand-dependent transcriptional factor expressed in over 30 cell types, which indicates its versatility.[4] This receptor functions by binding to vitamin D, an essential cholesterol-derived secosteroid that can come from dietary sources or be synthesized in the skin upon activation by sunlight.[5] VDR's activity is crucial in regulating interactions between immune and cancer cells, particularly by limiting the production of harmful, proinflammatory cytokines.[6] This regulation is important in the development of diseases such as CRC, where inflammation plays a key role. Low levels of plasma vitamin D are associated with CRC, whereas elevated levels decrease the risk of developing it. In CRC, abnormal adipose tissue secretes cytokines that fuel inflammation. Interestingly, adipose tissue itself acts as a storage site for vitamin D, and calcitriol, its activated form, can alter adipocyte physiology and suppress the release of inflammation-inducing cytokines. Therefore, when vitamin D levels are low, a prolonged inflammatory environment is created, potentially paving the way for the development of CRC.[5] This link emphasizes the importance of further examining VDR agonists, given their role in managing inflammation-related malignancies. A recent study reported that vitexin, a plant derivative, can protect VDR during inflammation and tumor growth. The use of vitexin is a potential therapeutic strategy to prevent the transformation of chronic intestinal inflammation into CRC by influencing macrophage behavior in the tumor microenvironment,[3] drawing attention toward its role in CRC via the VDR pathway.

Vitexin is a glycosylated flavone that exerts antiviral, antibacterial, analgesic, antiinflammatory, and antitumor effects and is present in multiple medicinal herbs. Vitexin has been established to suppress tumor growth in various malignancies, including endometrial, breast, ovarian, gastric, non-small cell lung, liver, and colon cancer and nasopharyngeal carcinoma by enhancing apoptosis and inhibiting tumor cell proliferation.[2,3] Studies have shown that vitexin can avert the development of CAC by reducing NFKB1 activity and COX-2 expression by adjusting macrophage polarization.[2] By targeting multiple signaling pathways, including PI3K-Akt, interleukin 17, tumor necrosis factor, and nuclear factor kappa B, via key proteins such as NFKB1, COX-2, MAPK1, MAPK3, and TP53, vitexin suppresses the cell cycle and promotes apoptosis in human colon cancer (HCT-116) cells.[2,7]

Research has confirmed vitexin's novel function as a VDR agonist, targeting VDR to induce its activity. This substance binds to amino acid motifs in the VDR-LBD region to promote the nuclear translocation of VDR, advancing its transcriptional activity onto genes such as *CYP24A1*. Immunofluorescence experiments using biotin-labeled vitexin probes have confirmed the colocalization of vitexin and VDR in THP-1 cells, which signifies their direct interaction. In addition, surface plasmon resonance (SPR) revealed binding affinity (KD=34.67 μM), and molecular docking identified that critical residues in VDR-LBD, particularly THR287, were imperative for this interaction.[3] Furthermore, vitexin has been shown to stabilize VDR

Corresponding author: Manahil Mubeen, Department of Cardiology, Dow Medical College, Dow University of Health Sciences, Karachi, Pakistan
e-mail: manahilmubeen4751@gmail.com

Received: October 30, 2024 **Accepted:** December 05, 2024 **Available Online Date:** May 05, 2025 • **DOI:** 10.4274/balkanmedj.galenos.2024.2024-10-105
Available at www.balkanmedicaljournal.org

ORCID iDs of the authors: M.M. 0009-0002-6211-9114; H.A. 0009-0006-7894-8397; S.S.Z. 0009-0007-0329-3223; A.K. 0009-0008-0513-2463.

Cite this article as: Mubeen M, Ali H, Zehra SS, Khan A. Harnessing the Power of Vitexin as a Vitamin D Receptor Agonist in Colorectal Cancer: A New Frontier. Balkan Med J.; 2025; 42(3):276-8.

by tightening its structural domain, which is crucial for maintaining its functional integrity during cellular signaling processes. Vitexin uses the VDR-PBLD pathway to regulate macrophage polarization by blocking their differentiation to the M2 phenotype (associated with tumor promotion). In contrast, vitexin stimulates the M1 phenotype proliferation, enhancing its antitumor properties and inhibiting the transition of chronic intestinal inflammation to CRC. Moreover, vitexin reduces tumor enlargement via the VDR pathway, improving the tissue form (Figure 1).[3]

Vitexin's anticancer role in CAC has been researched previously, and its function as a VDR agonist provides novel insights and has been experimentally validated by preclinical findings. Cellular thermal shift assay and drug affinity responsive target stability have confirmed the direct binding of vitexin to the VDR-LBD domain by demonstrating receptor stabilization upon interaction in mouse models. Furthermore, SPR has been used to quantify this interaction, and isothermal titration calorimetry has broadened our understanding of the thermodynamic properties of the binding,[3] forming the basis for further investigations.

Vitexin's potential as a VDR agonist provides a robust platform for its use in treating several other diseases involving the VDR pathway, specifically autoimmune diseases such as Bechet's disease, type 1 diabetes mellitus, and rheumatoid arthritis. This conclusion is drawn because VDR is present in virtually all immune cells. As mentioned above, vitamin D is responsible for the transcriptional repression of proinflammatory cytokines, with a role in the innate and adaptive immune response.[8] In addition, among the bone-related pathologies, age-dependent osteoporosis presented VDR as a vital player in its prevention and treatment, acting protectively.[9]

The effectiveness of other VDR agonists can be compared with that of vitexin. For instance, $1,25(OH)_2D_3$ is a natural VDR agonist with antiproliferative effects on cancer cells. However, its therapeutic use is limited by the risk of hypercalcemia, which can lead to tissue calcification. Synthetic analogs, such as calcipotriol (used for psoriasis), and anticancer agents, such as PRI-1907, PRI-1917, PRI-5201, and PRI-5202, have been developed to mitigate these side effects. Despite their efficacy, most of these analogs are susceptible to transformation by CYP24A1. The binding of these analogs to the LBD domain of VDR has also not yet been explored, and docking experiments are necessary to confirm their interaction with VDR.[10,11] On the contrary, vitexin stands out owing to its natural origin, metabolic stability, and direct, experimentally validated interaction with the VDR-LBD domain.[3]

Nevertheless, challenges exist in its applicability. Vitexin is administered orally in the form of capsules, pills, tablets, or powdered form in doses that depend on the condition being treated, the formulation being used, patient factors, and the plant from which it is derived.[12] For example, in CRC models, vitexin has been used in a time- and dose-dependent manner in combination with aspirin.[2] Despite being taken orally, the absorption is poor because of its limited solubility. Vitexin is primarily absorbed in the small intestine, where it rapidly disperses into tissues such as the liver. There, it undergoes glycosylation, becoming more water soluble and excretable in the urine.[12] To overcome the insolubility and low bioavailability of vitexin, β-cyclodextrin-vitexin (β-CD-vitexin) microspheres have been developed, providing a promising avenue to enhance its pharmacokinetics.[13]

Adverse effects of vitexin include gastrointestinal disturbances such as nausea, vomiting, and abdominal cramps. Furthermore, it alters

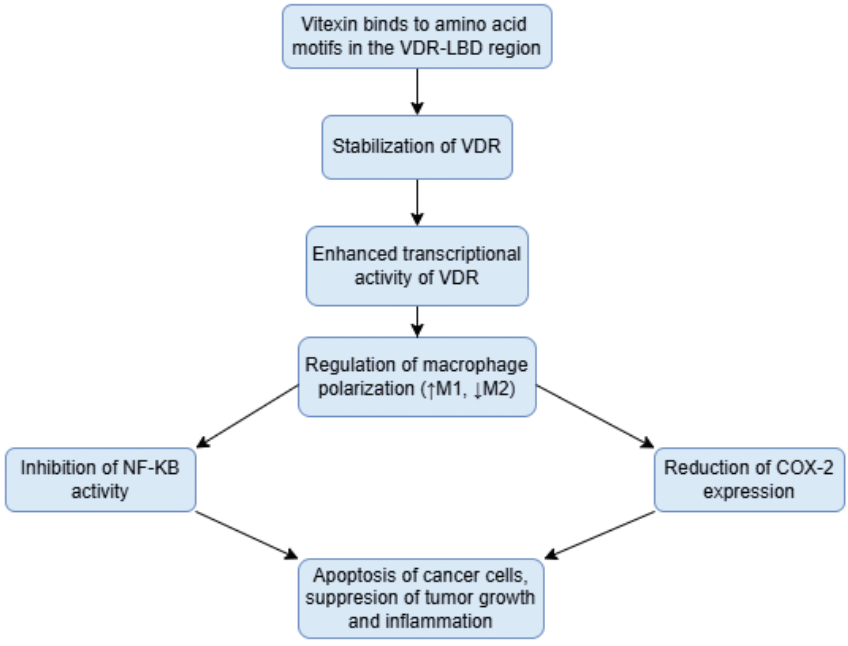

FIG. 1. Interaction of vitexin with the VDR pathway.
VDR, vitamin D receptor.

the level of estrogen in the bloodstream and might cause allergic reactions ranging from mild itching to severe anaphylaxis. Vitexin alters the levels of many drugs by interacting with liver enzymes, making some of them less effective while simultaneously increasing the toxic effects of others. Moreover, vitexin should be avoided in pregnant and breastfeeding women as limited data are available on teratogenicity or safety during pregnancy.[14] Therefore, despite its benefits, these pharmacokinetic and safety concerns highlight the need for careful dosing and monitoring in therapeutic applications.

Succinctly, this article has discussed the interaction of plant-derived vitexin with VDR, an intriguing discovery that underscores its role in preventing chronic IBD and its progression to CRC. Vitexin's mechanisms of action and therapeutic applications in CRC must be comprehended to develop effective therapeutic approaches that enhance the patient's quality of life and survival rates. Beyond CRC, it has potential in other VDR-regulated diseases. Therefore, further research on vitexin's potential as a VDR agonist is crucial to optimizing its therapeutic application, which could be beneficial in multiple pathologies by targeting inflammation and cancer cell proliferation pathways.

Authorship Contributions: Concept- M.M.; Design- M.M., H.A.; Supervision- M.M.; Data Collection or Processing- S.S.Z.; Literature Search- H.A., S.S.Z., A.K.; Writing- M.M., H.A., S.S.Z., A.K.; Critical Review- M.M.

Conflict of Interest: No conflict of interest was declared by the authors.

REFERENCES

1. Constantinou V, Constantinou C. Focusing on colorectal cancer in young adults (Review). *Mol Clin Oncol.* 2023;20:8. [CrossRef]
2. Chen D, Chen Y, Huang F, Zhang X, Zhou Y, Xu L. The underlying regulatory mechanisms of colorectal carcinoma by combining Vitexin and Aspirin: based on systems biology, molecular docking, molecular dynamics simulation, and in vitro study. *Front Endocrinol.* 2023;14:1147132. [CrossRef]
3. Chen Y, Liang J, Chen S, et al. Discovery of vitexin as a novel VDR agonist that mitigates the transition from chronic intestinal inflammation to colorectal cancer. *Mol Cancer.* 2024;23:196. [CrossRef]
4. Latic N, Erben RG. Vitamin D and cardiovascular disease, with emphasis on hypertension, atherosclerosis, and heart failure. *Int J Mol Sci.* 2020;21:6483. [CrossRef]
5. Castellano-Castillo D, Morcillo S, Clemente-Postigo M, et al. Adipose tissue inflammation and VDR expression and methylation in colorectal cancer. *Clin Epigenetics.* 2018;10:60. [CrossRef]
6. Knackstedt R. The importance of vitamin D, the vitamin D receptor (VDR) and retinoid X receptor alpha (RXRα) in murine colitis development and progression. Dissertation/ Thesis. 2013. [CrossRef]
7. Kuruvalli G, Lavanya L, Pulakuntla S, et al. Vitex negundo L. leaf extract suppresses the cell cycle and promotes apoptosis in colon cancer cells. *Indian J Biochem Biophys.* 2024;61:269-78. [CrossRef]
8. Agliardi C, Guerini FR, Bolognesi E, Zanzottera M, Clerici M. VDR gene single nucleotide polymorphisms and autoimmunity: a narrative review. *Biology (Basel).* 2023;12:916. [CrossRef]
9. Xu P, Lin B, Deng X, Huang K, Zhang Y, Wang N. VDR activation attenuates osteoblastic ferroptosis and senescence by stimulating the Nrf2/GPX4 pathway in age-related osteoporosis. *Free Radic Biol Med.* 2022;193:720-735. [CrossRef]
10. Powała A, Żołek T, Brown G, Kutner A. Structure and the anticancer activity of vitamin D receptor agonists. *Int J Mol Sci.* 2024;25:6624. [CrossRef]
11. Milczarek M, Chodyński M, Pietraszek A, et al. Synthesis, CYP24A1-dependent metabolism and antiproliferative potential against colorectal cancer cells of 1,25-dihydroxyvitamin D2 derivatives modified at the side chain and the A-ring. *Int J Mol Sci.* 2020;21:642. [CrossRef]
12. Ranjan R, Kishore K, Ranjan R, et al. Nutraceutical potential of vitexin: a flavone glycoside. *J Phytopharmacol.* 2023;12:44-50. [CrossRef]
13. Ding C, Li S, Wang D, et al. Preparation of β-CD-Vitexin microspheres and their effects on SW480 cell proliferation. *Curr Drug Deliv.* 2023;20:433-440. [CrossRef]
14. What are the side effects of vitexin? Synapse by patsnap. (July 12, 2024). Accessed November 24, 2024. [CrossRef]