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Review Article

Wnt/β-catenin signaling pathway is essential for the protective effect of Fat-soluble Vitamins (A, D, E, and K) on colorectal cancer

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Abstract

An essential regulatory pathway involved in many biological processes, such as embryonic development, tissue homeostasis, and cancer progression, is the Wnt/β-catenin signaling pathway. One of the main characteristics of Colorectal Cancer (CRC) is the dysregulation of the Wnt/β-catenin signaling pathway, which plays a significant role in tumor development, invasion, and metastasis. Adenomatous polyposis coli (APC) gene mutations account for 80–90% of sporadic cases of CRC. Typically, APC mutations occur early in the development of CRC. APC normally suppresses tumors by encouraging β-catenin degradation. Fat-soluble vitamins, such as A, D, E, and K, are essential for many physiological functions. They may also interact with signaling pathways like the Wnt/β-catenin pathway. The involvement of the Wnt/β-catenin signaling pathway in the protective effect of Fat-soluble vitamins against CRC is the main topic of this review. Moreover, a comprehensive understanding of the underlying molecular mechanisms of fat-soluble vitamins-mediated Wnt/β-catenin signaling pathway regulation is required to target therapeutic targets for CRC prevention and treatment effectively.

Keywords: Wnt/β-catenin signaling; fat soluble vitamins; colorectal cancer

Introduction

The Wnt/β-catenin signaling pathway is a crucial regulatory pathway involved in numerous biological processes, including embryonic development, tissue homeostasis, and disease [1]. Glycoproteins released into the bloodstream called wnt proteins attach to cell surface receptors to start a signaling cascade [2]. Axin, APC, glycogen synthase kinase 3β (GSK-3β), and casein kinase 1α (CK1α) comprise a destruction complex that phosphorylates β-catenin and targets it for proteasomal degradation in the absence of Wnt ligands [3-5].

Wnt ligands bind to a variety of receptors, including co-receptors like low-density lipoprotein receptor-related proteins (LRP5/6) and Frizzled (FZD) receptors [6,7]. When Wnt ligands attach to their receptors, a signaling cascade stabilizes and builds up β-catenin in the cytoplasm [8,9]. Moreover, β-catenin is stabilized when the Wnt pathway is active because its phosphorylation and subsequent degradation are inhibited [10,11]. Stabilized β-catenin moves into the nucleus after accumulating in the cytoplasm [12,13]. Consequently, β-catenin interacts with T-cell factor/lymphoid enhancer factor (TCF/LEF) transcription factors to activate the transcription of Wnt target genes in the nucleus [14,15]. These target genes often play key roles in cell proliferation, survival, and differentiation such as c-Myc, Cyclin D1, and Axin2 [16].

Most interestingly, The Wnt/β-catenin pathway is tightly regulated by various mechanisms, including post-translational modifications, feedback loops, and crosstalk with other signaling pathways. Wnt signaling inhibitors, such as Dickkopf (DKK) proteins and secreted frizzled-related

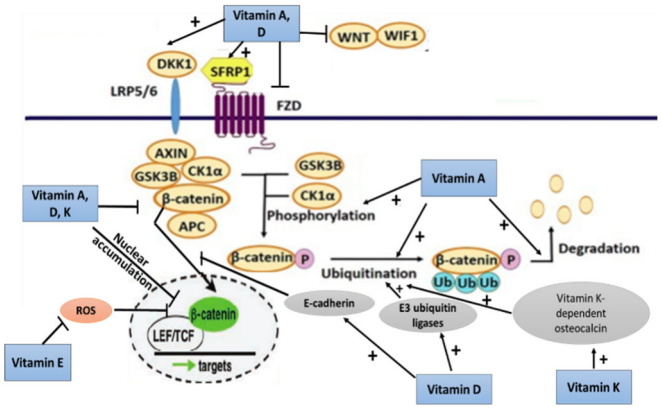

Figure 1. Graphical abstract of the protective effect of fat-soluble vitamins (A, D, E, and K) on colorectal cancer (CRC) involved Wnt/β-catenin signaling.

proteins (sFRPs), can obstruct receptor-ligand interactions or counteract Wnt ligands [17,18]. Moreover, the Wnt/β-catenin pathway is crucial for embryonic development because it controls functions like stem cell maintenance, tissue patterning, and cell fate determination [19]. Wnt/β-catenin pathway's dysregulation has been linked to several illnesses, including cancer, where tumor initiation, progression, and metastasis are all facilitated by aberrant Wnt signaling activation [20,21], as described in Figure 1.

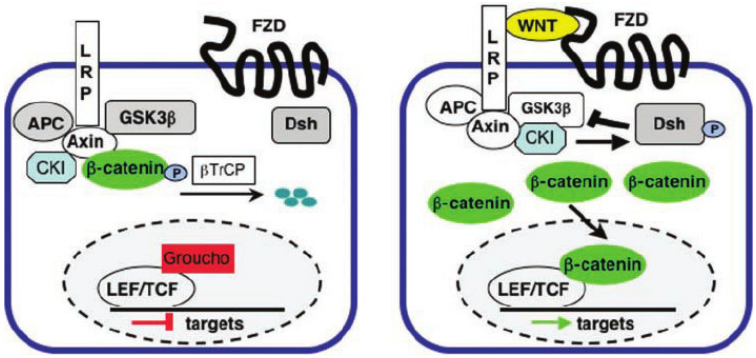

Figure 2. Diagrammatic representation of the signaling cascade of Wnt/β-catenin. (Left) When cytoplasmic β-catenin is not bound by a WNT ligand, it attaches itself to APC and Axin, is phosphorylated by GSK3 β and CKI, and is polyubiquitinated by the β TRCP complex before being degraded by proteasomes. In these circumstances, transcription factors called LEF/TCF, which are found in the nucleus, work in concert with transcriptional co-repressors like Groucho to inhibit the transcription of TCF target genes. (Okay) WNT ligand prevents β-catenin from being phosphorylated or broken down, allowing it to build up in the cytoplasm and enter the nucleus. To start the transcription of target genes, nuclear β-catenin interacts with several other transcription factors and transcriptional co-activators belonging to the LEF/TCF family. APC stands for adenomatous polyposis coli; GSK stands for glycogen synthase kinase CKI stands for casein kinase I; DSH, Disheveled; LEF/TCF, Lymphoid enhancer factor/T-cell factor [22].

Due to its critical role in cancer and other diseases, the Wnt/β-catenin pathway has emerged as an attractive target for therapeutic intervention [23]. Strategies that modulate Wnt signaling, such as small molecule inhibitors or monoclonal antibodies targeting Wnt ligands or receptors, are actively explored to treat Wnt-driven cancers and other disorders [24,25].

A malignant tumor called colorectal cancer (CRC) starts in the colon or rectum, which are sections of the large intestine [26]. It is one of the most common cancers worldwide and a leading cause of cancer-related morbidity and mortality [27,28]. Usually, a series of steps leading to the accumulation of genetic and epigenetic changes in healthy colonic epithelial cells causes colorectal cancer (CRC). The adenoma-carcinoma sequence, in which benign adenomatous polyps eventually turn into malignant carcinomas, is a well-known model for colorectal carcinogenesis [29,30]. Mutations in the APC gene, the (Kirsten rat sarcoma virus) KRAS and BRAF oncogenes, and changes in the (Tumor Protein 53) TP53 tumor suppressor gene are significant genetic abnormalities linked to CRC [31].

The relationship between CRC and the Wnt/β-catenin signaling pathway is fundamental to understanding CRC pathogenesis [32]. Wnt/β-catenin signaling pathway dysregulation is a hallmark of CRC, contributing significantly to tumor initiation, progression, and metastasis. Most intriguingly, 80–90% of sporadic cases of CRC are associated with mutations in the APC gene [33-35]. Typically, APC mutations occur early in the development of CRC. Normally, APC suppresses tumors by encouraging β-catenin degradation [36]. Most interestingly, APC mutations result in the cytoplasmic accumulation and stabilization of β-catenin, facilitating its nuclear translocation and activating Wnt target genes [37].

Fat-soluble vitamins A, D, E, and K are essential for many physiological functions. They may also interact with signaling pathways, like the Wnt/β-catenin pathway. Although the precise impact of fat-soluble vitamins on the Wnt/β-catenin pathway remains to be explored, there is growing evidence that these vitamins could potentially regulate Wnt/β-catenin signaling activity [38,39]. More interestingly, fat-soluble vitamins are chosen over other vitamins based on the previous review implicating the molecular mechanisms of vitamin supplementation in CRC, demonstrating that fat-soluble vitamins affect CRC via Wnt/β-catenin signaling more than other vitamins [40]. Overall, fat-soluble vitamins have the potential to influence Wnt/β-catenin signaling activity through various mechanisms, including direct interactions with pathway components or indirect effects on cellular processes that intersect with Wnt signaling.

Fat-soluble vitamins

A class of vitamins known as fat-soluble vitamins can dissolve in fats and oils. Unlike water-soluble vitamins, which are not stored and are eliminated in urine when consumed in excess, they are necessary for several physiological processes in the body. They are stored in fatty tissues and the liver [41]. The four fat-soluble vitamins are A, D, E, and K.

Vitamin A (retinol)

Immune system performance, reproduction, cellular communication, and vision all depend on vitamin A. It plays a vital role in vision by preserving retinal health and promoting the synthesis of rhodopsin, a pigment involved in low-light vision [42]. Vitamin A regulates gene expression, cell differentiation, and immune responses [43]. Food sources of vitamin A include liver, dairy products, fish oils, and fortified foods. Plant-based sources provide beta-carotene, a precursor that the body converts into active vitamin A [44].

Vitamin D (Calciferol)

Since the skin can produce vitamin D when exposed to sunlight, it is sometimes called the "sunshine vitamin". It regulates calcium and phosphate metabolism, promoting bone health by enhancing calcium absorption in the intestines and maintaining adequate levels of calcium and phosphate in the blood [45]. Vitamin D also affects immune function, cell growth and differentiation, and inflammation modulation. Egg yolks, fortified foods (like milk and cereal), fatty fish (like salmon and mackerel), and dietary supplements are examples of dietary sources of vitamin D [46].

Vitamin E (tocopherol)

Strong antioxidant vitamin E helps shield cells from oxidative stress and free radical damage. It promotes skin health, blood vessel integrity, and immunological function [47]. Vitamin E may also have anti-inflammatory properties and contribute to cardiovascular health. Food sources of vitamin E include nuts and seeds, vegetable oils (such as wheat germ, sunflower, and safflower oil), leafy green vegetables, and cereals with added nutrients [48].

Vitamin K (Phylloquinone and Menaquinones)

Blood clotting, bone metabolism, and cardiovascular health depend on vitamin K. It is essential for the liver's production of clotting factors, which are required for the coagulation cascade and wound healing [49]. Vitamin K also regulates calcium metabolism and bone mineralization by activating

proteins involved in bone formation. Dietary sources of vitamin K include leafy greens (such as kale, spinach, and broccoli), vegetable oils (such as soybean and canola oil), and fermented foods (which provide menaquinones, or vitamin K2) [50].

Wnt/β-catenin signaling pathway plays a role in health

The Wnt/β-catenin signaling pathway plays a crucial role in maintaining various aspects of health by regulating fundamental cellular processes throughout the body. During embryogenesis, the coordination of multiple methods, including limb development, neural tube formation, body axis patterning, and organogenesis, depends on the Wnt/β-catenin pathway [51]. Most importantly, the Wnt/β-catenin pathway must be activated at certain times and in specific spatial patterns for different tissues and organ systems to be formed during embryonic development [52].

The pathway of Wnt/β-catenin regulates the survival, proliferation, and differentiation of cells in adult tissues, which is essential for preserving tissue homeostasis [53]. Moreover, in tissues with high turnover rates, such as the skin and intestinal epithelium, Wnt/β-catenin signaling promotes stem cell and progenitor cell proliferation, ensuring the tissue's continuous renewal [54]. In the skin, stomach, and hematopoietic system, among other tissues, adult stem cells require the Wnt/β-catenin pathway to be maintained and able to self-renew [55]. Wnt signaling activation in stem cells encourages self-renewal and inhibits differentiation, preserving a pool of undifferentiated cells that can produce specialized cell types when required [56].

In bone tissue, osteoblast differentiation and bone formation are regulated by Wnt/β-catenin signaling [57]. When mesenchymal stem cells differentiate into osteoblasts, the new bone matrix is mineralized and deposited, activating the Wnt/β-catenin pathway [58]. In the nervous system, the Wnt/β-catenin pathway is involved in neurogenesis, axon guidance, and synaptic plasticity [59]. Wnt signaling regulates the proliferation and differentiation of neural progenitor cells during brain development and adult neurogenesis in specific brain regions, such as the hippocampus [60]. Wnt signaling also affects the development and function of synapses, affecting memory and learning [61]. Emerging evidence suggests that the Wnt/β-catenin pathway also affects immune regulation and inflammation [62]. Wnt signaling has been implicated in the development and function of immune cells, including T cells, B cells, and macrophages, as well as in regulating immune responses in various tissues [63].

Role of Wnt/β-catenin signaling pathway in diseases

Because the Wnt/β-catenin signaling pathway is involved in fundamental cellular functions like survival, differentiation, and proliferation, it is essential in several diseases [64]. Numerous disorders have been linked to the pathogenesis of Wnt/β-catenin signaling pathway dysregulation.

The most common cause of CRC cases, which has a well-studied association, may be mutations in components of the Wnt/β-catenin pathway, such as APC or β-catenin (CTNNB1) [65]. Atypical activation of Wnt/β-catenin signaling initiates, advances, and disseminates colorectal cancer. Furthermore, dysregulated Wnt/β-catenin signaling is linked to tumor growth, invasion, and a poor prognosis in hepatocellular carcinoma [66]. Furthermore, Wnt/β-catenin signaling has been linked to the development, metastasis, and initiation of tumors in breast cancer [67]. Additionally, it has been noted that prostate cancer activates Wnt/β-catenin signaling, which is linked to treatment resistance and tumor aggressiveness [68].

Osteoporosis is a condition marked by decreased bone density and an increased risk of fracture. It is linked to dysregulated Wnt/β-catenin signaling. Wnt/β-catenin signaling activation promotes osteoblast differentiation and bone formation [69]. Moreover, aberrant Wnt/β-catenin signaling activation is seen in osteosarcoma, a type of bone cancer, and is associated with tumor progression and a poor prognosis [70]. Furthermore, dysregulation of Wnt/β-catenin signaling has been associated with Alzheimer's disease, particularly with synaptic dysfunction and neurodegeneration [71]. Moreover, it has been observed that Wnt/β-catenin signaling is altered in Parkinson's disease; however, the precise function of this signaling in the disease's pathogenesis remains unclear [72].

The pathophysiology of inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, is linked to dysregulated Wnt/β-catenin signaling, which causes intestinal inflammation and tissue damage [73]. Furthermore, the pathophysiology of rheumatoid arthritis has been linked to Wnt/β-catenin signaling, specifically to synovial inflammation and joint destruction [74]. The pathophysiology of type 2 diabetes may be aided by the dysregulation of wnt/β-catenin signaling, which regulates insulin secretion and pancreatic β-cell function [75].

Implication of Wnt/β-catenin signaling pathway in colorectal cancer pathogenesis and progression

One of the most prevalent cancers in the world, colorectal cancer (CRC), is primarily caused by the Wnt/β-catenin signaling pathway [76]. One of the main characteristics of CRC is the dysregulation of the Wnt/β-catenin signaling pathway, which promotes tumor development, spread, and metastasis [77]. Most intriguingly, APC gene mutations are early events in tumorigenesis in most sporadic colorectal cancer cases [78]. Because these mutations impair the APC protein's function, β-catenin stabilizes and accumulates in the cytoplasm [79]. It is also possible for β-catenin (CTNNB1 gene) to undergo mutations, activating it constitutively without needing Wnt ligands [80].

Mutations in the APC or β-catenin genes can disrupt the Wnt/β-catenin signaling pathway, leading to its aberrant activation and the subsequent abnormal expression of downstream target genes such as c-Myc, cyclin D, Matrix metalloproteinase 7, and AXIN2 [81]. When β-catenin accumulates, it moves into the nucleus. It combines with TCF/LEF transcription factors to promote the expression of Wnt target genes essential for cell division, invasion, and survival [82]. Constitutive activation of the Wnt/β-catenin pathway stimulates the proliferation of intestinal epithelial cells, which in turn promotes the formation of adenomatous polyps, the precursor lesions of colorectal cancer [32,83]. Furthermore, dysregulated Wnt signaling promotes the growth of intestinal progenitor and stem cells, which aids in the clonal proliferation of tumor cells [84].

Activation of Wnt/β-catenin signaling promotes the epithelial-mesenchymal transition (EMT), a process by which tumor cells acquire invasive and metastatic properties [85]. Wnt signaling enhances the expression of EMT-inducing transcription factors and matrix metalloproteinases, facilitating tumor cell invasion into surrounding tissues and dissemination to distant sites [86]. Given the critical role of the Wnt/β-catenin pathway in CRC, targeting this pathway has emerged as a promising therapeutic strategy [87]. Among the therapeutic strategies explored are small molecule inhibitors that specifically target elements of the Wnt signaling pathway [88]. One example is PRI-724, a small Wnt signaling inhibitor that prevents β-catenin from interacting with CREB-binding protein (CBP), which is β-catenin's transcriptional coactivator. Humanized antibodies against Wnt ligands or receptors, like OncoMed's Vantictumab (OMP-18R5), which interacts with five FZD receptors to inhibit Wnt signaling, have emerged as a promising therapeutic approach [89,90]. Furthermore, worse clinical outcomes and a poor prognosis have been linked to dysregulation of Wnt/β-catenin signaling and the expression levels of its downstream target genes in CRC patients [87]. Furthermore, biomarkers related to Wnt pathway activity may have prognostic value and could potentially guide treatment decisions in CRC patients [91].

Vitamin A / Retinoic acid significantly modulate Wnt/β-catenin signaling pathway at different stages in colorectal cancer

Indeed, many studies suggest that vitamin A, specifically its active metabolite, retinoic acid, can inhibit the Wnt/β-catenin signaling pathway in CRC cells. Moreover, retinoids block the main signaling pathways that encourage the advancement of colorectal cancer. Every path is pursued to its full potential; retinoids reduce MMPs, cyclin D1, and other factors that promote cellular invasion or proliferation [92]. It has been demonstrated that retinoic acid reduces the expression levels of β-catenin, the Wnt signaling pathway's central effector, in colorectal cancer [92,93]. The reduction in β-catenin's nuclear accumulation and transcriptional activity results in a downregulation of Wnt target genes essential for cell survival and proliferation [94]. Moreover, vitamin A/retinoic acid treatment promotes the degradation of β-catenin through proteasomal and lysosomal pathways [95]. The signaling activity

of β-catenin is attenuated when retinoic acid increases its phosphorylation, marking it for ubiquitination and subsequent proteasomal degradation [96].

Furthermore, in CRC, retinoic acid can inhibit the expression of Wnt ligands and receptors, including FZD receptors [97]. Retinoic acid obstructs Wnt signaling cascade initiation by decreasing the availability of Wnt ligands and their receptors, preventing downstream signaling and β-catenin activation [98]. Furthermore, it has been demonstrated that retinoic acid increases the expression of Wnt antagonists in CRC, including sFRPs and DKK proteins [99]. Retinoic acid counteracts Wnt ligand-mediated pathway activation by increasing the expression of Wnt antagonists, which further inhibits β-catenin signaling [100]. Reducing Wnt/β-catenin signaling activity is linked to cellular differentiation, which is one way that retinoic acid promotes anticancer effects [92,101]. More details about the molecular mechanisms through which Vitamin A/ Retinoic acid can modulate the Wnt/β-catenin signaling pathway are mentioned in Table 1.

Vitamin D induces recruitment of β-catenin for degradation, upregulates the Wnt antagonist's expression, and upregulates the expression of E-cadherin in colorectal cancer

Research indicates that vitamin D may lessen the activity of Wnt/β-catenin signaling in colorectal cancer. It has been demonstrated that vitamin D encourages β-catenin degradation in CRC [102-104]. β-catenin is brought to the proteasome for degradation when vitamin D activates the vitamin D receptor (VDR) [105]. To reduce β-catenin levels and inhibit Wnt signaling, this process entails the upregulation of E3 ubiquitin ligases that target β-catenin for ubiquitination and subsequent proteasomal degradation [105].

Vitamin D can inhibit the expression of Wnt target genes, such as c-Myc and Cyclin D1, essential for cell survival and proliferation [106,107]. By downregulating the expression of these target genes, vitamin D inhibits the transcriptional activity of β-catenin-TCF/LEF complexes, leading to decreased Wnt/β-catenin signaling activity [108]. Additionally, vitamin D has been found to upregulate the expression of Wnt antagonists, including DKK proteins and sFRPs, in CRC [102, 106, 109]. Furthermore, increased expression of Wnt antagonists by vitamin D interferes with Wnt ligand-receptor interactions. It blocks the activation of the Wnt signaling pathway, decreasing β-catenin stabilization and transcriptional activity [110].

Most intriguingly, E-cadherin is a cell adhesion molecule whose down-regulation is linked to increased invasiveness and metastasis in colorectal cancer [108,111]. Vitamin D can positively regulate the expression of this molecule. β-catenin is prevented from nuclear translocation and transcriptional activity at the cell membrane by E-cadherin [112,113]. In preclinical models and clinical studies, vitamin D has been demonstrated to inhibit CRC cell proliferation, induce apoptosis, and suppress tumor growth and progression through its effects on Wnt/β-catenin signaling and other pathways involved in tumorigenesis. It has also provided evidence suggesting an association between low vitamin D levels and an increased risk of CRC [28,114]. More details regarding the molecular mechanisms of vitamin D on the Wnt/β-catenin signaling pathway are discussed in Table 1.

Wnt/β-catenin signaling was indirectly down-regulated by vitamin E in colorectal cancer

Compared to other vitamins like vitamin A and D, there is less research on how vitamin E affects Wnt/β-catenin signaling in colorectal cancer (CRC); however, some studies indicate that vitamin E may inhibit Wnt/β-catenin signaling in CRC. Well-known antioxidant vitamin E can scavenge reactive oxygen species (ROS) and lower oxidative stress, which are linked to promoting Wnt/β-catenin signaling activation in CRC [115]. Oxidative stress can stabilize β-catenin and enhance its transcriptional activity by inhibiting its degradation or promoting nuclear translocation. Vitamin E's antioxidant properties may counteract this effect and suppress Wnt/β-catenin signaling [116].

Upstream signaling molecules or pathways of Wnt/β-catenin signaling in colorectal cancer may interact with vitamin E. Vitamin E, for instance, has been shown to regulate the activity of the mitogen-activated protein kinase (MAPK) and protein kinase C (PKC) pathways, which can interact and affect

the activity of Wnt/β-catenin signaling [117]. These indirect molecular mechanisms were briefly discussed in Table 1.

Vitamin K moderately diminished Wnt/β-catenin signaling activity in colorectal cancer

Vitamin K is a fat-soluble vitamin that has been studied for its potential role in various physiological processes, including blood clotting, bone metabolism, and even cancer [118]. While research on the specific effects of vitamin K on Wnt/β-catenin signaling in CRC is somewhat limited, evidence suggests that vitamin K may have inhibitory effects on this pathway. Vitamin K has been shown to regulate the expression and activity of β-catenin in CRC [119]. Several studies have suggested that vitamin K can decrease the expression levels of β-catenin, the central effector of the Wnt/β-catenin pathway, in CRC cell lines [119]. By reducing β-catenin expression, vitamin K may inhibit its nuclear translocation and transcriptional activity, leading to decreased Wnt signaling activity.

Furthermore, vitamin K might encourage the CRC cells' β-catenin to degrade. It has been suggested that β-catenin's stability and signaling activity can be decreased by increasing the ubiquitination and degradation of the protein by activating the vitamin K-dependent protein osteocalcin [120]. According to reports, vitamin K can obstruct Wnt ligands or receptors, which may prevent Wnt signaling cascades from starting [121]. These direct and indirect molecular mechanisms are discussed briefly in Table 1.

Table 1. Molecular mechanisms of fat-soluble vitamins in modulating the Wnt/β-catenin signaling in colorectal cancer.

Type of fat – soluble vitamin	Detailed molecular mechanisms on Wnt/β-catenin signaling	Reference
Vitamin A (retinoic acid)	**Induction of E3 Ubiquitin Ligases:** The expression or activity of E3 ubiquitin ligases, which ubiquitinate β-catenin and subsequently subject it to proteasomal degradation, may be upregulated by vitamin D. It is well known that E3 ubiquitin ligases, like β-TrCP (beta-transducin repeat-containing protein), aid in the ubiquitination and proteasome-mediated degradation of β-catenin.	[95,96,122]
	Stimulation of Axin Expression: The scaffold protein Axin, which is involved in the formation of the β-catenin destruction complex, may be stimulated by vitamin D in terms of expression or activity. Axin, APC, GSK-3β, and CK1α make up the β-catenin destruction complex, which stimulates β-catenin's phosphorylation and eventual breakdown.	[123-125]
	Transcriptional Regulation: By attaching to retinoic acid receptors (RARs) and retinoid X receptors (RXRs), retinoic acid controls the expression of genes, which are ligand-activated transcription factors. RAR/RXR complexes bound to retinoic acid have the ability to directly bind to specific DNA sequences known as retinoic acid response elements (RAREs) in target gene promoter regions, thereby modulating target gene transcription. Numerous studies have reported the presence of RAREs in the regulatory regions of Wnt ligand genes (Wnt1, Wnt3a) and Frizzled receptor genes (FZD1, FZD2). This implies that retinoic acid might directly prevent these genes' transcription.	[97,98,126-128]
	Indirect Regulation via Transcriptional Repressors: Retinoic acid can indirectly regulate Wnt ligands and receptors by inducing the expression of transcriptional repressors that antagonize Wnt signaling. Retinoids, for example, have been shown to upregulate the expression of Dkk-1, a secreted protein that binds to LRP5/6 co-receptors to inhibit Wnt signaling pathway activation.	[99,105,129]
	Epigenetic Regulation: Retinoic acid can also exert epigenetic effects on gene expression by influencing chromatin structure and DNA methylation patterns. Transcriptional repression may result from retinoic acid-mediated modifications to DNA methylation and chromatin accessibility at the promoter regions of Wnt ligand and receptor genes. Furthermore, retinoic acid has the ability to control the activity of enzymes that modify histones, including histone methyltransferases (HMTs) and deacetylases (HDACs), which control the remodeling of chromatin and the expression of genes.	[130-132]

	Inhibition of β-Catenin Transcriptional Activity: Retinoic acid has been shown to suppress the transcriptional activity of β-catenin by preventing it from interacting with transcriptional coactivators and localizing nuclear. When the Wnt pathway is triggered, β-catenin moves into the nucleus and facilitates the transcription of target genes related to cell survival, proliferation, and differentiation.	[94,133]
Vitamin D (Cholecalciferol)	**Induction of β-Catenin Phosphorylation:** By activating GSK-3β, a kinase involved in the phosphorylation and subsequent degradation of β-catenin, vitamin D can stimulate the phosphorylation of β-catenin. When β-catenin is phosphorylated, it becomes susceptible to ubiquitination and proteasomal breakdown.	[106,134,135]
	Activation of the Proteasomal Degradation Pathway: Treatment with vitamin D can enhance β-catenin's ubiquitination, which leads to its proteasomal breakdown. The process of covalently attaching ubiquitin molecules to proteins to mark them for proteasome degradation is known as ubiquitination. Vitamin D may enhance the activity of E3 ubiquitin ligases, which catalyze the ubiquitination of β-catenin and consequently promote its proteasome-mediated degradation.	[105,136]
	Inhibition of β-Catenin Transcriptional Activity: One crucial downstream effector of the Wnt signaling pathway, β-catenin, has its transcriptional activity inhibited by vitamin D. Increased phosphorylation and β-catenin degradation can result from vitamin D's promotion of this destruction complex's activity. This leads to decreased transcriptional activation of Wnt target genes, including c-Myc and Cyclin D1, which are involved in cell proliferation and survival, and reduced nuclear accumulation of β-catenin.	[102,105,137]
	Induction of Wnt Antagonists: Vitamin D receptor induction can induce the expression of Wnt antagonists, such as Dkk-1, which bind to LRP5/6 co-receptors and inhibit the activation of the Wnt signaling pathway. Dkk-1 stops the Wnt-Frizzled-LRP5/6 complex from forming, inhibiting downstream signaling events mediated by β-catenin. By encouraging the expression of Dkk-1 and other Wnt antagonists, vitamin D can effectively suppress the transcriptional activity of β-catenin and the expression of its target genes involved in cell proliferation and survival.	[102,106,138,139]
	Modulation of Chromatin Structure and Transcriptional Regulation: Vitamin D can alter chromatin structure and transcription regulation by influencing the activity of histone-modifying enzymes and transcription factors. Vitamin D response elements, or VDREs, are target gene promoter regions in which the vitamin D receptor, or VDR, ligand-activated transcription factor, binds to specific DNA sequences. Cyclin D1 and c-Myc are two examples of Wnt target genes whose transcription can be suppressed by VDR, preventing cell division and survival. This is accomplished by utilizing corepressor complexes or preventing coactivators from acting.	[140,141]
	Transcriptional Regulation: Vitamin D can regulate the transcriptional expression of e-cadherin. To stimulate the transcription of the e-cadherin gene (CDH1), the vitamin D receptor, or VDR, can bind to specific DNA sequences known as vitamin D response elements (VDREs). By directly triggering the expression of E-cadherin, vitamin D enhances cell-cell adhesion and inhibits tumor cell invasion and metastasis.	[108,111,142]
	Inhibition of Epithelial-Mesenchymal Transition (EMT): Vitamin D can inhibit EMT, a cellular process linked to increased cancer metastasis and invasiveness. EMT encourages tumor cell migration and invasion by causing the loss of epithelial features, such as the down-regulation of E-cadherin and the acquisition of mesenchymal features. Vitamin D inhibits the effects of EMT and preserves epithelial integrity, which in turn prevents tumor metastasis by upregulating the expression of E-cadherin.	[143,144]

	Sequestration of β-Catenin: E-cadherin plays a crucial role in preventing β-catenin's nuclear translocation and transcriptional activity at the cell membrane. Without Wnt signaling, β-catenin forms complexes with E-cadherin and α-catenin at adherens junctions, stabilizing and holding itself at the cell membrane. By indirectly blocking β-catenin's nuclear translocation and transcriptional activity through the enhancement of E-cadherin expression, vitamin D inhibits Wnt/β-catenin signaling and tumor progression.	[112,113,145]
Vitamin E (Tocopherol)	**Antioxidant Properties:** Potent antioxidants, such as vitamin E, can reduce oxidative stress by scavenging reactive oxygen species (ROS). Oxidative stress has been connected to the Wnt/β-catenin signaling pathway's activation in colorectal cancer. By reducing oxidative stress, vitamin E may stop the abnormal activation of the Wnt/β-catenin signaling pathway, slowing the progression of CRC.	[115,146]
	Regulation of Gene Expression: Vitamin E has been shown to regulate the expression of genes associated with the Wnt/β-catenin signaling pathway. For example, vitamin E treatment has downregulated β-catenin expression and its target genes, such as Cyclin D1 and c-Myc, in CRC cells. This suggests that vitamin E may directly impact the transcriptional activity of β-catenin, thereby suppressing Wnt/β-catenin signaling.	[147]
	Regulation of Cell Cycle Progression: Vitamin E regulates how the cell cycle develops in CRC cells. The dysregulation of cell cycle progression is a primary feature of cancer, and the Wnt/β-catenin signaling pathway plays a crucial role in this process. It has been shown that administering vitamin E stops the cell cycle at the G1 phase and inhibits the expression of Cyclin D1, an essential G1/S transition regulator. These results suggest vitamin E may alter the cell cycle's progression, thereby blocking the Wnt/β-catenin signaling pathway.	[148,149]
	Protein Kinase C (PKC) Pathway: It has been shown that vitamin E regulates the activity of PKC, a family of serine/threonine kinases involved in several cellular processes, such as cell survival, differentiation, and proliferation. PKC can regulate the activity of the Wnt/β-catenin signaling pathway through various mechanisms. For example, PKC-mediated phosphorylation of β-catenin can regulate its subcellular location and stability, which in turn affects the protein's transcriptional activity. Moreover, PKC can phosphorylate Dishevelled (Dvl), a crucial component of the Wnt signaling pathway, activating and enhancing Wnt/β-catenin signaling. By altering PKC activity, vitamin E may indirectly impact the Wnt/β-catenin signaling pathway's activity and its subsequent effects on gene expression and cellular processes.	[117,150- 152]
	Mitogen-Activated Protein Kinase (MAPK) Pathway: Vitamin E has been shown to regulate the activity of the MAPK pathway, which is composed of several protein kinases, including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK, that are involved in cellular responses to extracellular stimuli like growth factors, cytokines, and stress. Crosstalk between MAPK pathways and Wnt/β-catenin signaling has been observed in various cellular environments. For instance, increased Wnt/β-catenin signaling activity can result from ERK activation promoting nuclear translocation and β-catenin stabilization. On the other hand, β-catenin's phosphorylation and degradation have been linked to the JNK and p38 MAPK pathways, which in turn inhibit Wnt/β-catenin signaling. Vitamin E may influence the balance between β-catenin stabilization and degradation by modulating the activity of the MAPK pathway, which in turn affects the activity of the Wnt/β-catenin signaling pathway.	[153-155]
Vitamin K	**Inhibition of Wnt/β-Catenin Signaling:** Vitamin K has been shown to inhibit the Wnt/β-catenin signaling pathway, a crucial step in the development and progression of colorectal cancer. β-catenin stabilizes and migrates into the nucleus in response to activation of Wnt	[119,156]

	signaling, where it serves as a transcriptional coactivator of target genes crucial for cell division, survival, and proliferation. Vitamin K may prevent β-catenin from accumulating and reduce its expression levels in CRC cells by inhibiting Wnt signaling.	
	Promotion of β-Catenin Degradation: It has been shown that vitamin K administration causes β-catenin to break down more quickly in CRC cells. β-catenin is subjected to proteasomal degradation after being phosphorylated by the destruction complex, which is made up of Axin, APC (adenomatous polyposis coli), GSK-3β (glycogen synthase kinase 3 beta), and CK1α (casein kinase 1 alpha). Vitamin K can facilitate the ubiquitination of β-catenin, which will cause its proteasomal breakdown and a drop in expression levels, or it can boost the activity of this destruction complex.	[119]
	Regulation of β-Catenin Target Genes: Vitamin K can regulate the expression of β-catenin target genes involved in cell survival, proliferation, and differentiation. By obstructing Wnt/β-catenin signaling, vitamin K may reduce the transcriptional activity of β-catenin and downregulate the expression of its target genes, such as c-Myc and Cyclin D1. This could contribute to the decrease in β-catenin expression levels and the inhibition of CRC cell growth and progression.	[119,157]
	Modulation of β-Catenin Stability: Osteocalcin is a vitamin K-dependent protein that plays a role in bone metabolism and has been connected to several cellular functions, including cancer. Once activated, the biological activity of osteocalcin is dependent on post-translational modifications such as carboxylation, which are dependent on vitamin K and can impact the stability of β-catenin directly or indirectly. This could occur through several mechanisms, including stimulating E3 ubiquitin ligases to ubiquitinate β-catenin or blocking its interaction with stabilizing factors.	[120,121,158]

Conclusion

One of the main characteristics of CRC is the dysregulation of the Wnt/β-catenin signaling pathway, which plays a significant role in the progression, proliferation, survival, and metastasis of cancers. From the previous review, it is evident that β-catenin expression levels are lowered and that β-catenin degradation via proteasomal and lysosomal pathways is promoted by retinoic acid, vitamin D, and vitamin K. Furthermore, retinoic acid and vitamin D can suppress Wnt ligand and receptor expression in CRC, which includes DKK proteins and sFRPs. Furthermore, Vitamin D can upregulate the expression of E-cadherin that sequesters β-catenin at the cell membrane, preventing its nuclear translocation and transcriptional activity. On the other hand, vitamin E can indirectly affect Wnt/β-catenin signaling, where it can scavenge ROS and reduce oxidative stress, which is implicated in promoting Wnt/β-catenin signaling activation in CRC. Additionally, it has been suggested that β-catenin's stability and signaling activity can be decreased by increasing the ubiquitination and degradation of the protein by activating the vitamin K-dependent protein osteocalcin. Fat-soluble vitamins, especially vitamins A and D, significantly protect CRC by modulating the Wnt/β-catenin signaling pathway in different sites. In contrast, vitamins E and K can modulate Wnt/β-catenin signaling via indirect mechanisms.

Recommendations and future directions

Evaluate the efficacy of nutritional interventions targeting fat-soluble vitamin supplementation in CRC prevention and treatment. Conduct randomized controlled trials to assess the impact of vitamin supplementation on Wnt/β-catenin signaling activity, tumor progression, and patient outcomes in CRC patients.

Identify biomarkers associated with fat-soluble vitamin status and Wnt/β-catenin signaling activity in CRC patients. These biomarkers could serve as diagnostic or prognostic indicators and help personalize treatment strategies based on individual vitamin profiles.

We will emphasize the necessity of conducting thorough clinical trials, identifying biomarkers, and investigating innovative treatment approaches that target fat-soluble vitamins and Wnt/β-catenin signaling in CRC.

Explore the development of novel therapeutic agents targeting the Wnt/β-catenin signaling pathway based on fat-soluble vitamin compounds. Investigate whether synthetic analogs or derivatives of these vitamins can selectively modulate Wnt/β-catenin signaling activity and inhibit CRC growth.

Explore potential synergistic or antagonistic interactions between fat-soluble vitamins in modulating Wnt/β-catenin signaling and CRC risk. Investigate whether combinations of these vitamins have additive or synergistic effects on β-catenin activity and CRC prevention.

Advocate for population-wide strategies to promote adequate intake of fat-soluble vitamins through dietary modifications or supplementation. Educate the public and healthcare providers about maintaining optimal vitamin levels for CRC prevention and overall health.

Authors contribution

The authors are responsible for performing and creating all aspects and components of this work.

Declaration of interest

The authors declare no conflict of interest.

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