Journal on Oncology

www.journalononcology.org

Review Article

Open Access, Volume 6

Vitamins as Radiosensitizers: Multifaceted Mechanisms and Therapeutic Potential in Cancer

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Abstract

Radiotherapy is a cornerstone of cancer management, yet its efficacy is often limited by variable tumor radiosensitivity and treatment-related toxicities. Vitamins, as readily available micronutrients, have emerged as promising agents to enhance radiosensitivity and improve therapeutic outcomes. This review systematically summarizes the multifaceted mechanisms-including the modulation of oxidative stress, DNA damage repair, cell cycle progression, and antitumor immunity-by which various vitamins potentiate the effects of radiotherapy. We further synthesize the current preclinical and clinical evidence supporting their use, address key challenges such as dose optimization and individual variability, and outline future translational research directions. This work aims to provide a foundation for developing novel, vitamin-based radio sensitization strategies to achieve more precise and effective radiotherapeutic interventions.

Keywords: Cancer; Radiotherapy; Radiosensitization; Vitamins; Micronutrients.

Introduction

The global incidence of cancer continues to rise, driven by factors such as population aging, lifestyle changes, and environmental influences. Radiotherapy exerts antitumor effects through ionizing radiation-induced biomolecular damage, cellular responses, and modulation of the tumor microenvironment, making it a widely utilized clinical modality. However, patient-specific factors, treatment-related toxicities, and inherent or acquired resistance often led to suboptimal radiosensitivity, limiting therapeutic efficacy. Emerging evidence indicates that vitamins can modulate oxidative stress, DNA repair, cell cycle progression, and immune responses, suggesting their potential as radiosensitizers. This review comprehensively examines the roles and molecular mechanisms of various vitamins in radio sensitization, summarizes relevant preclinical and clinical findings, discusses current challenges, and highlights future translational research directions.

Potential mechanisms of vitamins in modulating cancer radio sensitization: A multi-pathway regulatory framework

Vitamins exert multifaceted regulatory effects on tumor cell biology through diverse pathways and molecular targets, thereby modulating radiosensitivity.

The principal mechanisms involve the following aspects

Regulation of antioxidant and pro-oxidant balance: The influence of vitamins on Reactive Oxygen Species (ROS) is highly

Manuscript Information: *Received: Feb 03, 2026; Accepted: Feb 23, 2026; Published: Mar 02, 2026*

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Citation: *Zhou Y, Zhao A, Chen W, Wu B, Cao J, et al. Vitamins as Radiosensitizers: Multifaceted Mechanisms and Therapeutic Potential in Cancer. J Oncology. 2026; 6(1): 1198.*

context-dependent. At physiological concentrations, vitamins primarily exert antioxidant effects by scavenging free radicals, chelating metal ions, and enhancing the activity of antioxidant enzymes, thereby preserving cellular redox homeostasis and protecting normal tissues from radiation-induced damage. However, at high concentrations or in specific tumor microenvironments (e.g., high iron ion levels, acidic pH), vitamins (such as vitamin C and E) can act as pro-oxidants. Through processes like the Fenton reaction, they selectively increase ROS levels in tumor cells, inducing oxidative damage to DNA, proteins, and lipids, and potentiating radiotherapy-induced cell death [1].

Inhibition of DNA repair pathways: Radiotherapy primarily mediates its antitumor effects by inducing DNA damage, particularly double-strand breaks in DNA. The proficiency of tumor cells in activating DNA repair mechanisms-such as Base Excision Repair (BER), Nucleotide Excision Repair (NER), Homologous Recombination (HR), and Non-Homologous End Joining (NHEJ)-constitutes a major mechanism of radio resistance. Several vitamins, including nicotinamide (B3), vitamin C, and D, can interfere with DNA repair processes via various strategies, such as modulating the activity of repair enzymes like poly (ADP-ribose) Polymerase (PARP), depleting Adenosine Triphosphate (ATP) necessary for repair, or directly inflicting additional DNA damage. These interventions impede the restoration of radiation-induced DNA lesions and enhance radiosensitivity [2].

Cell cycle regulation: Cellular radiosensitivity varies across the cell cycle, with cells in the G2/M phase being most sensitive and those in the S phase exhibiting relative resistance. Vitamins-including All-Trans Retinoic Acid (ATRA), vitamin D, Vitamin E Succinate [VES], and vitamin K2-can modulate the expression of cyclins, cyclin-dependent kinase inhibitors (CDKIs; e.g., p21, p27), and associated signaling pathways, such as phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT). These actions induce cell cycle arrest in radiation-sensitive phases (e.g., G0/G1) and reduce the proportion of cells in the radioresistant phase, particularly the late S phase, thereby increasing the fraction of cells susceptible to radiation-induced cell death [3,4].

Remodeling of the immune microenvironment: The immunosuppressive nature of the Tumor Microenvironment (TME) is a contributor to radiotherapy resistance. Vitamins can potentiate radiotherapy responses through through multidimensional immunomodulatory effects: Preserving immune cell functionality (e.g., T cells, natural killer NK cells) via antioxidant activity [5], directing immune cell differentiation (e.g., promoting M1 over M2 macrophage polarization, enhancing dendritic cell function) [6,7], modulating cytokine secretion profiles (e.g., upregulating IL-12 and IFN-γ, downregulating immunosuppressive factors) [8], and Amplifying radiotherapy-induced Immunogenic Cell Death (ICD), facilitating tumor antigen release and presentation, and eliciting abscopal effects [9]. It is noteworthy that complex synergistic or antagonistic interactions may occur among different vitamins, which must be carefully considered when designing combination regimens [10].

Vitamin-targeted intervention strategies for radio sensitization: A mechanistic perspective

From a molecular standpoint, vitamins enhance tumor cell radiosensitivity through four main strategies, involving DNA damage response, redox homeostasis, cell cycle checkpoints, and the immune microenvironment.

Targeting DNA damage response: Nicotinamide (vitamin B3) modulates PARP1 activity by regulating the level of Nicotinamide Adenine Dinucleotide (NAD^+), inhibiting DNA break repair and potentiating radiation-induced DNA damage at high doses[11]. High-dose ascorbic acid (vitamin C, e.g., five mM) combined with radiation (e.g., 6 Gy) generates hydrogen peroxide (H_2O_2) via the Fenton reaction, causing oxidative DNA double-strand breaks and increasing radiosensitivity in glioblastoma cells ($p<0.05$) (Table 1) [12]. Vitamin D disrupts energy metabolism by impairing mitochondrial membrane potential, cytochrome C release, and reducing ATP levels. Energy depletion inhibits DNA repair pathways, preventing recovery from radiation-induced damage and enhancing sensitivity [13]. These vitamins act synergistically by inhibiting repair enzymes, mitigating additive damage, and promoting energy deprivation, thereby forming a multifaceted regulatory network that amplifies the efficacy of radiotherapy (Figure 1).

Regulating redox homeostasis for selective radio sensitization: Vitamins demonstrate dual roles in the tumor redox microenvironment. Vitamin A indirectly reduces ROS levels and enhances radiosensitivity, while protecting normal tissues [14]. Pharmacologic ascorbate exploits high tumor iron to generate H_2O_2 via the Fenton reaction, selectively damaging cancer cells and inactivating HIF-1 (Table 2) [15]. High-dose vitamin E exerts pro-oxidant effects, disrupting membrane integrity and enhancing radiation response [16,17]. Although vitamins C and E act on different targets (DNA vs. membranes), both promote ROS accumulation and selective radio sensitization (Figure 1).

Cell cycle intervention: Vitamin C downregulates Cyclin D1 in gastric cancer cells, thereby inhibiting CDK4/6 complex formation and preventing pRb phosphorylation, which leads to G0/G1 arrest. And autophagy via AMPK-mTOR or PI3K-AKT-mTOR modulation (Table 1) [18]. VES induces G0/G1 arrest in esophageal cancer cells via PI3K/AKT inhibition, reduces S-phase fraction, and promotes apoptosis through caspase activation (Table 1) [19]. Vitamin K2 arrests prostate cancer cells in the G0/G1 or early S-phase via cyclin-CDK modulation, p21 activation, and interference with Akt/NF-κB, thereby reducing the proportion of radioresistant cells and enhancing therapeutic synergy [20]. These vitamins promote G0/G1 arrest through diverse signaling pathways, achieving cell cycle redistribution and phase-specific radio sensitization (Figure 1).

Remodeling the tumor immune microenvironment: ATRA induces monocyte differentiation into M1 macrophages, promotes pro-inflammatory cytokine secretion (e.g., IL-12, TNF-α), and recruits effector T cells, enhancing antigen presentation and amplifying ICD and mediated abscopal effects (Table 1) [14]. Vitamin B5, via coenzyme A, modulates T cell metabolism and function, synergizing with PD-L1 inhibitors to enhance efficacy and promote abscopal responses [21]. Vitamin E enhances dendritic cells' antigen presentation by inhibiting SHP1, activating tumor-specific T cells, and strengthening adaptive immunity [7]. The metabolites of vitamins A and D both possess the ability to regulate T cells. However, when used in combination, they may lead to immunomodulatory antagonism due to pathway crosstalk, underscoring the need for precise dosing [22]. Similarly, vitamins C and E may

suppress DC function and promote Treg differentiation, potentially attenuating immune activation [23]. Thus, vitamins remodel the TME through immune phenotype switching, receptor regulation, and signaling crosstalk, forming a combined "local killing + systemic immunity" effect with radiotherapy (Figure 1)

Evidence for vitamins in cancer radio sensitization: From Preclinical to clinical studies

A growing body of evidence supports the radio sensitizing potential of various vitamins across tumor models.

Vitamin A: Preclinical studies demonstrate that ATRA, when combined with radiotherapy, inhibits tumor growth, reduces tumor volume, and prolongs survival in murine models by inducing M1 macrophage polarization and enhancing immune activity (Table 1) [14]. Vitamin A-containing nutritional formulations inhibit EGFR/VEGF pathways, attenuate angiogenesis and metastasis, and alleviate cachexia in Lewis lung cancer models (Table 1) [24]. Clinical studies directly evaluating its radio sensitizing effects are currently lacking.

B Complex vitamins

Inhibition of vitamin B1 metabolism-by knocking down thiamine pyrophosphokinase 1 (TPK1, a key rate-limiting enzyme for converting vitamin B1 to its active form thiamine pyrophosphate [TPP]), blocking the vitamin B1 transporter (THTR1), or using thiamine analogs (e.g., PyrH)-disrupts TPP production, energy metabolism disorders and damage to key proteins' function, causing energy failure and impaired DNA repair in lung, colorectal, and breast cancer cells, increasing radiosensitivity (Table 1) [25]. Nicotinamide (B3) with carbogen (a high-oxygen gas mixture) improves tumor oxygenation and radio Sensitization Ratios (SER) (Table 1) [26]. Despite promising mechanisms involving DNA repair inhibition and immune modulation, clinical evidence remains limited.

Vitamin C: Pharmacological ascorbate induces H_2O_2 accumulation, enhancing radiation-induced killing in pancreatic cancer and glioblastoma models by 40-60% (Table 1 and Table 2) [27]. Phase I/II clinical trials have demonstrated that high-dose intravenous vitamin C, when combined with chemoradiotherapy, is well-tolerated, prolongs survival in patients with advanced pancreatic cancer, and reduces hematological toxicity (Table 2) [28]. Efficacy may be cancer-type dependent, with no significant benefit observed in some breast cancer studies (Table 2) [29].

Vitamin D: Combined with radiotherapy, vitamin D inhibits clonogenicity, invasion, and metastasis in colorectal cancer models, induces apoptosis, reverses Epithelial-Mesenchymal Transition (EMT), reduces tumor volume by >40% and prolongs progression-free survival (Table 1) [30]. Mechanisms involve DNA repair regulation and immune modulation. Clinical evidence primarily focuses on vitamin D deficiency and prognosis, with limited direct clinical evidence on radio sensitization.

Vitamin E: Vitamin E can protect and enhance the anti-tumor immune function after radiotherapy, maintain the number and activity of white blood cells (mainly lymphocytes) in the peripheral blood of mice post-radiotherapy, and prevent immune cells from excessive exhaustion due to radiation exposure (Table 1) [31]. As a fat-soluble antioxidant, it can scavenge excessive Reactive Oxygen Species (ROS) induced by radiotherapy, reduce the chance of stress-induced damage repair in tumor cells, decrease the level of oxidative stress and inflammatory response in the tumor microenvironment, inhibit the expression of tumor angiogenesis-related factors, and suppress tumor growth [31]. No direct clinical radio sensitization studies are available.

Vitamin K: Vitamins K2, K3, and K5 inhibit tumor growth in colorectal cancer models via mitochondrial or death receptor-mediated apoptosis (Table 1) [32]. Subtype mechanisms vary, and research remains preclinical.

In summary, vitamins demonstrate radio sensitizing potential across various tumors by regulating oxidative stress, inhibiting DNA repair, inducing cell cycle arrest, remodeling the immune system, and reversing EMT. There is already some clinical evidence supporting vitamins C and D, while research on other vitamins remains focused primarily on basic studies. Further well-designed clinical trials incorporating molecular typing, microenvironment features, and genetic background are needed to advance precision applications.

Challenges in the application of vitamins for radio sensitization

Dosage and formulation optimization: Vitamins exhibit diverse pharmacokinetics. Excessive doses may cause toxicity (e.g., vitamin A hepatotoxicity, vitamin D hypercalcemia), while insufficient doses may lack efficacy [33,34]. Bioavailability varies between natural and synthetic forms, and patient-specific factors (e.g., gastrointestinal, hepatic, or renal function) further influence absorption and activity [35].

Individual variability: Genetic polymorphisms (e.g., vitamin D receptor, VDR; methylenetetrahydrofolate reductase, MTHFR; methionine synthase reductase, MTRR) affect vitamin metabolism, receptor function, and efficacy [36,37]. Comorbidities such as diabetes, inflammatory bowel disease, and chronic kidney disease can alter vitamin absorption and homeostasis [38-40]. Lifestyle factors, including diet, sun exposure, and smoking, also influence vitamin levels and responses, underscoring the need for personalized approach [41,42].

Complex interactions: Combinations of vitamins with radiotherapy, other vitamins, or targeted therapies may result in synergistic or antagonistic effects [43,44]. Antioxidant vitamins may reduce the efficacy of radiotherapy under certain conditions, and interactions with immunotherapy or chemotherapy require careful evaluation to ensure both safety and effectiveness [45].

Limitations in clinical evidence: Current clinical studies are often limited by small sample sizes, non-randomized designs, and short follow-up periods, which restrict the reliability and generalizability of their findings. The clinical application and promotion of vitamins in tumor radio sensitization face challenges due to the lack of support from large-scale, multi-center, and high-quality clinical research evidence.

Table 1: Summary of major vitamins in cancer radio sensitization research.

Vitamin Type	Radio sensitization mechanism	Preclinical findings	Current status of clinical research	Main challenges
Vitamin A	Redox balance; Cell cycle; Immune regulation	ATRA inhibits growth, induces M1polarization [14]; vitamin A formulas inhibit EGFR/VEGF and cachexia [24];	No direct clinical studies	Dose-dependent hepatotoxicity; potential antagonism with other agents (e.g., vitamin D); lack of individualized protocols
B complex Vitamins	DNA repair inhibition; Immune/ metabolic regulation	B1 inhibition enhances tumor radiosensitivity [25]; B3 improves oxygenation and SER [26];	No direct clinical studies	Subtype variability; unclear drug interactions; metabolic differences (e.g., MTHFR polymorphism)
Vitamin C	Redox balance; DNA damage; Immune regulation	enhances DNA breaks [12]; causes G0/ G1 arrest and autophagy [18]; induces H_2O_2 accumulation [27];	Phase I/II support in pancreatic cancer; mixed results in breast cancer [27]	Dose-response uncertainty; potential antagonism; tumor microenvironment variability (e.g., iron levels)
Vitamin D	DNA repair inhibition; Immune regulation; Apoptosis induction; EMT reversal	Reduces colony formation, invasion, and volume; reverses EMT [30];	Focus on deficiency and prognosis; limited direct evidence	VDR polymorphism; hypercalcemia risk; potential immunomodulatory antagonism
Vitamin E	Redox balance; Cell cycle; DNA protection	Synergizes with radiotherapy via oxidative stress modulation and apoptosis [19]; Protecting immune function [31];	No direct clinical studies	Selectivity unclear; high-dose toxicity; potential antagonism with other antioxidants.
Vitamin K	DNA repair inhibition; apoptosis; Immune regulation	K2, K3, and K5 induce apoptosis and inhibit growth in CRC models [32];	No direct clinical studies	Subtype variability; unclear targets; limited clinical exploration

ATRA: All-Trans Retinoic Acid; SER: Radio Sensitization Ratio; MTHFR: Methylenetetrahydrofolate Reductase; VDR: Vitamin D Receptor; EMT: Epithelial-Mesenchymal Transition; CRC: Colorectal Cancer.

Table 2: Representative clinical studies on vitamins-mediated radio sensitization.

Author, Year	Vitamin	Cancer Type	Sample size	Combination regimen	Conclusion
Alexander MS et al. 2018 [15]	C	Locally advanced pancreatic	N/A	Vitamin C + chemoradiotherapy	Induces tumor cell death via H_2O_2 and HIF hydroxylase regulation, with potential radio sensitizing properties.
Schoenfeld JD et al. 2017 [27]	C	Glioblastoma, NSCLC	23	High-dose IV vitamin C (20,000 μM) + chemoradiotherapy	Well-tolerated; increased chemo radiosensitivity
Boeddeker KL et al. 2024 [28]	C	Pancreatic (Stage Ⅳ)	34	IV vitamin C (75 g/session, 3×/week) + chemotherapy	Improved survival (16 vs. 8.3 months); reduced hematological toxicity
Khazaei S et al. 2022 [29]	C	Breast cancer	2017	Vitamin C + radiotherapy vs. radiotherapy alone	No significant sensitization; efficacy may depend on subtype and concentration

N/A: No information available; NSCLC: Non-Small-Cell Lung Cancer.

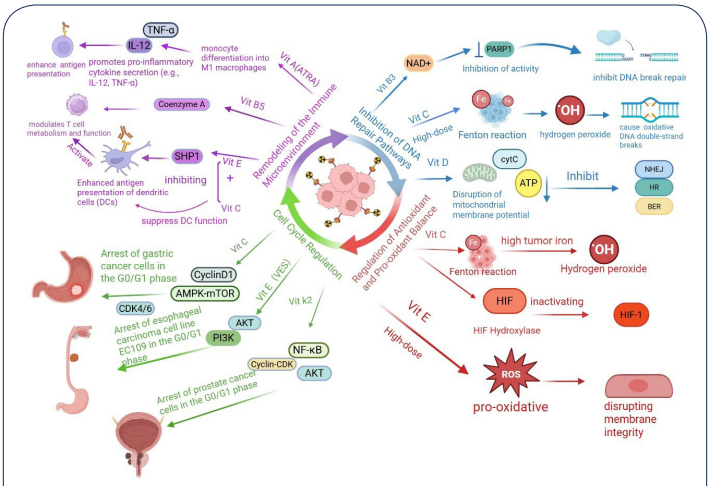

Figure 1: Mechanism network through which vitamins mediate radio sensitization via core pathways such as oxidative stress, DNA repair, cell cycle, and the immune microenvironment.

Conclusion and perspectives

Conclusion: Vitamins demonstrate significant potential to enhance tumor radiosensitivity through multi-mechanistic actions, including redox regulation, inhibition of DNA repair, cell cycle arrest, immune activation, and reversal of EMT. Certain preclinical and clinical evidence has been accumulated for vitamins C and D in some cancer types (e.g., pancreatic cancer, colorectal cancer), while others (B complex Vitamins, E, K) remain largely preclinical. Common challenges include dose individualization, formulation optimization, patient variability, and complex interactions among these factors.

Future directions

Based on current research limitations and challenges, future efforts should focus on the following areas:

Conduct large-scale, multi-center, randomized controlled trials to systematically evaluate the radio sensitizing effects of various vitamins-both as single-agent or in combination-across different

cancer types and radiotherapy regimens. These studies should aim to determine optimal administration routes, timing, and long-term safety profiles.

Enhance understanding of the dynamic mechanisms through which vitamins modulate the tumor microenvironment, with particular emphasis on their synergistic or antagonistic interactions with chemotherapy, targeted therapy, and immunotherapy. This will provide a theoretical foundation for optimizing combination strategies, for instance, by tailoring vitamin-immunotherapy combinations based on VDR genotype and PD-L1 expression levels.

Integrate multi-omics approaches (e.g., genomics, metabolomics) to identify patient subgroups most likely to benefit from vitamin-based radio sensitization, such as those with ATM/BRCA mutations [46], specific metabolic profiles [47], or particular gene expression signatures [48]. Develop tumor microenvironment-responsive nano delivery systems for vitamins to enhance local drug concentrations, reduce systemic toxicity, and enable personalized treatment [49,50].

Actively develop novel vitamin formulations with improved selectivity, stability, and bioavailability, such as nano-carriers and prodrug designs, to maximize efficacy and minimize adverse effects.

Closely evaluate the potential long-term risks associated with high-dose or prolonged vitamin use, including metabolic dysregulation, organ toxicity (e.g., niacin-related hepatotoxicity [51]), and potential carcinogenicity. Establish comprehensive safety assessment frameworks to support the clinical translation of new therapies.

Through interdisciplinary integration and in-depth investigation, vitamins are expected to facilitate more individualized and clinically meaningful advances in the field of tumor radio sensitization.

Declarations

Acknowledgement: Not applicable.

Funding: This research was funded by Science and Technology Department Basic Research Project of Shanxi [No. 202303021221239], and National Cancer Center Climbing Fund [NCC202404003], This research was funded by Science and Technology Department Basic Research Project of Shanxi[No. 202203021221282], the Research Project Supported by Shanxi Scholarship Council of China No. [2022]210, and The Science and Education Cultivation Fund of the National Cancer and Regional Medical Center of Shanxi Provincial Cancer Hospital (TD2023002), the Noncommunicable Chronic Diseases-National Science and Technology Major Project [2023ZD0502100].

Availability of data and materials: Not applicable

Authors' contributions: Yuying Zhou drafted the manuscript. Qnqi Zhao, Wenlu Chen and Baixue Wu conducted literature review. Wenbo Zhang, Ningning Yao and Meng Zhao was responsible for supervision and validation. Qing Hou, Shuangping Zhang, Jianchun Duan, Ning Li and Jianzhong Cao revised the manuscript. All authors contributed to the article, read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate: Not applicable.

Patient consent for publication: Not applicable.

Competing interests: The authors declare that they have no competing interests.

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