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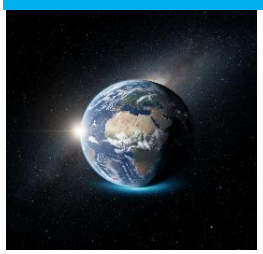

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Vitamins D and E as radiotherapy adjuncts - literature review of preclinical and clinical evidence

Ada Wiśniowska
Medical University of Warsaw
awisniowska2006@gmail.com
https://orcid.org/0009-0000-8703-8527

Maksymilian Wiśniowski[1]
Student Scientific Circle at the Department of Radiotherapy, Medical University of Lublin, Aleje Racławickie 1, 20-059 Lublin, Poland
makswisniowski@icloud.com
https://orcid.org/0009-0004-2470-307

Kacper Buczek
Student Scientific Circle at the Department of Radiotherapy, Medical University of Lublin, Aleje Racławickie 1, 20-059 Lublin, Poland
kbuczek@tlen.pl
https://orcid.org/0009-0005-0521-3536

Aleksandra Kozłowska
Department of Radiotherapy, Medical University of Lublin, Aleje Racławickie 1, 20-059 Lublin, Poland
olla.kozlowska@gmail.com
https://orcid.org/0009-0006-6900-2196

Abstract
Introduction: Radiotherapy (RT) is the fundamental method in cancer treatment, yet tumor resistance and normal tissue toxicity limit its efficacy. Vitamins D and E may modulate RT outcomes through radiosensitization, antioxidant effects, and immune regulation.
Methods and Materials: We reviewed preclinical and clinical studies from PubMed, ScienceDirect, ResearchGate, and Google Scholar using keywords like "radiotherapy", "radiation", "vitamin D", "vitamin E" and "radiosensitivity".
Results: Vitamin D enhances RT response via VDR-mediated DNA damage and reduces toxicity (e.g., mucositis), though hypercalcemia risk requires monitoring. Vitamin E (especially tocotrienols) alleviates mucositis and fibrosis, but excessive doses may compromise RT efficacy by neutralizing tumor-killing ROS.
Conclusions: Vitamins D and E show therapeutic potential in RT but require precise dosing and timing to avoid interference with treatment. Personalized strategies and robust clinical trials are needed to establish evidence-based guidelines for their adjuvant use.
Keywords: "radiotherapy", "radiation", "vitamin D", "vitamin E", "radiosensitivity"

1. Introduction

Cancer is the second leading cause of death worldwide, accounting for 9.6 million fatalities in 2018. According to projections, the annual incidence of new cancer cases could rise to 23.6 million by 2030. Despite major advancements in diagnostics and therapy, cancer is being stated with increasing frequency, particularly in developed countries. In the United States, it is estimated that over 2 million new cancer cases and over 600000 cancer-related deaths will occur in 2025 [1]. The rising incidence and complexity of cancer treatment necessitate the exploration of novel strategies to complement conventional therapeutic approaches.

Radiotherapy (RT) is one of the key modalities in cancer treatment, utilized in approximately 70% of oncology patients [2]. Alongside surgery and chemotherapy, RT is considered a principal cancer treatment strategy [3]. Its primary objective is the destruction of cancer cells

through the administration of high doses of ionizing radiation, such as X-rays, gamma rays (γ), alpha particles (α), beta particles (β), protons, and neutrons [4]. RT can be applied for both curative and palliative purposes, depending on the cancer type, disease stage, and the overall health condition of the patient. Radiotherapy faces significant challenges, including tumor resistance and collateral damage to healthy tissues [2-5,6]. RT functions through both direct and indirect mechanisms to damage cancer cells [7,8]. Directly, ionizing radiation induces DNA damage by causing single-strand breaks (SSB) and double-strand breaks (DSB), resulting in cell-cycle arrest, apoptosis, or necrosis [7]. Indirectly, RT promotes oxidative stress through the formation of reactive oxygen species (ROS), such as hydroxyl radicals (•OH), superoxide radicals ($O_2•^-$), and hydrogen peroxide (H_2O_2), which further damage DNA, proteins, and lipids, disrupting cellular functions and contributing to cell death [4,7,8]. ROS also activate apoptosis-associated signaling pathways, enhancing therapeutic outcomes [4]. However, cancer cells possess mechanisms to repair such damage, potentially leading to cell survival and treatment resistance [8]. Excessive oxidative stress, meanwhile, can adversely affect healthy tissues, causing inflammation, fibrosis, and organ dysfunction [2,7]. Managing oxidative stress levels is therefore essential to maximize therapeutic effectiveness and minimize toxicity.

Multiple factors influence RT efficacy, including cancer type, tumor localization, disease stage, patient age, overall health status and individual DNA repair capacities [9]. Notably, tissue oxygenation plays a crucial role, as hypoxic cancer cells exhibit increased radioresistance due to metabolic shifts toward glycolysis [10]. Additionally, resistance to RT can arise from the activation of survival signalling pathways, such as Wnt/β-catenin, NF-κB, and Akt/cyclin D1/CDK4 [11]. The presence of cancer stem cells (CSCs) further complicates therapy by contributing to disease recurrence and metastasis, highlighting a persistent therapeutic challenge [12]. Thus, enhancing the effectiveness of radiotherapy while minimizing its adverse effects remains a critical focus in contemporary oncology.

Dietary supplements, including vitamins, minerals, and natural product-derived supplements, are commonly used by cancer patients, particularly those undergoing treatments like chemotherapy and radiotherapy. The prevalence of supplement use varies across countries but is generally high among cancer patients. In the United States, a significant percentage of cancer survivors report using dietary supplements, with 70.4% incorporating them into their treatment regimens. Among these, multivitamins are the most commonly used [13]. In South Korea, 33.3% of cancer survivors use dietary supplements, compared to 22.1% of cancer-free individuals, highlighting the high prevalence among cancer patients [14]. Similarly, in Iran, 20.4% of cancer patients undergoing chemotherapy and 23.7% undergoing chemoradiation regularly use vitamins as part of their treatment [15]. In Germany, 56.4% of women with breast cancer report using dietary supplements post-diagnosis, compared to only 20.2% before diagnosis, indicating an increase in supplement use following cancer diagnosis [16]. In Mongolia, 47.9% of cancer patients use complementary and alternative medicine (CAM) modalities, including dietary supplements, often alongside conventional treatments such as chemotherapy or radiotherapy [17]. In the United Kingdom, a large cohort study found that 57.8% of cancer patients use dietary supplements, with this use being associated with a lower risk of all-cause and cancer-specific mortality [18]. In the United States, Fakhoury et al. conducted a study that found 82.0% of radiation oncology patients used complementary health approaches (CHAs), including dietary supplements, within the past 12 months. Despite the high use, only 35.9% of those patients disclosed their use of these supplements to their radiation oncologists. After attending an integrative medicine educational program, 67.4% of patients reported intending to disclose their use of CHAs, showing a marked increase in openness and self-efficacy regarding supplement use and health management during cancer treatment [19]. The study by Hauer et al. focusing on breast cancer patients revealed that 89.5% of participants used vitamin and mineral (VM) supplements, with 46.5% of them using at least three different VM products concurrently.

Natural products (NP), including probiotics, turmeric and fish oil, were used by 67.7% of participants, with a significant proportion of these individuals also using multiple NP products concurrently [20]. This study highlights the high reliance on supplements among breast cancer patients, underscoring the need for awareness of their potential interactions with cancer treatment methods. The reasons for using dietary supplements among cancer patients are varied, ranging from the desire to reduce treatment side effects such as fatigue and nausea to hope of enhancing treatment efficacy and improving overall well-being. Many patients, particularly those undergoing chemotherapy, use supplements to manage symptoms like fatigue, while others believe that supplements can help in boosting immune function or improving their quality of life during cancer treatment [13,14]. Despite the high rates of use, there are concerns about the potential interactions between supplements and cancer treatment methods. This underscores the need for healthcare providers to control the patients' use of supplements to ensure safety and avoid possible negative interactions with cancer therapies.

2. Materials and methods

Given the growing interest in vitamins among cancer patients and the absence of clear clinical guidelines on their use during radiotherapy, a critical evaluation of their effects on tissue radiosensitivity is warranted. This review aims to synthesize the available evidence on selected vitamin compounds, exploring their molecular mechanisms, potential therapeutic benefits and associated risk. Literature was sourced from PubMed, ScienceDirect, ResearchGate, and Google Scholar, using search terms including: radiotherapy, radiation, vitamin D, vitamin E and radiosensitivity.

3. Results

3.1. Vitamin D

Vitamin D is a fat-soluble setosteroid that plays a multifaceted role in human physiology, acting as a precursor to the biologically active form 1,25-dihydroxyvitamin D_3 [15,16]. It is synthesized in the skin upon exposure to ultraviolet B radiation and metabolized through hepatic and renal hydroxylation, ultimately influencing calcium-phosphorus homeostasis, bone health, immune function, and cellular differentiation [16-18]. While dietary sources and supplements can provide vitamin D, deficiency remains common due to limited sun exposure, aging, and lifestyle factors [15,19]. Beyond its classical roles, emerging research has highlighted vitamin D's potential in oncology, particularly as an adjuvant to radiotherapy and chemotherapy [15-17]. Experimental and epidemiological data suggest that adequate serum levels of 25-hydroxyvitamin D are associated with reduced incidence and improved prognosis in various cancers, including breast, colorectal, prostate, and lung cancers [16,20]. Notably, vitamin D exerts antiproliferative, pro-apoptotic, anti-inflammatory, and anti-angiogenic effects, while also modulating the tumor microenvironment (TME) and immune responses, thereby enhancing sensitivity to radiation and mitigating treatment-related side effects such as fatigue, neuropathy, and gastrointestinal disturbances [16-18,21]. In the context of radiotherapy, vitamin D operates through multiple molecular and cellular mechanisms. Firstly, it enhances radiosensitivity in tumor cells by modulating the expression and activity of vitamin D receptors (VDR), which in turn regulate genes involved in cell cycle arrest (e.g., p21, p27), DNA repair, and apoptosis [16,18]. It downregulates pro-survival pathways such as PI3K/Akt and MAPK/ERK, while upregulating pro-apoptotic factors like BAX and caspases, thereby intensifying radiation-induced cell death [16]. Moreover, vitamin D impairs DNA damage repair mechanisms in cancer cells by inhibiting homologous recombination, leading to

accumulation of double-strand breaks and enhanced cytotoxicity following ionizing radiation exposure [18]. Additionally, vitamin D mitigates radiation-induced oxidative stress in healthy tissues through its antioxidant properties, decreasing levels of reactive oxygen species (ROS) and upregulating protective enzymes like superoxide dismutase (SOD) and glutathione peroxidase (GPx) [22]. It also supports vascular integrity and epithelial barrier function, reducing radiation-related mucositis and enteritis [21,22]. Importantly, vitamin D reprograms the immunosuppressive TME by inhibiting the recruitment of myeloid-derived suppressor cells (MDSCs), enhancing cytotoxic T lymphocyte activity, and promoting dendritic cell maturation, all of which contribute to improved antitumor immune responses [18,21]. Vitamin D further affects the gut microbiota, a key modulator of systemic inflammation and radiation resistance. It helps maintain microbial diversity and reduces dysbiosis, which has been implicated in modulating host immunity and tumor progression in patients receiving radiotherapy [21].

Vitamin D demonstrates significant potential in modulating tumor response and mitigating normal tissue injury during radiotherapy. In vitro and in vivo studies have shown that the active form of vitamin D—1α,25-dihydroxyvitamin D_3 (calcitriol)—enhances radiosensitivity in various cancer cell types by activating specific molecular pathways involved in oxidative stress and apoptosis. For instance, Ji et al. demonstrated that calcitriol radiosensitized lung and ovarian cancer cells by upregulating NOX4, p22^phox^, and p47^phox^, components of the NADPH oxidase complex. This resulted in a 1.8-fold increase in intracellular ROS and a 2.1-fold increase in apoptotic cell populations. Antioxidant pretreatment reversed these effects, confirming ROS-mediated radiosensitization [22]. In hepatocellular carcinoma (HCC) models, calcitriol suppressed IL-6 expression by 60% and reduced cancer stemness markers (e.g., CD44 and CD133) by over 50% post-radiation. In vivo, mice treated with calcitriol plus 10 Gy radiation exhibited significantly smaller tumors (mean volume reduction of 48%) compared to radiation alone (23%). Immunohistochemical analysis revealed enhanced infiltration of $CD8^+$

T cells (2.3-fold) and a 44% reduction in MDSCs in tumors from the combination group [23]. In pancreatic ductal adenocarcinoma (PDAC), vitamin D reduced α-SMA expression in CAFs by 70%, thereby preventing fibroblast activation that typically promotes post-radiation metastasis. Supplementation also led to a 2-fold increase in radiosensitivity in vitro and suppressed tumor progression in orthotopic mouse models [24]. In breast cancer models, calcipotriol-loaded FAP-targeted nanoparticles restored CAFs to a quiescent state (via lipid droplet accumulation and p27Kip1 upregulation), reduced TGF-β expression, and enhanced radiation-induced tumor regression by 34.9% compared to radiation alone [25]. In normal keratinocytes, vitamin D pretreatment (100 nM) demonstrated dose-dependent radioprotection: it reduced caspase-3 activity by ~70% (4 Gy), ~75% (8 Gy), and ~80% (12 Gy), while completely blocking the apoptotic morphology induced by 4 Gy irradiation. Additionally, calcitriol suppressed radiation-induced MMP-9 secretion by ~50% at both 4 Gy and 10 Gy. The protective effects were observed whether vitamin D was administered before or after irradiation, with maximal efficacy seen in the 4-12 Gy dose range relevant to radiotherapy [26]. Endothelial cells pretreated with calcitriol showed a 45.7% reduction in senescence-associated β-galactosidase activity after 4 Gy irradiation and maintained SIRT1 expression (1.5-fold higher in proliferating cells), suggesting protection against radiation-induced senescence [27]. In murine models exposed to 8 Gy abdominal irradiation, vitamin D receptor (VDR) activation preserved villus length and reduced epithelial cell apoptosis. Mice treated with vitamin D analogs showed improved crypt regeneration and better weight maintenance compared to irradiated controls [28]. In melanoma cell lines exposed to proton beam radiation (0–5 Gy), calcitriol and calcidiol enhanced radiation sensitivity, reducing clonogenic survival and increasing apoptosis. The effect was dose-dependent, with higher vitamin D concentrations showing greater radiosensitization [29]. In prostate cancer models treated with 15 Gy radiation, calcitriol pretreatment suppressed IL-6 signaling and STAT3 activation. Tumor-bearing mice

receiving calcitriol plus radiation showed greater tumor regression than radiation alone. Calcitriol also increased DNA damage markers (γ-H2AX) and decreased clonogenic survival after irradiation [30]. Yu et al. showed that in colorectal cancer cells, calcitriol combined with 6 Gy radiation significantly decreased cell viability (inferred ~55% reduction vs. ~23% with radiation alone). EMT reversal was evidenced by a 2.8-fold increase in E-cadherin and a ~70% decrease in Snail. In vivo, the combination reduced tumor volume by 59% without toxicity [31]. In cervical cancer, Zhang et al. reported that calcitriol enhanced radiation-induced apoptosis, downregulating autophagy markers (LC3B-II) by ~60% and increasing cleaved caspase-8 (2.6-fold). In vivo, tumor volume was reduced by 68% (vs. 31% with radiation alone) [32]. Trémezaygues et al. found that $1,25(OH)_2D_3$ reduced γ-H2AX foci by ~40% at 2 Gy (suggesting DNA protection) but increased foci at 5 Gy, indicating a dose-dependent dual role [33].

Clinical investigations in cancer patients undergoing radiotherapy support the potential role of vitamin D in modifying treatment outcomes, including toxicity, quality of life, and tumor response. In a randomized controlled trial of 45 head and neck cancer patients, topical oral vitamin D gel significantly reduced the severity of radiation-induced oral mucositis (RIOM). After 6 weeks of radiotherapy, 33.5% of the control group experienced high-grade mucositis, compared to only low-grade or remissive mucositis in the vitamin D and combination therapy groups. Pain scores were also significantly lower in the vitamin D-treated groups, confirming a protective effect against RIOM [34]. Anand et al. examined the impact of vitamin D supplementation on quality of life (QOL) in 45 patients with advanced oral cancer undergoing chemoradiotherapy. Vitamin D significantly reduced treatment-related toxicities, including oral mucositis and dysphagia, and improved overall QOL. Additionally, they found that vitamin D receptor (VDR) expression was elevated in premalignant and malignant oral lesions, while serum vitamin D levels were significantly lower in cancer patients compared to healthy controls ($p = 0.002$) [35]. A prospective observational study in patients with head and neck squamous

cell carcinoma (HNSCC) receiving chemoradiotherapy found that suboptimal serum 25-hydroxy vitamin D levels were associated with a significantly higher incidence of mucositis ($p = 0.0011$) and radiation dermatitis ($p = 0.0505$). Only 28.6% of patients had optimal vitamin D status at follow-up, underscoring widespread deficiency and its clinical implications [36]. In breast cancer patients, a randomized trial compared calcipotriol (vitamin D analog) ointment versus Aqua cream for prevention of radiation dermatitis. Although no significant difference in skin toxicity was observed between the two treatments, the study confirmed the safety of topical vitamin D application and highlighted the need for larger studies to assess efficacy [37]. Fassio et al. analyzed vitamin D status in 394 breast cancer patients within 12 months of diagnosis. Hypovitaminosis D (<20 ng/mL) was present in 39% of all patients, but in 60% of those not receiving supplementation. Chemotherapy, obesity, and southern geographic residence were associated with higher deficiency rates. These deficiencies were relevant given the role of vitamin D in bone health, immune function, and possibly breast cancer prognosis [38]. In another study involving 107 breast cancer patients, vitamin D blood levels (mean 20.9 ng/mL) were found to be below normal in the majority of participants. However, no statistically significant correlation was found between vitamin D status and severity of radiotherapy-induced skin toxicity, suggesting limited predictive value for dermatologic side effects in this context [39]. A study by Moghaddam et al. on 98 cancer patients receiving pelvic radiation found that vitamin D deficiency significantly increased the risk of developing radiation-induced acute proctitis. Patients with low vitamin D levels had a higher RTOG score (median 2 vs. 1, $p = 0.037$), and deficiency was an independent predictor of grade ≥2 proctitis (OR = 3.07; 95% CI: 1.27–7.50; $p = 0.013$) [40]. Deng et al. evaluated patients with nasopharyngeal carcinoma and late delayed radiation-induced brain injury (RBI), finding significantly lower serum $25(OH)D_3$ levels in RBI patients versus healthy controls (40.39 ± 22.11 vs. 64.54 ± 19.89 nmol/L, $p < 0.001$). Lower vitamin D levels correlated with increased RBI severity

(LENT/SOMA score ≥3, p = 0.010) and shorter latency period (p = 0.015) [41]. Genetic factors may also influence response to radiotherapy. In a cohort of 256 patients with differentiated thyroid cancer (DTC) receiving radioiodine-131, VDR gene polymorphisms (particularly rs7975232 and rs10735810) were associated with both treatment efficacy and toxicity. Patients with the CC genotype at rs7975232 had better therapeutic responses and fewer adverse reactions, highlighting a potential role for VDR genotyping in personalizing treatment [42]. Nejatinamini et al. demonstrated in head and neck cancer patients that lower plasma 25(OH)D levels were significantly associated with both increased mucositis and greater skeletal muscle loss during treatment. Patients with vitamin D deficiency had an average muscle loss of 3.4 kg and significantly lower dietary and plasma vitamin A and D levels compared to those without mucositis ($p < 0.02$) [43]. In a randomized controlled trial of patients with advanced cervical cancer (FIGO stages IIB–IVA), daily supplementation with 10,000 IU of cholecalciferol during a 7-week radiotherapy course and 12-week post-treatment period significantly improved treatment response. Complete response was achieved in 82.6% of the treatment group, compared to 64.8% in the control group—a 14.32% increase in efficacy. Moreover, patients in the vitamin D group reported fewer adverse effects, including reduced rates of bleeding (2.9% vs. 35.2%) and discharge (36.2% vs. 55.6%) [44]. Yamada et al. conducted a study on 146 pancreatic ductal adenocarcinoma (PDAC) patients, showing that those receiving preoperative chemoradiation therapy (CRT) had significantly lower bone density—a predictor of distant metastasis. Multivariate analysis revealed a hazard ratio (HR) of 2.17 for bone density decrease (p = 0.04), while CRT was associated with a 5.8-fold higher risk of bone loss in patients with low vitamin D levels. Although low vitamin D (<20 pg/mL) was only a weak predictor of metastasis (p = 0.08), it was significantly associated with bone density change (p = 0.04), indicating the potential value of supplementation [45]. Nguyen et al. reported rapid relief from acute radiation dermatitis using oral high-dose vitamin D (50,000–100,000 IU). In two patients,

symptoms such as erythema and swelling improved significantly within 3–7 days post-treatment, when prior steroid therapy had failed. One patient achieved disease remission, while the other experienced partial improvement before disease progression [46]. A similar case series by Nguyen et al. supported the use of high-dose vitamin D (hdvD) in managing acute radiation dermatitis. Patients receiving hdvD showed faster symptom resolution compared to standard care, with significant reductions in skin inflammation and no reported adverse effects [47].

Vitamin D supplementation is generally considered safe and well-tolerated in cancer patients undergoing radiotherapy, especially when used at physiological or moderately elevated doses. Several clinical studies report minimal toxicity, with most adverse events being mild and manageable. However, a few reports highlight potential concerns, particularly at higher doses. For example, in a phase II trial involving breast cancer patients receiving adjuvant chemotherapy, 29.5% developed asymptomatic grade 1 hypercalciuria, which led to discontinuation of vitamin D in some cases, although renal function remained unaffected [48]. High doses of calcitriol (1,25-dihydroxyvitamin D_3) have also been associated with the risk of hypercalcemia, especially when used in combination with chemotherapy or calcium supplementation [49]. Nevertheless, other studies emphasize the favorable safety profile of vitamin D-containing interventions, reporting reduced rates of nausea, neutropenia and other chemotherapy-related side effects in patients receiving supportive nutritional regimens including vitamin D [48]. Overall, vitamin D appears to be a promising adjunct in cancer care, but supplementation should be personalized and monitored to avoid rare but possible complications such as hypercalcemia or hypercalciuria. Although preclinical and clinical research suggests that vitamin D may support better radiotherapy outcomes—through immune modulation, tumor suppression, and protection against radiation-induced toxicity—official guidelines do not currently recommend vitamin D as part of routine cancer treatment. The recommended daily intake remains 600–800 IU depending on age, with a safe upper limit of

4000 IU/day. Supplementation may be beneficial in patients with documented deficiency (serum 25(OH)D <30 nmol/L), but indiscriminate high-dose use is not advised. Further large-scale clinical trials are needed before vitamin D can be formally integrated into oncologic practice guidelines [50].

3.2. Vitamin E

Vitamin E is a fat-soluble compound with potent antioxidant activity, occurring in eight natural isoforms—four tocopherols (α, β, γ, δ) and four tocotrienols (α, β, γ, δ).

Vitamin E is widely distributed in nature: tocopherols are predominantly found in green leafy vegetables, nuts (e.g., almonds, hazelnuts), sunflower seeds, and plant oils such as soybean and canola oil. In contrast, tocotrienols are primarily found in palm oil, rice bran oil, barley, oats, rice, and annatto seeds—one of the richest natural sources of these vitamin E isoforms. Cereal- and oil-derived products may vary in their content of specific isomers; for example, palm oil contains up to 70% tocotrienols and only 30% tocopherols [51]. Although α-tocopherol has historically attracted the most attention due to its bioavailability, it is tocotrienols—particularly γ- and δ-tocotrienol—that demonstrate the strongest biological activities, including antioxidant, anti-inflammatory, and anticancer effects [51,52]. Studies indicate that tocotrienols inhibit signalling pathways involved in cancer cell proliferation, angiogenesis, and metastasis while inducing apoptosis and autophagy in various types of cancer cells, including breast, prostate, pancreatic, and lung cancers. Notably, tocotrienols may act selectively, damaging cancer cells without affecting normal tissues [52]. The mechanism of action of vitamin E involves its ability to neutralize free radicals, such as reactive oxygen species (ROS), thereby protecting cells from oxidative stress and DNA damage [51,53]. Additionally, vitamin E modulates the expression of genes involved in inflammatory responses by reducing the activity of transcription factors such as NF-κB and decreasing levels of pro-inflammatory cytokines like TNF-α and IL-6 [51]. In the context of radiotherapy, both tocopherols and tocotrienols exhibit radioprotective

properties, mitigating the harmful effects of ionizing radiation. This protective mechanism includes the scavenging of ROS, reduction of inflammation, and promotion of DNA repair and cell survival [53]. Moreover, vitamin E supplementation is associated with a reduced risk of cancers such as lung cancer—each additional 2 mg/day of vitamin E may lower this risk by up to 5% [54].

Studies on human hematopoietic progenitor cells (CD34+) and murine models have shown that δ-tocotrienol enhances post-radiation cell survival via activation of the ERK1/2 and mTOR signalling pathways. These activations lead to increased translation of proteins crucial for cell growth and survival, including eIF4E and ribosomal protein S6. Furthermore, δ-tocotrienol reduces the formation of γ-H2AX foci—markers of DNA damage—and increases colony-forming units, indicating enhanced DNA repair and anti-apoptotic activity [55]. In nonhuman primates, γ-tocotrienol (GT3) was shown to shorten the duration of radiation-induced neutropenia and thrombocytopenia. At doses of 5.8 and 6.5 Gy, GT3 completely prevented thrombocytopenia, with the higher dose (75 mg/kg) proving more effective than the lower (37.5 mg/kg), albeit associated with mild local skin reactions. These effects were dose-dependent, suggesting GT3's potential for human application as a radioprotector [56]. In hepatocellular carcinoma (HCC) and endothelial (HUVEC) cell lines, γ-tocotrienol was also identified as a potent antiangiogenic agent. It inhibited VEGF-induced activation of the VEGFR2 receptor, thereby blocking the downstream AKT/mTOR signalling pathway. This resulted in reduced endothelial cell migration, invasion, and capillary-like structure formation, as well as suppression of tumor growth in an orthotopic mouse model of HCC [57]. Other studies using CD2F1 mouse models demonstrated that GT3 has the highest dose-reduction factor (DRF = 1.29) among known tools. Its radioprotective effect was linked to ROS scavenging and accelerated hematopoietic regeneration. GT3-treated mice exhibited significantly higher post-radiation levels of white blood cells, neutrophils, monocytes, platelets, and reticulocytes

compared to controls [58]. Research by Kulkarni et al. further confirmed that GT3 protects hematopoietic stem and progenitor cells from radiation-induced injury. Flow cytometry analysis showed that within 7 days post-irradiation, the number of progenitor cells (HPC) in the GT3 group recovered to 90% of normal levels, compared to just 30% in the control group even after 13 days. Additionally, a greater number of regenerative foci and reduced micronucleus frequency in erythrocytes were observed, indicating diminished long-term DNA damage [59]. A subsequent study by the same team revealed that GT3 strongly induces hematopoietic cytokine production, notably G-CSF, IL-6, IL-1α, and MIP-1α. G-CSF levels exceeded 5000 pg/mL within 12–24 hours post-injection, correlating with maximal radioprotective efficacy when GT3 was administered 24 hours before irradiation [60]. In a preclinical model of radiation necrosis induced by stereotactic radiosurgery (Gamma Knife), vitamin E (administered at 30 mg/kg/day) reduced expression of HIF-1α and VEGF—key mediators of hypoxia and angiogenesis. This resulted in a lower number of VEGF-positive cells in the perinecrotic zone and reduced contrast enhancement on MRI, suggesting that vitamin E may also exert vascular-protective effects [61]. Anzai et al introduced γ-tocopherol-N,N-dimethylglycine ester (GTDMG), a water-soluble γ-tocopherol prodrug. In mice subjected to lethal whole-body X-irradiation (7.5 Gy), GTDMG (100 mg/kg) significantly improved 30-day survival to 97.6% when administered immediately post-exposure. GTDMG remained effective even when administered up to 24 hours post-irradiation (36.7% survival) and demonstrated a high DRF of 1.25. Hematologic recovery included increased RBC, WBC, and platelet counts, as well as endogenous spleen colony formation, confirming potent radiomitigative properties [62].

In a randomized, double-blind clinical trial conducted by Chung et al., the efficacy of vitamin E and C supplementation was evaluated in patients undergoing radiotherapy for head and neck cancers. The intervention group (n = 25) received 200 IU of vitamin E and 1000 mg of vitamin C daily during treatment. After six months, participants showed a significant reduction in

radiation-induced xerostomia symptoms compared to the placebo group (n = 20), although no difference was noted in overall survival between groups. The treatment was well-tolerated, with no significant adverse effects reported. There were no indications of increased toxicity or interference with radiotherapy efficacy, suggesting a favorable safety profile for combined antioxidant supplementation in this context [63]. In a study by Ferreira et al., the use of a topical α-tocopherol oil mouthwash (400 mg) significantly reduced the frequency and severity of oral mucositis in patients undergoing radiotherapy for cancers of the oral cavity and pharynx. Symptomatic mucositis occurred in 21.6% of the vitamin E group, compared to 33.5% in the placebo group ($p = 0.038$). Moderate to severe pain (grade 2–3) was reported in only 3 out of 28 patients in the vitamin E group, compared to 14 out of 26 in the control group ($p = 0.0001$). No adverse reactions or mucosal irritation were observed during the study. The topical application of vitamin E was safe and well-tolerated, with no instances of hypersensitivity or other complications [64]. Hosseini et al. investigated a combination mouthwash containing vitamin E, triamcinolone, and hyaluronic acid in comparison to triamcinolone alone for managing radiation-induced oral mucositis. In this four-week randomized trial involving 60 patients, the vitamin E combination group showed a significant reduction in both mucositis severity and pain across all weekly assessments ($p < 0.001$). The formulation was well-tolerated, and no local or systemic side effects were reported. These results suggest a synergistic therapeutic effect with excellent tolerability [65]. In the context of breast cancer, Jacobson et al. examined the use of oral vitamin E (400 IU/day) in combination with pentoxifylline (400 mg three times daily) for six months following radiotherapy. Among the 26 patients in the intervention group, a significant reduction in radiation-induced fibrosis was observed, as measured by tissue compliance, compared to 27 patients in the control group (mean difference: 0.88 mm vs. 2.10 mm; $p = 0.0478$). The combination therapy was associated with minor gastrointestinal discomfort in a few cases, primarily nausea, but no participant withdrew due to

adverse events. Treatment adherence was high, and the overall safety profile was acceptable [66]. A systematic review by Person et al. further supports the use of pentoxifylline and vitamin E for reducing radiation-induced fibrosis in breast cancer patients. The authors reviewed clinical trials specifically targeting fibrosis prevention or treatment and concluded that this combination may be beneficial, though larger, better-controlled trials are necessary to validate its efficacy. The review noted that most reported side effects were mild, with pentoxifylline occasionally causing gastrointestinal upset, dizziness, or headaches. Vitamin E alone was consistently well-tolerated across studies [67]. In a randomized controlled trial by Sayed et al., the combination of pentoxifylline (400 mg twice daily) and vitamin E (1000 mg daily) was evaluated in 60 patients with head and neck cancers undergoing radiotherapy. The intervention significantly reduced the severity and duration of oral mucositis and dysphagia. Patients in the combination group required fewer hospitalizations and radiotherapy interruptions and reported better quality of life outcomes ($p < 0.01$). Adverse effects were infrequent and primarily involved mild gastrointestinal symptoms, such as gastric discomfort. No severe toxicities were noted, and locoregional tumor control remained uncompromised [68]. In a pilot study by Schmidt et al., topical application of a nanoparticle cream containing 2% vitamin E was assessed for its effectiveness in preventing radiodermatitis among breast cancer patients. Although all participants developed some form of radiodermatitis, the onset was significantly delayed in the vitamin E group ($p = 0.03$), and milder erythema was observed, particularly in the inframammary region ($p = 0.04$). The formulation was well-tolerated, with no reports of adverse dermatologic or systemic reactions. The findings support the safety of topical nanoencapsulated vitamin E in radiotherapy-induced skin toxicity prevention [69]. Additionally, a phase II clinical trial (ClinicalTrials.gov ID: NCT01871454) is underway at the University of Louisville to assess the safety and efficacy of pentoxifylline and vitamin E in patients with non-small cell lung cancer undergoing stereotactic ablative radiotherapy (SABR) after prior thoracic

irradiation. The objective is to evaluate whether this combination can reduce radiation-induced toxicity during re-irradiation. While final results are pending, earlier reports suggest that the regimen is generally well-tolerated. Preliminary observations indicate mild gastrointestinal side effects—primarily gastric irritation—in some patients. No severe adverse events have been linked to the intervention thus far.

Despite encouraging preclinical and clinical evidence suggesting the protective role of vitamin E in mitigating radiation-induced toxicities such as mucositis, fibrosis, and radiodermatitis, vitamin E is not routinely implemented in standard oncologic practice. Several clinical trials have shown beneficial effects, particularly when vitamin E is administered topically or in combination with pentoxifylline [66,68,69]. However, systemic high-dose supplementation has raised safety concerns. The Selenium and Vitamin E Cancer Prevention Trial (SELECT), which enrolled over 35,000 healthy men, demonstrated that supplementation with 400 IU/day of α-tocopheryl acetate was associated with a statistically significant 17% increase in the risk of prostate cancer compared to placebo (HR = 1.17; 99% CI, 1.004–1.36; p = 0.008). This increased risk persisted after discontinuation of supplementation and became apparent after approximately two years of use. The co-administration of selenium appeared to mitigate this risk, indicating potential interaction effects [70]. Although vitamin E is generally well tolerated in short-term use or at physiological doses, higher doses have been linked to potential adverse outcomes. These include altered redox signalling, interference with chemotherapeutic efficacy, and displacement of other isoforms such as γ-tocopherol, which may have superior anti-inflammatory properties [51,71]. There is also concern that supraphysiological antioxidant supplementation may counteract the cytotoxic effects of radiotherapy or chemotherapy by neutralizing reactive oxygen species that are essential to cancer cell killing [71,72]. Given these findings, high-dose vitamin E supplementation during cancer treatment should be approached

cautiously. Additional robust clinical trials are needed to establish the safe therapeutic window and clarify the balance between benefit and risk in oncologic settings.

4. Conclusions

Vitamins D, and E have demonstrated considerable potential in enhancing the efficacy of radiotherapy while reducing associated side effects. Vitamin D enhances tumor response to radiation and protects normal tissues, but excessive supplementation can lead to complications such as hypercalcemia. Vitamin E, especially tocotrienols, provides radioprotection and alleviates side effects like skin toxicity but may interfere with the cytotoxic effects of radiation at high doses. The current evidence data suggest these vitamins could play important roles in optimizing radiotherapy outcomes, but several challenges remain. The timing, dosage, and combination of vitamins with radiotherapy require careful consideration to avoid interfering with treatment efficacy. The potential for antioxidant vitamins to protect tumor cells remains a theoretical concern that needs further investigation. Future research should focus on well-designed clinical trials to establish evidence-based guidelines for vitamin use in radiation oncology. Personalized approaches, considering individual patient factors and tumor characteristics, will likely be key to realizing the full potential of these nutritional adjuvants in cancer treatment.

5. Disclosure

Author Contribution Statement

Conceptualization: AW, MW; methodology: AW, MW; software: n/a; check: MW, ; formal analysis: MW, AK; investigation: MW, AW; resources: MW; data curation: AW; writing - rough preparation: AW, MW, KB; writing - review and editing: AW, MW; visualization: MW, AW; supervision: AK; project administration: AW; receiving funding: n/a. All authors have read and agreed with the published version of the manuscript.

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