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Vitamins A and C as radiotherapy adjuncts - literature review of preclinical and clinical evidence

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Abstract

Introduction: Radiotherapy (RT) is a cornerstone in cancer treatment, but its success is often hindered by tumor radioresistance and normal tissue toxicity. Vitamins A and C are being investigated as potential adjuvants to modulate RT outcomes through radiosensitizing, radioprotective, and immune-regulatory mechanisms.

Methods and Materials: We reviewed preclinical and clinical studies from PubMed, ScienceDirect, ResearchGate, and Google Scholar using keywords like “radiotherapy”, ”radiation”, “vitamin A”, “vitamin C”, “retinol”, “β-carotene”, “α-carotene”, “β-cryptoxanthin”, “ascorbic acid” and “radiosensitivity”.

Results: Vitamin A, particularly all-trans retinoic acid (ATRA), enhances radiosensitivity by promoting immune-mediated tumor regression, impairing DNA repair in cancer stem cells, and reducing radiation-induced normal tissue damage. However, clinical data on β-carotene suggest potential risks, including increased recurrence in some populations (e.g., smokers). Vitamin C shows dose-dependent effects: at physiological levels, it protects normal tissues via antioxidant activity, while at pharmacological intravenous doses, it selectively sensitizes tumors through pro-oxidant mechanisms. Clinical trials indicate potential for mitigating RT toxicity, such as improved

xerostomia, but evidence is currently limited.
Conclusions: Vitamins A and C may enhance the therapeutic ratio of radiotherapy via distinct biological mechanisms. However, their clinical use requires careful consideration of dose, timing, and patient-specific factors. Further research through well-designed trials is needed to establish optimal protocols and identify which patients are most likely to benefit.
Keywords: “radiotherapy”, ”radiation”, “vitamin A”, “vitamin C”, “retinol”, “β-carotene”, “α-carotene”, “β-cryptoxanthin”, “ascorbic acid”, “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 signaling 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 A", "vitamin C", "retinol", "β-carotene", "α-carotene", "β-cryptoxanthin", "ascorbic acid" and "radiosensitivity".

3.Results

3.1.Vitamin A

Vitamin A is a group of fat-soluble compounds essential for numerous physiological functions in humans, including vision, immune regulation, cellular differentiation and reproduction. It occurs in two primary forms in nature: preformed vitamin A (retinol and its derivatives), which is found in animal-based food, such as liver, dairy, and eggs, and provitamin A carotenoids (like β-carotene, α-carotene, and β-cryptoxanthin), which are abundant in colorful fruits and vegetables such as carrots, sweet potatoes, and leafy greens [21,22]. Preformed vitamin A, especially in the form of retinyl esters, is efficiently absorbed in the

intestine and stored in the liver, while carotenoids require enzymatic cleavage for conversion to retinol, with β-carotene being the most potent precursor [21]. Carotenoids must contain at least one unsubstituted β-ionone ring to serve as vitamin A precursors [21,23]. Biologically, vitamin A exerts its action predominantly via its active metabolite, all-trans-retinoic acid (ATRA), which acts as a ligand for nuclear receptors—retinoic acid receptors (RARs) and retinoid X receptors (RXRs). These receptors form heterodimers that bind to retinoic acid response elements (RAREs) in the promoter regions of target genes, regulating transcription of genes involved in cell proliferation, differentiation, apoptosis, and oxidative stress response [23]. This genomic mechanism distinguishes vitamin A from classical antioxidants, as its antioxidant effects are largely indirect, mediated through the transcriptional regulation of antioxidant enzymes and pathways such as NRF2/KEAP1 [23]. Furthermore, carotenoids—while distinct from vitamin A—possess direct antioxidant properties by quenching reactive oxygen species (ROS) and singlet oxygen. These effects contribute to the health benefits of carotenoid-rich diets and are independent of their conversion to retinoids [22,23]. Therefore, while dietary carotenoids may act as antioxidants, vitamin A itself functions primarily as a transcriptional regulator with indirect antioxidant capacity [23].

Vitamin A and its active metabolite all-trans retinoic acid (ATRA) exhibit diverse biological effects in cancer and radiotherapy settings, including radiosensitization, tumor suppression, and protection of normal tissues. In MC38 colon carcinoma-bearing mice, combination therapy with ATRA and 15 Gy ionizing radiation resulted in complete tumor regression in 89% of animals, compared to partial responses in monotherapy arms. This effect was immune-mediated: $iNOS^+$/TNF-α^+ macrophage accumulation, a 2.4-fold increase in $CD8^+$/Treg ratio, and elevated IFN-γ production contributed to tumor rejection and abscopal effects. Notably, $CD4^+$ T cell depletion abolished efficacy, underlining the immunologic dependency [24]. In radioresistant SAOS400 osteosarcoma cells, carotenoid-enriched nanoemulsions (CEN) combined with 10

Gy γ-radiation induced >60% cell death at 96 hours (vs minimal death with radiation alone), mediated by lethal autophagy (LC3-II/LC3-I ratio increase). β-carotene alone failed to replicate this effect, highlighting synergy within the carotenoid mixture [25]. In male germline stem cells, ATRA-induced differentiation significantly increased radiosensitivity. After 4 Gy irradiation, apoptosis increased by ~45%, and DNA repair gene RAD51 expression decreased by >40%. Differentiated spermatogonia showed impaired DNA repair and higher γ-H2AX foci accumulation, confirming increased radiation vulnerability [26]. In mice exposed to 2 Gy gamma radiation, vitamin A pre-treatment (100 mg/kg) reduced micronuclei formation in bone marrow polychromatic erythrocytes by 2.62-fold compared to irradiated controls, demonstrating significant radioprotective effects without altering bone marrow cell proliferation rates. The micronucleus reduction was comparable at 400 mg/kg (2.56-fold), suggesting a plateau in protective efficacy beyond 100 mg/kg [27]. In allogeneic hematopoietic stem cell transplant models, 8 Gy total-body radiation increased RALDH2 (RA-synthesizing enzyme) expression 3.1-fold. This upregulated α4β7 integrin on donor T cells 2.5-fold, enhancing gut homing and potentially modulating GVHD development post-irradiation [28]. In lung and ovarian cancer stem-like cells, ATRA decreased ALDH1 and CD133 expression and clonogenic capacity by ~45%, and when combined with cisplatin, prevented therapy-induced enrichment of resistant subpopulations by ~50% [29]. Kang et al. demonstrated that 2 Gy cranial irradiation in mice caused a 4-fold increase in hippocampal transthyretin (TTR) expression, which inhibited retinol-mediated neurogenesis by blocking PAK1 signaling. This led to reduced BrdU+/NeuN+ and DCX+ neuronal progenitor cells and increased depressive-like behaviors [30].

Mei et al. showed that 40 μM all-trans retinoic acid (ATRA) reduced viability of CD133+ thyroid cancer stem cells by 50%, inhibited colony formation, and induced apoptosis in 41.2% of cells. While ATRA downregulated stemness markers (OCT4, GLUT1), it failed to restore

differentiation markers (NIS, TG, TPO). Radiation (131I) transiently enriched CD133+ cells, though ATRA was not tested in combination with radiation [31]. Fu et al. reported that ATRA cleared senescent astrocytes after 10 Gy radiation in vitro, decreasing γH2AX and SA-β-gal positivity. In vivo, daily ATRA (450 μg/kg) increased survival by 41% and improved behavioral outcomes in irradiated mice. ATRA also restored blood-brain barrier markers (VE-cadherin, ZO-1) and reduced IL-6 and IL-1β, acting via the AKT/mTOR/PPARγ/Plin4 pathway [32].

Clinical studies in cancer patients receiving radiotherapy suggest that vitamin A status—especially in the forms of retinol and β-carotene—may influence treatment-related toxicity, recurrence risk, and antioxidant defense. In a prospective study of 230 women with breast cancer, Matos et al. observed a significant post-radiotherapy decline in serum retinol (from 45.1 ± 18.2 to 27.1 ± 11.7 μg/dL, $p < 0.001$) and β-carotene (from 209.0 ± 153.6 to 47.7 ± 25.5 μg/L, $p < 0.001$). Vitamin A inadequacy increased from 17.8% to 70.4% for retinol and from 16% to 63.4% for β-carotene, with stage III patients showing the most pronounced deficiencies [33]. Rosa et al. confirmed this trend, demonstrating that breast cancer patients undergoing chemotherapy and breast-conserving surgery had the highest baseline deficiencies in retinol and β-carotene. Moreover, they found a synergistic correlation with zinc status, implying that deficits in one nutrient may amplify others during cancer treatment [34]. In a randomized trial of 540 head and neck cancer patients, Meyer et al. showed that β-carotene (30 mg/day) and vitamin E (400 IU/day) supplementation significantly reduced severe acute toxicity (OR = 0.38; 95% CI: 0.20–0.74) during radiotherapy. However, a higher rate of local recurrence was observed in the supplement group (HR = 1.56; 95% CI: 0.79–3.07), raising concerns about long-term safety [35]. In an associated observational analysis, higher dietary β-carotene intake was linked to reduced severe toxicity (OR = 0.61; 95% CI: 0.40–0.93) and lower local recurrence (HR = 0.67; 95% CI: 0.45–0.99), with even stronger effects among patients actively supplementing (HR = 0.54; 95% CI: 0.32–0.91) [36]. Corbi et al.'s meta-analysis of 31 randomized trials showed no overall effect of β-carotene supplementation on cancer mortality (RR = 0.98; 95% CI: 0.90–1.07) but found a significant increase in mortality among

lung cancer patients (RR = 1.14; 95% CI: 1.02–1.27), particularly in smokers and those exposed to asbestos [37]. In a large Canadian trial by Bairati et al., post-radiotherapy supplementation with β-carotene and vitamin E in head and neck cancer patients led to a higher incidence of second primary tumors and increased all-cause mortality (HR = 1.38; 95% CI: 1.03–1.85), suggesting potential harm when antioxidants are used during or after treatment [38]. In a randomized trial of 180 women undergoing pelvic radiotherapy for cervical cancer, Delia et al. found that treatment with low-molecular-weight hyaluronic acid significantly reduced mucosal toxicity. At the end of radiotherapy, nearly 90% of patients in the HA group reported no or mild symptoms, versus moderate to severe symptoms in the control group. Pain scores were also significantly lower (1.88 ± 1.02 vs. 6.85 ± 0.94) [39].

Vitamin A and its derivatives, including beta-carotene, are generally considered safe when consumed within recommended dietary limits. However, clinical evidence highlights the importance of dose, patient population, and treatment context in determining their safety profile during cancer therapy. Some trials have demonstrated that high-dose beta-carotene supplementation may pose risks, particularly among smokers and asbestos-exposed individuals, where an increased risk of lung cancer incidence and mortality was observed (RR 1.14; 95% CI 1.02–1.27) [38]. In contrast, moderate dietary intake or supplementation in non-high-risk populations did not consistently show harmful effects, and in some cases, beta-carotene contributed to reduced inflammation and improved antioxidant status, potentially supporting tissue repair during radiotherapy [22,23]. Nevertheless, a meta-analysis involving over 216,000 participants found no overall mortality benefit from beta-carotene supplementation and suggested caution in its use, particularly at pharmacological doses [39]. Clinical trials assessing carotenoid supplementation during radiotherapy have reported generally good tolerability, but isolated cases of adverse events such as skin discoloration (carotenodermia) and gastrointestinal discomfort have been noted at higher intakes. Moreover, the pro-oxidant effects of beta-carotene under certain conditions—especially in oxidative stress-rich environments such as radiotherapy—may counteract its antioxidant benefits [21]. Given the variability in response, individual risk stratification is advised. Beta-carotene supplementation should be approached

cautiously in patients with lung cancer risk factors or a history of smoking. Ongoing trials and future studies are essential to establish optimal dosages and identify populations that may benefit most from vitamin A derivatives during oncologic treatment.

3.2.Vitamin C

Vitamin C (ascorbic acid, VC) is a water-soluble antioxidant abundantly found in fruits and vegetables such as oranges, kiwifruit, broccoli, and red peppers. In the human body, it plays critical roles in collagen synthesis, immune function, iron absorption, and protection against oxidative stress [40]. Recent evidence suggests VC also exerts a dual antioxidant and pro-oxidant function, depending on its concentration and the cellular redox environment [40,41]. Vitamin C is proposed to exert radioprotective effects by scavenging reactive oxygen species (ROS) generated during ionizing radiation, thus preventing oxidative DNA damage in normal tissues [42,43]. However, it can also enhance radiation-induced tumor cell killing through pro-oxidant mechanisms, especially when administered at high pharmacological doses [40,44,45]. As such, the balance between its protective and cytotoxic effects is of key interest in cancer therapy.

On the cellular level, Hosokawa et al. demonstrated that ascorbic acid (AsA) scavenges hydroxyl radicals produced during X-ray exposure and induces apoptosis in HL60 human leukemia cells at concentrations above 1 mM, independent of irradiation. Electron spin resonance showed that OH radicals were effectively eliminated at intracellular AsA concentrations of 75 μM, obtained after extracellular application of 5 mM. Importantly, co-treatment of HL60 cells with AsA and radiation did not reduce radiation-induced cytotoxicity, suggesting the radioprotective effect is selective for non-tumoral tissues [46]. Maeda et al. confirmed similar findings using Chinese hamster ovary (CHO) cells. Pretreatment with ascorbic acid-2-glucoside (AA2G), a stabilized vitamin C derivative, protected wild-type CHO cells and radiosensitive xrs5 mutants against ionizing radiation-induced DNA damage and cell

death [47]. The protection was observed even after gamma-ray and neutron exposure, and was also effective post-irradiation, presumably by scavenging long-lived radicals [47,48]. Ito et al. extended these observations in vivo using AY-27 bladder tumor-bearing rats receiving pelvic radiotherapy (8 fractions, 40 Gy). Oral administration of AA2G (250 mg/kg/day) reduced radiation-induced intestinal mucosal injury but did not impair tumor control. DNA double strand breaks (53BP1 foci) and antitumor effects were comparable in treated and control groups, while increased ratios of CD163+/CD68+ macrophages suggested improved tissue repair and inflammation resolution [49]. In a mouse model of radiation-induced pulmonary fibrosis (RIPF), Ma et al. demonstrated that high-dose VC (administered for 6 weeks starting 2 days before radiation) attenuated fibrosis without impairing tumor control in Lewis lung carcinoma (LLC) models. The mechanism involved inhibition of fibroblast-to-myofibroblast transition via suppression of S100A8/S100A9 derived from neutrophils, as identified via RNA-seq and histopathology [44]. Du et al. found that pharmacologic VC selectively sensitized pancreatic cancer cells (PANC-1, MIA PaCa-2, AsPC-1, 403, and 339s) to ionizing radiation through H2O2-mediated oxidative stress, increasing DNA damage and γ-H2AX signaling, while sparing non-tumorigenic ductal cells (H6c7). In xenograft models, the combination therapy significantly reduced tumor volume and increased survival without increased systemic toxicity [45]. Yamamoto and Kinoshita also demonstrated that high-dose VC mitigated radiation-induced gastrointestinal syndrome and bone marrow aplasia in irradiated mice, both pre- and post-exposure, especially via intraperitoneal administration [50]. Similarly, Sato et al. confirmed increased survival and reduced apoptosis in bone marrow after administration of 3 g/kg VC post-irradiation [51].

Liu et al. conducted a randomized, single-blind, controlled trial involving 72 thyroid cancer patients who received therapeutic 131I (radioiodine) for thyroid remnant ablation. The aim was to assess whether salivary stimulation with vitamin C would reduce the salivary absorbed dose

of 131I and potentially protect salivary glands from radiation injury. Patients were divided into four groups receiving 100 mg of vitamin C every 4 hours starting at 1, 5, 13, or 25 hours post-131I ingestion. The study found no statistically significant differences in salivary gland radiation doses among the groups. These findings suggest that vitamin C administration as a sour stimulant has a limited effect on the absorbed radiation dose to salivary glands and may not offer the protective benefits often assumed in clinical settings [52]. Chung et al. conducted a randomized placebo-controlled trial in 45 head and neck cancer patients. Those receiving 100 IU vitamin E + 500 mg vitamin C twice daily during RT reported improved xerostomia scores at 6 months post-treatment, with better oral salivary function indices measured by scintigraphy compared to placebo. No differences in survival were noted [53]. Park et al. retrospectively evaluated 424 breast cancer patients receiving postoperative radiotherapy. Among them, 70 received intravenous vitamin C (IVC) twice weekly during RT. In the high-dose group (>1 g/kg), neutrophil–lymphocyte ratio (NLR), a marker of systemic inflammation, decreased significantly across time points, suggesting anti-inflammatory and possibly protective effects of IVC during RT [54]. Zarakowska et al. assessed intracellular vitamin C (iVC) levels and 8-oxodG (a marker of oxidative DNA damage) in prostate cancer patients undergoing RT. Although plasma VC remained stable, iVC levels varied: some patients showed depletion (possibly releasing VC to plasma), others had increased intracellular accumulation (possibly as a protective response). These dual patterns support the hypothesis that iVC serves as both a reservoir and a safeguard against RT-induced oxidative stress [55]. Overall, these findings suggest that VC—depending on dosage, delivery route, and timing—may offer protective effects to normal tissues without compromising antitumor efficacy. However, the outcomes are context-dependent and require careful clinical validation. Several reviews note the complexity of interactions between antioxidants and radiation response, including modulation of NF-κB, Nrf2, MAPK, and PI3K/AKT/mTOR pathways [41,56]. According to a systematic review by

Hoppe et al., oral VC showed minimal efficacy in oncology patients, while intravenous administration demonstrated more promising, though heterogeneous, results. Most studies were of moderate quality and lacked statistical power to support broad recommendations. Nevertheless, VC was generally well tolerated with few adverse effects reported [57].

Scientific societies, including Cancer Research UK and American Society of Clinical Oncology, do not currently recommend routine VC supplementation during radiotherapy due to insufficient high-quality evidence. Patients are advised to consult healthcare providers before initiating antioxidant therapy during cancer treatment [43,52,57].

4.Conclusions

Vitamins A and C have demonstrated significant potential as adjuncts to radiotherapy, offering both radiosensitizing and radioprotective effects. Vitamin A, particularly in the form of its active metabolite all-trans retinoic acid (ATRA), enhances tumor radiosensitivity by modulating immune responses, impairing DNA repair in cancer cells, and promoting differentiation of cancer stem cells. However, clinical evidence suggests that high-dose β-carotene supplementation may increase recurrence risk in certain populations, particularly smokers and lung cancer patients, underscoring the need for cautious dosing and patient selection.

Vitamin C exhibits a dual role—acting as a radioprotectant in normal tissues by scavenging free radicals and reducing radiation-induced fibrosis, while at high pharmacological doses, it may selectively radiosensitize tumors through pro-oxidant mechanisms. Clinical studies indicate that intravenous vitamin C shows more promise than oral supplementation in mitigating radiation toxicity, though current evidence remains insufficient for broad recommendations.

Despite promising preclinical findings, key challenges remain in translating these benefits into clinical practice. Optimal dosing, timing, and administration routes must be carefully tailored

to avoid interference with radiotherapy efficacy. Additionally, the potential for antioxidant vitamins to inadvertently protect tumor cells requires further investigation. Future research should prioritize well-designed clinical trials to establish evidence-based guidelines, with a focus on personalized approaches that account for individual patient factors, tumor biology, and treatment regimens. By addressing these gaps, vitamins A and C could become valuable tools in optimizing radiotherapy outcomes while minimizing treatment-related toxicity.

5.Disclosure

Author Contribution Statement

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

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