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# Polyphenols and radiotherapy: literature review of preclinical and clinical evidence

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**Abstract**

**Introduction and aim:** Radiotherapy is a fundamental component of cancer treatment but is limited by tumor radioresistance and damage to healthy tissues. Polyphenols—plant-derived compounds with antioxidant, anti-inflammatory, and anticancer properties—have gained attention for their potential to modulate radiotherapy outcomes. This review aims to evaluate preclinical and clinical evidence on the effects of selected polyphenols in combination with radiotherapy.

**Materials and methods:** A comprehensive literature search was conducted using PubMed, ScienceDirect, ResearchGate, and Google Scholar, focusing on studies from the last two decades. Search terms included: radiotherapy, radiation. polyphenols, curcumin, genistein, chrysin, ellagic acid, resveratrol, quercetin, apigenin, epicatechin, kaempferol, caffeic acid, gallic acid. Both in vitro and in vivo studies were included, as well as available clinical trials.

**Results:** Several polyphenols—including curcumin, genistein, ellagic acid, resveratrol, and quercetin—demonstrated the ability to enhance radiosensitivity in tumor cells or protect normal tissues. Curcumin and genistein have shown early clinical benefits, particularly in head and neck and prostate cancer patients. However, most polyphenols remain in the preclinical stage.

**Conclusion:** Polyphenols show promise as adjuncts to radiotherapy, with context-dependent radiosensitizing or radioprotective effects. Further clinical trials are necessary to validate efficacy, safety, and optimal dosing before integration into standard oncology protocols.

**Keywords:** Radiotherapy; Radiation; Polyphenols; Curcumin; Genistein; Chrysin; Ellagic Acid; Resveratrol; Quercetin; Apigenin; Epicatechin; Kaempferol; Caffeic acid; Gallic acid

## 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 advancements in diagnostics and therapy, cancer is being diagnosed with increasing frequency, particularly in developed countries. In the United States, it is estimated that 2,041,910 new cancer cases and 618,120 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 [2–6]. 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.

Polyphenols, a diverse group of plant-derived compounds with notable antioxidant and anti-inflammatory properties, are increasingly studied for their potential role in cancer therapy. As key constituents of many fruits, vegetables, teas, and medicinal herbs, polyphenols are widely consumed as part of the human diet and through supplementation [13]. Their use has gained popularity among oncology patients, with reports indicating that approximately 22% of cancer patients incorporate plant-based products, including polyphenols, during treatment [14]. Motivations include the desire to enhance therapeutic efficacy, alleviate treatment-related side effects, improve quality of life, or based on anecdotal recommendations from peers or family members [14,15].

Despite their natural origin, the use of polyphenols during radiotherapy remains controversial. Their potent antioxidant capacity may protect normal tissues from radiation-induced oxidative stress; however, there is concern that this same mechanism could also shield cancer cells, potentially reducing the effectiveness of radiotherapy [9,16]. The current body of evidence presents conflicting findings—some studies demonstrate enhanced radiosensitivity and therapeutic synergy, while others suggest a risk of treatment interference [9,16–21].

## 2. Materials and Methods

Given the growing interest in polyphenols 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 polyphenolic compounds, exploring their molecular mechanisms, potential therapeutic benefits, and associated risks. Literature was sourced from PubMed, ScienceDirect, ResearchGate, and Google Scholar, using search terms including: radiotherapy, radiation. polyphenols, curcumin, genistein, chrysin, ellagic acid, resveratrol, quercetin, apigenin, epicatechin, kaempferol, caffeic acid, gallic acid.

## 3. Results

**Curcumin (diferuloylmethane)**, the principal polyphenol in turmeric rhizome (2–8% of turmeric composition), exhibits diverse pharmacological properties, including antioxidant, anti-inflammatory, pro-apoptotic, and anticancer effects through modulation of intracellular signaling pathways [22,23]. It exerts anti-inflammatory action by inhibiting COX-2, lipoxygenase, and NOS enzymes, reducing prostaglandins and cytokines such as TNF-α [22,24]. Its antioxidant properties stem from the neutralization of ROS including superoxide anions, $H_2O_2$, and NO [22]. Curcumin also modulates monoamine neurotransmitters and inhibits MAO, contributing to its analgesic profile.

At the cellular level, curcumin enhances radiosensitivity across various cancer models. In A549 lung cancer cells, 10 μM curcumin inhibited EGFR and reduced EMT, migration, and invasion; 20 μM induced apoptosis in xenograft models [25–27]. In nasopharyngeal carcinoma, curcumin (10–20 μM) downregulated MDR1 and modulated circRNAs; 100 mg/kg pre-irradiation

suppressed tumor growth in mice [28,29]. In breast cancer, 2.5–10 μM curcumin influenced apoptosis-related pathways; 30 μM with radiation inhibited HIF-1α and HSP90 in stem cells [30,31]. In cervical cancer, 40 μM enhanced radiation cytotoxicity in vitro; 4 g/day in clinical settings reduced survival in 75% of patients [32,33]. In prostate cancer, curcumin upregulated miR-143, downregulated DNMT1/3B, and enhanced apoptosis (0.1–30 μM) post-radiation [34,35]. Curcumin also showed efficacy in gliomas (5–20 μM), where it inhibited Hedgehog signaling, arrested cells in G2/M, and suppressed tumor growth in vivo [36–38]. In esophageal cancer, 10 μM curcumin inhibited NF-κB and reduced tumor mass following irradiation [39]. In colorectal cancer, 2.5 μM curcumin modulated DNA repair genes and inhibited tumor growth [40]. Similar effects were observed in pancreatic (6–12 μM), renal (5–80 μM), and bladder cancer (10 μM) models, where curcumin increased radiosensitivity through diverse molecular mechanisms [41–43].

Despite robust preclinical data, clinical studies evaluating curcumin during radiotherapy remain limited. Table 1 summarizes existing clinical trials assessing its efficacy in patients undergoing radiotherapy.

Table 1. Summary of clinical studies assessing the effects of curcumin during radiotherapy in cancer patients.

| | Form / dosage | Duration | Sample size (n) | Clinical outcome | Reference |
|---|---|---|---|---|---|
| Head and neck squamous cell carcinoma | 0.1% mouthwash, 10 mL | 3x/day for 6 weeks | n=68 (33 curcumin, 35 benzydamine) | Delayed onset of ROM by 2 weeks vs. benzydamine | 44 |
| ROM in head and neck cancer | 0.1% mouthwash, 10 mL or 40 mg oral | 3x/day or 40 mg daily for 3 weeks | n=37 (13 rinse, 13 oral, 12 control) | Significant reduction in mucositis severity (WHO) and pain (NRS) vs. control after 3 weeks. | 22 |
| Head and neck squamous cell carcinoma | 500 mg orally | 3x daily until completion of radiotherapy | n=61 (30 curcumin, 31 placebo) | From week 3, ROM severity significantly reduced in curcumin group | 45 |
| Head and neck cancer | 80 mg orally | 1 capsule daily during radiotherapy | n=32 (16 curcumin, 16 placebo) | Significant reduction in mucositis incidence and severity; at week 2, 100% in placebo vs. 32% in curcumin group developed mucositis; curcumin group had less weight loss. | 46 |
| Head and neck cancer | 650 mg curcumin + 13 mg piperine | 3x daily for 2 months post-radiotherapy | n=204 (109 curcumin, 95 placebo) | Curcumin significantly reduced mucositis frequency, delayed its onset, and shortened duration—affecting 51% vs. 92% in the control group. More patients completed radiotherapy without interruption (89% vs. 53%). | 47 |
| Breast cancer | 80mg orally | 2x daily for 7 weeks | n=42 (21 curcumin, 21 control) | Significant reduction in breast/chest pain and radiation-induced skin toxicity (RTOG scale) at week 7 vs. placebo; no significant changes during the first 6 weeks. | 48 |
| Breast cancer (RT + CTH) | 80 mg orally | 2x daily for 7 weeks | n=50 (25 curcumin, 25 control) | Oral mucositis symptoms were notably milder than in the control group at weeks 1, 4, and 7; patients also reported less pain, especially in week 7. | 49 |
| Breast cancer | 500 mg orally | 12x daily throughout RT and 1 week post-RT | n=578 (283 curcumin, 295 control) | Curcumin did not significantly reduce radiation-induced skin toxicity at the end of treatment compared to placebo. However, fewer patients had RDS > 3.0 in the curcumin group (7.4% vs. 12.9%, p = 0.082), suggesting a trend toward symptom relief. No significant differences in pain, symptoms, or quality of life were observed between groups. | 50 |
| Prostate cancer | 3 g/day (6 × 500 mg capsules) | 1 week before and throughout RT (~8 weeks) | n=40 (20 curcumin, 20 control) | Increased total antioxidant capacity (TAC) in the curcumin group ($p < 0.001$); decreased superoxide dismutase (SOD) activity ($p=0.018$); no effect on treatment outcomes (PSA levels, disease progression, or MRI/MRS findings). | 51 |

Clinical studies suggest that curcumin may effectively alleviate the symptoms of radiation-induced oral mucositis (ROM) and reduce the severity of radiotherapy-related side effects in oncology patients. In studies on head and neck cancers, both topical (mouthwashes) and oral forms of curcumin have been shown to reduce the intensity and delay the onset of mucosal inflammation [22,44-46]. For example, curcumin prolonged the time to the onset of ROM by 2 weeks compared to a 0.15% benzydamine solution, and curcumin nanomicelles limited the development of ROM to 32% of patients as early as the second week of radiotherapy [44,46]. In the study by Arun et al., as many as 73.3% of patients receiving curcumin presented with only mild ROM in the fourth week of therapy, compared to 68% of patients with moderate or severe ROM in the placebo group [45]. In the context of breast cancer radiotherapy, the effects of curcumin are less conclusive. Smaller studies demonstrated a reduction in pain symptoms and alleviation of skin inflammation, whereas a larger study (578 patients) did not confirm a significant reduction in skin-related symptoms [48-50]. In the case of prostate cancer radiotherapy, curcumin improved antioxidant parameters, but did not significantly affect oncological treatment outcomes [51].

Despite promising results in mitigating radiation-induced oral mucositis (ROM), curcumin is not currently recommended by major clinical guidelines, such as those of the Multinational Association of Supportive Care in Cancer (MASCC) or the International Society of Oral Oncology (ISOO) [52]. Nevertheless, curcumin is not contraindicated during radiotherapy. It is generally regarded as a safe supplement; however, high doses and long-term use may lead to adverse effects. In predisposed individuals, curcumin may promote kidney stone formation by increasing oxalate excretion [53]. Rare cases of hepatotoxicity and cardiac arrhythmias (e.g., atrioventricular blocks) associated with high doses have also been reported [53,54]. Additionally, curcumin may interfere with the metabolism and efficacy of various medications, including anticoagulants and chemotherapeutics [55]. Although curcumin represents a promising phytochemical, further research is required to establish safe dosing regimens and confirm its therapeutic benefits in clinical oncology.

**Ellagic acid (EA)**, a naturally occurring polyphenol found in pomegranates, berries, nuts, and seeds, exists both freely and as ellagitannins, which are hydrolyzed in the gut to enhance bioavailability [56,57]. EA exerts potent antioxidant, anti-inflammatory, and anticancer effects via multiple pathways that inhibit tumor growth, angiogenesis, and metastasis while promoting apoptosis and cell cycle arrest [56-58]. Key mechanisms include suppression of the PI3K/AKT/mTOR and NF-κB pathways, ROS-mediated apoptosis, and modulation of cell cycle regulators such as p21, CDK4/6, and p53.

At the cellular level, EA shows broad antitumor activity. In breast cancer (MCF-7, MDA-MB-231), 10-100 μM EA activated caspase-3/9, increased Bax, decreased Bcl-2, and induced G0/G1 arrest, reducing tumor volume by 60% in vivo (50 mg/kg) [57]. In liver cancer (HepG2, HCC), 10-50 μM EA enhanced ROS generation, activated caspase-3, inhibited NF-κB, and suppressed VEGF-mediated angiogenesis; 100 mg/kg reduced tumor burden by 70% in vivo [58]. In colorectal cancer (HT-29, Caco-2), EA (20-50 μM) induced mitochondrial apoptosis, modulated CDK4/6 and p21, and improved gut microbiota composition through urolithin metabolites; in vivo, 100 mg/kg reduced tumor count by 65% [57]. In pancreatic cancer (PANC-1, AsPC-1), 25-100 μM EA promoted apoptosis via Bax upregulation and caspase activation, blocked TGF-β/Smad3 signaling, and induced G1 arrest; 50 mg/kg reduced tumor growth and angiogenesis markers [57].

Although preclinical studies suggest potential radiosensitizing effects, no clinical trials have evaluated EA in combination with radiotherapy. Its clinical utility remains unconfirmed due to lack of human data and regulatory endorsement. At doses ≥200 mg/kg, EA has demonstrated nephrotoxicity and cardiotoxicity in animal models; the $LD_{50}$ in rats is 630 mg/kg [57]. Weight loss has also been observed following intraperitoneal administration in female rats. Further

clinical studies are necessary to determine safety, efficacy, and therapeutic viability in radiotherapy contexts.

**Resveratrol** (3,5,4'-trihydroxystilbene) is a stilbene-type polyphenol produced by plants under stress, functioning as a phytoalexin with antioxidant, anti-inflammatory, and anticancer properties. It is abundant in grape skins, peanuts, and berries (e.g., blueberries, cranberries), and is highly concentrated in red wine due to fermentation processes [59,60]. Resveratrol modulates key oncogenic pathways (NF-κB, STAT3, PI3K/Akt/mTOR), suppresses pro-proliferative genes, upregulates Bax and caspase-3, and inhibits angiogenesis via VEGF and MMP downregulation [61-63].

At the cellular level, resveratrol induces G1/S and G2/M cell cycle arrest, downregulating cyclins D1/B and CDKs 2/4 across various cancer cell lines [8]. In colorectal cancer, 50 μM resveratrol inhibits Wnt/β-catenin signaling, while 20-100 μM activates TRAIL and Fas-mediated apoptosis through mitochondrial destabilization [61,63]. As a radiosensitizer, resveratrol (10-50 μM) enhances radiation-induced DNA damage by delaying repair (via ATM and H2A.X inhibition), increasing apoptosis and G2/M arrest [61].

Resveratrol also exhibits dual redox behavior: it acts as an antioxidant in normal cells by upregulating SOD2 and GPX1, and as a pro-oxidant in cancer cells, enhancing ROS accumulation and apoptosis, particularly at 50-200 μM [59]. In breast cancer, resveratrol reduces TNF-α and IL-6 via NF-κB inhibition, attenuating inflammation-associated tumor progression [61].

Despite strong preclinical evidence, no clinical trials have assessed resveratrol in conjunction with radiotherapy. Its dual antioxidant/pro-oxidant nature necessitates further study to determine optimal dosing and therapeutic windows. Adverse effects reported in clinical contexts include nephrotoxicity, gastrointestinal symptoms, and hormonal alterations. Notably, a trial in multiple myeloma using oral SRT501 was terminated due to toxicity [61,63]. At present, resveratrol lacks formal recommendations for use in radiotherapy, and clinical validation remains essential to confirm its efficacy and safety in oncology settings.

**Chrysin**, a flavonoid of the flavone subclass characterized by hydroxyl groups at C5 and C7 [64], is widely distributed in plants, fruits, and bee products such as honey and propolis-where it is most concentrated (up to 25 g/L) [65]. Despite broad pharmacological activity-anticancer, antioxidant, anti-inflammatory, and neuroprotective-its clinical utility is constrained by poor water solubility and bioavailability [64-66].

Mechanistically, chrysin induces apoptosis via caspase activation and mitochondrial membrane permeabilization, increases ROS generation, and modulates key signaling pathways including PI3K/Akt, MAPK, and NF-κB [64-66]. It also exhibits immunomodulatory activity by upregulating calreticulin (CRT), ATP, and HMGB1, which enhance dendritic cell and T cell activation, while suppressing STAT3 and PD-L1 to counteract immune evasion [67]. Additionally, chrysin interferes with cancer cell metabolism by inhibiting mitochondrial complex II and HIF-1α, thereby impairing ATP synthesis and angiogenesis under hypoxic conditions [68].

At the cellular level, chrysin demonstrates radiosensitizing effects. In B16-F10 melanoma cells, 60 μM chrysin induced 48.2% apoptosis, which increased to 81.4% when combined with 4 Gy radiation. ROS production and ICD marker expression (CRT, ATP) were also significantly elevated under combined treatment. Chrysin-mediated STAT3 and PD-L1 inhibition further augmented immune recognition and cytotoxic T cell activation. These findings suggest its potential as a radiosensitizer through combined pro-apoptotic, oxidative, and immunogenic mechanisms [67].

To date, no clinical trials have evaluated chrysin in conjunction with radiotherapy. Limitations include low systemic bioavailability and potential cytotoxicity to normal cells at high doses. Excessive ROS generation may lead to off-target DNA and mitochondrial damage.

Furthermore, chrysin inhibits cytochrome P450 enzymes, raising concerns about drug-nutrient interactions and altered metabolism of co-administered agents [68]. While in vitro data highlight promising radiosensitizing properties, clinical evidence is currently lacking, and chrysin remains unendorsed by scientific guidelines for use in radiotherapy.

**Caffeic acid (CA)**, a hydroxycinnamic acid from the phenolic acid group, is widely distributed in fruits, vegetables, herbs, coffee, tea, and red wine. It is synthesized from tyrosine or phenylalanine and plays a protective role in plants against oxidative stress and pathogens. CA exhibits potent antioxidant, anti-inflammatory, and immunomodulatory properties and is under investigation as a therapeutic adjuvant in oncology and chronic disease management [69,70]. A key derivative, caffeic acid phenethyl ester (CAPE), found in propolis, further enhances its therapeutic potential, particularly in cancer and radioprotection [69].

CA neutralizes ROS and RNS and activates the Nrf2/ARE pathway, inducing antioxidant enzymes such as HO-1, GST, and NQO1. In HepG2 cells, 50-100 μM CA reduced oxidative stress induced by t-BHP [70]. CA also inhibits NF-κB and STAT3, thereby downregulating IL-6, IL-1β, and COX-2, as shown in lung fibroblasts treated with 40-80 μM CA [71]. Both CA and CAPE exhibit anticancer activity by inducing apoptosis, blocking cell cycle progression (S and G2/M phases), and reducing metastatic potential [69].

As a radiosensitizer, CAPE (25-50 μM) increases sensitivity in NSCLC cell lines by inhibiting NF-κB and enhancing ROS-mediated apoptosis. It depolarizes mitochondrial membranes and promotes cell death in prostate and colorectal cancer models. Radioprotective effects of CAPE have been demonstrated in murine models, where 100 mg/kg reduced radiation-induced oxidative stress and pro-inflammatory cytokine levels [71]. Additionally, CAPE (50 μM) reduced DNA strand breaks in irradiated human fibroblasts, indicating protective effects on normal tissues [69].

Despite encouraging preclinical evidence, no clinical trials have evaluated CA or CAPE in the context of radiotherapy. High doses of CAPE (>100 μM or 100 mg/kg) have been associated with nephrotoxicity, hepatotoxicity, and enhanced toxicity when combined with certain chemotherapeutic agents due to drug metabolism interference [69,71]. At present, no official guidelines support the clinical use of CA or CAPE during radiotherapy, and further research is required to establish their safety, optimal dosing, and therapeutic role in oncology.

**Gallic acid (GA)** is a trihydroxybenzoic acid found in free and bound forms-primarily as hydrolyzable tannins-in various fruits, herbs, and beverages, including tea, wine, berries, and sumac [72]. It is synthesized via the shikimate pathway and exhibits potent antioxidant, anti-inflammatory, antimicrobial, anticancer, neuroprotective, and radioprotective activities [72,73]. GA exerts its biological effects by scavenging reactive oxygen species (ROS), enhancing the activity of antioxidant enzymes (e.g., SOD, CAT, GPx), and influencing signaling pathways involved in oxidative stress, inflammation, and apoptosis [72]. It downregulates NF-κB and pro-inflammatory cytokines (e.g., TNF-α, IL-6), while promoting apoptosis through the mitochondrial pathway by upregulating Bax, downregulating Bcl-2, and activating caspases. Anticancer effects are also achieved via inhibition of proliferation and modulation of AKT and MAPK signaling [73].

Evidence from animal models supports GA's radioprotective potential. Pre-irradiation administration of GA (100 mg/kg) significantly reduced micronuclei and chromosomal damage in erythrocytes and bone marrow cells [73]. These protective effects are linked to oxidative stress reduction and stimulation of DNA repair mechanisms.

In vitro, GA demonstrates efficacy at concentrations ranging from 5 to 200 μM, with outcomes varying by cancer cell type and experimental conditions. Despite encouraging preclinical findings, no clinical trials have yet investigated GA in combination with radiotherapy. Additionally, high doses (e.g., 100 mg/kg) have been associated with altered hematologic parameters, including reduced hemoglobin and hematocrit levels, indicating a potential risk of

hemolytic anemia with prolonged use [73]. Although GA holds promise as a radioprotective agent, its clinical applicability remains uncertain in the absence of human studies. Further research is warranted to validate its therapeutic role, establish dosing safety, and explore its integration into oncologic care.

**Epicatechin (EC)** is a flavanol-class polyphenol found in cocoa, green tea, grapes, berries, and other plant-based foods [74-77]. It is especially abundant in cocoa and green tea, where it contributes significantly to their antioxidant capacity. EC is recognized for its antioxidant, anti-inflammatory, cardioprotective, and anticancer properties.

EC exerts its effects primarily through ROS scavenging and modulation of redox-sensitive pathways. It activates the Nrf2 pathway, enhancing expression of antioxidant enzymes such as catalase and SOD, while inhibiting NF-κB-mediated pro-inflammatory cytokines like TNF-α and IL-6 [74]. In cancer models, EC inhibits proliferation and induces apoptosis via caspase-3 activation, Bax upregulation, and Bcl-2 suppression. It also regulates the cell cycle through PI3K/Akt and MAPK signaling, contributing to tumor growth inhibition [77].

Preclinical studies support EC's radiosensitizing potential. In Panc-1 cells, EC (200 μM) increased COX activity and upregulated p21 and phosphorylated Chk2, leading to G2/M arrest. Combined treatment with 20 μM EC and 6 Gy radiation enhanced p21 (62%) and Chk2 phosphorylation (43%), while promoting caspase-3 activation [77]. In Panc-1, U87, and MIA PaCa-2 cell lines, EC (20 μM) reduced post-irradiation survival to 58%, 51%, and 52%, respectively, suggesting improved radiotherapy efficacy via modulation of mitochondrial function, ROS production, and DNA damage responses [77].

Despite promising in vitro data, no clinical studies have evaluated EC in combination with radiotherapy. Its safety profile appears favorable-EC is classified as GRAS by the FDA and is generally well tolerated, though gastrointestinal symptoms and rare allergic reactions have been reported [74]. Potential interactions with hepatic drug-metabolizing enzymes warrant caution in polypharmacy contexts. The absence of human data limits definitive conclusions on efficacy or safety in oncology, and no clinical guidelines currently recommend EC as a radiosensitizing agent [75,77]. Further research is needed to validate EC's therapeutic role, define optimal dosing, and clarify its impact on treatment outcomes in radiotherapy.

**Kaempferol**, a flavonol-type polyphenol, is widely distributed in plant-based foods including tea, kale, apples, citrus fruits, broccoli, onions, legumes, and herbs such as dill and tarragon. It possesses a broad spectrum of biological activities-antioxidant, anti-inflammatory, anticancer, cardioprotective, neuroprotective, and antidiabetic-attributed to its capacity to neutralize free radicals, activate antioxidant enzymes (e.g., SOD, CAT), and inhibit pro-oxidant enzymes like xanthine oxidase [78].

Kaempferol modulates key cellular signaling pathways, contributing to its anticancer effects. In HepG2 cells, it attenuates oleic acid-induced oxidative stress and lipid accumulation by downregulating SREBP1, FAS, SCD-1, and adipogenic transcription factors (PPARγ, C/EBPβ), supporting its role in metabolic regulation [79]. In cervical cancer (HeLa), 10-50 μM kaempferol inhibited PI3K/Akt and telomerase activity, induced G2/M arrest, and activated caspase-3/9 with Bax upregulation and Bcl-2 suppression [78]. In lung cancer (A549), pre-treatment with 14 μM kaempferol enhanced radiotherapy response by inhibiting PI3K/Akt and ERK signaling and triggering mitochondrial apoptosis pathways [80]. In colorectal cancer cells (HCT116, HT-29), 10-50 μM kaempferol induced G2/M arrest and apoptosis via Bax/Bcl-2 modulation and caspase activation. In ovarian cancer (OVCAR-3, SKOV-3), it sensitized cells to TRAIL-induced apoptosis through JNK/ERK-CHOP pathway activation and regulation of DR4/DR5 receptors. Similarly, in breast cancer (MCF-7, MDA-MB-231), kaempferol suppressed proliferation by inducing cell cycle arrest and activating caspases 3, 7, and 9, while downregulating NF-κB and c-Myc [78].

Although extensive in vitro and in vivo evidence supports kaempferol's anticancer and radiosensitizing potential, clinical validation is currently lacking. Limited bioavailability following dietary intake may restrict therapeutic efficacy, underscoring the need for pharmacokinetic optimization and clinical dose-finding studies. Toxicological assessments indicate low cytotoxicity toward normal cells (e.g., human monocytes, MRC-5), suggesting a favorable safety profile with $IC_{50}$ values ranging from 69.87 to 383.6 μg/mL [81]. At present, no formal recommendations support kaempferol's clinical use as a radiosensitizer, and further investigation is warranted to assess its utility in oncologic radiotherapy protocols.

**Quercetin** is a flavonoid polyphenol widely distributed in fruits, vegetables, and medicinal herbs, with high concentrations in onions, apples, grapes, red wine, and tea [76,82]. Typically occurring in glycosylated forms, its bioavailability is influenced by sugar moieties such as rhamnose and glucose [83]. Quercetin possesses strong antioxidant, anti-inflammatory, and anticancer properties, attributed to its ability to scavenge free radicals, regulate redox-sensitive enzymes, and modulate cell signaling pathways [84,85].

Its antioxidant activity involves upregulation of SOD and catalase, while anti-inflammatory effects are mediated through inhibition of COX, LOX, and suppression of cytokines like TNF-α and IL-6 [84,85]. Quercetin induces apoptosis via mitochondrial pathways and influences the PI3K/Akt, mTOR, and SIRT1/AMPK signaling axes. It also regulates cell cycle checkpoints and may affect glucose metabolism, suggesting broader therapeutic relevance [84].

In vitro, quercetin exhibits cytotoxic and anti-proliferative activity across multiple cancer types. In colorectal cancer cells (HCT-15, RKO), quercetin (0-300 μM) inhibited growth in a time- and dose-dependent manner. In breast cancer lines (MCF-7, MDA-MB-231), 30 μM quercetin reduced migration, suppressed MMP-2/-9, and modulated autophagy [84]. Prostate (PC3) and ovarian cancer cells showed reduced viability at 100-150 μM and 50-130 μM, respectively, via apoptosis induction and cell cycle arrest [84]. In primary effusion lymphoma (PEL), quercetin (12-100 μM) decreased viability through mTOR/Akt inhibition and nuclear fragmentation. In NSCLC cells (A549, H1299), it activated autophagy and caspases via the SIRT1/AMPK pathway [82]. In liver cancer (HepG2), quercetin arrested cells in G1 phase by upregulating p21 and p27 [85].

Although preclinical studies suggest quercetin may act as a radiosensitizer-enhancing apoptosis, impairing DNA repair, and protecting normal tissues-no clinical trials have confirmed its efficacy or safety in combination with radiotherapy. Concerns persist regarding potential pro-oxidant behavior at high concentrations, which may exacerbate oxidative damage in both cancerous and normal cells [85]. Chronic high-dose intake (>1000 mg/day) has been associated with hepatotoxicity and nephrotoxicity in animal models [86].

Quercetin is generally well tolerated at dietary levels, but it may interfere with drug metabolism through cytochrome P450 enzyme modulation, raising the possibility of pharmacokinetic interactions [76]. Currently, no formal clinical guidelines endorse its use in oncology or radiotherapy settings. Rigorous clinical studies are needed to evaluate its therapeutic potential and define safe, effective dosing strategies.

**Apigenin** (4',5,7-trihydroxyflavone) is a naturally occurring flavone-class flavonoid found in a wide variety of fruits, vegetables, and herbs. Rich dietary sources include parsley, celery, chamomile, onions, citrus fruits, and tea [87-89]. Structurally composed of two aromatic rings linked by a heterocyclic oxygen-containing ring, apigenin exhibits strong antioxidant, anti-inflammatory, anticancer, and radioprotective activities [88].

Apigenin acts primarily by scavenging reactive oxygen species (ROS) and enhancing antioxidant enzymes such as catalase and glutathione peroxidase, mitigating oxidative stress [87]. It also modulates tumorigenesis-associated signaling pathways including PI3K/Akt/mTOR, MAPK/ERK, NF-κB, STAT3, and Wnt/β-catenin, resulting in cell cycle arrest, apoptosis induction, angiogenesis inhibition, and suppression of tumor cell migration

[87,89]. Anti-inflammatory effects are mediated through downregulation of COX-2, iNOS, and cytokines such as TNF-α, IL-1β, and IL-6. Additionally, apigenin has demonstrated genoprotective properties against radiation-induced DNA damage [87].

In vitro, apigenin exhibits dose- and time-dependent antiproliferative effects across gastric cancer models. In SGC-7901 cells, 20-80 μM apigenin inhibited proliferation (up to 99%) and induced apoptosis, with a peak apoptotic rate of 29.3% at 80 μM [88]. Similar findings were observed in HGC-27 and AGS cells, with increased sensitivity in poorly differentiated tumors and an $IC_{50}$ of 5.1 μg/mL [88]. In A549 lung cancer cells, 37.2 μM apigenin suppressed gamma radiation (3 Gy)-induced ROS, while 25 μM reduced radiation-induced chromosomal aberrations in human lymphocytes [87]. In UVB-irradiated human keratinocytes, 15 μM apigenin reduced DNA damage and downregulated pro-apoptotic proteins Bax and caspase-3 [87].

Despite promising preclinical findings, no clinical trials have been conducted to evaluate apigenin in oncology or radiotherapy settings. Toxicological studies report low toxicity, with high doses (up to 5000 mg/kg orally or 200 mg/kg intraperitoneally in mice) producing no significant adverse effects [87]. However, a lack of human data and formal recommendations currently limits its clinical application. Further studies are needed to establish optimal dosing, bioavailability, safety, and therapeutic efficacy of apigenin in radiotherapy and cancer treatment protocols.

**Genistein** (4',5,7-trihydroxyisoflavone) is a soy-derived isoflavone found in legumes such as soybeans, chickpeas, lentils, and in smaller amounts in fruits, vegetables, and herbs (e.g., red clover) [86,90].

It exerts anticancer, antioxidant, anti-inflammatory, and radiomodulatory effects via both estrogen receptor-dependent and -independent mechanisms. Genistein modulates ERβ signaling, which regulates tumor growth in hormone-sensitive cancers. In normal tissues, it functions as a radioprotective agent by scavenging ROS and reducing oxidative DNA damage, while in tumor cells, it acts as a radiosensitizer by inhibiting DNA repair and inducing G2/M phase arrest, thereby enhancing radiation efficacy [90-92]. It also suppresses pro-inflammatory cytokines (TNF-α, IL-6, TGF-β), contributing to reduced radiotherapy-related toxicity [86].

In vitro, genistein inhibits proliferation and induces apoptosis in a wide range of cancer models. In MCF-7 breast cancer cells, genistein (50-100 μM) reduced viability via ERβ-mediated signaling, whereas in ER-negative MDA-MB-231 cells, 20-50 μM induced G2/M arrest and ROS-dependent apoptosis [90]. In PC-3 and DU145 prostate cancer cells, 10-60 μM genistein suppressed PI3K/Akt, NF-κB, and Wnt/β-catenin pathways, increased caspase activity, and reduced Bcl-2 expression, enhancing radiosensitivity [90,92]. In A549 lung and U87-MG glioma cells, 25-50 μM genistein increased ROS, inhibited EGFR/Akt signaling, and impaired DNA repair, thereby potentiating radiation-induced cytotoxicity [92].

A clinical trial in prostate cancer patients receiving radiotherapy showed that daily supplementation with 200 mg soy isoflavones (including genistein) significantly reduced radiation-related side effects-urinary incontinence, diarrhea, and defecation pain-while preserving erectile function at 3 and 6 months post-treatment [93]. However, genistein combined with decitabine in advanced solid tumor trials revealed dose-limiting toxicities such as neutropenia, anemia, and febrile neutropenia in NSCLC patients [91].

Although preclinical and early clinical findings support genistein's dual role as a radiosensitizer and radioprotector, its use remains investigational. Conflicting evidence regarding its estrogenic effects-particularly in hormone-sensitive cancers-warrants caution. The American Institute for Cancer Research and World Cancer Research Fund report indicated possible survival benefits in breast cancer, but also noted data suggesting tumor-promoting effects under certain conditions [90]. Further randomized trials are required to define its clinical utility,

optimal dosing, and safety in oncology.

## 4. Conclusions

Polyphenols, a diverse group of plant-derived compounds with well-documented antioxidant, anti-inflammatory, and anticancer properties, are increasingly recognized for their potential role in modulating the efficacy and toxicity of radiotherapy. This comprehensive literature review has synthesized current preclinical and limited clinical evidence on several polyphenolic agents—including curcumin, ellagic acid, resveratrol, chrysin, caffeic acid, gallic acid, epicatechin, kaempferol, quercetin, apigenin, and genistein—highlighting their mechanistic diversity and relevance in the context of radiation oncology.

Collectively, in vitro and in vivo data suggest that many polyphenols exert radiosensitizing effects in tumor cells through various mechanisms, including inhibition of DNA repair, induction of oxidative stress, modulation of apoptosis-related pathways, cell cycle arrest, and immune system activation. Simultaneously, some compounds also display radioprotective properties in normal tissues, often through ROS scavenging and the upregulation of endogenous antioxidant defenses. Among these compounds, curcumin and genistein have progressed furthest toward clinical evaluation, with early trials indicating symptom relief and reduced radiation-associated toxicity, particularly in prostate and head and neck cancer patients. However, the vast majority of polyphenols remain at the preclinical stage of investigation.

Despite promising findings, translational gaps persist due to limited bioavailability, poor pharmacokinetics, potential pro-oxidant effects at high concentrations, and the lack of standardized dosing protocols. In addition, interactions with chemotherapeutics and cytochrome P450 enzymes raise concerns regarding the safe integration of polyphenols into conventional treatment regimens. The dual roles of polyphenols—as both potential radiosensitizers and radioprotectors—highlight the need for context-dependent application. Their impact is influenced not only by compound-specific pharmacodynamics but also by tumor type, radiation dose, treatment timing, and the patient's physiological status. The variability of outcomes across models underscores the necessity of rigorous, controlled clinical trials to evaluate efficacy, safety, and optimal therapeutic windows.

In conclusion, polyphenols represent a promising but as yet unproven class of adjunctive agents in radiotherapy. While their favorable safety profiles and multifaceted biological activity justify continued investigation, the current body of evidence is insufficient to support their routine clinical use. Future research should prioritize well-designed clinical trials, the development of bioavailable formulations, and mechanistic studies that delineate compound-specific interactions with radiation-induced cellular pathways. Only with such evidence can polyphenols be confidently integrated into evidence-based oncologic care.

## 5. Disclosure

### Author Contribution Statement

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

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