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Advancements in delivery systems for dietary polyphenols in enhancing radioprotection effects: challenges and opportunities

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Radiotherapy, a widely employed cancer treatment, often triggers diverse inflammatory responses such as radiation enteritis, pulmonary injury, pelvic inflammation, dermatitis, and osteitis. Dietary polyphenols have recently emerged as promising agents for mitigating radiation-induced inflammation. However, their clinical application faced challenges related to variable bioavailability, individual pharmacokinetics, optimal dosing, and limited clinical evidence. Current researches revealed the efficacy of bioactive small molecule polyphenols in addressing radiation-induced inflammation. In this review, along with a comprehensive examination of the etiology and categories of radiation-induced inflammatory conditions, the diversity of polyphenols and elucidating their anti-inflammatory mechanisms are explored. This study emphasizes the recent progresses in delivery systems for dietary polyphenols, aiming to enhance radioprotection effects. The optimized utilization of polyphenols, with a theoretical framework and reference guide, is of paramount relevance. Through diverse delivery mechanisms, the more effective and safer radioprotective strategies become achievable. This endeavor aspires to contribute to breakthroughs in the dietary polyphenols' application, significantly enhancing human health protection during radiotherapy. These comprehensive insights presented here also support (pre)-clinical practices in navigating the complexities of utilizing dietary polyphenols for radioprotection, fostering advancements in the field and improving patient outcomes.

In the contemporary era marked by rapid socio-economic advancements, the incidence of cancer has been escalating, positioning it as a predominant cause of global morbidity and mortality, projected to lead from 2008 through 2030[1,2]. In response, there is a continuous exploration of cancer treatment options. Among the most promising therapeutic methods, radiation therapy has gained widespread use in clinical practice. Approximately 50% of cancer patients undergo radiotherapy during their treatment, and it accounts for 40% of cancer cure treatments[3]. However, the efficacy of radiation therapy is often counterbalanced by its adverse effects, notably radiation-induced inflammation and tissue damage. These side effects significantly impair the quality of life of patients and can adversely affect the overall success of the treatment. As a result, the development of effective radioprotection measures has become an area of critical concern in oncological research, seeking to mitigate these detrimental impacts while enhancing therapeutic efficacy.

Dietary polyphenols, natural substances derived from plants, have garnered attention due to their potent antioxidant and anti-inflammatory effects[4]. Polyphenols exhibit antioxidant effects by regulating reactive oxygen species (ROS) production and promoting ROS clearance, making them effective dietary supplements in combating cellular oxidative stress. Their anti-inflammatory effects are primarily achieved through the modulation of inflammatory signaling pathways and the release of inflammatory factors[5]. In the context of radiation inflammation, polyphenols can alleviate patient

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discomfort by reducing the inflammatory response caused by radiation injury. Moreover, they can promote tissue repair, regeneration, and accelerate the healing process at the injury site[6]. These properties position polyphenols as potential candidates for the treatment of radiation inflammation. However, dietary polyphenols are typically found in low quantities in foods and exhibit low bioavailability, largely due to poor stability and solubility[7]. Furthermore, individual differences in the intake and metabolism of dietary polyphenols need to be considered to determine the optimal dosage and usage for different populations[8,9]. Additionally, dietary polyphenols have multitarget properties, making their bioactivity and clinical application complex, necessitating consideration of their interactions with multiple biomolecules and signaling pathways, as well as potential side effects and safety issues[7].

To address these challenges, researchers have begun exploring novel delivery systems for polyphenol treatment. Based on relevant literature, new delivery systems such as biomaterials can enhance the solubility and stability of dietary polyphenols, improve their permeability and targeting, prolong their half-life in the body, and enhance their therapeutic effects by modifying release rates and metabolic pathways[10]. Biological delivery systems can also extend the duration of action and improve drug bioavailability by altering the release rate and metabolic pathway of dietary polyphenols.

This review delves into the mechanisms and challenges of radiation-induced inflammation, the effectiveness of dietary polyphenols, and the utilization of biological delivery systems. It emphasizes the potential of polyphenols in mitigating radiation-induced inflammation and enhancing their bioavailability through diverse delivery systems. This discussion pointed out opportunities for more research and advances in the field of polyphenols for the alleviation of radiation-induced inflammation, with the ultimate goal of providing innovative ideas and approaches to improve treatment efficacy and enhance the quality of life for the patients with radiation-induced inflammation (Fig. 1).

Radiotherapy and radiation-induced inflammation

In the face of the challenging treatment landscape presented by cancer, the continuous advancements in science and medical treatment have led to ongoing updates and improvements in radiation therapy. Currently, radiation treatments encompass various methods, including external radiotherapy, internal radiotherapy, nuclide internal radiation therapy, and heavy ion radiotherapy. We will review below the rationale and advantages of the more common and promising approaches, including X-rays, flash high-dose-rate radiation therapy (FLASH), proton heavy-ion therapy, and internal irradiation therapy.

While these methods offer precise targeting and therapeutic effects, it is important to acknowledge that radiotherapy can still result in inevitable damage to normal human tissue cells, potentially leading to radiation-induced inflammation. In this section, we will also primarily discuss common forms of radiation-induced inflammation, including radiation enteritis, radiation pneumonia, radiation dermatitis, and radiation osteitis, exploring their production mechanisms and impact on the body.

Radiotherapy

In the current landscape of radiotherapy, the main modalities include external radiotherapy, which encompasses X-ray, FLASH radiotherapy, proton heavy ion therapy, and internal radiotherapy, including selective internal therapy and internal radiation therapy. X-ray radiotherapy functions by utilizing the high energy penetration force of X-rays to damage the DNA of cancer cells within the tumor area, thereby impeding their division and growth. Advancements in diagnostic imaging technology have enabled more accurate targeting and reduced damage to healthy tissue, achieving the goals of high precision, high permeability, low dosage, and minimized harm[11].

Compared to X-rays, FLASH proton therapy marks a significant advancement in radiotherapy technology, representing a substantial breakthrough in future tumor therapy. This method employs specialized equipment, like an electron accelerator, to administer radiation at an

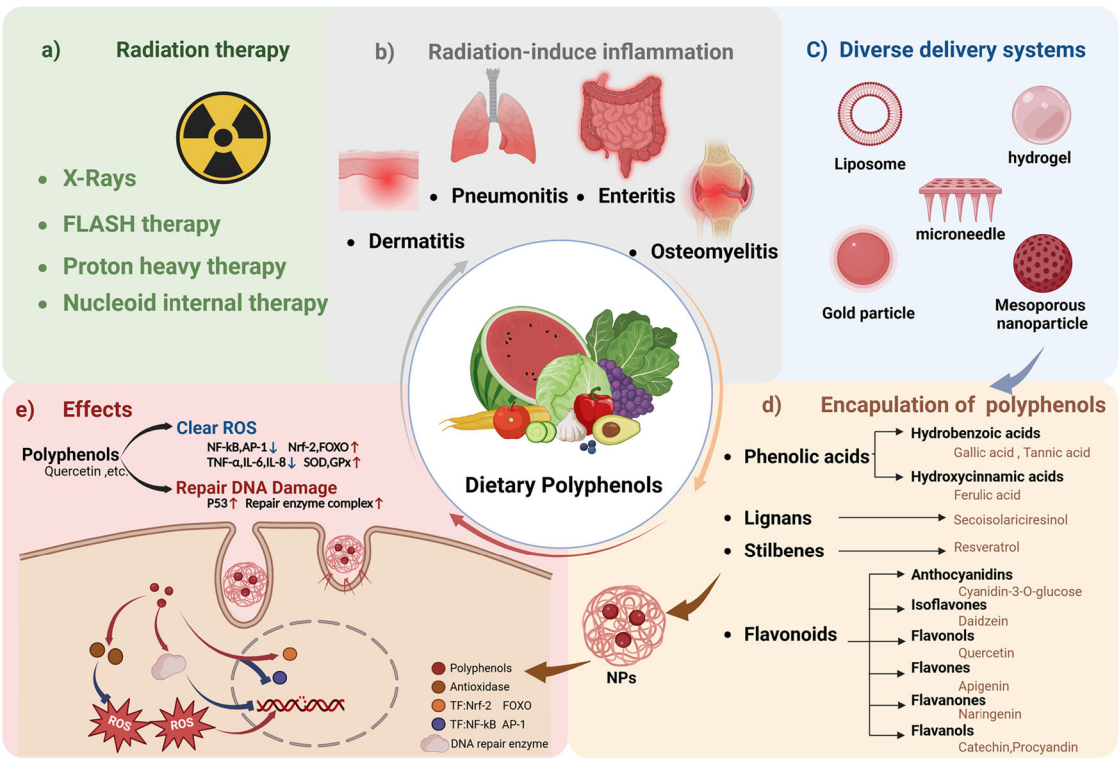

Fig. 1 | Schematic overview of polyphenol delivery systems for enhanced radiation protection and treatment efficacy. a Spectrum of prevalent radiation therapies; **b** Principal categories of radio-induced inflammation; **c** Varied delivery systems for polyphenols; **d** Taxonomy of polyphenols based on chemical structure; **e** The mechanistic action of polyphenols in radioprotection.

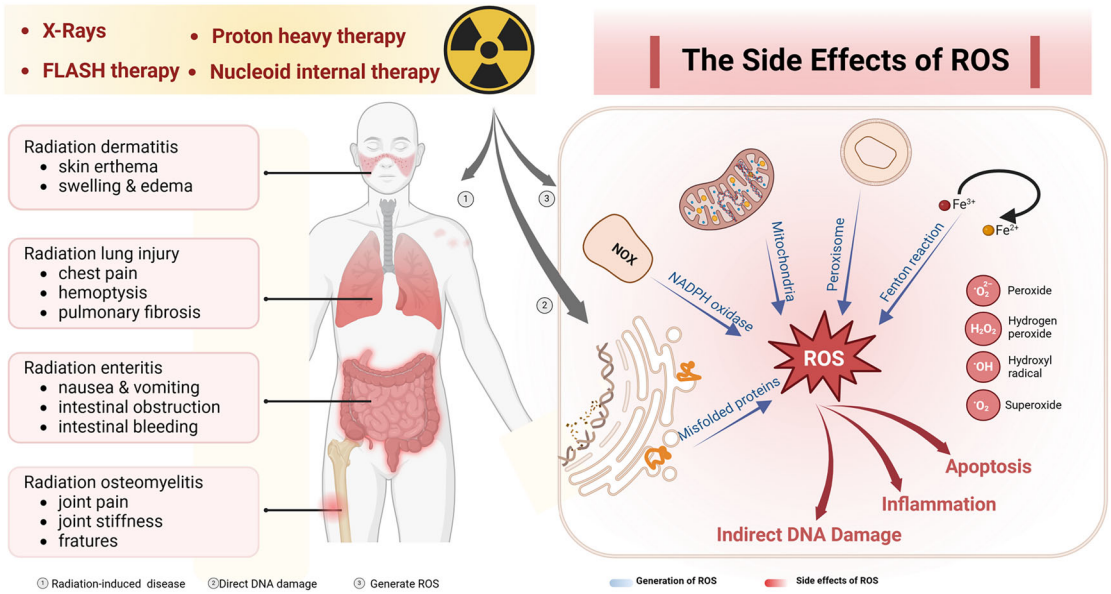

Fig. 2 | Left: Comparative analysis of radiotherapy modalities and radio-inflammation pathogenesis. Right: versus reactive oxygen species (ROS) production and associated adverse effects. ROS originate from multiple sources, including mitochondria, peroxisomes, the Fenton reaction, and misfolded proteins, leading to significant cellular detriments such as DNA damage, inflammatory responses, and apoptosis.

exceptionally high dose rate, offering higher therapeutic efficiency, minimal damage to normal tissue, and enhanced antitumor effects relative to conventional X-ray therapy[12].

Proton heavy ion therapy, another high-precision tumor therapy, utilizes charged particles (such as protons or heavy ions) to directly target tumor cells. With accurate positioning and controlled radiation dose delivery, it reduces damage to normal tissue and minimizes radiotherapy's side effects[13]. Compared to traditional X-ray therapy, proton therapy offers improved treatment outcomes for both deep-seated tumors and those near critical organs.

As a kind of internal radiation therapy, selective internal therapy involves the treatment of tumors by releasing radiation from a radioactive source (such as radioactive particles or agents) directly within or near the area of the tumor[14]. Nucleoid internal radiotherapy (Radionuclide therapy) uses a radionuclide or radiolabeled material introduced into the patient to treat the disease by releasing radiation through radioactive decay[15]. These two internal radiation therapy methods release radiation energy into the tumor cells by targeting the specific receptor or lesion site, destroying the structure of their nucleic acid and protein, resulting in the death of the tumor cells. Compared to conventional radiotherapy, internal radiation therapy ensures more accurate radiation dose delivery and minimizes damage to normal tissue, offering a more precise radiation range, fewer side effects, and enhanced postoperative survival rates. Since internal radiation therapy relies on the decay of radioactive sources within the body to generate radiation, the precision of targeting and dosage are vital to avoiding damage to normal tissues[16].

Despite recent advances in external and internal radiotherapy, which have improved targeting accuracy and reduced side effects, radiation damage and inflammation remain inevitable. For instance, treating pelvic or abdominal tumors can cause radiation enteritis, while head and neck cancer treatments may lead to radioactive oral mucositis, and treating superficial tumors might result in radiation dermatitis among other forms of radiation-induced inflammation. In the following, we will discuss the primary forms of radiation inflammation—radiation enteritis, radiation pneumonia, radiation dermatitis—including their causes and clinical manifestations, along with radiation osteitis.

Radiation-induced inflammation

When irradiating cancer cells, radiotherapy inevitably irradiates normal issue cells and produces damage. Radiation causes oxidative stress in normal tissue cells resulting in high levels of ROS and damage to DNA or, indirectly damage to DNA from the ROS produced. Thus, radiotherapy leads to inflammatory damage to the skin, bones, internal organs as well as cardiovascular tissues and organs. In this review, we focus on radiation-induced enteritis, pneumonia, dermatitis, and osteitis (Fig. 2).

Radiation enteritis is the damage and inflammatory response to the intestinal tissue caused by radiation during the course of radiation therapy. Radiation directly affects intestinal tissue, leading to cell damage and DNA structure destruction, which interferes with normal cell function, resulting in tissue damage and inflammation. Patients may experience abdominal pain, diarrhea, nausea, vomiting, loss of appetite and weight, intestinal obstruction, and intestinal bleeding. Additionally, radiation generates oxygen-free radicals, highly oxidizing compounds that further damage intestinal tissue, triggering an inflammatory response. Furthermore, radiation causes damage to intestinal microvascular endothelial cells and epithelial cells, resulting in edema and mucosal damage, potentially exacerbating gastrointestinal inflammation[17].

Radiation pneumonia is the damage and inflammatory response of lung tissue following radiation therapy or accidental radiation exposure. In addition to direct damage and oxygen-free radical impact on lung tissue, radiation can induce fibrotic reactions in the lungs, leading to structural and functional changes in non-tissues. Patients may exhibit symptoms such as cough, difficulty breathing, chest pain, hemoptysis, decline in pulmonary function, and pulmonary fibrosis[18].

Radioactive dermatitis results from the damage and inflammatory response of skin tissue caused by radiation. Patients may present with skin erythema, ecchymosis, dry and desquamated skin, blisters, ulcers, pain, itching, swelling, and edema. Radiodermatitis primarily stems from direct radiation damage and the production of oxygen-free radicals. Additionally, radiation can disrupt skin microcirculation, leading to vascular permeability and vasoconstriction, resulting in skin tissue ischemia and hypoxia[19].

Radioactive osteitis is the damage and inflammatory response of bone tissue caused by radiation after radiotherapy. In addition to direct damage and oxygen-free radical production, the presence of radiation causes microcirculatory dysfunction in bone tissue, leading to increased vascular permeability and vasoconstriction, which in turn leads to the side effect of ischemia and hypoxia in bone tissue[20]

While radiotherapy is an effective treatment for cancer, its common side effects, including the previously mentioned radiation inflammation and

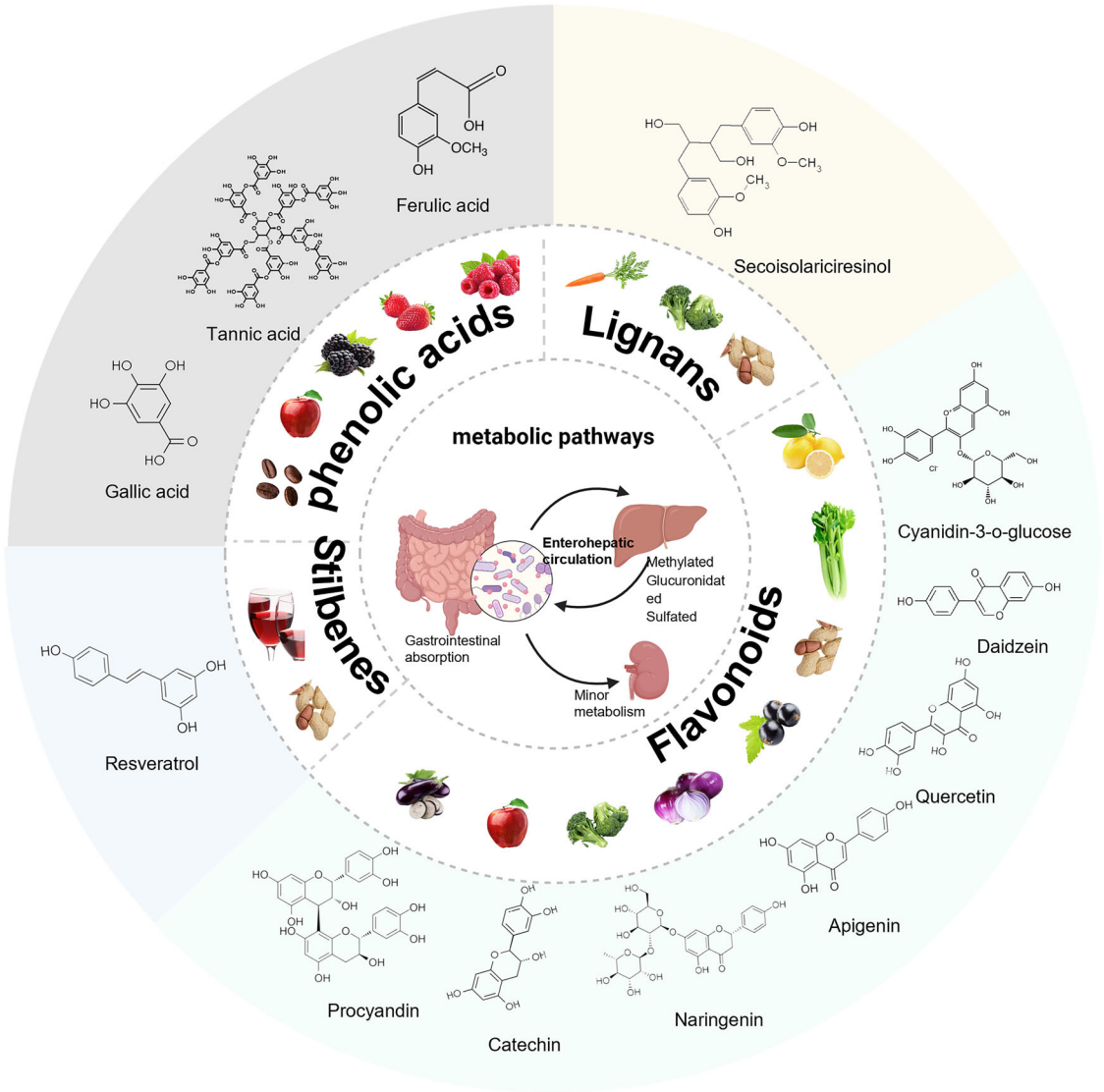

Fig. 3 | Biological sources, classification, and brief metabolic processes of dietary polyphenols. Dietary polyphenols, having a wide range of biological sources, are mainly categorized as phenolic acids, lignans, flavonoids, and stilenes. Polyphenols are generally absorbed through the gastrointestinal tract, metabolized into the body circulation by hepatic methylation, glucuronidation, and sulfation reactions, and partially metabolized by intestinal microbial biotransformation in the colon by intestinal hepatic circulation.

damage, cannot be overlooked. Thus, protecting patients undergoing radiotherapy is paramount. Currently, the protective role of dietary polyphenols in radiation therapy is a significant area of research interest. In the subsequent section, we will explore the sources, classification, and anti-inflammatory mechanisms of dietary polyphenols.

Dietary polyphenols for radiotherapy protection

Dietary polyphenols are natural compounds found in many plants, offering various health benefits and showing promise in protecting against the effects of radiation therapy. In this chapter, we will explore dietary polyphenols from three perspectives: monomeric polyphenols and their classification, polyphenol complexes, and the mechanisms of modified polyphenols in alleviating radiation-induced inflammation. Additionally, we will briefly discuss the application of different types of dietary polyphenols in radiotherapy protection[21].

Monomeric polyphenols, known for a wide range of biological activities and complex metabolic pathways, are mainly categorized as flavonoids, phenolic acids, stilbenes, and lignans. Flavonoids are the largest and most diverse group of polyphenols, and include compounds such as quercetin, catechins, and anthocyanins. Flavonoids can further be classified into anthocyanins, flavonols, flavanols, flavanones, and isoflavones, each sourced from various plants such as berries, grapes, tea, and soybeans. Phenolic acids, on the other hand, are simpler in structure and include compounds such as caffeic acid and ferulic acid. Stilbenes, such as resveratrol, are another class of polyphenols that have gained attention for their potential health benefits. Finally, lignans are polyphenols found in high-fiber foods such as flaxseeds and sesame seeds (Fig. 3).

Polyphenolic complexes and the modified polyphenols

Dietary polyphenol complexes are a group of compounds found in a variety of plant-based foods and beverages that have gained attention for their potential health benefits. Complex mixtures of polyphenols found in foods like wine, tea, and fruits exhibit synergistic effects, also providing potent antioxidant and anti-inflammatory properties. Modified polyphenols are produced through various processes such as esterification, glycosylation, acylation, and structural modification, which also have the ability to alleviate radiation-induced inflammation. In the study of Yamanishi et al., oligo polyphenols complexes extracted from litchi effectively inhibited NF-κB activation and nuclear translocation and inhibited the expression of these inflammatory genes, providing further evidence for the application of

polyphenol complexes in radiotherapy protection[22]. In another study, resveratrol (RV) was used and five structurally modified RV analogs, namely, butyric, isobutyric, palmitic, acetic, and diacetic acids, were compared. In this experiment, they showed that of the five modifiers of resveratrol, only diacetate was able to contribute to the alleviation of inflammation (17% higher gene expression stimulating SIRT-1 than resveratrol). It is evident that modified polyphenols also have good biological functions, but the effect is average[23].

Dietary polyphenols, including polyphenol complexes, monomers, and modified forms, hold promise in radiotherapy protection and treatment. Further research will contribute to a better understanding of their mechanisms and provide guidance for their application in health management and disease treatment. In the following sections, we will delve into the specific mechanisms by which dietary polyphenols can alleviate radiation-induced inflammation.

Protective mechanism of polyphenols in radiation therapy

Dietary polyphenols are extensively utilized in radiation therapy protection because of their inherent properties. These compounds principally act by enhancing the clearance of ROS and facilitating DNA repair. In this section, we will concentrate on these two pathways to elucidate the mechanisms through which polyphenols mitigate the effects of radiation therapy (Table 1).

Polyphenols reduce the toxicity of ROS. ROS are required for normal physiological metabolism in humans. However, overproduced ROS can cause harm to healthy tissue. After radiotherapy, cells in the human body undergo oxidative stress, leading to increased free radicals, especially oxygen free radicals[24]. ROS include hydroxyl radicals, superoxide anion, and hydrogen peroxide. Endogenous ROS are mainly derived from the activity of mitochondrial metabolism, peroxisomes, and the transmembrane NADPH-oxidase family. Through a review of the relevant literature, we have identified both direct and indirect mechanisms by which ROS are mitigated, including the direct reduction of mitochondria and mammalian target of rapamycin (mTOR) activity produced by ROS. Indirectly, ROS clearance is facilitated through the inhibition of the NF-κB pathway, which consequently downregulates the expression of inflammatory mediators and cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-8 (IL-8). This action helps to prevent the amplification of inflammatory signals and diminishes ROS production. Polyphenols have been found to modulate these pathways effectively[25]. The next sections will detail how polyphenolic compounds contribute to the reduction of ROS levels, mainly in the pathways that inhibit ROS generation and promote the elimination of existing ROS in the body (Fig. 4).

Inhibition of ROS generation. ROS is mainly generated directly in the mitochondrial oxidative respiratory chain, NADPH oxidase, and partially in peroxisomes, endoplasmic reticulum misfolded proteins, and Fenton reaction. Dietary polyphenols can reduce ROS production by directly blocking these pathways, thereby reducing the production of inflammatory mediators and cytokines, alleviating the inflammatory and tissue damage side effects of radiotherapy.

For example, resveratrol has been demonstrated to inhibit NOX 4 and reduce oxidative stress caused by radiation therapy. Azmoonfar et al. showed that resveratrol can inhibit NADPH oxidase 4 (NOX 4) (producing superoxide) and thus reduce its derived reactive oxygen species ROS, which can reduce the oxidative stress caused by radiation therapy[26]. It is well known that hydroxyl radicals generated by the Fenton reaction are important members of ROS. The experiments of Lopez-Burillo et al. verified that resveratrol could inhibit the Fenton reaction to reduce ROS[27]. Other compounds such as gallic acid and tea polyphenols also have metal chelation properties, which can reduce cellular inflammation and damage caused by radiation. These findings collectively demonstrate various strategies for mitigating oxidative stress and preventing the generation of ROS, offering potential avenues for therapeutic intervention.

Upregulation of antioxidant enzyme expression or activity. Antioxidant enzymes, such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione reductase (GR), convert reactive oxygen species (ROS) into harmless substances, thereby reducing cellular oxidative stress and mitigating radiotherapy-induced inflammation[28].

The transcription factor Nrf-2 promotes the expression of antioxidant enzymes[29]. Thus, the key to the upregulation of antioxidant enzyme activity by dietary polyphenols lies in the upregulation of transcription factor activity. Not only that, but Zhang et al. showed that Nrf-2 is a major regulatory pathway of oxidative stress, which is considered to be an ideal target for attenuating radiation damage in endothelial cells (EC). The ability of dietary polyphenols to modulate Nrf-2 has been of great interest in the study of mitigating radiation-induced inflammation by modulating Nrf-2 and thus being able to reduce radiation enteritis caused by oxidative stress and apoptosis[30]. Zhang et al. demonstrated that resveratrol activated the intracellular Nrf-2 pathway, upregulated the expression of SOD, GPx, removed ROS, and attenuated inflammatory damage due to oxidative stress in endothelial cells. The data showed that rats subjected to resveratrol intervention produced more superoxide dismutase and glutathione peroxidase, which was respectively recorded as 274.30 ± 11.22 U/mg protein, 5.33 ± 0.01 μmol/mg protein, and the corresponding data for the control group were 271.67 ± 13.62U/mg protein and 5.31 ± 0.05μmol/mg protein[31]. Similarly, quercetin mitigates oxidative damage via the Nrf-2-mediated antioxidant pathway, effectively reducing ROS by modulating Nrf-2 signaling and facilitating intestinal epithelial repair in Zhu's radiation mouse model[32]. Similarly, according to Ha's research, Q-3-G significantly enhanced the expression level of Nrf2 upon UVB irradiation compared to the control in a concentration-dependent manner, up to 10 μM[33].

The FOXO signaling pathway also contributes to ROS reduction by enhancing the expression of antioxidant enzymes, promoting ROS clearance, and regulating cellular redox balance. In a γ-radiation mouse model, resveratrol was used for radiation protection, significantly regulating the FOXO signaling pathway to diminish ROS and alleviate liver damage caused by radiation[34].

Downregulation of inflammatory mediators and cytokines. Radiation causes damage to normal cells and tissues and produces many inflammatory mediators, which in turn induce radiation-induced inflammation. These inflammatory mediators commonly include TNF-α, IL-1β, IL-6, and so on. We know that NF-κB and AP-1 as upstream transcription factors can regulate the expression of these factors. Therefore, dietary polyphenols targeting the above two transcription factors can also alleviate radiation-induced inflammation[35]. Zhang et al. verified by radiation-induced rat model that resveratrol downregulated the inflammatory response and apoptosis through NF-κB signaling pathway in rats, and alleviated the post-radiation inflammation and injury in rats. Upregulation of TNF-α mRNA expression in the radiation group was assessed by qRT-PCR and Western blot. However, the level of TNF-α expression decreased after RSV treatment. Meanwhile, experimental analysis of RSV treatment in rats in the RAD group decreased NF-κB protein levels. The researchers showed that activated NF-κB induced the overexpression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. Thus, resveratrol can reduce inflammatory mediators by inhibiting NF-κB expression[31]. Furthermore, Ha et al. employed a luciferase assay to confirm that Q-3-G increased AP-1-mediated luciferase activity and NF-κB-mediated luciferase activity. They demonstrated that quercetin 3-O- β -D-glucuronide (Q-3-G) decreases ROS through NF-κB pathway, exhibiting significant anti-inflammatory and antioxidant properties, with promising therapeutic potential for radiation-induced skin inflammation[33]. Beyond resveratrol, Wang et al. in a radiation-treated mouse model found that quercetin also lowered NF-κB levels and reduced ROS, consequently alleviating lung injury in irradiated mice[36]. In another study, quercetin liposomes protect against radiation-induced pulmonary injury in a murine model.

Table 1 | Primary mechanisms of polyphenol-mediated mitigation of radiation-induced inflammation and damage are explored, with a focus on conditions such as radiation-induced enteritis, pneumonia, dermatitis, and osteitis

Polyphenolic compounds	Experiment system	Dosage	Way of administration	Main outcome	Reference
Resveratrol	In vitro	0–5 μM	/	SIRT1↑, p53↓, mTOR↓, PI3K/AKT/mTOR ↓	134
Resveratrol	Vivo	100 mg/kg	Oral	Sirt1↑, SOD2↑, GPx↑, NF-κB↓	26
Resveratrol	Vivo	4 mg/kg	Gavage	NOX4↓, SOD2↑, GPx1↑	135
Resveratrol	Vivo	6 mg/kg	Intraperitoneal injection	SIRT-1↑, FOXO-1↓	34
Resveratrol	Vivo	2 mg/kg	Intragastric administration	MAPK↓, Nrf2↑	136
Resveratrol	In vitro	25, 50, 100 μM	/	MAPK↓, NF-κB↓	137
Resveratrol	Vivo	20 mg/kg	Oral	PI3K/Akt/mTOR↓	43
Resveratrol	Vivo	25 mg/kg	Oral	SIRT1↑, NF-κB↓	138
Resveratrol	In vitro	0, 50, 100, 200 μM	/	SIRT1↑	139
Quercetin	Vivo	20 mg/kg	Injection after decapitation	Repair DNA damage	140
Quercetin	Vivo	50 mg/kg	Intragastric administration	Nrf2↓	141
Quercetin	Vivo	20 mg/kg	IV	NF-κ B↓	36
Quercetin	Vivo	10 mg/kg	Intramuscular injection	NF-κ B↓	142
Curcumin	Vivo	200 mg/kg	Intragastric administration	NF-κ B↓	143
Curcumin	Vivo	50 mg/kg, 150 mg/kg	Intraperitoneal injection	SIRT1↑	144
Curcumin	Vivo	150 mg/kg	intraperitoneal injection	Repair of alveolar epithelial cells	145
Curcumin	In vitro	10 μM	/	NF-κ B ↓PI3K/Akt/mTOR ↓	146
EGCG	Vivo	25 mg/kg	Oral	Regulate the intestinal microenvironment	147
EGCG	Vivo&In vitro	12.5, 25 mg/kg 1, 2, 5, 10, 20, 40 μM	Intraperitoneal injection	Repair DNA damage, Fenton Death ↓ , Nrf2↑	148
EGCG	In vitro	10, 20, 50 μM	/	Repair DNA damage	149
Anthocyanin	In vitro	2.5, 5, 10 μM	/	MAPK↓, Akt↓, Nox4↓	150
Anthocyanin	In vitro	5 mg/cm^2	Application	MAPK↓, NF-κB↓, Nrf-2↑	151
Anthocyanin	In vitro	0, 250, 500 μM	Application	Repair DNA damage NF-κ B ↓	152
Anthocyanin	In vitro	5, 10.20 μM	/	NF-κ B↓, AP-1↓, MAPKs↓	153
Caffeic acid	Vivo	100 mg/kg	Oral	MAPKs↓	154
Epicatechin	Vivo	80 mg/kg	Oral	Repair DNA damage	155

Composite polyphenols	Experiment system	Dosage	Way of administration	Main outcome	Reference
Seabuckthorn extract	Vivo	100 μg/ml		Repair DNA damage	156
Litchi extract	In vitro	8 μg /ml	/	NF-kB↓	22
Propolis flavonoid complex	Vivo	100 mg/kg	intraperitoneal injection	Repair DNA damage	157

Modified polyphenols	Experiment system	Dosage	Way of administration	Main outcome	Reference
Resveratrol as well as the methoxy derivatives	In vitro	40, 80, 120 μM	/	Repair DNA damage	158
Caffeic acid phenethyl ester	Vivo	20 mg/kg	Intraperitoneal injection	NF-κ B↓	159
Caffeic acid phenethyl ester	Vivo	15 mg/kg	Intraperitoneal injection	NF-κ B↓	160

Activator Protein 1 (AP-1), a family of transcription factors composed of different subunits, including members such as c-Fos, c-Jun, JunB, JunD, and so on, has a similar effect to NF-κB. For instance, resveratrol blocks the AP-1 pathway associated with NF-κB inhibition, and simultaneous inhibition of both routes has a common effect on reducing inflammatory factors and alleviating radiation-induced inflammation[37]. Li et al. found that quercetin indirectly prevents inflammation by enhancing peroxisome proliferator-activated receptor γ activity, thereby opposing NF-κB or AP-1 mediated transcription of inflammatory genes, collectively obstructing the TNF-α-mediated inflammatory cascade and reducing inflammation damage from radiation therapy[38].

Indirect modulation of signaling pathways reduces ROS. Above, we summarized that dietary polyphenols alleviate radiation-induced inflammation by regulating transcription factors, and in this section, we will focus on some additional regulatory proteins.

SIRT-1 enhances the stability and activity of Nrf-2 by deacetylation. SIRT-3 regulates the expression of various genes via downstream transcription factors, including FOXO, thereby improving cellular oxygen resistance[39]. Moreover, SIRT-1 inhibited the activity of NF-κB, which reduces the transcriptional expression of several inflammation-related genes, and reduces inflammatory mediators and inflammatory cytokines such as TNF- α and IL-8[40]. Said et al. verified by γ-radiation mouse model that resveratrol suppressed oxidative stress induced by ionizing radiation by activating SIRT-1 and others, alleviating radiation pelvic inflammation[41]. Guo et al.'s found that quercetin attenuates oxidative stress-induced cell apoptosis through SIRT-1/AMPK mediated inhibition of ER stress, thus mitigating radiation-induced inflammatory damage[42].

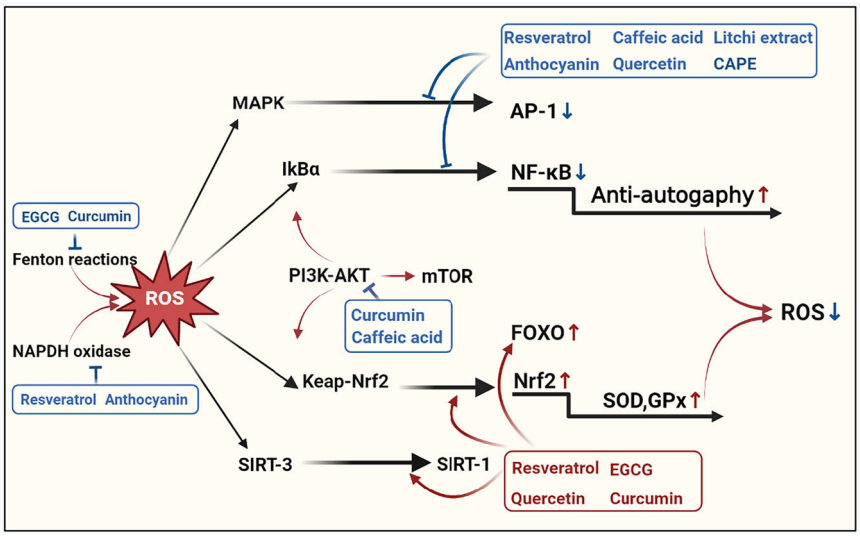

Fig. 4 | Polyphenolic mediation in the attenuation of ROS accumulation. This figure delineates how polyphenols modulate the activity of key transcription factors (AP-1, NF-κB, FOXO, Nrf2) and ancillary signaling cascades to mitigate ROS-induced cellular damage.

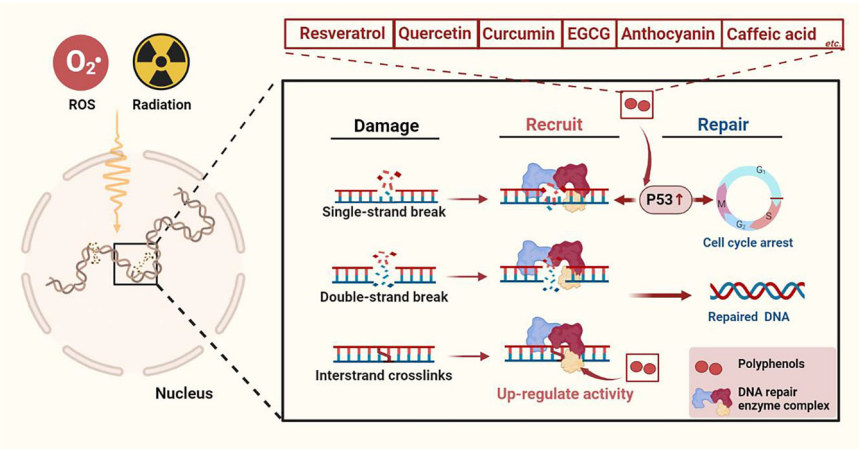

Fig. 5 | Mechanisms by which polyphenols promote damaged DNA repair. Polyphenols are shown to augment the functionality of DNA repair enzyme complexes and enhance the expression of the tumor suppressor protein P53, critical for cellular integrity and tumor suppression.

Beyond the SIRT-3/SIRT-1 pathways, the PI3K/AKT/mTOR pathway also influences the aforementioned transcription factors. This pathway interacts with these factors to upregulate Nrf-2 and FOXO expression while downregulating AP-1 and NF-κB. The PI3K/Akt pathway is known to enhance NOX 4 expression and ROS production; conversely, its inhibition suppresses NOX 4-mediated ROS generation. For instance, Radwan and Karam et al. in a rat model of radiation enteritis, showed that resveratrol downregulates the PI3K/Akt/mTOR pathway, thereby reducing ROS post-radiation and effectively alleviating radiation enteritis[43].

Promoting the DNA damage repair. Radiation can also directly or indirectly lead to DNA damage, including single-strand breaks, double-strand breaks, base damage, *etc*[44]. As mentioned before, polyphenols reduce ROS to minimize DNA damage. Moreover, polyphenols possess the capability to directly facilitate the repair of damaged DNA, a critical process for preserving genomic integrity and stability[45]. Based on the literature review, we summarize the mechanisms by which polyphenols promote DNA damage repair after radiation

Enhance the activity of DNA repair enzymes

Polyphenols can increase the activity of DNA repair enzymes, such as nucleotide excision repair (NER) and base excision repair mechanisms[46]. Polyphenols can interact with DNA repair enzymes to enhance their structure and function, thus accelerating the repair process of DNA damage[47]. Nambiar et al. demonstrated that resveratrol can enhance the activity of DNA repair enzymes involved in base excision repair, nucleotide excision repair, and double-strand break repair mechanisms, helping cells repair radiation-induced DNA damage and reducing radiation inflammation and damage[48,49]. Not only resveratrol, but also polyphenol monomers such as quercetin, epigallocatechin gallate (EGCG), anthocyanins, and caffeic acid have good functions to repair radiation-induced DNA damage.

Regulate DNA damage repair gene expression

Polyphenols can regulate the expression of genes related to DNA damage repair, such as p53[50]. By regulating the expression of these genes, polyphenols can enhance the efficiency of DNA damage repair[49,51,52]. When cells are exposed to radiation-induced DNA damage, the p53 protein is activated and accumulates in the nucleus. Once activated, the p53 protein will initiate a series of responses to protect the cells from further damage. Soltani et al. found that curcumin recruits ATR, ATM, and other proteins associated with NER to sites of DNA damage through the p53/XPC/DDB 2 pathway to initiate and complete the DNA damage repair process[53] (Fig. 5).

Polyphenols for dietary supplement: metabolism and bioavailability

As mentioned above, although polyphenols can have a wide range of promising applications as dietary supplements for protection against radiation therapy, especially in the alleviation of inflammation—one of the side effects

caused by radiation therapy, their low absorption and oral bioavailability in the human body seriously limit further clinical applications of dietary polyphenols. Numerous studies have demonstrated the mechanisms by which dietary polyphenols are metabolized and transformed in the human body leading to low bioavailability, mainly including the following aspects.

Phase I-II reactions in intestinal tissue and liver. The reaction involves two phases of polyphenolic compounds in the intestine and liver, respectively, and consists mainly of a combination of reactions including absorption as well as glucuronidation, sulfation, and methylation, to be converted into more water-soluble metabolites and rapidly metabolized so that they can be removed by urine and bile and readily excreted from the body[54]. Due to the physicochemical nature of the polyphenols, either extremely low absorption or extremely rapid metabolism, the bioavailability of dietary polyphenols is low. In addition, according to relevant studies, dietary polyphenols are bio-transformed by the liver and intestines, and their metabolized derivatives have certain biological activities, which will be described in detail below[55,56]. Summarizing the above, it is easy to see that this reaction allows for the rapid absorption and metabolism of dietary polyphenols into metabolic derivatives, thus reducing the bioavailability of dietary polyphenols.

Gut microbe-mediated biotransformation

There is an extensive and complex two-way connection between dietary polyphenols and gut flora. The gut flora can undergo biotransformation—converting dietary polyphenols into other metabolic derivatives, usually smaller, simpler molecules, and into the bloodstream (we'll explain this in more detail below)[55]. At the same time, dietary polyphenols also modulate the composition of the intestinal flora, which is also relevant to the anti-inflammatory mechanism of dietary polyphenols in relieving radiation enteritis by handing over the intestinal flora that we have mentioned above. However, in this section, we emphasize that it is this gut flora biotransformation that limits the bioavailability of dietary polyphenols in plasma. Taking resveratrol as an example to explain, only 75% of resveratrol entering the human gastrointestinal tract can enter the intestinal cells, and the rest is directly excreted. And even more unfortunately, only 1.5% of resveratrol can escape from bio-transformation and enter the bloodstream[54]. From this, it is easy to see that the biotransformation of dietary polyphenols in the gastrointestinal flora is one of the most important reasons for limiting the bioavailability of dietary polyphenols.

After entering the bloodstream via the intestine, dietary polyphenols undergo enterohepatic circulation and, to a lesser extent, renal metabolism, and are bio-transformed several times until they are excreted in bile and urine. After such a metabolic process as described above, there is no doubt that the metabolism of dietary polyphenols in the human body makes their bioavailability far less than that of direct use in vitro. Moreover, due to the gastrointestinal metabolism of the human body, the bioavailability of dietary polyphenols is low and their bioactivity is more complex.

In the next articles, we will focus on the topic of intestinal metabolism, metabolic derivatives, and bioavailability of several dietary polyphenols that have been widely investigated for the alleviation of radiation-induced inflammation (mainly focus on resveratrol, curcumin, quercetin, and proanthocyanidins), the possible solutions, and the expression of expectations to increase their bioavailability for a really wide range of applications.

Resveratrol. Resveratrol, widely derived from grapes, wine, peanuts, and peanut products, is a fat-soluble natural molecule with low water solubility and high membrane permeability for rapid absorption and metabolism.

According to research data, the absorption rate of oral dietary polyphenols is about 70–75%, mainly by trans-epithelial diffusion. After extensive metabolism in the intestine and liver, the bioavailability is far less than 1%[54,57]. The main metabolites of resveratrol after intestinal and hepatic metabolism are resveratrol glucosides and sulfates. Specifically, uridine 5'-diphospho-glucuronosyltransferases catalyze the binding of resveratrol with glucuronic acid, mainly producing resveratrol-3-O-glucuronide (R3G) and resveratrol-4'-O-glucuronide (R4G); sulfotransferases catalyze the formation of resveratrol-3-O-sulfate (R3S), resveratrol-O-sulfate, and resveratrol disulfate[58,59].

However, there is still doubt about whether these abundant metabolites have the same favorable anti-inflammatory activity as dietary polyphenols. Experimental data showed that 10 μM resveratrol completely inhibited the release of the inflammatory mediator IL-6, while resveratrol-3-sulfate and resveratrol-disulfate decreased by 84.2 ± 29.4% and 52.3 ± 39.5%, respectively, and the release of TNF-α was reduced by 48.1 ± 15.4%, 33.0 ± 10.0%, and 46.7 ± 8.7%, respectively, in macrophage assays in vitro[60]. In another experiment, R3G and R4G upregulated SIRT-1 mRNA by 22.7 ± 17.9% and 22.8 ± 16.9% respectively, showing anti-inflammatory properties[61].

As seen above, the abundant metabolites of resveratrol in the human body also have some anti-inflammatory effects. However, the anti-inflammatory effects of the metabolites may not be superior to those of resveratrol, thus reinforcing the need to improve the bioavailability of the polyphenols themselves. In addition to this, relevant experiments conducted so far have mainly focused on the local anti-inflammatory molecular level, but little attention has been paid to the overall mitigating effect in models of radiation-induced inflammation. This also provides ideas for further pharmacokinetic studies.

Curcumin. Curcumin, a small natural molecule found in turmeric, is a common spice and herb that is widely used in cooking and traditional herbal medicine[62]. Curcumin is also less than 1% bioavailable in vivo and is rapidly metabolized in the body with limited absorption and low blood entry. In an in vivo study, curcumin failed to establish detectable plasma levels even at an oral dose of 180 mg[63].

In the intestinal and hepatic phase I reactions, curcumin can be metabolized into dihydrocurcumin, tetrahydrocurcumin, hexahydrocurcumin (HHC), and octahydrocurcumin (OHC) by alcohol dehydrogenases. Similarly, curcumin undergoes glucuronidation, sulfation, and methylation during metabolism. Recent studies have shown that curcumin, like other dietary polyphenols, undergoes biotransformation through the gut microbiota[64–66].

In terms of anti-inflammatory pathways and mitigating effects, most of the above metabolites have been shown to have anti-inflammatory effects, with HHC having the strongest anti-inflammatory activity among the diarylheptanes or diarylheptylamine analogs of curcumin[67]. In contrast, Pan et al. revealed that OHC also has anti-inflammatory potential, but lower than curcumin by inhibiting NF-κB activating[68].

However, curcumin and its bioactive metabolites are likely to be formed at trace levels in human metabolism, which not only makes their detection and identification a challenge, but indeed makes the clinical use of curcumin severely limited. It is not difficult to see the urgency of addressing its low bioavailability.

Quercetin. Quercetin, a typical representative of flavonoids, is commonly found in lettuce, peppers, onions, black cherries, tomatoes, broccoli and apples[69]. Quercetin generally has poor oral bioavailability due to its low water solubility, poor stability, and low membrane permeability. Like curcumin, quercetin has a low plasma content[9,69,70]. Quercetin is absorbed in the small intestine mainly by passive diffusion or with membrane transport proteins. In enterocytes, quercetin is mainly glucuronidated, sulfated, and methylated[71,72].

Small amounts of unmetabolized quercetin are metabolized in the hepatic and intestinal circuits and enter the systemic circulation or are excreted in the bile. In intestinal flora metabolism and biotransformation, quercetin is mainly used as a substrate by several intestinal bacteria, which produce C-ring cleavage and dehydroxylation reactions that metabolize the quercetin to make it more readily available for absorption[72–74].

Although studies evaluating the anti-inflammatory effects of quercetin metabolites are limited, some metabolites, such as resorcinol, have been suggested to have intrinsic anti-inflammatory properties. It regulates the

activity of several mediators or transcription factors involved in the inflammatory process, such as TNF-a, IL-6, IL-1b, and NF-κB[75]. In an experiment in our lab, it was similarly shown that quercetin has good anti-inflammatory properties[2].

At this stage, the research on quercetin is limited. Relevant researchers still have a long way to go regarding quercetin pharmacokinetics. In addition, the metabolism of quercetin is characterized by individual variability, which makes it difficult to study and improve it further[9,74].

Proanthocyanidins. Proanthocyanidins, also condensed tannins, pigment compounds widely found in plants, sources include cinnamon bark, blueberries, sorghum grains, grapeseeds, chocolate, and hazelnuts[75].Due to their polymeric nature and high structural complexity, the absorption and metabolism of proanthocyanidins are complex. As a result, little is known about the absorption, metabolism, and intestinal microbial effects of proanthocyanidins. A brief overview of bioavailability and metabolite anti-inflammatory correlations will be presented below[76–78].

Poor bioavailability of proanthocyanidin polymers, especially those of plant origin, which may be highly digested by intestinal microorganisms, has also made the intestinal metabolism of proanthocyanidins a hot research topic[79]. During biotransformation in the gut, proanthocyanidins rely on the hydrophilic paracellular pathway, or endocytosis, to enter the systemic circulation due to the lack of proanthocyanidin receptors in cell membranes. The main biotransformation modes are likewise glucuronidation, sulfation and methylation[79,80].

Under the action of intestinal flora, proanthocyanidins are mainly metabolized to phenylpentanolide and phenolic acid, which can be reabsorbed in the blood, and most of them as well as the metabolites are excreted in the feces[81]. Among them, several metabolites of quercetin exhibit strong biological activity, for example, phenyl-γ-valerolactone can inhibit inflammation and counteract inflammation induced by NF-kB activation[82].

Proanthocyanidins have been shown to alter gut flora in recent decades. As we mentioned above one of the mechanisms for relieving radiation enteritis is by regulating the intestinal flora. However, more research is still needed to fully prove it. On top of that, proanthocyanidins are much more difficult to study due to their complexity. In view of the favorable biological properties of proanthocyanidins, we also propose a vision for further in-depth research on proanthocyanidins.

In summary, dietary polyphenols have good anti-inflammatory bioactivity as dietary supplements and are very promising natural substances. However, with the brief description of the pharmacokinetics of dietary polyphenols above, it is easy to know that the main reason why dietary polyphenols stopped in animal studies is their low bioavailability. Thus, we propose the need to improve the bioavailability of dietary polyphenols. With the advances in nanomaterials research, encapsulation of dietary polyphenols using different bio-delivery systems is an extremely promising approach. We will present this in detail in the next section.

Diverse delivery systems for dietary polyphenol encapsulation

Although it was mentioned in the previous chapter that polyphenols exhibit significant anti-inflammatory and antioxidant properties, their further development is constrained by issues such as instability, limited bioavailability, and low biological activity. This chapter focuses on exploring delivery systems—such as liposomes, inorganic nanoparticles, organic nanocarriers, hydrogels, and microneedle systems—to enhance the bioavailability of dietary polyphenols, thereby mitigating radiation-induced inflammation and damage (Fig. 5).

liposome

Despite Phase I clinical trials confirming the safety of polyphenolic compounds at high doses, challenges such as low bioavailability, poor absorption, rapid metabolism, and quick systemic clearance impede their clinical and preclinical applications. Substances like curcumin, resveratrol, and quercetin are notably poorly absorbed in the gastrointestinal tract and swiftly metabolized in the liver[83]. However, liposomes present a viable solution to these issues. (Fig. 6).

Liposomes, usually being classified as emulsion-type ones and solid ones, are small spherical structures composed of components such as phospholipids and cholesterol. Emulsion-type liposomes are emulsion-type structures consisting of aqueous and oil phases. Due to the dietary polyphenols wrapped in liquid oil droplets and their aqueous characteristics, nano-emulsion has the advantages of high drug load, good biocompatibility, and regulated release properties[84]. Solid liposomes (Solid Lipid Nanoparticles, SLNs) are nanoparticles composed of solid lipids and surfactants. However, in despite of the greater advantage in maintaining the stability of dietary polyphenols, solid nanoliposomes are not as biocompatible as the emulsion-type one due to solid structure[84,85].

As discussed above, characterized with great biocompatibility, non-toxic property and non-immunogenic feature[86,87], liposome is a great delivery system for dietary polyphenols and exhibit excellent encapsulation properties such as good aqueous solubility and slow release ability to enhance the bioavailability of dietary polyphenols[88].

With extensive studies and statistics, liposomes have been fully convinced in their ability to improve the bioavailability and bioactivity of dietary polyphenols. Li et al. prepared Solid lipid nanoparticles (QT-SLNs) coated with quercetin, which were confirmed to have fair edge in high biocompatibility, high bioavailability, controlled release, and overcoming problems associated with different routes of administration[89]. Basnet et al. selected vesicles with a size range of about 200 nm for stability and cell experiments and found that the liposomal curcumin was two to six times as potent as the corresponding curcumin[90]. The same for EGCG[91]. Similarly, Arora et al. demonstrated that solid liposomes coated with curcumin showed enhanced anti-inflammatory effects[92], providing ideas for the remission and treatment of radiation osteitis. Another piece of evidence provided by Zhou et al. demonstrated that liposomal drugs coated with anthocyanin reduce the production of ROS in early radioactive lung injury. The study data showed that these liposomes have excellent free radical clearance ability, and it is worth noticing that the number of infiltrating neutrophils (the main host cell producing ROS) in lung tissue by X-irradiation after treatment with this drug decreased significantly, which was more effective in the treatment of radiation lung injury[93]. Liu et al. used a C6BL/16J mouse model undergoing total thoracic radiotherapy (57 Gy) and protected with quercetin liposomes. The test data showed that quercetin was more effective in preventing radiation-induced acute hepatitis and advanced fibrosis[94].

There are also many studies confirming that liposomes perform well in slowing the release and increasing the water solubility of dietary polyphenols to improve polyphenols' absorption and bioavailability in vivo. Li et al. developed and characterized QT-SLN. They used solid lipid nanoparticles (SLNs), carrying the poor water-soluble drugs, as oral delivery and conducted pharmacokinetic studies in rats. They proved that SLN, as an oral delivery carrier, is of great value to enhance the intestinal absorption of quercetin[89]. The research provides evidence that it is advantageous for the liposomes to improve the bioavailability of quercetin.

In addition to the above advantages, liposomes can also improve the targeting of polyphenols, facilitating their specific delivery to target tissues and reducing side effects and toxic reactions. Sun et al. utilized vesicles as drug carriers and the mouse model verified that liposomes reduce the significant side effects caused by off-target effects. Their specificity creates opportunities for treating many inflammation-related diseases[95].

Despite many advantages, liposomes still have certain drawbacks, particularly in terms of stability and drug encapsulation efficiency, which are influenced by factors such as temperature, pH, and ionic strength. To address these limitations, researchers have sought to enhance liposome stability and drug encapsulation efficiency by utilizing polymer-coated liposomes. Among the various polymers, chitosan is commonly employed for encapsulating liposomes. For instance, Caddeo et al. utilized chitosan in complex with sodium triphosphate to coat liposomes, and conducted a comprehensive characterization of the system's effectiveness and feasibility.

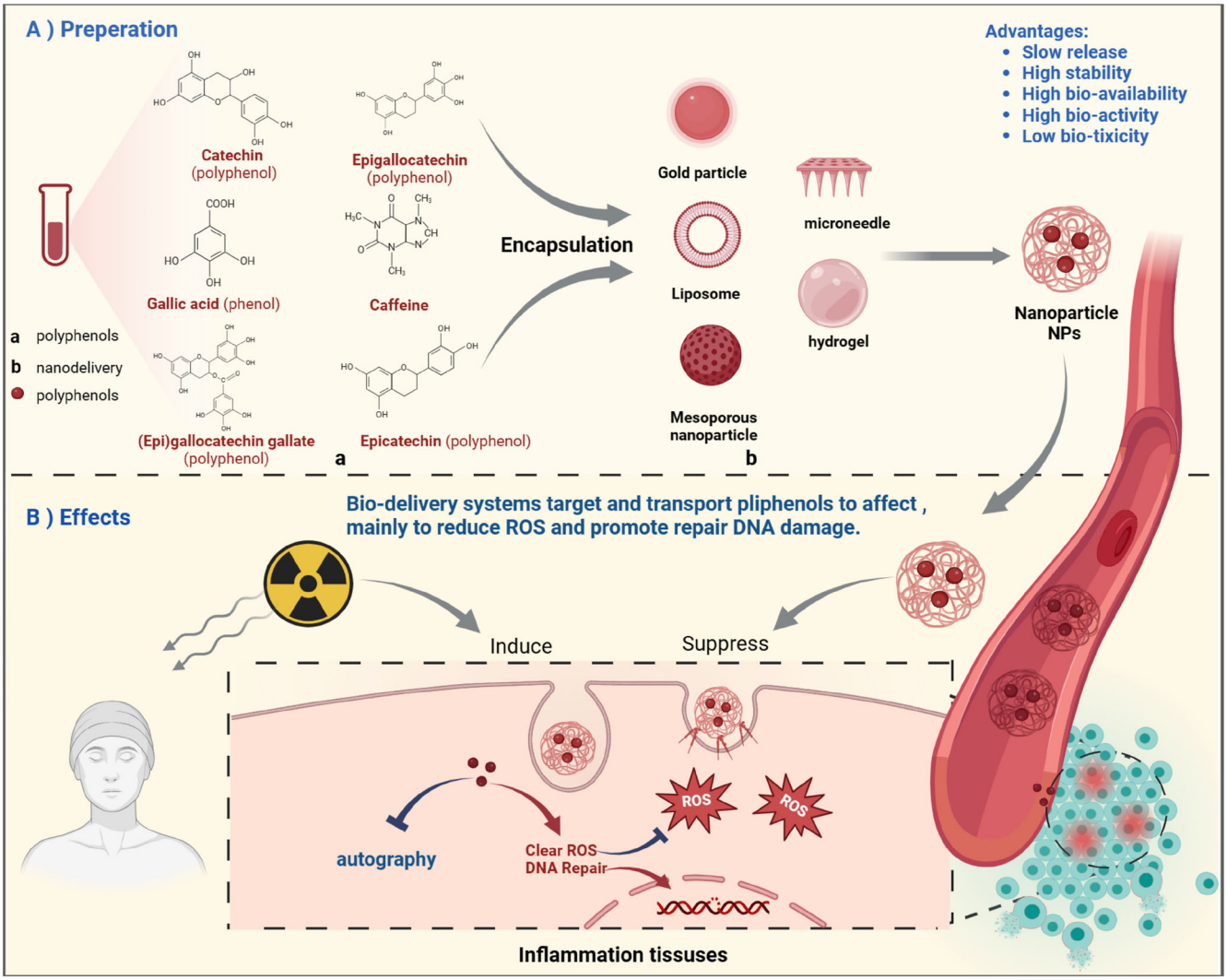

Fig. 6 | The types and advantages of delivery systems which encapsulate and deliver polyphenols to enhance radioprotection effects. A Preparation: Schematic of encapsulating polyphenols into carriers. Key advantages include slow release, high stability, bioactivity retention, and low toxicity. **B** Therapeutic effects: Targeted delivery to inflamed tissues reduces ROS and promotes DNA repair.

Furthermore, they investigated the system's ability to release quercetin under conditions simulating gastric and intestinal pH. The data revealed that encapsulated liposomes enhance the bioavailability of quercetin and optimize its release rate in the gastrointestinal tract[96]. In a subsequent study, Caddeo et al. prepared succinic anhydride-based chitosan-coated liposomes, and experimental data demonstrated that these sugar-modified liposomes serve as an effective delivery system for encapsulating. Moreover, the succinic anhydride-based chitosan-modified liposomes do not compromise their internal properties[97]. Series of experiments have shown that in addition to highlighting anti-inflammatory and antioxidant function, optimized liposomes can improve their stability and encapsulation efficiency to some extent without affecting their normal function.

Along with the chitosan packaging method, the researchers also have explored other optimization options to solve this problem. For example, WU et al. utilized hyaluronic acid-optimized solid lipid nanoparticles to investigate the anti-inflammatory effects after encapsulating EGCG, showing potential applications in enhancing the stability of EGCG for the treatment of radiation-induced inflammation and injury[91]. Also of great importance is the fact that liposome administration has been shown to be relatively safe. Shi et al. demonstrated the effectiveness of liposomal curcumin in preventing radiation damage and reducing pulmonary fibrosis after irradiation, and the systemic administration of liposomal curcumin was found to be safe, suggesting its potential for further clinical applications[98].

Inorganic nanoparticles

Inorganic nanoparticles, a delivery system with superior stability and excellent physicochemical properties, are among the most commonly used delivery systems at the current stage of research on dietary polyphenol delivery to alleviate radiation-induced inflammation. Comparatively, liposomes, as nanoparticles encapsulated in lipid membranes, are more susceptible to the properties of these membranes and the drugs they carry. In contrast, inorganic nanoparticles typically exhibit higher stability, maintaining their properties across different environments. As an emerging drug delivery system, inorganic nanoparticles at the nanometer scale can serve as carriers to encapsulate drugs, enabling precise drug delivery[99]. Along with their enhanced stability, inorganic nanoparticle delivery systems offer numerous advantages and are widely used in mitigating and treating radiation-induced inflammation and injury[100], as discussed below.

Currently, inorganic nanoparticles for delivering dietary polyphenols can be broadly categorized into metal nanoparticles, metal oxide nanoparticles, and metal sulfide nanoparticles.

1. Metal nanoparticles, such as gold, silver, and copper nanoparticles, have been found to effectively deliver dietary[101], for treating radiation-

induced diseases through their photothermal and fluorescence properties[102]. Crisan et al. demonstrated that locally delivered polyphenols-coated silver and gold nanoparticles significantly reduced the release of NO, IL-12, and TNF- α release compared to traditional dietary polyphenols[103]. While the study aimed to alleviate inflammation in a psoriasis plaque model, it provides a basis for delivering polyphenols using metal nanoparticles due to similar signaling pathways for inflammation relief.

2. Metal oxide nanoparticles, including titanium dioxide, iron oxide, and zinc oxide nanoparticles, have successfully delivered multiple dietary polyphenols to radiation lesions, reducing radiation damage by inhibiting oxidative stress and inflammatory reaction[104]. Modified magnetic core-shell mesoporous silica nanoparticles encapsulated with quercetin exhibited superior antioxidant activity compared to traditional dietary polyphenols and demonstrated better efficacy in reducing radiation-induced ROS[105].
3. Metal sulfide nanoparticles, such as iron sulfide and copper sulfide nanoparticles, have been used to encapsulate dietary polyphenols. Researchers found that nickel cobalt sulfide (NiCoS) nanoparticles exhibited good peroxidase-like activity and antioxidant capacity[106]. It has been verified that metal sulfides themselves have antioxidant effects and can synergistically alleviate radiation-induced inflammation with polyphenols, offering potential for using inorganic biological delivery systems to encapsulate polyphenols for alleviating radiation inflammation[106].

Furthermore, inorganic nanoparticle delivery systems can also achieve precise drug delivery by controlling release[107]. By adjusting the structure and material properties of particles, slow drug release can be achieved, thereby prolonging the duration of drug action and reducing dosage[108]. For example, Nday et al. encapsulated quercetin with modified silica nanoparticles and determined the release curve of quercetin through relevant experimental methods. The results showed that using inorganic nanoparticles to encapsulate quercetin in the treatment of Alzheimer's disease can prolong the release time of quercetin[109]. Given that current methods for treating Alzheimer's disease include radiation therapy, the use of inorganic nanoparticle delivery systems may have a synergistic effect in releasing polyphenols to alleviate Alzheimer's disease and inflammation caused by radiation therapy.

In addition to the above, dietary polyphenols are also dependent on the targeting and controllability of inorganic nanoparticles for targeted delivery to the site of radiation-induced inflammation, which improves their utilization and bio-availability[110]. For instance, Zhou et al. prepared mesoporous hydroxyapatite nanoparticles which were hydrothermally synthesized from hexametaphosphate and tea polyphenols, and found that tea polyphenols delivered by inorganic nanoparticles exhibit higher biological activity[111]. Moreover, mesoporous hydroxyapatite particles mentioned above, composed of natural apatite, demonstrate good biocompatibility with human tissues, showing further evidence for the feasibility and great perspective of inorganic nanoparticle delivery of dietary polyphenols.

However, many challenges remain in the current research on nanoparticle delivery systems to alleviate radiation-induced inflammation and injury, especially in terms of unsatisfactory biocompatibility, low drug delivery rates, and lack of long-term stability. To address these challenges, researchers often employ methods such as surface modification and functionalization, as well as the design of controlled release systems, to effectively improve their shortcomings. Ge et al. altered the biocompatibility by modifying the surface shape of nanoparticles. They investigated the antioxidant effects and cell compatibility of ceria nanoparticles with different shapes, such as rod and cube. Polyethylene glycol functionalization of ceria nanoparticles reduced protein adsorption, but did not induce cell compatibility[112]. These improvements are validated and refined through preclinical and clinical studies[113]. To some extent, the stability of inorganic nanoparticles has been improved, offering insights into the stable delivery of dietary polyphenols using biological delivery systems.

Inorganic nanoparticles, as an emerging delivery system, despite its own favorable physicochemical properties and feasibility in dietary polyphenol delivery for mitigating radiation-induced inflammation relief, it still lack sufficient experimental studies as described in this review. We envision that, by virtue of their inherent advantages, inorganic nanoparticles can be studied more extensively in the field of delivering dietary polyphenols to alleviate radiation-induced inflammation.

Organic nanoparticles

Organic nanoparticle delivery systems have been extensively studied and shown promising results in targeting the delivery and enhancing the utilization of dietary polyphenols for inflammation relief[114]. Organic nanoparticles hold significant potential in drug delivery, particularly in the treatment of radiation-induced inflammation and diseases.

The methods for preparing organic nanoparticle delivery systems for encapsulating dietary polyphenols mainly include self-assembly, solvent evaporation, and the oil-in-water method, etc[115]. Self-assembly allows for control over particle size, shape, and dispersion by adjusting drug and organic material concentrations, solvent properties, and temperature[116]. This method also achieve high drug loading and targeted delivery[117]. The solvent evaporation method is suitable for poorly soluble drugs, involving dissolving drugs and organic materials in organic solvents and then evaporating the solvent to form nanoparticles[115]. Nanoparticles prepared using this method exhibit high drug loading and good stability[118]. The oil-in-water method is suitable for water-soluble drugs, involving the dissolution of drugs and organic materials in the oil phase, followed by conversion to an aqueous phase through emulsification or ultrasound, resulting in the formation of nanoparticles with good dispersibility and stability[119].

According to the present research, the encapsulation of polyphenols within organic nano-delivery systems offers several advantages as below. Firstly, it protects drugs against environmental influences, enhancing their stability and bioavailability. For instance, Ji et al. encapsulated curcumin within organic nanoparticles and conducted in vivo pharmacokinetic studies and in situ intestinal perfusion, revealing improvements in the gut microbiota environment and alleviation of oxidative stress and inflammation caused by ROS. This approach showed promise in alleviating various inflammations, including radiation-induced enteritis[120]. Similarly, Yang et al. encapsulated tea polyphenols within organic nanoparticles, demonstrating enhanced stability in water and biological culture medium compared to traditional dietary polyphenols, along with excellent free radical scavenging performance[121]. Ullah et al. encapsulated lignin within organic nanoparticles, resulting in improved antioxidant and biological activity[122]. These findings suggest broad application prospects in the treatment of radiation-induced inflammation and injury. Zhang et al. demonstrated that encapsulating dietary polyphenols in biopolymer nanoparticle delivery systems can enhance their bioavailability and biological activity, showing promise in antioxidant and anti-inflammatory applications[123].

In addition to improving stability, the surface of organic nanoparticles can be modified and functionalized to achieve targeted controlled release and prolong drug action. For example, Anwer et al. developed a quercetin nanoparticle based on polylactide glycolic acid (PLGA), which exhibited higher bioavailability and biological activity compared to traditional dietary polyphenols, while also extending the release time of quercetin to some extent[124]. This nanoparticle holds promise as a potential choice for delivering quercetin to alleviate radiation-induced inflammation and damage.

Organic nano-delivery systems represent a promising drug delivery method that enhances drug delivery efficiency and targeting. The incorporation of polyphenolic small molecules within organic nano-delivery systems achieves drug packaging and stability while exerting antioxidant and anti-inflammatory effects.

However, organic nanoparticles also have drawbacks, such as complex preparation processes, the need to control multiple parameters. As a result, continued research and optimizations are necessary to enable the widespread application of organic nanoparticle delivery systems in clinical settings.

Hydrogels and microneedles

Hydrogel is a gel system composed of water molecules and high molecular polymers. Its characteristics include high water content, three-dimensional network structure, reversibility, controllability, and biocompatibility. When polyphenols are added to a natural extracellular matrix and hydrogel in a hydration environment, they form an ideal material for skin wound healing. Compared with traditional dietary polyphenols, hydrogel delivery of dietary polyphenols has many advantages in the treatment of radiation inflammation and injury. After consulting relevant literature, we have summarized the following three points:

Improve the bioavailability of polyphenols

Hydrogels can stabilize polyphenols, preventing their premature degradation and excretion in the body. Additionally, hydrogels can slow down the release rate of polyphenols, allowing them to persist in damaged tissues for a longer time. For instance, Zhao et al. used a hydrogel loaded with resveratrol, which prolonged the release time of resveratrol, inhibited inflammation, promoted the healing of skin wounds, and showed promise in the treatment of skin damage caused by radiation dermatitis[125]. Similarly, Zhou et al. used tannic acid cross-linked and mixed soft conductive polymer hydrogel for the repair of spinal cord injury, indicating considerable application prospects for the treatment of radiation osteoarthritis[126]. In another study, Zhu et al. used a composite hydrogel encapsulated with resveratrol, which effectively promoted the repair of endothelial cytokines, providing a basis for the repair of radiation-induced enteritis and dermatitis[126].

Enhance the stability of polyphenols

Polyphenols are easily affected by external factors such as light, heat, and oxygen, leading to a decrease in their activity. Hydrogel can provide a protective layer to prevent polyphenols from contacting the external environment, thus enhancing their stability. For example, Chen et al. encapsulated tea polyphenol nanospheres in PVA/alginate saline gel, which improved the stability of tea polyphenols. Animal experiments showed that the hydrogel promoted the elimination of inflammation by regulating the PI3K/AKT pathway, demonstrating a good therapeutic effect on alleviating radiation inflammation and injury[127]. In the research of Zhang et al., they pointed out that curcumin and EGCG can be stably released from hydrogel, significantly weakening the development of skin damage and accelerating the healing process. Therefore, researchers believe that hydrogel provides an effective strategy for the clinical management and treatment of ionizing radiation-induced skin injury[128].

Increase the local concentration of polyphenols

Hydrogel can fix polyphenols on the surface of damaged tissues, allowing them to reach a higher concentration in local areas. This helps to improve the therapeutic effect of polyphenols.

Compared to the above three delivery systems, hydrogels have the advantages of high water content, controllability, biocompatibility, and biodegradability. They provide good biocompatibility and tissue compatibility, possess good biodegradability, and do not cause long-term effects on the human body. However, the limitations of hydrogels include low mechanical strength, poor stability, and complex preparation methods. Researchers may use surface modification methods to address this shortcoming. For example, Joraholmen et al. used chitosan hydrogel to encapsulate dietary polyphenols to alleviate pelvic inflammation. Data show that chitosan hydrogel has a synergistic effect on the anti-inflammatory effect of preparations, demonstrating stronger anti-inflammatory activity[129].

A microneedle is a needle-like device with a small size and tip, usually used to deliver drugs or other therapeutic substances to the skin or tissue, and is also a commonly used method of drug delivery. The structure of microneedles can be divided into two types: solid and hollow. Solid microneedles are usually made of metal or ceramic materials and have a certain penetration force, suitable for thicker skin or tissues. Hollow microneedles have a hollow structure that can deliver drugs or other therapeutic substances through a central channel[130,131].

The therapeutic principle of microneedle delivery of polyphenols is to deliver polyphenols to the skin or tissue through the insertion of the microneedle tip. The size of microneedles is usually between tens to hundreds of micrometers, which is small enough to avoid causing obvious pain or trauma. Once microneedles penetrate the skin or tissue, polyphenols will be released through the channels of the microneedles and penetrate into the inflamed area or damaged tissue, exerting therapeutic effects. The penetration of microneedles can also stimulate the regeneration and repair of skin or tissue, promoting the healing of inflammation. Microneedle delivery can also significantly increase the local concentration of drugs and enhance therapeutic efficacy. Chen et al. used a double-layer PLGA/HA system as a good formula for polyphenols, which has better anti-inflammatory effects and provides an idea for the effective treatment of radiation dermatitis[132].

Microneedle delivery of polyphenols is an innovative treatment method for radiation inflammation and diseases. The definition, structure, and preparation method of microneedles provide technical support for the delivery of polyphenols. Compared with traditional drug delivery methods, microneedle delivery of polyphenols has several advantages, including painlessness, controllable drug release, simplicity, and reusability. They can provide a painless treatment experience and have controllable drug release performance[133].

The ongoing research and development in this area hold promise for the future use of microneedles as a delivery system for polyphenols in the treatment of radiation-induced inflammation and related conditions.

Conclusion and future perspective

In this review, we present an overview of radiation therapy modalities and their associated inflammatory responses, with a particular focus on elucidating the pathogenesis and clinical manifestations of radiation-induced enteritis, radiation pneumonitis, radiation pelvic inflammatory disease, radiation dermatitis, and radiation-induced osteoarthritis. Responding to the challenge of radiation-induced inflammation, we delve into the potential application of dietary polyphenols in radioprotection. We delineate the classification, sources, and mechanisms underlying the action of dietary polyphenols in mitigating radiation-induced inflammation. Specifically, we emphasize that dietary polyphenols mitigate radiation-induced inflammation primarily through robust ROS scavenging pathways and DNA damage repair mechanisms. Nonetheless, notwithstanding the considerable efficacy of dietary polyphenols in alleviating radiation-induced inflammation, their limited bioavailability and intricate, rapid metabolic processes pose significant hurdles. Consequently, we contend that these limitations should not impede the further integration of polyphenols into clinical practice. Instead, we advocate for a targeted approach to address challenges such as enhancing bioavailability. Among the viable and promising strategies, various bio-delivery systems stand out as potential solutions. Thus, we comprehensively summarize the most extensively researched delivery materials to date, encompassing liposomes, organic nanoparticles, inorganic nanoparticles, polymers, and microneedles. Drawing upon insights from peer-reviewed studies, we assert that diverse delivery systems hold the capacity to enhance the activity, bioavailability, and targeted delivery of dietary polyphenols, thereby opening new avenues for their clinical implementation.

While various bio-delivery systems offer potential avenues for enhancing the bioavailability and biological efficacy of dietary polyphenols, it is imperative to address the bio-toxicity and biocompatibility concerns associated with these systems as exogenous antigens. Current solutions to mitigate these challenges, primarily involving surface modification techniques, remain relatively limited. Despite highlighting the advantages and opportunities afforded by packaged systems, it is crucial to acknowledge their inherent limitations and the constraints of existing solutions. Confronted with these challenges, we are tasked with the responsibility of continuing the refinement and advancement of these systems to ensure their safe integration into clinical practice.

In conclusion, this review offers researchers novel insights into enhancing the bioavailability of dietary polyphenols through innovative

delivery systems. We anticipate further research and optimization efforts aimed at augmenting polyphenol bioavailability through chemical modifications and leveraging artificial intelligence for improved targeting and delivery. Advancements in our understanding of radiobiology mechanisms hold the promise of identifying more efficacious dietary polyphenols for enhanced delivery. The utilization of bio-delivery systems for dietary polyphenols is poised to emerge as a potent strategy for radiation protection, safeguarding human health and life. Looking ahead, dietary polyphenol bio-delivery systems have the potential to revolutionize treatment paradigms by tailoring interventions based on individual patient variations and disease profiles, thus heralding a new era of personalized medicine. This personalized treatment model is poised to offer more precise and efficacious therapeutic options in radiotherapy, thereby enhancing treatment success rates. Moreover, the deployment of nano-delivery systems for dietary polyphenols holds the promise of extending therapeutic durations and enhancing disease control, offering patients the prospect of long-term disease management and recurrence prevention. This represents a promising avenue for mitigating radiation therapy side effects in the future. Additionally, the use of bio-delivery systems ensures safety considerations are addressed, rendering bio-delivered dietary polyphenols widely accessible, cost-effective, and safe protective agents against radiation therapy side effects.

Abbreviations

AP-1	Activator protein-1
CAPE	Caffeic acid phenethyl ester
EC	Endothelial cell
EGCG	Epigallocatechin gallate
FLASH Therapy	Flashed High-dose Rate Radiotherapy
FOXO	Forkhead box
GPx	Glutathione peroxidase
GR	Glutathione reductase
IL-8	Interleukin-8
IV	Intravenous
NOX	NADPH oxidase
NF- κ B	NF-kappa B
Nrf2	Nuclear factor-E2-associated factor 2
PI3K-AKT-mTOR	Phosphoinositide 3-kinase\ Protein Kinase B\ Mammalian Target of Rapamycin
ROS	Reactive oxygen species
REV	Resveratrol
SOD	Superoxide dismutase
TNF- α	Tumor necrosis factor-alpha
DHC	Dihydrocurcumin
THC	Tetrahydrocurcumin
HHC	Hexahydrocurcumin
OHC	Octahydrocurcumin

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Competing interests

The authors declare no competing interests.

Additional information

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