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Research Progress on the Relationship between Radiation Enteritis and the Gut Microbiota

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Abstract

Radiotherapy remains a cornerstone treatment for pelvic and abdominal malignancies; however, radiation-induced intestinal injury, known as Radiation Enteritis (RE), represents a major complication that negatively affects patients' quality of life. Emerging evidence indicates that gut microbiota dysbiosis plays a critical role in promoting the initiation and progression of RE. Recent biomedical research demonstrates that gut microbiota dysbiosis is an active, critical driver that promotes and amplifies the pathogenesis, severity, and chronicity of RE. This comprehensive review synthesizes the contemporary global scientific literature to delineate the multifaceted roles, molecular mechanisms, and therapeutic potentials of the gut microbiota in the occurrence and progression of RE.

Keywords

Radiation Enteritis, Gut Microbiota, Dysbiosis, Probiotics, Fecal Microbiota Transplantation

1. Introduction

Radiotherapy is widely applied in the treatment of pelvic and abdominal malignancies, including cervical, prostate, colorectal, and endometrial cancers. Despite advances in techniques such as intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT), normal intestinal tissues remain vulnerable to radiation-induced damage due to their high proliferative activity. From a radiobiological perspective, cells that are structurally undifferentiated, rapidly dividing, and characterized by intense metabolic activity exhibit an exceptionally high sensitivity to ionizing radiation [1]. This fundamental vulnerability renders the human gastrointestinal tract, particularly the epithelial layer lined with highly

active crypt stem cells (such as Lgr5+ intestinal stem cells), an organ that is profoundly susceptible to acute and chronic radiation-induced trauma.

This review focuses on radiation enteritis associated with pelvic and abdominal radiotherapy, as these treatment sites are closely related to the occurrence of intestinal radiation injury. Although radiotherapy has become an essential component in the management of many pelvic and abdominal malignancies, radiation exposure to surrounding intestinal tissues remains an important clinical concern [2]. Improvements in radiation delivery techniques have reduced unnecessary irradiation to normal tissues; however, intestinal complications continue to occur in a proportion of treated patients.

Radiation enteritis may present with various gastrointestinal symptoms and, in some cases, develop into persistent intestinal dysfunction that affects patient recovery and daily life. The occurrence and progression of RE involve multiple biological processes, and increasing attention has been directed toward understanding the factors contributing to its development. Therefore, RE remains a clinically important complication that requires further investigation to improve prevention and management strategies. Epidemiological data and clinical registries indicate that RE has transitioned into one of the most widespread and severe adverse events associated with pelvic radiotherapy, which profoundly undermines the patient's overarching quality of life and clinical compliance. Although modern clinical paradigms have introduced an array of prophylactic and therapeutic strategies—ranging from highly optimized prescription dose fractionation schemes and radical surgical interventions to advanced pharmacological agents such as corticosteroids, mucosal protectants, and hyperbaric oxygen therapies [3] [4]—the clinical burden remains substantial. Clinical studies have reported that a considerable proportion of patients receiving pelvic radiotherapy develop persistent gastrointestinal symptoms, including diarrhea, fecal urgency, abdominal pain, and altered bowel habits, which can significantly impair long-term quality of life, particularly among survivors of gynecological and colorectal malignancies [5] [6].

2. Importance of the Gut Microbiota

The human gut microbiota represents an incredibly dense, highly diverse, and metabolically sophisticated microbial community that predominantly inhabits the complex luminal spaces of the small and large intestines of the host organism [7] [8]. Extensive metagenomic and cellular evaluations have consistently indicated that the cumulative number of microorganisms thriving within an adult human intestine reaches an astonishing magnitude of approximately 30 trillion, a numerical figure that slightly surpasses the absolute total number of human somatic cells comprising the host body. Bacteria represent the predominant component of this complex microbial ecosystem, accounting for more than 99% of the total microbial population [7] [9]. In healthy adults, the intestinal microbiota consists of a diverse range of bacterial phyla, with several genera showing relatively high abundance and functional significance, including Bifidobacterium, Lactobacillus, Bac-

teroides, Clostridium, Escherichia, Streptococcus, and Ruminococcus [8] [10] [11].

Based on their interactions with the host and their physiological roles, intestinal microorganisms can be broadly categorized into different groups. These microbial populations include beneficial bacteria with probiotic characteristics, relatively stable commensal microorganisms, and potentially harmful pathogenic species. Under physiological conditions, these microbial communities coexist in a dynamic equilibrium, with continuous interactions among different populations contributing to the maintenance of intestinal homeostasis and normal host functions. Under baseline healthy physiological states, these highly diverse microbial species participate in continuous, complex biochemical competition and mutual restriction, thereby sustaining an optimized, resilient state of dynamic equilibrium that is crucial for host survival.

The collective structural components of the gut microbiota, alongside the complex array of microbial metabolites they synthesize, possess the capacity to directly or indirectly modulate a diverse spectrum of essential physiological functions, immunological homeostatic mechanisms, and metabolic pathways within the host organism. These functions encompass the extraction of energy from indigestible dietary fibers, the biosynthesis of vital vitamins and micronutrients, the maintenance of the structural integrity of the intestinal mucosal barrier, and the structural maturation and functional priming of the host mucosal immune system.

Furthermore, the delicate architectural composition and functional stability of the gut microbiota are continuously subjected to, and remodeled by, an intricate network of intrinsic genetic variables and extrinsic environmental factors, including host dietary patterns, stress levels, pharmacological exposures, and geographic habitats as well as host age and sex [12] [13]. This intricate configuration is deeply rooted in early-life microbial assembly and succession [14]-[17]. Once severe gut microbiota dysbiosis is triggered by overwhelming external insults, the collapse of this balanced microbial network invariably precipitates local mucosal degradation and systemic metabolic disturbances. Therefore, the complex interrelationships among individual microbial species, as well as the reciprocal crosstalk between the collective microbiota and the host, are profoundly interdependent and structurally interactive, effectively forming an inseparable community of shared destiny defined by dynamic biological equilibrium.

3. Gut Microbiota Dysbiosis in Radiation Enteritis

This section summarizes current evidence on gut microbiota dysbiosis in radiation enteritis (RE), including changes in microbial composition observed in clinical and experimental studies and the limitations of current microbiome research. Available studies have shown that radiation exposure is associated with alterations in the abundance and diversity of intestinal microorganisms, with a general tendency toward the loss of beneficial commensal bacteria and an increase in potentially harmful species. These microbial changes have also been associated with the

severity of intestinal toxicity and radiation-induced intestinal injury. However, differences in patient characteristics, treatment regimens, concomitant medications, dietary factors, sampling time points, and sequencing methods may affect the reported microbiome profiles. Therefore, the current evidence should be interpreted with consideration of these potential confounding factors.

3.1. Evidence of Radiation-Induced Gut Microbiota Dysbiosis

Increasing evidence from both experimental models and clinical studies indicates that exposure to ionizing radiation is closely associated with changes in gut microbial composition. Research conducted in different settings has consistently shown that radiation can disturb intestinal microbial homeostasis, resulting in alterations in bacterial abundance and diversity. These changes are generally characterized by an increase in opportunistic pathogenic microorganisms and a reduction in beneficial commensal bacteria.

In a clinical study, Wang *et al.* collected and analyzed longitudinal fecal samples from 18 cervical cancer patients receiving pelvic radiotherapy [18]. High-throughput sequencing analysis showed that patients who developed clinical manifestations of radiation enteritis exhibited significant alterations in their gut microbial profiles. Specifically, radiation-associated intestinal injury was accompanied by marked microbial imbalance, suggesting that disruption of the intestinal microbiota may contribute to the progression of RE. Specifically, patients suffering from RE exhibited a pronounced, disproportionate elevation in the relative abundance of the phylum Proteobacteria and the class Gammaproteobacteria, coupled with a dramatic, concomitant reduction in the representation of the phylum Bacteroidetes. The investigators concluded that the delivery of pelvic radiotherapy directly catalyzed a catastrophic reduction in beneficial commensal bacteria alongside an aggressive, opportunistic expansion of endotoxin-producing pathogenic taxa. This microbial shift significantly exacerbated local mucosal inflammatory cascades and profoundly impaired the endogenous physiological repair capacities of the damaged intestinal epithelial cells, thereby directly inducing and exacerbating the classical clinical manifestations of radiation enteritis, such as severe diarrhea [18]. Furthermore, transplantation experiments suggested that microbiota derived from patients with RE may contribute to epithelial inflammation and barrier dysfunction in experimental systems, supporting a potential pathogenic role for radiation-associated dysbiosis.

Further supporting these findings, Jiang *et al.* investigated gut microbiota changes in 34 cervical cancer patients undergoing pelvic radiotherapy [19]. According to the severity of acute intestinal toxicity, patients were divided into two groups: a mild toxicity group (Group M) and a severe toxicity group (Group S). After microbial DNA extraction, 16S rRNA gene sequencing was performed to compare microbial characteristics between the two groups.

The results demonstrated that the relative abundance and diversity of Firmicutes were higher in group M than in group S, whereas Proteobacteria showed the opposite pattern. Patients with severe intestinal toxicity exhibited increased levels

of potentially harmful bacteria, including Shigella, together with a reduction in beneficial butyrate-producing bacteria such as Faecalibacterium. LEfSe analysis further identified distinct microbial signatures between the two groups, indicating that different degrees of radiation enteritis severity are associated with specific patterns of gut microbiota alteration [19].

To further investigate whether radiation-induced microbial changes directly contribute to intestinal injury, Gerassy-Vainberg *et al.* established a mouse model using 454 pyrosequencing to monitor longitudinal changes in gut microbiota following localized rectal irradiation [20]. Their findings showed that microbial disturbances increased progressively after radiation exposure. LEfSe analysis revealed that changes in specific bacterial taxa, particularly the enrichment of Akkermansia and Bacteroides, were positively associated with the severity of radiation-induced intestinal damage. To definitively ascertain whether this post-radiation dysbiotic microbiota was a primary driver of tissue damage or merely a passive consequence of tissue injury, the researchers executed a seminal fecal microbiota transplantation (FMT) experiment [20]. Fecal microbiota harvested from either irradiated donor mice or completely healthy, non-irradiated control mice were transplanted into separate cohorts of completely germ-free (GF) recipient mice. Following the successful engraftment of the respective microbiotas, both cohorts of recipient mice were subsequently exposed to identical doses of ionizing radiation.

The experimental results revealed that the recipient mice that had been colonized with the dysbiotic microbiota derived from irradiated donors exhibited profoundly more severe, extensive, and accelerated pathological manifestations of radiation-induced intestinal injury compared to the mice colonized with a normal, healthy microbiota [20]. These findings provide strong experimental evidence that radiation-induced alterations in gut microbiota may transmit inflammatory susceptibility and exacerbate intestinal injury in recipient animals.

Taken together, evidence from clinical studies and preclinical animal models consistently supports an important association between gut microbiota dysbiosis and the development of radiation enteritis. The severe disruption of microbial proportions, the loss of taxonomic alpha and beta diversity, and the profound alterations in overall microbial composition may contribute to the onset and progression of RE. The severity and clinical course of radiation enteritis appear to be associated with the specific characteristics, compositional resilience, and metabolic output of the host intestinal microbiota.

3.2. Limitations of Current Microbiome Studies

Although increasing evidence has indicated an association between gut microbiota dysbiosis and radiation enteritis, the interpretation of these findings should take into account several potential confounding factors. Patients receiving radiotherapy are frequently exposed to additional interventions, including chemotherapy, antibiotics, or corticosteroids, and treatment-related dietary changes may also occur. These factors can independently influence gut microbial composition

and may contribute to the differences observed among studies. In addition, variations in radiation dose, fractionation schedules, cancer types, sampling time points, sequencing methods, and patient characteristics may further affect the reported microbiome profiles. Therefore, future investigations should employ more standardized study designs and consider these variables more carefully to improve the reproducibility and clinical applicability of microbiome-related findings in radiation enteritis.

The contribution of gut microbiota dysbiosis to radiation enteritis involves interactions among multiple biological processes, including cellular responses, immune regulation, and alterations in microbial metabolism.

4. Mechanisms by Which Gut Microbiota Dysbiosis Promotes Radiation Enteritis

The intricate pathophysiological pathways through which gut microbiota dysbiosis drives, amplifies, and perpetuates the development of radiation enteritis are highly multifaceted, involving an integrated network of cellular, immunological, and metabolic signaling axes. Fundamentally, radiation enteritis manifests as an intense, uncoordinated intestinal inflammatory response that is initially triggered by direct ionizing tissue damage and subsequently amplified by a cascade of pro-inflammatory cytokines. Radiobiological research has demonstrated that when ionizing radiation penetrates the soft tissues of the intestine, it interacts with intracellular water molecules, inducing rapid radiolysis that generates an overwhelming surge of intracellular reactive oxygen species (ROS). This initial wave of intense oxidative stress acts as a primary molecular trigger that rapidly activates a series of highly conserved, downstream cellular signaling pathways within the intestinal tissue, most notably the Nuclear Factor-kappa B (NF-KB), Extracellular Signal-Regulated Kinase/Mitogen-Activated Protein Kinase (ERK/MAPK), Phosphoinositide 3-Kinase/Protein Kinase B (PI3K/AKT), and Stress-Activated Protein Kinase/Jun Amino-Terminal Kinase (SAPK/JNK) pathways.

The structural and transcriptional activation of these complex signaling cascades severely disrupts the delicate physiological equilibrium between pro-inflammatory and anti-inflammatory cytokines, initiating a self-perpetuating inflammatory cascade. Within this highly unstable cellular microenvironment, radiation-induced gut microbiota dysbiosis systematically exploits and accelerates these activated pathways through several highly specific, interconnected molecular mechanisms:

4.1. Intestinal Barrier Dysfunction

The profound gut microbiota dysbiosis induced by radiation exposure acts as a primary cause of structural damage to the host intestinal mucosal barrier, which normally serves as an impermeable defensive wall separating the luminal microbial mass from the sterile sub-epithelial layers. When the commensal microbiota is disrupted, the severe loss of protective species leads to a rapid degradation of

the protective mucus layer, facilitating the direct adherence and opportunistic translocation of pathogenic bacteria and their highly toxic metabolic byproducts, such as lipopolysaccharides (LPS) and peptidoglycans, into the underlying mucosal lamina propria. The translocation of these microbial products into the mucosal tissue can activate local inflammatory responses through their interaction with host pattern recognition receptors (PRRs), including Toll-like receptors (TLRs). Activation of these innate immune pathways further contributes to disruption of intestinal epithelial integrity.

Persistent inflammatory signaling after radiation exposure may impair the function of epithelial tight junction complexes, including Occludin, Claudins, and Zonula Occludens-1 (ZO-1), which regulate the permeability between adjacent epithelial cells [21]-[23]. The resulting barrier impairment facilitates increased microbial penetration, promotes epithelial cell injury and apoptosis, and creates a favorable environment for the expansion of opportunistic pathogenic bacteria within the damaged intestinal mucosa.

In addition, radiation-associated dysbiosis may influence the expression of key regulatory cytokines, including Transforming Growth Factor-β (TGF-β), and interfere with important signaling pathways involved in intestinal repair and regeneration, such as the Wnt/β-catenin and Notch pathways. Because the Wnt and Notch pathways are fundamentally required to orchestrate the proliferation, differentiation, and migration of the Lgr5+ intestinal stem cells residing within the crypts of Lieberkühn, their radiation-induced disruption cripples the normal physiological response and regenerative mechanisms of the intestinal mucosa. This severely impairs the self-renewal capacity of the epithelial lining, prevents the structural healing of the intestinal villi, and profoundly amplifies the severity of radiation-induced intestinal tissue degradation.

Gerassy-Vainberg *et al*., utilizing a highly controlled bacteria-epithelial cell co-culture experimental model to evaluate localized epithelial inflammatory responses, demonstrated that the transcriptomic expression of key pro-inflammatory cytokines, specifically Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-1 beta (IL-1β), was significantly and selectively upregulated when epithelial cells were exposed to a dysbiotic microbial environment [20]. Their mechanistic evaluations further elucidated that the gut microbiota, when altered under the destructive influence of ionizing radiation, directly drives and programs host intestinal epithelial cells to dramatically scale up their endogenous synthesis and secretion of IL-1β [20]. Within the complex clinical architecture of RE, IL-1β is universally acknowledged as a pivotal, non-redundant molecular driving factor that orchestrates downstream tissue damage, microvascular thrombosis, and extensive mucosal ulceration.

4.2. Inflammatory Activation

As detailed extensively in the preceding evaluations, the post-radiation dysbiotic microbiota functions as a continuous biological trigger that directly ignites and

chronically perpetuates mucosal tissue inflammation. By continuously prompting the robust, unregulated secretion of key pro-inflammatory cytokines such as IL-1β, TNF-α, and TGF-β, the dysbiotic microbiota establishes a highly cytotoxic localized microenvironment. This intense inflammatory activation cascade actively suppresses and impairs the physiological transcription of critical cellular pathways required for DNA damage repair and cellular homeostasis. Consequently, the chronic persistence of damaged epithelial cells within a pro-inflammatory microenvironment may contribute to tissue degeneration and impaired mucosal healing. However, the potential relationship between radiation-associated dysbiosis and malignant transformation remains insufficiently understood and requires further investigation.

4.3. Alterations in Microbial Metabolism

Beyond executing direct structural disruption upon the physical architecture of the intestinal barrier, radiation-induced gut microbiota dysbiosis profoundly alters the functional metabolic output of the intestinal tract, thereby eliminating protective biochemical signals while generating cytotoxic metabolites. Under normal physiological conditions, a healthy gut microbiota produces a diverse range of chemical compounds through the fermentation of dietary substrates, including Short-Chain Fatty Acids (SCFAs, primarily acetate, propionate, and butyrate), tryptophan metabolites (such as indole derivatives), taurine, deoxycholic acid, lactate, spermine, and histamine. These microbial metabolites act as important regulators of intestinal epithelial barrier function, immune activity, and metabolic balance. They support intestinal homeostasis through several mechanisms, including modulation of host G-protein-coupled receptor (GPCR) signaling, regulation of transcription factors such as Hypoxia-Inducible Factor-1α (HIF-1α), alteration of mucosal cytokine production, and promotion of epithelial tight junction protein expression.

Following radiation exposure, disruption of the gut microbiota can interfere with these metabolic functions. The reduction of key anaerobic bacterial populations, particularly members of the classes Clostridia and Bacteroidia, is associated with decreased production of protective metabolites, including short-chain fatty acids (SCFAs). Reduced butyrate availability, which provides an important energy source for colonocytes, may impair epithelial metabolic activity and contribute to local hypoxia, epithelial injury, and decreased generation of regulatory T cells (Tregs). These changes may further weaken the mechanisms responsible for maintaining control of intestinal inflammation.

The influence of gut microbiota on intestinal radiosensitivity was investigated by Crawford *et al.*, who compared germ-free (GF) mice with conventional microbiota-colonized mice after exposure to the same dose of ionizing radiation [24]. Their study demonstrated that GF mice showed reduced apoptosis of intestinal vascular endothelial cells and resident lymphocytes, which was associated with improved survival following radiation exposure. These findings suggest that dif-

ferences in microbial composition can modify host responses to radiation and may play a role in the development of radiation enteritis [24].

Overall, radiation therapy induces intestinal injury through both direct tissue damage and microbiota-associated mechanisms. Radiation-induced reactive oxygen species (ROS) initiate inflammatory responses, while subsequent changes in gut microbial composition may further impair intestinal barrier function and tissue repair. The resulting dysbiosis creates a less favorable environment for intestinal recovery, promotes epithelial cell apoptosis, and contributes to the progression of radiation enteritis.

5. Therapeutic and Preventive Effects of Gut Microbiota

Modulation

With a growing understanding of the molecular links between gut microbiota dysbiosis and the development of radiation enteritis (RE), microbiota-targeted therapeutic strategies have attracted increasing interest. Approaches designed to restore the altered microbial community, particularly probiotic supplementation and Fecal Microbiota Transplantation (FMT), have demonstrated potential therapeutic value in both clinical and experimental studies. These interventions may help alleviate RE-related symptoms, improve intestinal barrier function, and modulate mucosal inflammatory responses.

5.1. Probiotics

Probiotics are defined as live, non-pathogenic microorganisms that provide health benefits to the host when administered in adequate amounts [25]. In current clinical practice, commonly studied probiotic strains mainly belong to the genera *Lactobacillus*, *Streptococcus*, and *Bifidobacterium*, which have demonstrated protective effects in experimental models of radiation-induced intestinal injury [26]. Previous clinical studies have also suggested that probiotics may provide benefits in gastrointestinal disorders, including recurrent *Clostridioides difficile* infection, ulcerative colitis, Crohn's disease, and irritable bowel syndrome (IBS) [27] [28].

In the context of radiation enteritis prevention and treatment, probiotics may exert their effects through several mechanisms. These include competing with pathogenic microorganisms for adhesion sites, producing antimicrobial substances such as bacteriocins, reducing intestinal pH through lactic acid production, and limiting the colonization and translocation of opportunistic bacteria [29] [30]. Clinical studies have reported that probiotics may reduce radiation-associated gastrointestinal symptoms, including diarrhea and abdominal discomfort, while helping maintain patients' quality of life [30].

In a randomized, double-blind, placebo-controlled clinical trial conducted by Linn *et al.*, 54 cervical cancer patients receiving pelvic radiotherapy were randomly assigned to either a probiotic intervention group or a placebo control group [30]. Patients in the intervention group received oral probiotic capsules containing a combination of *Lactobacillus acidophilus* LA-5 and *Bifidobacterium ani-*

malis three times daily throughout the radiotherapy period. Each capsule contained at least 1.75 billion viable lyophilized bacteria, whereas the placebo capsules contained inert starch [30].

In a randomized, double-blind, placebo-controlled clinical trial conducted by Linn *et al.*, a cohort of 54 cervical cancer patients undergoing standardized courses of pelvic radiotherapy was randomly allocated into either an active probiotic intervention group or a matched placebo control group [30]. The intervention group received oral probiotic capsules explicitly containing a high-dose combination of Lactobacillus acidophilus LA-5 and Bifidobacterium animalis three times daily throughout the entire duration of their radiotherapy regimen [30]. Crucially, each individual capsule was standardized to contain a precise minimum concentration of 1.75 billion lyophilized viable bacteria, whereas the placebo cohort received identical capsules filled entirely with inert starch [30].

The clinical results demonstrated that the overarching incidence of radiation-induced diarrhea in the active probiotic cohort was significantly lower than that documented within the placebo group (53.8% versus 82.1%) [30]. Concurrently, the total utilization rate of the standard opioid-receptor agonist antidiarrheal medication, loperamide, was drastically reduced among patients receiving probiotics, and the absolute number of days that patients suffered from debilitating episodes of acute abdominal pain was markedly shortened [30].

However, it is critically noteworthy from a clinical safety perspective that because these probiotics are formulated as live bacterial preparations, extreme caution, rigorous monitoring, and strict risk-benefit evaluations must be systematically exercised when administering these interventions to severely immunocompromised or profoundly neutropenic oncology populations, given the small but severe potential risk of inducing iatrogenic bacteremia or systemic opportunistic infections.

5.2. Fecal Microbiota Transplantation

In addition to the administration of standardized probiotic strains, Fecal Microbiota Transplantation (FMT)—defined as the transfer of a completely functional, highly diverse microbial ecosystem harvested from the filtered feces of a thoroughly screened, healthy human donor into the gastrointestinal tract of a diseased patient—has emerged as a highly revolutionary and effective clinical intervention for refractory RE.

Wang *et al.* documented a seminal clinical case study wherein they performed two sequential, highly targeted FMT interventions in a 64-year-old cervical cancer patient suffering from severe, chronic, and treatment-resistant radiation enteritis [31]. Prior to the initiation of the transplantation protocol, deep metagenomic sequencing of the patient's fecal DNA revealed a striking, catastrophic taxonomic divergence when compared against the healthy donor's microbial baseline [31]. The RE patient's gut microbiota was found to be almost entirely dominated by aggressive, pathogenic, and pro-inflammatory bacterial species, most notably Esche-

richia fergusonii and members of the genus Romboutsia [31]. In contrast, the healthy donor's intestinal landscape exhibited an optimized, harmonious distribution of beneficial taxa, characterized by a high abundance of Enterococcus faecalis, diverse saccharolytic bacterial communities, Cytophaga, and Bifidobacterium longum [31].

Following the successful execution of the FMT protocol, the patient's intestinal microbial architecture underwent a rapid, radical structural shift, successfully adopting the highly diverse and stable configuration of the healthy donor [31]. Metagenomic monitoring confirmed a massive increase in core beneficial commensal bacteria, such as the anti-inflammatory genus Blautia, coupled with a complete, simultaneous eradication of the dominant pathogenic clusters [31]. Clinically, the patient's severe RE-associated symptoms—including chronic abdominal pain, constant diarrhea, and recurrent, life-threatening hematochezia—were completely relieved during both the immediate short-term follow-up and throughout extended long-term post-transplantation monitoring, with zero documented adverse events or infectious complications [31].

These profound clinical outcomes have been deeply reinforced by mechanistic insights obtained in animal experiments. Tu *et al.* conducted a preclinical study in which C57BL/6J mice were exposed to localized abdominal irradiation at a dose of 9 Gy and subsequently treated with FMT derived from healthy donor mice or saline as a control [32]. Their analyses showed that FMT treatment restored several beneficial bacterial populations, particularly members of the family *Lactobacillaceae*, which had been reduced after radiation exposure [32]. Metabolomic analysis further demonstrated that FMT increased the levels of important tryptophan-derived metabolites in intestinal tissues, including indole-3-carboxaldehyde (I3A) and N-acetyl-5-hydroxytryptamine [32]. These microbial metabolites can act as ligands for the Aryl Hydrocarbon Receptor (AhR) expressed on intestinal epithelial cells and local innate lymphoid cells (ILCs), thereby influencing downstream protective responses [32]. The activation of the AhR signaling pathway directly drives the transcription of protective genes that accelerate tight junction assembly, stimulate mucus production, and promote the localized secretion of Interleukin-22 (IL-22), which is critically required to drive crypt stem cell regeneration [32]. These comprehensive insights provide definitive evidence that FMT exerts its powerful protective and curative effects against RE by systematically remodeling the taxonomy of the microbiota and restoring its protective metabolic outputs [32].

5.3. Comparison between Probiotics and FMT

Although both probiotics and fecal microbiota transplantation aim to restore intestinal microbial balance, these two approaches differ in their underlying mechanisms, clinical applications, and current levels of supporting evidence. Probiotics involve the administration of selected beneficial microbial strains, providing a relatively simple and controllable method for modifying intestinal microbial composi-

tion. In contrast, FMT introduces an entire microbial community derived from healthy donors, which may enable broader reconstruction of the gut microbiota.

From a clinical perspective, probiotics have been more extensively studied and are currently more commonly used as supportive interventions for gastrointestinal complications. Their advantages include convenient administration, relatively favorable safety profiles, and greater accessibility in clinical practice. However, the effects of probiotics may differ according to the specific strains administered, dosage, treatment duration, and individual patient characteristics.

FMT has received increasing attention due to its ability to introduce diverse microbial populations and potentially restore multiple components of intestinal ecosystem function. However, several challenges remain, including donor selection, procedure standardization, potential safety issues, and the limited availability of clinical evidence.

Therefore, although FMT represents a promising therapeutic option for radiation enteritis, further large-scale clinical studies are needed to clarify its long-term efficacy and determine its appropriate clinical application.

Overall, probiotics currently demonstrate greater clinical readiness for routine supportive care, whereas FMT remains a promising but investigational strategy that requires further validation through well-designed clinical trials.

6. Conclusions and Future Perspectives

In conclusion, the human gut microbiota represents a complex and metabolically active ecosystem that is closely involved in the occurrence, severity, and pathological progression of radiation enteritis (RE). Through its interactions with the host, the gut microbiota contributes to the maintenance of intestinal barrier integrity and mucosal immune homeostasis.

The systemic correction of radiation-induced gut microbiota imbalance through precisely engineered microecological interventions represents a promising, highly innovative strategy for RE therapy. By actively modulating microbiota dysbiosis, clinicians can enhance the localized anti-inflammatory defense mechanisms and self-repair capacities of the intestinal mucosa. This therapeutic approach decreases the risk of RE onset, alleviates debilitating radiotherapy-related symptoms, improves patient tolerance and compliance, and optimizes long-term oncology outcomes and overall quality of life.

Future studies should further explore microbial signatures associated with radiation sensitivity, establish more standardized protocols for FMT, and investigate targeted personalized postbiotic strategies to facilitate the development and clinical application of microbiota-based therapies in radiation oncology.

Author Contributions

Y.X.W. contributed to the conceptualization, literature search, investigation, and writing of the original draft. Y.S.S. contributed to the supervision, critical revision, and editing of the manuscript. Both authors contributed to the interpretation of

the literature, reviewed and approved the final version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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