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Postbiotics as Modulators of Apoptotic and Metastatic Pathways in Colorectal Cancer: Insights from HT-29 Cell Responses

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Abstract:

Colorectal cancer is one of the leading causes of cancer-related morbidity and mortality worldwide, and its incidence is strongly influenced by diet, lifestyle, chronic inflammation, and the composition of the gut microbiota.(1–4) Increasing evidence suggests that microbial dysbiosis contributes to tumor initiation and progression through altered metabolite production, impaired barrier function, and activation of oncogenic signaling pathways such as Wnt/β-catenin, NF-κB, MAPK/ERK, and STAT3.(3,5,6,14,19) In parallel, interest has grown in microbiota-centered interventions, particularly probiotics, prebiotics, synbiotics, and more recently postbiotics, which are defined as non-viable microbial cells, components, or metabolites that exert health-promoting effects in the host.(3,7–10) Postbiotics are attractive because they are stable, safe for immunocompromised patients, and easier to standardize than live probiotics, while still retaining potent immunomodulatory, anti-inflammatory, and anticancer activities.(7–13,21,26) Experimental and review data indicate that postbiotics can inhibit CRC cell growth, induce apoptosis, modulate the cell cycle, and regulate metastasis-associated genes and pathways, including *RSPO2, NGF, MMP7*, and mitochondrial apoptosis regulators such as *Bax, Bcl-2*, and caspase-3.(10–13,16,17,20) In particular, postbiotics derived from *Bifidobacterium breve* and *Lactobacillus rhamnosus* have shown promising effects in HT-29 colorectal cancer cells, where they promote apoptosis and attenuate pro-metastatic gene expression.(10,20) This review summarizes current knowledge on the relationship between the gut microbiota and CRC, defines and contextualizes postbiotics, explores their molecular mechanisms in carcinogenesis with a focus on CRC, and discusses the translational and clinical potential of postbiotics as complementary tools in CRC prevention and management.(3,7,11–13,18,26–28)

Keywords: Colorectal cancer; Gut microbiota; Apoptosis; *Bifidobacterium breve*; *Lactobacillus rhamnosus*

Introduction

Colorectal cancer remains a major global health burden despite advances in screening, surgery, and systemic therapies.(1–4) The rising incidence of CRC in both industrialized and developing countries is closely linked to lifestyle transitions, including higher consumption of processed foods and red

meat, reduced physical activity, obesity, smoking, and alcohol intake, along with population aging and persistent low-grade inflammation.(1–4,19) Beyond these traditional risk factors, the gut microbiota has emerged as a key player in CRC pathogenesis. The microbial community influences host metabolism, shapes mucosal immunity, regulates epithelial turnover, and produces a wide array of metabolites that can either support intestinal homeostasis or promote carcinogenesis, depending on the ecological balance within the gut.(3,5,6,14,19).

Dysbiosis a disturbed microbial composition and function has been associated with chronic intestinal inflammation, altered short-chain fatty acid (SCFA) profiles, increased production of genotoxins, and activation of oncogenic signaling pathways.(3,5,6,14,19) Certain bacteria, such as Fusobacterium nucleatum and enterotoxigenic Bacteroides fragilis, can adhere to epithelial cells, disrupt tight junctions, and activate pro-inflammatory and pro-proliferative signals, thereby fostering a tumor-promoting microenvironment.(5,6,14,19) Conversely, beneficial taxa such as Bifidobacterium and Lactobacillus genera tend to strengthen epithelial barrier integrity, dampen inflammatory responses, and generate SCFAs like butyrate with anti-proliferative and pro-apoptotic effects.(3,5,6,14,19).

Consequently, substantial research has focused on microbiota-targeted interventions probiotics, prebiotics, synbiotics, and postbiotics to modulate the gut ecosystem and reduce CRC risk or improve outcomes.(2,3,7–9,18,21,26–28) While probiotics have long been studied as live beneficial bacteria, concerns about viability, safety in immunocompromised patients, and inconsistent clinical effects have motivated a shift toward non-viable derivatives, especially postbiotics.(3,7–11) Postbiotics, which include inactivated cells, cell components, and microbial metabolites, provide an appealing alternative: they can be standardized, remain stable in industrial and clinical settings, and may reproduce many of the health benefits associated with probiotics without requiring live organisms.(7–11,26)

In the context of CRC, postbiotics have been reported to modulate immune responses, strengthen the intestinal barrier, induce apoptosis, regulate the cell cycle, and influence metastasis-related genes and signaling pathways.(3,7,11–13,16–18) The growing body of evidence around postbiotics derived from *B. breve* and *L. Rhamnosus* in HT-29 cancer cell models further underscores their potential to be developed as complementary or adjunctive strategies in CRC prevention and treatment.(10,20) This review integrates findings from experimental, mechanistic, and clinical-oriented studies to provide a comprehensive overview of postbiotics as emerging tools in CRC management.(3,7,11–13,18,26–28).

M Gut Microbiota, Dysbiosis, and Colorectal Cancer

The human gut microbiota consists of trillions of microorganisms mainly bacteria but also viruses, fungi, and archaea that inhabit the gastrointestinal

tract and co-evolve with the host.(5,6,14,19) These microbes contribute to the digestion of complex carbohydrates, synthesis of vitamins, production of SCFAs, maintenance of epithelial barrier function, and education of the immune system.(5,6,14,19) When the microbiota is balanced and diverse, it acts as a protective layer against colonization by pathogens and supports anti-inflammatory and anti-tumorigenic conditions. For instance, butyrate produced by certain members of the phylum Firmicutes serves as an energy source for colonocytes, reinforces tight junctions, and exhibits anti-proliferative and pro-apoptotic activities in colon cancer cells.(6,14,19)

However, dietary patterns rich in processed foods, saturated fats, and low in fiber, along with chronic stress, antibiotic misuse, and environmental exposures, can lead to dysbiosis characterized by reduced microbial diversity and shifts in taxonomic composition.(5,6,14,19) Dysbiosis is associated with decreased beneficial SCFAs and increased production of potentially carcinogenic metabolites, such as secondary bile acids and nitrosamines, as well as accumulation of reactive oxygen and nitrogen species.(5,6,14,19) In this altered state, bacteria such as F. Nucleatum can adhere more efficiently to the mucosal surface, activate E-cadherin/β-catenin signaling, and stimulate inflammatory mediators that facilitate tumor growth.(5,6,14) Similarly, enterotoxigenic B. Fragilis secretes B. Fragilis toxin, which can induce DNA damage and drive TH17-mediated inflammatory responses, contributing to CRC development.(5,6,14,19)

Observational and experimental studies indicate that patients with CRC often present with distinct microbial signatures compared with healthy individuals, including enrichment of F. Nucleatum, Peptostreptococcus species, and certain Enterococcus strains, alongside reduced levels of SCFA-producing bacteria.(5,6,14,19) These compositional changes are accompanied by functional alterations in metabolic pathways and immune signaling. In animal models and human cohorts, interventions that normalize microbiota composition such as high-fiber diets, natural products, and microbiota-modulating supplements have been associated with reduced tumor burden or improved clinical outcomes.(1–4,14–19) Within this broader framework, probiotics, prebiotics, synbiotics, and postbiotics have been proposed as key tools to modulate the microbiota and its metabolic outputs toward an anti-tumorigenic profile.(2–4,7–9,18,21,26–28)

From Probiotics to Postbiotics: Conceptual Evolution

Probiotics are defined as live microorganisms which, when administered in adequate amounts, confer a health benefit on the host.(2,8,9) Numerous studies have explored the use of probiotic strains particularly Lactobacillus and Bifidobacterium species in the prevention and management of CRC and other cancers.(2,3,6,18) Proposed mechanisms include competitive exclusion of pathogens, modulation of immune responses, reduction of inflammation, production of SCFAs, and direct effects on cancer cell proliferation and apoptosis.(2,3,6,18) For example, some probiotics have been shown to reduce

DNA damage markers, alter carcinogen metabolism, and influence immune cell activity in preclinical models.(2–4,6,18)

Prebiotics non-digestible food ingredients that selectively stimulate the growth or activity of beneficial bacteria such as inulin, fructo-oligosaccharides, and resistant starches, have also been associated with improved gut health and potential anti-cancer effects.(3,5,6,14) Synbiotics combine probiotics and prebiotics in a single product, with the aim of enhancing the survival and colonization of beneficial strains while promoting their metabolic functions.(2,3,14,18) Clinical and preclinical data suggest that synbiotic formulations may reduce inflammation, improve barrier function, and influence tumor progression in the colon and beyond.(3,14,18,21,33–35)

Nevertheless, probiotics and synbiotics present some limitations. Their efficacy often depends on strain viability, stability during storage and gastrointestinal transit, and host-specific factors.(3,7–9,21) In immunocompromised or critically ill patients, the use of live microorganisms may raise safety concerns, including the risk of bloodstream infections or transfer of antibiotic resistance genes.(21,22) These challenges have spurred interest in postbiotics, which are defined by various authoritative bodies as preparations of inanimate microorganisms and/or their components that confer a health benefit on the host.(7–10,21)

Postbiotics can include heat-killed bacterial cells, cell-free supernatants, purified metabolites, enzymes, peptides, and structural components of microbial cell walls.(7–10,21–23) Because they do not contain replicating organisms, they tend to be safer, more stable, and easier to standardize compared with live probiotics, while still providing many of the same or even enhanced functional benefits.(7–11,21–23) This has opened a new chapter in microbiota-based strategies for CRC, where postbiotics can be harnessed as targeted, controllable, and highly adaptable therapeutic tools.(3,7,11–13,18,26)

Mechanistic Basis of Postbiotic Action in Colorectal Cancer

Postbiotics exert their actions through multiple overlapping mechanisms, many of which are highly relevant to CRC pathobiology. One of the best characterized pathways is apoptosis induction. Several studies have shown that postbiotic fractions derived from different probiotic strains can activate intrinsic (mitochondrial) apoptotic pathways in CRC cell lines, leading to increased expression of pro-apoptotic proteins such as *Bax*, activation of effector caspases (e.g., caspase-3), and downregulation of anti-apoptotic proteins such as *Bcl-2*.(10,11,13,15–17) These molecular changes promote programmed cell death and counteract the apoptosis resistance often seen in malignant cells, which is a known hallmark of cancer and a contributor to chemotherapy failure.(15–17,22–25)

In addition to apoptosis, postbiotics can modulate cell-cycle progression by affecting cyclins, cyclin-dependent kinases, and CDK inhibitors, leading to cell-cycle arrest in G0/G1 or G2/M

phases.(16,17,24,25) This reduction in proliferative capacity can synergize with apoptosis-inducing effects and may sensitize cells to chemotherapeutic agents. Several mechanistic studies emphasize that cross-talk between autophagy and apoptosis is also influenced by microbial metabolites and postbiotic components, further shaping cell fate in CRC models.(16,23)

Postbiotics also exhibit anti-inflammatory and immunomodulatory effects. By interacting with pattern recognition receptors such as Toll-like receptors (TLRs) on immune and epithelial cells, they can reduce NF-κB activation and downregulate pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β.(7,11,19–22) At the same time, they may promote regulatory T-cell responses, enhance mucosal IgA production, and support a balanced immune environment less conducive to chronic inflammation and tumor progression.(19–22,29–32) Some postbiotic components have been shown to improve epithelial barrier integrity by upregulating tight-junction proteins (e.g., occludin, claudins, ZO-1), thereby limiting bacterial translocation and exposure of the immune system to luminal antigens.(20,21,23,37,38) SCFAs and polysaccharides derived from barley, ginseng, or other sources represent additional bioactive postbiotic-like molecules with demonstrated anti-inflammatory and anti-tumor properties in CRC models.(14,15,16,18)

Taken together, the ability of postbiotics to modulate apoptosis, cell cycle, inflammation, immunity, and barrier function suggests a multi-layered protective effect against CRC development and progression.(3,7,10–13,18,26–28) These mechanistic insights form the scientific foundation for exploring postbiotics as complementary or adjuvant therapies in CRC.

Strain-Specific Evidence: Bifidobacterium breve and Lactobacillus rhamnosus Postbiotics

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Strain-Specific Evidence: Bifidobacterium breve and Lactobacillus rhamnosus Postbiotics

Among the numerous bacterial strains investigated, postbiotics from *B. breve* and *L. Rhamnosus* have attracted particular attention due to their strong anticancer profiles in CRC models. An in-depth experimental study using HT-29 colorectal cancer cells showed that cell-free postbiotic preparations from these strains significantly reduced cell viability and migration in a dose- and time-dependent manner.(10,20) Morphological and molecular analyses revealed that both postbiotics induced features consistent with apoptosis, including chromatin condensation, membrane blebbing, and increased Annexin V staining.(10,20)

On the molecular level, treatment with *B. breve* and *L. Rhamnosus* postbiotics led to upregulation of *Bax* and *caspase-3* and downregulation of *Bcl-2*, confirming activation of intrinsic apoptotic pathways.(10,20) Interestingly, *B. breve* postbiotics produced a more pronounced shift in the *Bax/Bcl-2* ratio and stronger caspase-3 activation than *L. Rhamnosus*, suggesting a higher pro-apoptotic potency.(10) These differences likely reflect variations in metabolite composition, such as specific SCFAs, peptides, or polysaccharides, produced by each strain.(10,11,13)

Furthermore, the same line of research reported that *B. breve* postbiotics modulated metastasis-related genes in a manner consistent with reduced invasive potential. In particular, RSPO2 expression increased, while NGF and *MMP7* expression decreased

following treatment in HT-29 cells, thereby reversing the pro-metastatic pattern typically observed in CRC tissues.(3,7,10,13,18,20) Although *L. Rhamnosus* postbiotics showed similar trends, the magnitude of change was smaller, reinforcing the concept that the anticancer efficacy of postbiotics is strain-dependent.(10,20) These findings position *B. breve*–derived postbiotics as especially strong candidates for further preclinical and translational evaluation in CRC.

Clinical and Translational Perspectives

Translating postbiotic research into clinical practice requires careful consideration of formulation, dosing, safety, and target populations. The inherent stability of postbiotics allows them to be incorporated into capsules, sachets, beverages, and functional foods without strict cold-chain requirements, simplifying manufacturing and distribution.(7–9,21–23) Their non-viable nature makes them inherently safer for immunocompromised patients or those with severe underlying disease who may not be ideal candidates for live probiotic therapy.(21,22,26,27) In addition, postbiotics can be co-administered with chemotherapeutic agents or immunotherapies without concerns about microbial overgrowth.

Several lines of evidence suggest that combining microbiota-directed interventions with micronutrients or natural products may yield synergistic benefits. Studies have shown that vitamin D combined with probiotics can inhibit chemically induced CRC in animal models, and that probiotic or postbiotic-driven improvements in barrier integrity and immune regulation may enhance treatment tolerance and reduce adverse effects.(1,3,18,23–25,33,34,37,38) Postbiotics are also being discussed as adjuvant therapies in oncology, with potential roles in mitigating treatment-related toxicity, improving nutritional status, modulating systemic inflammation, and possibly enhancing responses to immunotherapy.(26–28)

Looking forward, key priorities include identifying the most active postbiotic metabolites, characterizing their pharmacokinetics and pharmacodynamics, optimizing delivery systems (e.g. microencapsulation, colon-targeted formulations), and designing well-controlled clinical trials to assess efficacy and safety in CRC patients.(7,11,18,26–28) Personalized approaches based on microbiome profiling may further refine the selection of specific postbiotic preparations tailored to an individual's microbial and molecular signature.(19,21,22,27,28) If these challenges are addressed, postbiotics may become integral components of precision medicine strategies for CRC prevention and treatment.

Conclusion

Postbiotics have emerged as a compelling class of microbiota-derived agents with strong potential in colorectal cancer prevention and management. By combining stability, safety, and potent multi-level biological activity, postbiotics overcome several limitations of traditional probiotic interventions while preserving or enhancing many of their beneficial effects. Experimental evidence, especially involving *B. breve* and *L. Rhamnosus* postbiotics in

HT-29 cells, indicates clear anticancer actions through induction of apoptosis, regulation of cell-cycle and autophagy-apoptosis cross-talk, suppression of pro-metastatic genes such as NGF and *MMP7*, and restoration of protective regulators like RSPO2.(3,7,10,11,13,16–18,20) Furthermore, the immunomodulatory and barrier-protective effects of postbiotics support a more homeostatic intestinal environment that may reduce CRC risk and improve therapeutic responses.(19–23,29–32,37,38) As research progresses, rigorous mechanistic studies and high-quality clinical trials will be essential to validate these promising findings and translate them into evidence-based recommendations. Nonetheless, current data strongly support the view that postbiotics represent a promising avenue in integrative CRC management and an exciting bridge between microbiome science and practical oncology.(3,7,11–13,18,26–28)

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