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THE ROLE OF POSTBIOTICS IN COLORECTAL CANCER: MECHANISMS, EVIDENCE, AND FUTURE PROSPECTS

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ABSTRACT

Colorectal cancer (CRC) remains a major global health concern, with gut microbiota playing a crucial role in its development and progression. Postbiotics, bioactive compounds derived from probiotic fermentation, have emerged as promising therapeutic agents due to their stability, safety, and beneficial health effects. This review explores the mechanisms by which postbiotics influence CRC, including apoptosis induction, inhibition of cancer cell proliferation, enhancement of gut barrier integrity, immune modulation, and microbiota regulation. Furthermore, postbiotics show synergistic potential with chemotherapy and immunotherapy, offering a novel approach to CRC treatment. Clinical studies suggest that postbiotics may be a safer and more effective alternative to probiotics for gut microbiome modulation and disease management. While research supports their anti-cancer properties, further large-scale studies and clinical trials are required to establish their efficacy and safety in CRC treatment.

KEYWORDS: Postbiotics, Colorectal Cancer, Gut Microbiota, Apoptosis, Short-Chain Fatty Acids, Immune Modulation.

1. INTRODUCTION

1.1 The human gut microbiota plays a crucial role in maintaining overall health, influencing digestion, immunity, and even mental well-being. The balance of beneficial and harmful microorganisms in the gut is essential, and disruptions in this balance, known as

dysbiosis, have been linked to various diseases, including inflammatory disorders and cancer. To support and restore gut health, three main dietary strategies have emerged: probiotics, prebiotics, and postbiotics. (Ji Y et al. (2023).

Probiotics are live beneficial microorganisms, such as Lactobacillus and Bifidobacterium species, that, when administered in adequate amounts, provide health benefits to the host. They help modulate gut microbiota composition, enhance immune function, and inhibit pathogenic bacteria. (Ji Y et al. (2023).

Prebiotics are non-digestible food components, primarily dietary fibers and oligosaccharides, that selectively stimulate the growth and activity of beneficial gut bacteria. Common prebiotic sources include inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS).

These compounds improve gut health by promoting the production of short-chain fatty acids (SCFAs), which have anti-inflammatory and protective effects. (Ji Y et al. (2023).

Postbiotics are bioactive compounds derived from probiotic fermentation. Unlike probiotics, postbiotics are non-living microbial metabolites that exert health benefits without the need for live bacteria. Examples include SCFAs (such as butyrate), exopolysaccharides, bacteriocins, enzymes, and cell wall fragments. Postbiotics have gained significant interest in recent years due to their stability, safety, and potential therapeutic applications in conditions such as colorectal cancer, metabolic disorders, and immune regulation. (Ji Y et al. (2023).

Together, probiotics, prebiotics, and postbiotics represent a holistic approach to gut health and disease prevention, offering promising interventions for gastrointestinal and systemic diseases, including colorectal cancer. (Ji Y et al. (2023).

1.2 Evolution of Postbiotics (Year-wise Development)

Year / Period	Terminology / Concept Used	Key Development	Scientific Significance	Key References
Pre-1990s	Fermentation by-products	Health effects of fermented foods observed (yogurt, kefir, kimchi)	Foundation for understanding microbial metabolites	Metchnikoff, 1907
1995–2000	Non-viable probiotics	Heat-killed probiotics shown to exert immune benefits	First evidence that live microbes are not always necessary	Salminen et al., 1999
Year / Period	Terminology / Concept Used	Key Development	Scientific Significance	Key References
2000–	Bacterial	Identification of SCFAs,	Shift from live	Marteau &

2005	metabolites	bacteriocins, enzymes as bioactive compounds	bacteria to microbial products	Shanahan, 2003
2006	Paraprobiotics	Term introduced for inactivated microbial cells	Differentiation between live and non-live probiotics	Taverniti & Guglielmetti, 2011
2011–2013	Postbiotics (emerging term)	First formal use of "postbiotics" in literature	Conceptual clarity begins	Tsilingiri & Rescigno, 2013
2015	Functional microbial metabolites	Postbiotics shown to improve gut barrier and immunity	Recognition of safety advantage over probiotics	Aguilar-Toalá et al., 2015
2018	Defined bioactive compounds	Systematic characterization (SCFAs, EPS, peptides)	Expansion into functional foods	Aguilar-Toalá et al., 2018
2019	Postbiotic mechanisms	Anti-inflammatory, antioxidant, metabolic roles identified	Strong mechanistic evidence	Żółkiewicz et al., 2020
2021	ISAPP Consensus	Official definition of postbiotics published	Global standardization of the term	Salminen et al., 2021
2022	Clinical application	Human trials in gut health, immunity, PCOS, IBS	Translational research phase	Wegh et al., 2022
2023	Nutraceutical & pharma use	Use in supplements, infant formula, women's health	Regulatory and industrial acceptance	Moradi et al., 2023
2024–2025	Targeted postbiotics	Precision nutrition & disease-specific postbiotics	Future-oriented personalized nutrition	De Marco et al., 2024

1.3 Types of Postbiotics and their mechanism

Postbiotics range from cell wall fragments to metabolites, bacterial lysates, extracellular vesicles, and short-chain fatty acids (SCFAs). They are classified by their chemical Composition, origin, and functional properties (Figure 1)

(Balendra V et al. (2024)

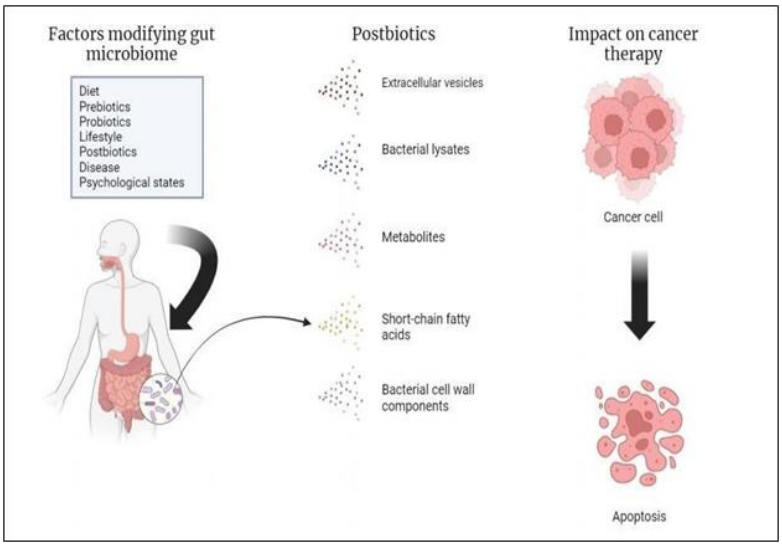

Figure 1: Factors that modify the gut microbiome, including the various types of postbiotics. Our own Elaboration based on the data in [8,11–13]. This figure was

created using Biorender.com (accessed on 1 July 2024). (Balendra V et al. (2024).

Type of Postbiotic	Examples / Source	Primary Mechanism in Colorectal Cancer	Anticancer Effects	Key References
Short-Chain Fatty Acids (SCFAs)	Butyrate, acetate, propionate (produced by *Lactobacillus*, *Bifidobacterium*)	• Histone deacetylase (HDAC) inhibition • Activation of apoptosis Pathways • Energy source for colonocytes	• Induces apoptosis in CRC cells • Suppresses tumor growth • Reduces inflammation	Donohoe et al., 2011; Louis & Flint, 2017
Bacterial Cell Wall Components	Peptidoglycan, lipoteichoic acid	• Activation of pattern recognition receptors (TLRs, NODs) • Immune modulation	• Enhances anti-tumor immune response • Reduces chronic inflammation	Tsilingiri & Rescigno, 2013; Żółkiewicz et al., 2020
Exopolysaccharides (EPS)	EPS from *Lactobacillus*, *Bifidobacterium*	• Antioxidant activity • Immune cell activation (macrophages, NK cells)	• Inhibits CRC cell proliferation • Enhances immune surveillance	Hidalgo-Cantabrana et al., 2014
Bacteriocins	Nisin, plantaricin	• Membrane pore formation in cancer cells • Induction of apoptosis	• Selective cytotoxicity against CRC cells • Inhibits tumor cell growth	Chumchalová & Smarda, 2003; Kamarajan et al., 2015
Microbial Enzymes	β-galactosidase, proteases	• Detoxification of carcinogens • Reduction of pro-carcinogenic enzymes	• Decreases carcinogen activation in colon	Rowland et al., 2018

Type of Postbiotic	Examples / Source	• Primary Mechanism in Colorectal Cancer	Anticancer Effects	Key References
Microbial-Derived Peptides	Bioactive peptides from fermented foods	• Anti- inflammatory signaling • Cell cycle arrest	• Suppresses CRC cell proliferation	Aguilar-Toalá et al., 2018
Indole Derivatives (Tryptophan Metabolites)	Indole-3-propionic acid, indole-3-aldehyde	• Activation of AhR pathway • Strengthening of gut barrier	• Reduces tumor-Promoting inflammation • Enhances epithelial integrity	Roager & Licht, 2018
Heat-Killed Microbial Cells (Paraprobiotics)	Inactivated *Lactobacillus*, *Bifidobacterium*	• Immune stimulation without infection risk	• Suppresses CRC progression via immune modulation	Taverniti & Guglielmetti, 2011
Secondary Bile Acid Modulators	Microbial metabolites altering bile acid metabolism	• Regulation of FXR and TGR5 signaling	• Reduces bile- acid–induced carcinogenesis	Ridlon et al., 2016

1.4 Postbiotics affecting Gut Microbiota

Postbiotics, which include metabolites, enzymes, peptides, and other bioactive compounds derived from probiotic bacteria, play a significant role in shaping gut microbiota composition and function. Unlike probiotics, which require colonization and viability, postbiotics exert

direct effects on the gut environment without concerns about survivability. They interact with intestinal microbes by promoting beneficial bacterial growth, inhibiting pathogenic species, and enhancing microbial diversity. (Zhang W et al. (2024).

One key mechanism through which postbiotics affect gut microbiota is by increasing the production of short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate. SCFAs serve as an energy source for colonocytes, help maintain intestinal barrier integrity, and modulate immune responses. Butyrate, in particular, has been shown to promote the growth of beneficial bacteria like Lactobacillus and Bifidobacterium, while suppressing inflammation-associated microbes such as *Escherichia coli* and *Clostridium species*. (Zhang W et al. (2024).

Postbiotics also influence gut health by modulating inflammatory pathways. Certain postbiotic compounds, including peptidoglycans and bacteriocins, have been found to downregulate proinflammatory cytokines such as TNF-α, IL-6, and IL-1β, while upregulating anti-inflammatory cytokines like IL-10. This shift in immune response contributes to a balanced gut microbiota, reducing the risk of inflammatory bowel diseases and colorectal cancer. (Zhang W et al. (2024).

A recent study Investigated the effects of postbiotics on gut microbiota composition in a rat model of colitis. Researchers found that postbiotic supplementation not only improved gut barrier integrity but also significantly altered microbial diversity. Beneficial bacteria, particularly butyrate-producing species, increased, while harmful bacteria associated with colonic inflammation were reduced. Additionally, fecal metabolomic analysis revealed an increase in antiinflammatory metabolites, further supporting the role of postbiotics in gut microbiota modulation. (Zhang W et al. (2024).

2. Mechanism of Action of Postbiotics on Colorectal Cancer

2.1 Postbiotic effects of butyrate-producing probiotics in colon cancer cells

Butyrate induces apoptosis (programmed cell death) in colorectal cancer cells by inhibiting histone deacetylase (HDAC) activity. Butyrate enhances the expression of pro-apoptotic gene (e.g., Bax, caspase-3) and reduces anti-apoptotic factors (e.g., Bcl-2). It also modulates cell cycle arrest in the G1 phase, limiting cancer cell proliferation. Butyrate's anti-inflammatory properties help maintain gut homeostasis, reducing cancer-promoting inflammation. (Aguilar-Toalá JE et al. (2018).

2.2 Postbiotic produced by Lactobacillus casei modulates colorectal cancer cell growth and differentiation

Postbiotics from Lactobacillus casei suppress cancer cell growth by downregulating AKT/mTOR signaling, which is vital for cancer cell survival and proliferation. The postbiotics trigger apoptosis by activating caspase-dependent pathways and enhance cell differentiation, reducing cancer cell malignancy. The presence of short-chain fatty acids (SCFAs) like butyrate and acetate leads to a reduction in proinflammatory cytokines, limiting the inflammatory environment that promotes cancer growth. (Salminen S et al. (2020).

2.3 Anti-proliferative effects of Lactobacillus fermentum postbiotics on colorectal cancer cells

Lactobacillus fermentum postbiotics contain exopolysaccharides and peptidoglycans that inhibit cancer cell proliferation by disrupting the cell cycle. These postbiotics induce mitochondrial membrane depolarization, leading to intrinsic apoptosis through the activation of the caspase-9 pathway. They also upregulate p53 tumor suppressor protein, which controls cell cycle arrest and apoptosis. Additionally, postbiotics reduce pro-inflammatory cytokine (IL-6, TNFα) levels, creating an anti-cancer microenvironment in the colon. (Alizadeh M et al. (2019).

2.4 Postbiotic activity of Lactobacillus plantarum inhibits colon cancer cell proliferation via downregulation of AKT signaling

Postbiotics from Lactobacillus plantarum specifically downregulate the AKT and PI3K signaling pathways, which are key regulators of cancer cell growth and survival. This leads to increased apoptosis in cancer cells through caspase-3 and caspase-9 activation.They also induce autophagy, a cellular process that degrades damaged proteins and organelles, inhibiting cancer progression. The postbiotics reduce oxidative stress, lowering reactive oxygen species (ROS) that drive DNA mutations and cancer development. (Kim MJ et al. (2020).

2.5 Inhibition of colorectal cancer growth by postbiotic metabolites from Lactobacillus acidophilus

Postbiotic metabolites from Lactobacillus acidophilus, such as SCFAs (butyrate, propionate), inhibit the activation of NF-κB, a transcription factor that promotes cancer cell proliferation and survival. These metabolites trigger caspase-8 and caspase-9, leading to apoptosis via both intrinsic and extrinsic pathways. They also inhibit angiogenesis (formation of new blood

vessels that feed tumors) by downregulating VEGF (vascular endothelial growth factor). The metabolites modulate the gut microbiota to reduce inflammation and restore immune balance, reducing tumor growth. (Huang T et al. (2020).

2.6 Postbiotics produced by *Bifidobacterium bifidum* reduce cancer cell proliferation and modulate immune responses

Postbiotics from *Bifidobacterium bifidum* enhance immune surveillance by activating dendritic cells (DCs) and T cells. These metabolites reduce IL-6 and TNFα, cytokines that promote tumor growth, while increasing IL-10 and TGF-β, which suppress inflammation. Butyrate produced by *Bifidobacterium* triggers apoptosis in colorectal cancer cells by modulating the Wnt/β-catenin pathway, which controls cell proliferation. They also inhibit cell migration and metastasis by downregulating matrix metalloproteinases (MMPs) involved in tumor invasion. (Arboleya S et al. (2021).

2.7 Lactobacillus-derived postbiotics exhibit antitumor effects on colon cancer cells

Postbiotics from Lactobacillus species induce apoptosis in colon cancer cells by activating p38 MAPK and JNK signaling pathways, which are involved in stress responses and cell death. They promote G0/G1 phase arrest in the cell cycle, preventing uncontrolled cell proliferation. The postbiotics also induce autophagy, a process that helps eliminate cancerous cells by degrading cellular components. They reduce levels of pro-inflammatory cytokines and limit the pro-tumor immune response in the tumor microenvironment. (Chen P et al. (2021).

2.8 Postbiotic extract from *Akkermansia muciniphila* induces apoptosis in colorectal cancer cells

Postbiotics from *Akkermansia muciniphila* trigger apoptosis through the caspase-3 and caspase-9 pathways. The extract downregulates pro-survival Bcl-2 proteins and upregulates pro-apoptotic Bax proteins, inducing cell death. Postbiotics inhibit Wnt/β-catenin signaling, reducing cancer cell proliferation and stemness. They enhance the gut barrier function, reducing inflammation and protecting against cancer-promoting toxins. (Wang J et al. (2019).

2.9 Postbiotic metabolites of Lactobacillus rhamnosus inhibit colorectal cancer cell invasion by modulating Wnt/β-catenin signaling

Postbiotic metabolites from *Lactobacillus rhamnosus* modulate Wnt/β-catenin signaling, leading to reduced cancer cell proliferation, invasion, and metastasis. The metabolites also

promote E- cadherin expression, which is involved in maintaining cell-cell adhesion and preventing cancer cell migration. They down regulate matrix metalloproteinases (MMPs), enzymes that degrade the extracellular matrix and facilitate cancer invasion. By reducing pro-inflammatory cytokines, the postbiotics create a less favorable environment for cancer progression. (Zhang Y et al. (2021).

2.10 Antitumor activity of postbiotic derived from *Lactococcus lactis* on colorectal cancer through modulating NF-kB signaling pathway

Postbiotics from *Lactococcus lactis* inhibit NF-kB signaling, which plays a key role in inflammation and cancer cell survival. They reduce the production of proinflammatory cytokines (TNF-α, IL-6) that promote tumor growth. The postbiotics enhance the expression of p53, a tumor suppressor protein that induces cell cycle arrest and apoptosis. These metabolites also modulate gut microbiota composition, promoting beneficial bacteria and reducing pathogenic microbes linked to colorectal cancer. (Yu J et al. (2022)

Key Contradictions in Current Evidence

Current evidence on the role of postbiotics in colorectal cancer (CRC) is promising but marked by several important contradictions that limit clear therapeutic translation. One of the most debated issues is the so-called butyrate paradox. In a healthy colon, butyrate serves as the primary energy source for colonocytes, supporting epithelial barrier integrity, promoting mucin production, and maintaining anti-inflammatory signaling. However, in cancerous colonocytes, cellular metabolism is reprogrammed toward glycolysis (the Warburg effect), reducing butyrate oxidation. As a result, intracellular butyrate can accumulate and act as a histone deacetylase (HDAC) inhibitor, leading to cell cycle arrest and apoptosis. Paradoxically, under certain conditions—particularly in hypoxic tumor regions or early-stage lesions where oxidative metabolism is partially retained—butyrate may be metabolized as a fuel source, potentially supporting tumor cell survival rather than suppressing it. This context-dependent behavior complicates the positioning of butyrate as a universally beneficial anticancer postbiotic and highlights the need to consider tumor stage, oxygen availability, and metabolic phenotype when interpreting outcomes (Donohoe et al., 2011; Kaiko et al., 2016).

Another major area of inconsistency lies in immune modulation by postbiotics. Several microbial metabolites have been shown to enhance antitumor immunity by increasing cytotoxic T-cell activity, improving antigen presentation, and reducing pro-tumor inflammation. Conversely, some postbiotics—particularly SCFAs—can promote the

expansion of regulatory T cells (Tregs), which are essential for immune tolerance but may suppress effective antitumor immune responses in the tumor microenvironment. While Treg induction may be protective in inflammatory conditions such as colitis-associated cancer, in established CRC it may inadvertently favor immune evasion by tumor cells. This dual immune role suggests that the timing, dosage, and disease context critically determine whether postbiotics exert protective or permissive effects on tumor progression (Furusawa et al., 2013; Tanoue et al., 2019).

The dependence on baseline gut microbiome composition further adds to the variability observed in postbiotic efficacy. Individual differences in microbial diversity, SCFA-producing capacity, diet, and antibiotic exposure lead to substantial variation in endogenous postbiotic levels. Consequently, identical postbiotic interventions can produce divergent biological effects across individuals, ranging from tumor suppression to minimal or no benefit. This heterogeneity challenges the concept of postbiotics as universally effective agents and suggests that personalized or microbiome-guided approaches may be necessary for consistent outcomes in CRC prevention and therapy (Louis & Flint, 2017; Zmora et al., 2018).

Finally, delivery-related contradictions remain unresolved. While oral postbiotic supplementation demonstrates clear anticancer and anti-inflammatory effects in animal models, human trials often report limited efficacy due to rapid metabolism, poor colonic availability, or degradation before reaching the target site. Emerging strategies such as microencapsulation, pH-sensitive coatings, and colon-targeted delivery systems show promise, but these approaches remain largely experimental and lack robust clinical validation. Until delivery challenges are addressed, translating preclinical success into reproducible human benefits will remain difficult (Wegh et al., 2022; Salminen et al., 2021).

Scope of Future development of postbiotics

- The future development of postbiotics in the field of colorectal cancer is expected to progress steadily as research shifts from observational findings to targeted therapeutic applications.
- With growing understanding of the gut microbiome and its metabolites, postbiotics such as short-chain fatty acids, microbial peptides, and indole derivatives are increasingly being explored for their direct role in regulating inflammation, immune responses, and tumor cell behavior in the colon.

- Unlike live probiotics, postbiotics offer greater safety, stability, and consistency, making them suitable for long-term use, especially in immunocompromised colorectal cancer patients.
- Future research is likely to focus on precision-based postbiotic formulations tailored to individual microbiome profiles, allowing more personalized prevention and treatment strategies.
- In addition, postbiotics may be developed as supportive agents alongside chemotherapy and immunotherapy to enhance treatment efficacy while reducing adverse effects.
- Advances in delivery systems, including colon-targeted and nano-encapsulated formulations, are also expected to improve local bioavailability at tumor sites.
- Overall, postbiotics hold strong potential not only as adjunct therapeutic agents but also as preventive tools in high-risk populations, marking a shift toward safer, microbiome-driven approaches in colorectal cancer management.

CONCLUSION

Overall, the anti-cancer effects of postbiotics are multifaceted, including induction of apoptosis, inhibition of tumor proliferation, enhancement of gut barrier integrity, immune modulation, and synergistic effects with conventional therapies. These mechanisms highlight the potential of postbiotics as promising adjunctive agents in colorectal cancer (CRC) management. However, further research is required to elucidate the precise mechanisms through which probiotics and postbiotics influence host health. Large-scale preclinical animal studies and well-designed human clinical trials are necessary to confirm the proposed safety advantages of postbiotics over live probiotics. Additional research should also focus on defining the clinical efficacy of postbiotics in CRC prevention and treatment, as well as establishing standardized classification and nomenclature based on microbial source and molecular characteristics. Furthermore, large-scale, randomized, double-blind clinical trials are essential to support their clinical application. Investigations into strain- and dose-specific effects are needed to ensure the efficacy and safety of traditional probiotics, next-generation probiotics (NGPs), and postbiotics. Finally, comprehensive animal and clinical studies are required to validate safety before administering NGPs and postbiotics to oncology patients.

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