Molecular Mechanisms of Probiotics in the Treatment of Gastrointestinal Cancers

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ABSTRACT

Probiotics have emerged as promising agents in gastrointestinal (GI) cancer therapy due to their ability to modulate signaling pathways, induce apoptosis, produce bioactive compounds, and enhance immune responses. This review synthesizes current evidence on the molecular mechanisms by which probiotics exert anticancer effects, focusing on their regulation of PI3K/AKT, Wnt, and MAPK pathways, induction of cell cycle arrest and apoptosis, production of short-chain fatty acids (SCFAs) and bacteriocins, and mitigation of oxidative stress. These findings underscore the therapeutic potential of probiotics as adjuncts in GI cancer management.

Keywords: **Probiotics, gastrointestinal cancer, signaling pathways, apoptosis, SCFA, immune modulation, oxidative stress.**

Introduction

Gastrointestinal (GI) cancers, encompassing malignancies of the stomach, colon, pancreas, and esophagus, represent a major global health burden due to their high incidence and mortality rates. Among these, gastric cancer is particularly lethal, often diagnosed at advanced stages and influenced by multifactorial etiologies including genetic predisposition, environmental exposures, and lifestyle factors (Zhang et al., 2017; Kumar et al., 2021). Helicobacter pylori infection, classified as a Group 1 carcinogen, plays a pivotal role in gastric carcinogenesis by inducing chronic inflammation, oxidative stress, and activating oncogenic pathways such as NF-κB, PI3K/AKT, and Wnt/β-catenin (Ding et al., 2010; Hardbower et al., 2013). Dietary habits also contribute significantly to GI cancer risk. High intake of salted, smoked, and processed foods has been correlated with increased gastric cancer incidence, whereas diets rich in fruits, vegetables, garlic, and soy

products exhibit protective effects (Kim et al., 2002; Fang et al., 2015). Tobacco and alcohol consumption further exacerbate cancer risk through synergistic mechanisms involving oxidative damage and inflammation (Sung et al., 2007; Hansson et al., 1994). Additionally, obesity and sedentary behavior have been linked to gastric cardia adenocarcinoma, highlighting the role of metabolic and inflammatory pathways in tumor development (Crew & Neugut, 2006; Friedenreich et al., 2021). Conventional cancer therapies such as chemotherapy, radiotherapy, and immunotherapy often face limitations due to adverse effects and resistance mechanisms. These challenges have prompted the exploration of adjunctive strategies, including the use of probiotics live microorganisms that confer health benefits when administered in adequate amounts (Marcason, 2013). Probiotics have demonstrated promising roles in modulating gut microbiota, enhancing intestinal barrier integrity, regulating immune responses, and producing bioactive compounds with anticarcinogenic properties (Plaza-Diaz et al., 2019; Bermudez-Brito et al., 2012). Recent evidence suggests that probiotics may influence cancer progression by interacting with host signaling pathways, reducing chronic inflammation, and restoring microbial equilibrium. Their ability to regulate cytokine secretion, strengthen tight junctions, and inhibit pathogen adhesion positions them as potential therapeutic agents in GI oncology (Zheng et al., 2022; Lim & Shin, 2020). However, further clinical trials and molecular investigations are required to fully elucidate their mechanisms and optimize their integration into cancer treatment protocols (Serban, 2014).

Regulation of Signaling Pathways (PI3K/AKT, Wnt, MAPK)

Probiotics exert significant influence on key oncogenic signaling pathways that drive gastrointestinal (GI) cancer progression. These pathways—PI3K/AKT/mTOR, Wnt/β-catenin, and MAPK—are frequently dysregulated in gastric and colorectal cancers, contributing to uncontrolled cell proliferation, resistance to apoptosis, and chronic inflammation. Emerging evidence suggests that specific probiotic strains can modulate these pathways, thereby inhibiting tumor growth and enhancing therapeutic outcomes.

PI3K/AKT/mTOR Pathway

This pathway plays a central role in regulating cell survival, proliferation, and metabolism. Its hyperactivation is commonly observed in gastric and colorectal cancers and is associated with poor prognosis and resistance to therapy. Probiotics such as *Lactobacillus acidophilus* have demonstrated the ability to downregulate PI3K/AKT signaling, thereby suppressing tumor cell proliferation and promoting apoptosis (Fattahi et al., 2020). Additionally, *Bifidobacterium* strains have shown potential in modulating this pathway through epigenetic mechanisms and immune regulation (Mohseni et al., 2021).

Wnt/β-Catenin Pathway

The Wnt signaling cascade is crucial for maintaining intestinal homeostasis and stem cell renewal. Aberrant activation of Wnt/β-catenin is a hallmark of colorectal cancer, leading to increased β-catenin accumulation and transcription of oncogenes. Probiotic-derived P8 protein has been shown to induce β-catenin degradation via GSK3β activation, resulting in cell cycle arrest and reduced proliferation in DLD-1 colon cancer cells (An et al., 2023). This mechanism highlights the therapeutic potential of engineered probiotic proteins in targeting Wnt-driven malignancies.

MAPK Pathway

The MAPK pathway mediates cellular responses to stress, cytokines, and growth factors. Its dysregulation contributes to inflammation, angiogenesis, and tumor progression. *Saccharomyces boulardii*, a probiotic yeast, has been shown to inhibit ERK1/2 MAPK activation, thereby reducing inflammation and protecting against toxin-induced enteritis (Chen et al., 2006). This anti-inflammatory effect is particularly relevant in the context of Clostridioides difficile-associated colitis and inflammation-driven carcinogenesis.

Table 1. Probiotic Modulation of Signaling Pathways.

Pathway	***Mechanism of Action***	***Probiotic Example***	***Reference***
PI3K/AKT/mTOR	Downregulates cell proliferation and survival	*L. acidophilus*, *Bifidobacterium* spp.	Fattahi et al., 2020; Mohseni et al., 2021
Wnt/β-Catenin	Promotes β-catenin degradation via GSK3β	P8 protein from probiotics	An et al., 2023
MAPK	Suppresses ERK1/2 activation, reduces inflammation	*S. boulardii*	Chen et al., 2006

Induction of Apoptosis and Cell Cycle Arrest

Apoptosis, or programmed cell death, is a tightly regulated process essential for maintaining tissue homeostasis. In cancer, this mechanism is often disrupted, allowing malignant cells to evade death and proliferate uncontrollably (Plati et al., 2008; Goldar et al., 2015). Probiotics have demonstrated the ability to restore apoptotic signaling in gastrointestinal cancers through both intrinsic and extrinsic pathways, as well as by inducing cell cycle arrest.

Intrinsic Apoptotic Pathway

The intrinsic pathway is regulated by BCL-2 family proteins and involves mitochondrial outer membrane permeabilization (MOMP), leading to the release of cytochrome c and activation of caspase-9 and caspase-3 (Wu & Bratton, 2013; Kale et al., 2018). *Lactobacillus rhamnosus* has been shown to upregulate pro-apoptotic genes such as **Bax** and **Casp3** in HT-29 colon cancer cells, promoting mitochondrial-mediated apoptosis (ZibasazTalebi & Ahmadizadh, 2020). This modulation of BCL-2 proteins presents a promising therapeutic strategy for colorectal cancer (Ramesh & Medema, 2020).

Extrinsic Apoptotic Pathway

This pathway is initiated by death ligands (e.g., FasL, TNF) binding to their receptors, forming the death-inducing signaling complex (DISC), and activating caspase-8 and caspase-3 (Ashkenazi, 2015; Caulfield & Lathem, 2014). *Bifidobacterium lactis* and *Lactobacillus sporogenes* have been shown to activate Fas-mediated apoptotic cascades in colorectal cancer cells, enhancing the expression of Fas, FADD, and cleaved caspases (Budu et al., 2022; Gomes et al., 2011). Additionally, *Bifidobacterium longum D42* induces apoptosis via ROS generation and mitochondrial dysfunction (Zhang et al., 2024).

Cell Cycle Arrest

Probiotics can halt cancer cell proliferation by interfering with cell cycle checkpoints. The supernatant of *L. rhamnosus* inhibits HT-29 cell growth by inducing G0/G1 phase arrest and downregulating **cyclin D1**, **cyclin E**, and **ERBB2** genes (Dehghani et al., 2020). Similarly, probiotic-derived **P8 protein** promotes β-catenin degradation via GSK3β activation, leading to cell cycle arrest in DLD-1 cells (An et al., 2023).

Table 2. Apoptotic and Cell Cycle Effects of Probiotics.

Mechanism	***Description***	***Probiotic Example***	***Reference***
Intrinsic Apoptosis	Bax/Casp3 activation; mitochondrial-mediated apoptosis	*L. rhamnosus*	ZibasazTalebi & Ahmadizadh, 2020
Extrinsic Apoptosis	Fas/FADD/caspase-8 pathway; activation of death receptors	*B. lactis*, *L. sporogenes*	Budu et al., 2022; Gomes et al., 2011
ROS-Mediated Apoptosis	Disruption of mitochondrial potential; induction of oxidative stress	*B. longum D42*	Zhang et al., 2024
Cell Cycle Arrest	Downregulation of cyclin D1, cyclin E, ERBB2; G0/G1 phase arrest	*L. rhamnosus*, P8 protein	Dehghani et al., 2020; An et al., 2023

Production of Bioactive Compounds

Probiotics, particularly strains from *Bifidobacterium* and *Lactobacillus* genera, are capable of synthesizing a diverse array of bioactive compounds that contribute to gastrointestinal health and exhibit anticancer properties. These compounds include short-chain fatty acids (SCFAs), bacteriocins, vitamins, enzymes, and immunomodulatory agents, each playing a distinct role in modulating the tumor microenvironment and enhancing host defense mechanisms.

Short-Chain Fatty Acids (SCFAs)

SCFAs primarily acetate, propionate, and butyrate—are produced through the fermentation of undigested carbohydrates by gut microbiota. Among these, **butyrate** is particularly significant due to its ability to:

- Regulate colonic physiology and epithelial cell differentiation
- Induce apoptosis in colorectal cancer cells via mitochondrial pathways
- Serve as an energy source for colonocytes and maintain mucosal integrity (Ríos-Covián et al., 2016; Markowiak-Kopeć & Śliżewska, 2020)

The production of SCFAs is influenced by dietary fiber intake and can be enhanced through targeted probiotic supplementation, offering a promising strategy for cancer prevention and therapy.

Bacteriocins

Bacteriocins are antimicrobial peptides secreted by probiotic bacteria, especially lactic acid bacteria (LAB), which:

- Inhibit the growth of pathogenic microorganisms
- Promote the proliferation of beneficial gut flora
- Modulate immune responses and reduce inflammation (Anjana & Tiwari, 2022)

These peptides act selectively, targeting harmful bacteria without disrupting the commensal microbiota, thereby restoring microbial balance and reducing carcinogenic risk.

Other Bioactive Compounds

Probiotics also produce a range of additional compounds with therapeutic potential:

- **Vitamins**: Such as B-group vitamins and vitamin K, which support metabolic and immune functions
- **Enzymes**: That aid in digestion and detoxification of carcinogens
- **Immunomodulatory agents**: Including exopolysaccharides and organic acids that enhance mucosal immunity and reduce oxidative stress (Kumar & Morya, 2022; Chugh & Kamal-Eldin, 2020)

These compounds contribute to the overall resilience of the gastrointestinal tract and may synergize with conventional therapies to improve outcomes in cancer patients.

Table 3. Bioactive Compounds Produced by Probiotics.

Compound	*Function*	*Probiotic Example*	*Reference*
SCFA (Butyrate)	Induces apoptosis, regulates colonic physiology	*Bifidobacterium* spp.	Ríos-Covián et al., 2016; Markowiak-Kopeć & Śliżewska, 2020
Bacteriocins	Inhibit pathogens, restore microbial balance	Lactic acid bacteria (LAB)	Anjana & Tiwari, 2022
Vitamins	Support immune and metabolic functions	*L. acidophilus*	Kumar & Morya, 2022
Enzymes	Detoxify carcinogens, aid digestion	*Lactobacillus* spp.	Chugh & Kamal-Eldin, 2020
Immunomodulators	Enhance mucosal immunity, reduce oxidative stress	*Bifidobacterium* spp.	Kumar & Morya, 2022

Immune Modulation and Oxidative Stress Reduction

Probiotics play a pivotal role in modulating the host immune system and mitigating oxidative stress, both of which are critical in the pathogenesis and progression of gastrointestinal (GI) cancers. Their immunomodulatory effects are mediated through interactions with epithelial cells, dendritic cells (DCs), and regulatory T cells, while their antioxidant properties help preserve intestinal barrier integrity and prevent DNA damage.

Cytokine Regulation

Probiotics, particularly strains of *Bifidobacterium bifidum*, have demonstrated the ability to elevate anti-inflammatory cytokines such as **interleukin-10 (IL-10)** and suppress pro-inflammatory cytokines including **tumor necrosis factor-alpha (TNF-α)** and **interleukin-6 (IL-6)**. These effects are crucial in reducing chronic inflammation associated with cancer development (Lim & Shin, 2020). In patients with Crohn's disease, *B. bifidum* enhances the expression of co-stimulatory molecules **CD80** and **CD86** in dendritic cells, promoting a tolerogenic immune profile (Ghavami et al., 2020). Such modulation may also influence the gut-brain-immune axis and contribute to systemic immune balance (Forsythe & Bienenstock, 2010).

Antioxidant Activity

Oxidative stress is a key driver of carcinogenesis, leading to DNA damage, lipid peroxidation, and disruption of cellular signaling. Probiotics such as *Lactobacillus rhamnosus* have been shown to enhance the activity of antioxidant enzymes and reduce reactive oxygen species (ROS) levels in intestinal epithelial cells (Zheng et al., 2022).This strain also strengthens tight junctions by upregulating proteins like **ZO-1** and **occludin**, thereby improving barrier integrity and reducing inflammation caused by lipopolysaccharide (LPS)-induced damage (Zheng et al., 2022; Miyauchi et al., 2009).

T-cell Activation and Immune Surveillance

Probiotics contribute to enhanced immune surveillance by stimulating cytotoxic immune cells. *Lacticaseibacillus rhamnosus Probio-M9* has been shown to increase infiltration of **CD8+ T cells** and **natural killer (NK) cells** into tumor tissues, thereby boosting antitumor immunity (Mao et al., 2020; Gao et al., 2023). These effects are particularly relevant in the context of immune checkpoint blockade therapies, where probiotics can improve the efficacy of anti-PD-1 treatments by modulating gut metabolites and enhancing interferon signaling (Gao et al., 2023; Zuo et al., 2024).

Table 4. Immunological and Antioxidant Effects of Probiotics.

Mechanism	*Description*	*Probiotic Example*	*Reference*
Cytokine Modulation	↑ IL-10, ↓ TNF-α, IL-6; modulation of DCs and Tregs	*B. bifidum*	Lim & Shin, 2020; Ghavami et al., 2020
Antioxidant Defense	Enhances tight junctions, reduces ROS, protects against LPS	*L. rhamnosus*	Zheng et al., 2022; Miyauchi et al., 2009
Immune Activation	↑ CD8+ T cells, NK cell stimulation, boosts anti-PD-1 therapy	*Probio-M9*	Mao et al., 2020; Gao et al., 2023

Discussion

The therapeutic potential of probiotics in gastrointestinal (GI) cancer management is increasingly supported by molecular and clinical evidence. Their mechanisms of action are multifaceted and highly strain-specific, encompassing modulation of oncogenic signaling pathways, induction of apoptosis, production of bioactive compounds, and enhancement of immune responses (Plaza-Diaz et al., 2019; Fattahi et al., 2020). One of the most compelling aspects of probiotic therapy is its ability to interfere with dysregulated cellular signaling. For instance, *Lactobacillus acidophilus* and *Bifidobacterium* spp. have been shown to suppress the PI3K/AKT/mTOR pathway, which is frequently activated in gastric and colorectal cancers (Fattahi et al., 2020; Mohseni et al., 2021). Similarly, engineered probiotic-derived proteins such as P8 can target the Wnt/β-catenin axis, promoting β-catenin degradation and halting cell cycle progression in colon cancer cells (An et al., 2023). In addition to signaling modulation, probiotics induce apoptosis through both intrinsic and extrinsic pathways. *L. rhamnosus* upregulates Bax and Casp3, while *B. lactis* and *L. sporogenes* activate Fas-mediated cascades, demonstrating their ability to restore programmed cell death in cancer cells (ZibasazTalebi & Ahmadizadh, 2020; Budu et al., 2022). These effects are further complemented by cell cycle arrest mechanisms, such as downregulation of cyclin D1 and ERBB2, which inhibit uncontrolled proliferation (Dehghani et al., 2020). Probiotics also produce bioactive compounds like short-chain fatty acids (SCFAs), bacteriocins, and vitamins, which contribute to their anticancer properties. Butyrate, for example, induces apoptosis and regulates colonic physiology, while bacteriocins selectively inhibit pathogenic bacteria and promote microbial balance (Ríos-Covián et al., 2016; Anjana & Tiwari, 2022). Moreover, their immunomodulatory effects are significant. *B. bifidum* increases IL-10 and reduces TNF-α and IL-6, while *L. rhamnosus* enhances antioxidant defenses and tight junction integrity (Lim & Shin, 2020; Zheng et al., 2022). These actions not only reduce inflammation but also improve mucosal immunity and epithelial resilience. In tumor models, *Probio-M9* has demonstrated the ability to enhance CD8+ T cell infiltration and NK cell activity, suggesting a role in boosting antitumor immunity (Gao et al., 2023). Despite these promising findings, several challenges remain. The efficacy of probiotics is highly dependent on strain specificity, dosage, and the host's baseline microbiota composition (McFarland et al., 2018). Inter-individual variability in microbial profiles and immune responses necessitates

personalized approaches to probiotic therapy. Furthermore, the lack of standardized clinical protocols and regulatory frameworks limits their integration into mainstream oncology (Serban, 2014; Arora et al., 2019). Future research should prioritize the identification of strain-specific molecular targets, optimization of delivery systems, and integration with conventional therapies such as chemotherapy and immunotherapy. Advances in microbiome sequencing and synthetic biology may also enable the development of engineered probiotics with enhanced anticancer efficacy (Chattaraj et al., 2023; Zhao et al., 2023).

Conclusion

Probiotics have emerged as promising adjuncts in the prevention and treatment of gastrointestinal (GI) cancers due to their multifaceted biological activities. By modulating gut microbiota, reinforcing intestinal barrier integrity, and regulating immune responses, they offer a holistic approach to mitigating cancer progression. Their ability to influence key oncogenic pathways—such as NF-κB, PI3K/AKT/mTOR, and Wnt/β-catenin—further underscores their therapeutic potential. Moreover, probiotics can induce apoptosis, inhibit tumor proliferation, and alleviate side effects associated with chemotherapy and immunotherapy. However, their efficacy is highly strain-specific and influenced by dosage, formulation, and individual microbiota composition. Safety concerns, particularly in immunocompromised patients, and regulatory inconsistencies also pose challenges to their clinical application.

To fully harness the anticancer potential of probiotics, future research must focus on:

- Identifying strain-specific molecular mechanisms
- Conducting large-scale, randomized clinical trials
- Developing standardized protocols for dosage and delivery
- Exploring engineered probiotics and paraprobiotics as safer alternatives

Ultimately, probiotics represent a convergence point between microbiology, immunology, and oncology, offering a novel frontier in personalized cancer therapy. Their integration into conventional treatment regimens could redefine therapeutic strategies and improve patient outcomes in GI malignancies.

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