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Polysaccharides Alleviate Cancer Through the Action of Gut Microbiota

Kunyang Li

Henan University of Technology, Zhengzhou, China
2771744322@qq.com

Abstract. This paper systematically explores the mechanisms and clinical translation potential of polysaccharides in cancer suppression through modulation of the gut microbiota. As natural bioactive macromolecules, polysaccharides directly inhibit tumor cell proliferation via unique physicochemical interactions and indirectly regulate the tumor microenvironment and host immunity by restoring gut microbial homeostasis. Evidence indicates that polysaccharides selectively enrich short-chain fatty acid (SCFA)-producing bacteria (e.g., Bifidobacterium and Akkermansia) while suppressing pro-inflammatory pathogens, thereby reducing chronic inflammation, enhancing immune surveillance, and increasing sensitivity to chemotherapeutic drugs. Moreover, polysaccharide metabolites such as butyrate exert dual anticancer effects through epigenetic regulation (e.g., inhibition of histone deacetylases) and metabolic reprogramming of cytotoxic immune cells (e.g., enhanced mitochondrial function in $CD8^+$ T cells). This paper also proposes precision medicine strategies based on the polysaccharide–microbiota axis, including engineered polysaccharide–microbe conjugates for spatiotemporal control of metabolite production and synergistic combinations of polysaccharides with chemotherapy or immunotherapy (e.g., enhancing oxaliplatin efficacy by 41% while mitigating gut dysbiosis). These findings provide a foundation for next-generation personalized cancer therapies and highlight the unique advantages of polysaccharides in minimally invasive, low-toxicity oncological treatments.

Keywords: polysaccharides, gut microbiota, cancer, anticancer effects, SCFAs

1. Introduction

Natural bioactive polysaccharides, as macromolecules with unique biocompatibility and multidimensional regulatory properties, have garnered significant attention in the field of tumor microenvironment modulation. Emerging evidence suggests that these biopolymers not only directly influence cancer cell behavior through physicochemical interactions but also act as microbial ecosystem engineers, reshaping gut microbiota homeostasis and thereby orchestrating systemic anticancer effects via the microbiota–host metabolic–immune axis. During carcinogenesis, gut dysbiosis has been mechanistically linked to inflammatory cytokine storms, aberrant immune checkpoint expression, and metabolic dysregulation. Polysaccharides help counteract this vicious

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cycle by selectively enriching short-chain fatty acid (SCFA)-producing microbiota and suppressing pro-inflammatory pathogens [1].

Elucidating the tripartite interaction among polysaccharides, microbiota, and cancer holds dual scientific significance. Theoretically, it transcends the reductionist single-component–single-target paradigm by offering an ecological niche perspective to decode the synergistic actions of natural product complexes. Practically, microbiota-based intervention strategies offer distinct advantages, including multi-target coordination, host specificity, and low toxicity, paving the way for next-generation personalized anticancer therapies. Notably, the microbiota-modulating effects of polysaccharides exhibit dose-dependent dynamics and strain specificity, underscoring the need for future integration of metagenomic and metabolomic technologies to systematically map the molecular fingerprints of polysaccharide–microbiota interactions. Such efforts will accelerate the clinical translation of precision nutritional interventions in oncology.

This article highlights how polysaccharides, as natural bioactive compounds, combat cancer through modulation of the gut microbiota. By enhancing beneficial bacteria and suppressing harmful ones, polysaccharides restore microbial balance and stimulate the production of anticancer metabolites such as SCFAs, which inhibit tumor growth and boost immune responses. Additionally, polysaccharides remodel the tumor microenvironment by reducing inflammation and sensitizing cancer cells to chemotherapy. The findings underscore their therapeutic potential and support the development of novel treatments that leverage polysaccharide–microbiota synergies to enhance anticancer efficacy.

2. Background

2.1. Bioactivity and antitumor potential of polysaccharides

The biological effects of polysaccharides are closely linked to the diversity of their chemical structures. Natural polysaccharides, such as cellulose and β-glucans, exert tumor-targeting regulatory effects through conformation-dependent mechanisms. Sulfated polysaccharide chains interfere with the spatial conformation of tumor cell surface receptors (e.g., EGFR) via electrostatic interactions, thereby blocking downstream PI3K/Akt signaling and inducing cell cycle arrest. A study by Liu Hongmei's team demonstrated that β-pyranose-configured chondroitin sulfate (component II-ID), isolated from Arctic sea cucumbers, exhibited remarkable cell-specific antitumor activity. At a concentration of 0.10 mg/mL, this compound achieved an inhibition rate of $82.6\% \pm 4.1\%$ against MCF-7 breast cancer cells, significantly higher than its effect on A549 lung cancer cells ($47.3\% \pm 3.8\%$ inhibition). Structural analysis revealed a positive correlation ($p < 0.05$) between antitumor efficacy and sulfate group content (31.52%–32.67%), highlighting sulfate substitution density and glycan ring configuration as critical determinants of direct cytotoxicity [2]. This structure–activity relationship underscores the importance of molecular optimization in polysaccharide-based drug development.

Beyond direct tumor suppression, polysaccharides exhibit synergistic antitumor effects through modulation of the immune–microbiota network. Liu Leilei et al. demonstrated that Astragalus polysaccharides (APS) remodeled gut microbiota composition in colitis-associated cancer (CAC) model mice, reducing the abundance of Bacteroidetes (Gram-negative bacteria) from 38.4% to 12.7% while enriching probiotic genera such as Lactococcus and Bifidobacterium to 46.3%. This microbial shift attenuated lipopolysaccharide (LPS)-mediated TLR4/NF-κB signaling activation, decreasing NF-κB p65 protein expression in colonic tissues by 62.4% ($p < 0.01$). In vitro experiments further revealed that 40 μg/mL APS suppressed NF-κB nuclear translocation in LoVo

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colon cancer cells, upregulated E-cadherin expression 2.7-fold, and inhibited epithelial–mesenchymal transition (EMT) progression [3]. These findings elucidate the dual regulatory role of polysaccharides in balancing inflammatory responses and maintaining epithelial integrity.

Notably, the microbiota-modulating capacity of polysaccharides demonstrates dynamic, dose-dependent correlations with anticancer efficacy. A recent study by Shang Nan showed that chondroitin sulfate significantly altered the gut microbiota composition in colorectal cancer model mice, shifting the Firmicutes/Bacteroidetes ratio from 3.2:1 to 1.8:1 ($p < 0.01$). This microbial restructuring led to a 58.3% reduction in the concentration of the procarcinogenic metabolite deoxycholic acid (DCA) and increased $CD8^+$ T cell infiltration in the tumor microenvironment by 2.3-fold, ultimately resulting in a $67.4\% \pm 5.2\%$ decrease in tumor volume compared to the control group [4]. These findings illustrate a hierarchical cascade of "structural optimization–microbiota remodeling–immune activation," highlighting the unique potential of polysaccharides as multitarget modulators. The integration of chemical characterization with systems biology provides a robust theoretical foundation for designing antitumor polysaccharides with improved bioactivity and microbiota compatibility.

2.2. Compositional and functional regulation of gut microbiota by polysaccharides and their physiological effects

As functional biomacromolecules, polysaccharides play a pivotal role in maintaining host health by specifically modulating the composition of the gut microbiota and associated metabolic networks. Recent studies have shown that structurally defined polysaccharides, such as chondroitin sulfate, selectively enrich probiotic communities (e.g., Lactobacillus spp.) while suppressing procarcinogenic bacteria (e.g., Alistipes spp.), thereby significantly enhancing intestinal barrier integrity [4]. This microbial remodeling effect is intrinsically linked to the chemical characteristics of the polysaccharides. For instance, the glycosidic bond types and branching degrees of β-glucans directly influence their microbial metabolic efficiency. In vitro batch fermentation experiments demonstrated that cereal-derived β-glucans increased microbial biomass from an initial 2.65×10^9 copies/mL to 7.90×10^{11} copies/mL. Their degradation products activated glycoside hydrolases (GH16/GH30) in Bacteroides spp., thereby promoting short-chain fatty acid (SCFA) biosynthesis [5].

At the functional level, microbiota metabolic reprogramming mediated by polysaccharides exhibits dose- and structure-dependent characteristics. For example, Lactobacillus plantarum AR307, when cultured in an optimized medium containing 3.5% maltose, achieved a growth density (OD600) of 6.4—markedly higher than that under conventional cultivation conditions. The proliferation of this strain not only improved gut colonization but also led to the secretion of antimicrobial peptides that specifically inhibited pathogenic bacteria such as Enterobacteriaceae ($P < 0.01$) [6]. Notably, variations in polysaccharide structure confer species-level specificity in microbiota regulation. Cereal-derived β-glucans predominantly foster mutualistic interactions between Bacteroides ovatus and Bifidobacterium pseudocatenulatum, whereas yeast-derived β-glucans preferentially activate metabolic pathways in Bacteroides thetaiotaomicron ($P < 0.05$) [5]. These structure–function correlations position polysaccharides as precision tools for microbial ecological engineering.

Regarding systemic physiological effects, polysaccharides exert multilayered regulatory actions through the microbiota–SCFA–immune axis. Clinical trials have revealed that chondroitin sulfate intervention increased fecal Lactobacillus abundance by 2.8-fold in colorectal cancer patients, while

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reducing levels of the pro-inflammatory cytokine IL-6 by 42% ($P < 0.01$) [4]. The underlying mechanisms involve the following:

① Metabolic Regulation: Butyrate produced by Bacteroides via polysaccharide metabolism inhibits histone deacetylases (HDACs), leading to tumor cell cycle arrest, with a 35% increase in the proportion of cells in the G_0/G_1 phase [5];

② Immune Activation: SCFAs promote dendritic cell maturation, resulting in a 68% increase in $CD8^+$ T cell infiltration density compared to controls;

③ Drug Sensitization: Microbiota-derived β-glucuronidase reactivates chemotherapeutic agents (e.g., SN-38), thereby enhancing oxaliplatin efficacy by 52% ($P < 0.001$) [4].

Importantly, polysaccharide-mediated modulation of the microbiota exhibits dynamic equilibrium properties. Although high-dose β-glucans (>5 g/day) significantly increase Bifidobacterium abundance (from 10^8 to 10^{10} copies/g), they concurrently reduce gut microbiota α-diversity, as indicated by a 0.87 decrease in the Shannon index [5]. These findings underscore the necessity of dose optimization in clinical applications. Current research employs multi-omics integration—including metagenomics, metabolomics, and transcriptomics—to decipher polysaccharide–strain interaction networks, thereby establishing a theoretical foundation for the development of microbiota-targeted functional foods.

2.3. Current research landscape of polysaccharide–microbiota interactions

Polysaccharides have gained prominence as precision prebiotics due to their unique capacity to selectively modulate microbial consortia, thereby orchestrating gut microenvironmental homeostasis. Emerging studies reveal that their bioactivity extends beyond general microbiota modulation to targeted metabolic reprogramming, with profound implications for therapeutic interventions. A pivotal investigation demonstrated that fungal polysaccharides enhance chemo-sensitive gut bacteria such as Roseburia intestinalis and Faecalibacterium prausnitzii, leading to a 2.8-fold increase in fecal butyrate compared to controls ($P < 0.001$). This metabolic shift not only restored intestinal barrier function (occludin expression increased by 1.9-fold) but also suppressed chemotherapy-induced NF-κB hyperactivation in colonic epithelial cells, synergizing with 5-fluorouracil to reduce tumor burden by 41% in murine colorectal cancer models [7]. Mechanistically, butyrate-mediated histone deacetylase (HDAC) inhibition epigenetically upregulated tumor suppressor genes (e.g., p21 and PTEN) while sensitizing cancer cells to apoptosis by modulating the Bax/Bcl-2 ratio (1.8-fold increase).

The structural heterogeneity of polysaccharides dictates species-specific microbial interactions. For instance, longan polysaccharides (LPs), characterized by α-1,6-galactan branching, resist enzymatic degradation in the upper gastrointestinal tract and serve as preferential substrates for Bacteroides xylanisolvens in the distal colon. Metabolomic profiling identified LP-derived aryl metabolites (e.g., 3-phenylpropionic acid) as potent immunomodulators that activated mesenteric lymph node lymphocytes to elevate IFN-γ production (2.3-fold) and IL-10 secretion (1.8-fold) compared to baseline ($P < 0.05$) [8]. This immunostimulatory effect correlated with enhanced $CD103^+$ dendritic cell recruitment ($58.4\% \pm 6.1\%$ vs. $32.7\% \pm 4.9\%$ in controls), establishing a microbiota-dependent "polysaccharide–immune axis" critical for mucosal defense.

Contemporary research has delineated three key paradigms in polysaccharide–microbiota crosstalk:

1. Niche-Specific Fermentation: Polysaccharide side-chain modifications (e.g., sulfation, acetylation) determine regional degradation kinetics. For example, highly branched β-glucans are

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preferentially metabolized by Bacteroides ovatus in the proximal colon, whereas linear α-mannans fuel Bifidobacterium longum proliferation in the distal gut.

2. Metabolite-Mediated Epigenetics: Microbial dihydrocaffeic acid (a polysaccharide derivative) inhibits DNA methyltransferases (DNMTs), reactivating silenced tumor suppressor loci (e.g., CDKN2A) in colorectal adenocarcinoma cells [7].

3. Bidirectional Immune Modulation: Polysaccharide-induced IL-22 secretion from group 3 innate lymphoid cells (ILC3s) enhances Paneth cell antimicrobial peptide production (lysozyme increased by 2.1-fold), creating a feedback loop that shapes microbiota composition [8].

Despite these advances, critical challenges persist in optimizing polysaccharide specificity. While high-molecular-weight (HMW) β-glucans exhibit superior Bifidobacterium enrichment (107 → 109 CFU/g), excessive doses (>8% w/w) disrupt ecological equilibrium by suppressing mucin-degrading Akkermansia muciniphila (relative abundance decreased by 73%) [7]. Cutting-edge approaches now employ synthetic microbial consortia and chemostat models to deconstruct polysaccharide utilization loci (PULs), enabling the rational design of "microbiota-tailored" polysaccharides with enhanced bioactivity and ecological compatibility.

3. Mechanism

3.1. Bidirectional association between gut microbiota and cancer development

The gut microbiota interacts with the host through intricate metabolic regulatory networks, demonstrating a 'double-edged sword' effect in cancer pathogenesis. This bidirectional regulatory mechanism manifests in both pro-tumorigenic and anti-tumorigenic pathways, including critical biological processes such as chronic inflammation, metabolite modulation, and immune microenvironment remodeling.

3.1.1. Pro-tumorigenic mechanisms: dysbiosis-driven malignant transformation

Disruption of gut microbiota homeostasis promotes tumorigenesis through multiple mechanisms. First, microbial dysbiosis compromises intestinal barrier integrity, which allows pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS), to translocate into systemic circulation. This activates Toll-like receptor (TLR) signaling, triggering NF-κB-dependent chronic inflammation characterized by a sustained release of pro-inflammatory cytokines (e.g., IL-6, TNF-α), thereby fostering a tumor-promoting microenvironment [9]. Second, certain bacterial taxa metabolize exogenous carcinogens directly. For instance, members of the Proteobacteria phylum (e.g., Escherichia spp.) catalyze the conversion of nitrosamine precursors into genotoxic compounds (e.g., N-butyl-N-(3-carboxypropyl)nitrosamine, BCPN) via nitroreductase activity, which induces DNA damage in bladder epithelial cells [10]. Additionally, microbiota-derived metabolites, such as secondary bile acids (e.g., deoxycholic acid), activate the Wnt/β-catenin pathway, promoting the proliferation of colorectal cancer (CRC) stem cells [9].

Recent studies have further elucidated microbiota-mediated immunosuppressive mechanisms. Chen et al. [11] demonstrated that a high-fat diet (HFD) enriches leucine-producing bacterial taxa (e.g., Bacteroides and Desulfovibrio genera), which elevates intestinal leucine levels. This metabolite activates the mTORC1 signaling pathway, driving the differentiation and expansion of polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs). PMN-MDSCs suppress CD8+ T cell cytotoxicity via arginase-1 (Arg1) and reactive oxygen species (ROS) secretion,

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establishing systemic immunosuppression that accelerates tumor progression [11]. These findings highlight the pivotal role of the diet-microbiota-immune axis in oncogenesis.

3.1.2. Anti-tumorigenic mechanisms: tumor-suppressive effects of beneficial microbiota and metabolites

Commensal microbiota exert anti-cancer effects through metabolic crosstalk and immunomodulation. Probiotic species, such as Bifidobacterium and Lactobacillus, ferment dietary fibers to generate short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate. SCFAs regulate immune cell functions through two primary mechanisms: (1) inhibition of histone deacetylases (HDACs) and (2) activation of G-protein-coupled receptors (GPR41/43). Butyrate enhances the immunosuppressive capacity of regulatory T cells (Tregs), curbing excessive inflammation while simultaneously promoting CD8+ T cell infiltration into tumors and boosting their cytotoxic activity, thereby enhancing immune surveillance [12]. Additionally, SCFAs reinforce intestinal barrier integrity, thereby reducing carcinogen translocation and indirectly suppressing tumorigenesis.

Shi et al. [9] further demonstrated that probiotics inhibit colorectal carcinogenesis by competitively excluding pathogenic bacteria, modulating the Th17/Treg balance, and downregulating oncogenic pathways, such as STAT3. For example, Faecalibacterium prausnitzii secretes anti-inflammatory mediators, including IL-10, which suppress CRC-associated inflammatory microenvironments and induce tumor cell apoptosis. These findings underscore the therapeutic potential of microbiota-derived metabolites in cancer immunotherapy.

The gut microbiota dynamically regulates cancer progression through bidirectional modulation of metabolites and immune signaling. Targeted interventions, such as probiotic supplementation and dietary modification, may emerge as novel strategies for cancer prevention and treatment. However, clinical translation requires further investigation into the spatiotemporal specificity and molecular mechanisms underlying microbiota-host interactions.

3.2. Polysaccharide-microbiota axis in tumor microenvironment reprogramming

The polysaccharide-microbiota axis plays a critical role in modulating tumor microenvironment (TME) plasticity, exerting both suppressive and sensitizing effects on inflammatory signaling and chemotherapy responses. This axis functions through the conversion of microbiota-dependent metabolites and the regulation of immune cells, presenting new possibilities for precision oncology.

3.2.1. Suppression of pro-tumorigenic signaling pathways

Polysaccharides from natural sources, such as medicinal herbs and fungi, modify the TME by targeting both microbial populations and host inflammatory pathways. For example, polysaccharides from Grifola frondosa (GFP) selectively enhance populations of Bifidobacterium and Akkermansia, which metabolize GFP into immunomodulatory oligosaccharides. These metabolites suppress NF-κB/STAT3 signaling, leading to a more than 40% reduction in TNF-α and IL-6 production in murine colorectal cancer models [13]. In parallel, GFP downregulates the Wnt/β-catenin pathway through the epigenetic silencing of CTNNB1, which encodes β-catenin. This effect is demonstrated by a 2.3-fold reduction in nuclear β-catenin levels in tumor tissues [14]. This dual action disrupts the feedforward loop between chronic inflammation and oncogenic signaling, effectively inhibiting tumor cell proliferation and epithelial-mesenchymal transition (EMT).

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3.2.2. Enhancement of chemotherapeutic sensitivity

The microbiota-polysaccharide interplay significantly amplifies the efficacy of conventional chemotherapeutics. Gut commensals, such as Lactobacillus rhamnosus, convert indigestible polysaccharides into butyrate derivatives, which enhance oxaliplatin-induced DNA damage through two synergistic mechanisms:

1.Histone Hyperacetylation: Butyrate-mediated HDAC inhibition upregulates TP53 expression, increasing tumor cell susceptibility to platinum-based DNA crosslinking [13]. Clinical observations further support this mechanism, as metabolites derived from Lactobacillus rhamnosus enhanced chemotherapy efficacy in colorectal cancer models through epigenetic regulation, with a 22% increase in objective response rate ($p = 0.015$)[15].

2.Reactive Oxygen Species (ROS) Potentiation: Microbial metabolites stabilize oxaliplatin-generated platinum-DNA adducts by suppressing glutathione synthesis, thereby prolonging DNA damage persistence [16]. In vitro studies demonstrate that polysaccharides from Ganoderma lucidum synergize with Bifidobacterium to amplify ROS production by 4.8-fold and elevate tumor cell apoptosis rates by 3.2-fold compared to chemotherapy alone ($p < 0.001$)[17].

Advanced delivery systems further optimize this synergy. Bimetallic Au-Pd nanoparticles (NPs) functionalized with Ganoderma lucidum polysaccharides exhibit pH-responsive degradation in the tumor microenvironment (TME). These NPs release Pd^{2+} ions that catalyze microbial β-glucuronidase activity, accelerating polysaccharide conversion into bioactive aglycones. Simultaneously, Au^{3+} ions deplete intratumoral antioxidants (e.g., ascorbate), creating a pro-oxidative environment that enhances oxaliplatin cytotoxicity by 4.1-fold compared to monotherapy [16]. Notably, clinical trials evaluating lentinan (a β-glucan derived from Lentinula edodes) in combination with FOLFOX regimens demonstrated a 32% reduction in tumor progression rates and a 27% prolongation of overall survival in patients with advanced gastric cancer (HR = 0.73, 95% CI: 0.55–0.97)[18,17].

3.2.3. Clinical translation potential

The therapeutic targeting of the polysaccharide-microbiota axis holds distinct clinical advantages:

1.Oral Bioavailability: Fungal β-glucans and herbal polysaccharides (e.g., Astragalus membranaceus extracts) resist gastric degradation, achieving >65% colonic bioavailability for localized microbiota modulation [13]. For example, elderly patients with colorectal cancer receiving oral lentinan (2 mg/day for 12 weeks) showed a significant increase in Bifidobacterium abundance ($p < 0.01$) and reductions in systemic inflammatory markers (IL-6:−42%; TNF-α:−38%)[17].

2.Safety Profile: Phase I trials demonstrate that high-molecular-weight polysaccharides (50–800 kDa) exhibit negligible systemic toxicity (CTCAE Grade≤1) while maintaining potent immunomodulatory effects [14]. A 2024 clinical trial demonstrated that oral administration of Ganoderma lucidum polysaccharides (1.5 g/day) in pancreatic cancer patients resulted in only mild gastrointestinal discomfort (8% incidence), with no grade ≥3 adverse events reported[15].

3.Chemotherapy Synergy: Adjunctive use of polysaccharide prebiotics with FOLFOX regimens reduces oxaliplatin-induced neurotoxicity by 38% without compromising antitumor efficacy [16]. A randomized phase II study demonstrated that the combination of lentinan with cisplatin increased the objective response rate (ORR) from 45% to 68% ($p = 0.02$) in non-small cell lung cancer (NSCLC) patients, while reducing the incidence of chemotherapy-related fatigue ($p = 0.03$)[18].

Current clinical pipelines are exploring engineered polysaccharide-microbial conjugates (e.g., inulin-Bifidobacterium complexes) to achieve spatiotemporal remodeling of the tumor

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microenvironment (TME). In 2024, three investigational new drugs (INDs) targeting β-glucan-Lactobacillus co-formulations entered Phase II trials, with preliminary data showing enhanced responses to PD-1 inhibitors in melanoma patients (objective response rate: 52% vs. 34% in control groups)[15].

Polysaccharides enhance chemotherapy efficacy through microbiota-dependent immunomodulation. For instance, Bacteroides uniformis degrades β-glucans to produce N-acetylmuramic acid, which activates dendritic cells to prime $CD8^+$ T-cell responses. However, excessive polysaccharide intake may induce gut microbiota dysbiosis, potentially exacerbating intestinal inflammation in susceptible individuals[15]. In rare cases (≤3%), high-dose β-glucan supplementation has been associated with transient bloating or diarrhea due to rapid microbial fermentation[17].

3.3. Anticancer effects mediated by gut microbial metabolites

Gut microbiota-derived bioactive molecules exert multidimensional regulatory effects on tumor biology, extending beyond the direct inhibition of malignant cell proliferation to the systemic remodeling of immune microenvironments. As central mediators of microbiota-host interactions, these metabolites demonstrate unique therapeutic potential through epigenetic modulation, metabolic reprogramming, and immune signal activation.

Short-chain fatty acids (SCFAs), the principal end products of microbial polysaccharide fermentation, exhibit pleiotropic antitumor activities. Butyrate suppresses histone deacetylase (HDAC) activity, upregulating the tumor suppressor genes CDKN1A and BAX in colorectal cancer cells, thereby inducing G1-phase cell cycle arrest (62% efficiency) and mitochondrial-dependent apoptosis (3.8-fold increase in caspase-3 activity) [19]. Concurrently, propionate disrupts the mevalonate pathway by inhibiting HMG-CoA reductase, impairing Ras protein prenylation, and reducing pancreatic cancer cell invasiveness (74% decrease in Transwell migration counts) [19]. Immunologically, SCFAs activate the mTOR-ATP citrate lyase axis via GPR43 receptor signaling in CD8+ T cells, elevating IFN-γ secretion (2.5-fold increase) and enhancing mitochondrial oxidative phosphorylation (180% increase in basal OCR), thereby amplifying cytotoxic T cell-mediated immune surveillance [19].

Mushroom-derived polysaccharides orchestrate cascading antitumor networks through the activation of innate immune receptors. Grifola frondosa β-glucan engages TLR4 on dendritic cells (DCs), triggering MyD88-IRAK4-TRAF6 signaling, which drives NF-κB nuclear translocation and IL-12p70 secretion (1.2 ng/mL). IL-12 promotes Th1 cell differentiation via STAT4 phosphorylation and enhances NK cell CD107a degranulation (58% increase), thereby achieving synergistic killing of ovarian cancer organoids (81% growth inhibition) [20]. In parallel, Lentinus edodes polysaccharides modulate the macrophage iNOS/ARG1 balance through activation of the PI3K/AKT/mTOR pathway, inducing nitric oxide (NO) synthesis (≥35 μM). The peroxynitrite ($ONOO^-$) generated from the interaction between NO and superoxide (O_2^-) causes DNA strand breaks (3.2-fold increase in comet tail moment) while suppressing angiogenesis through VEGF-A and HIF-1α downregulation (67% and 73% mRNA reduction, respectively), as evidenced by an 82% reduction in endothelial tube length in Matrigel assays [20].

Notably, rare medicinal fungal metabolites exhibit multitarget precision in cancer intervention. Ergosterol, isolated from Amauroderma rude, binds to the catalytic domain of DNA methyltransferase 3A (DNMT3A), reversing the promoter hypermethylation (42% reduction) of tumor suppressors PTEN and RASSF1A to restore their transcriptional activity [20]. This compound also inhibits the nuclear translocation of the Hedgehog effector Gli1 (64% decrease in fluorescence

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intensity), reduces CD44+/CD24- breast cancer stem cell populations from 12.3% to 3.8%, and reverses multidrug resistance through O-GlcNAcylation-mediated ABCB1 efflux pump regulation (resistance index decline from 8.7 to 1.3) when combined with 5-fluorouracil [20]. These findings underscore the unique role of microbial metabolites in epigenetic regulation and cancer stem cell targeting, establishing a theoretical foundation for metabolomics-driven combination therapies.

4. Conclusion

The multifaceted role of polysaccharides in cancer suppression through gut microbiota modulation has been systematically deciphered, revealing their capacity to orchestrate microbial composition, metabolic output, and immune crosstalk. As potent prebiotic agents, polysaccharides selectively enrich commensal taxa (e.g., Bifidobacterium, Akkermansia) while suppressing pathobionts, thereby reshaping microbial ecosystems toward tumor-suppressive states. This ecological remodeling drives the biosynthesis of bioactive metabolites—particularly short-chain fatty acids (SCFAs)—which perform dual anticancer functions: epigenetic regulation of oncogenic pathways (e.g., Wnt/β-catenin, STAT3) and metabolic reprogramming of cytotoxic immune cells (e.g., enhancing mitochondrial oxidative phosphorylation in CD8+ T cells). Concurrently, polysaccharide-mediated TLR4/MyD88 signaling activation amplifies IL-12-dependent antitumor immunity while suppressing NF-κB-driven chronic inflammation, collectively establishing an immune-permissive tumor microenvironment.

Future investigations should prioritize two translational axes as follows:

1. Precision Microbiota-Polysaccharide Therapeutics: Developing engineered polysaccharide conjugates (e.g., inulin-Faecalibacterium complexes) customized to individual microbial enterotypes. This approach would enable spatial and temporal control of SCFA production and localized immune activation.

2.Synergistic Treatment Paradigms: Conducting systematic exploration of polysaccharide-chemotherapy/immunotherapy combinations, particularly with DNA-damaging agents (e.g., oxaliplatin) and immune checkpoint inhibitors (e.g., anti-PD-1). Proof-of-concept studies have shown that fungal β-glucans enhance the efficacy of FOLFOX by 41%, while reducing chemotherapy-induced intestinal dysbiosis. This suggests that microbiome-targeted adjuvants could redefine standard oncology regimens.

These advancements position polysaccharides as pivotal molecules bridging microbiome science with precision oncology, offering a sustainable strategy to enhance anticancer responses while minimizing treatment-associated toxicity. The integration of multi-omics profiling and synthetic microbial consortia design will be critical to unlocking their full clinical potential in the era of microbiota-driven cancer therapeutics.

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