Cancer Biol Med 2026. doi: 10.20892/j.issn.2095-3941.2025.0511

REVIEW

Postbiotics: emerging bioactive agents in cancer therapy

Sihan Li[1]*, Fashun Li[1]*, Jiasheng Tu[1], Lei Jiang[1], Xiqun Jiang[2]

[1]NMPA Key Laboratory for Research and Evaluation of Pharmaceutical Preparations and Excipients and Department of Pharmaceutics, School of Pharmacy, China Pharmaceutical University, 24 Tong Jia Xiang, Nanjing 210009, China; [2]MOE Key Laboratory of High-Performance Polymer Materials and Technology, Department of Polymer Science & Engineering, College of Chemistry & Chemical Engineering, Nanjing University, Nanjing 210093, China

ABSTRACT Postbiotics, considered the functional successors of live probiotics, retain most of probiotics' structural and/or bioactive properties, and are key mediators of probiotic–environment interactions. Beyond influencing tumor proliferation, metastasis, and immune regulation, postbiotics can enhance the effectiveness of current anti-cancer treatments. Postbiotic-based cancer therapy represents an advanced evolution of bacterial treatment with improved safety and treatment potential. However, the field is limited by postbiotics' imprecise definition and lack of standardized manufacturing methods, which together hinder their clinical application. Here, we establish a systematic classification of postbiotics based on their formation processes, focusing on the complex mechanisms underlying their activity in anti-tumor therapy, their therapeutic promise, and their current clinical use and challenges. Our aim is to guide future research, translation, and industrial development.

KEYWORDS Postbiotics; antitumor; classification of postbiotics; adjuvant therapy; immunotherapy; tumor metabolic reprogramming

Introduction

Postbiotics are genetically defined, non-viable microbial entities (such as heat-inactivated cells, lysed-cell fractions, and purified fermentation metabolites) that confer health benefits on the host[1]. Unlike live probiotics, postbiotics resist gastric acid, are easily stored, and exhibit superior stability and safety profiles, while providing precisely quantifiable dose–response relationships and scalable, standardized manufacturing routes[2]. Over the past decade, postbiotics have emerged as next-generation therapeutic ingredients in microbiome-based interventions; their molecular diversity underpins their immunostimulatory, gut-modulating, anti-inflammatory, and anti-tumor activities[3]. In oncology therapeutics, postbiotics, distinguished by an exceptional safety margin, multimodal synergistic mechanisms, and precise immunomodulation, have provided a transformative therapeutic paradigm. Postbiotic nanostructures are natural, self-assembled targeting platforms built around bacterial membrane vesicles and metabolite supramolecular assemblies. This review synthesizes current mechanistic insights, as well as pre-clinical and clinical advances in postbiotic-based anti-cancer strategies, to provide a comprehensive framework for the rational development and clinical deployment of postbiotic anti-tumor therapeutics.

*These authors contributed equally to this work.
Correspondence to: Lei Jiang and Xiqun Jiang
E-mail: lei.jiang@cpu.edu.cn and jiangx@nju.edu.cn
ORCID ID: https://orcid.org/0000-0003-3831-9044 and https://orcid.org/0000-0003-0483-0282
Received August 31, 2025; accepted January 12, 2026;
published online February 19, 2026.
Available at www.cancerbiomed.org
©2026 The Authors. Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0)

Classification of postbiotics

Postbiotics can be taxonomically classified according to their mode of biogenesis, into metabiotics and paraprobiotics, both of which have a pleiotropic range of bioactivities[4]. The modes of postbiotic biogenesis are illustrated in **Figure 1**, and the characteristics of postbiotics are summarized in **Table 1**.

Metabiotics

Metabiotics are composed of live bacteria-derived metabolites and soluble factors, including short-chain fatty acids, exopolysaccharides (EPS), and bile acids. These molecules have antitumor effects by reprogramming tumor metabolism and modifying the immune system microenvironment[16].

Paraprobiotics

Paraprobiotics, also called parabiotics, are non-living forms of bacteria that can improve human health. These include

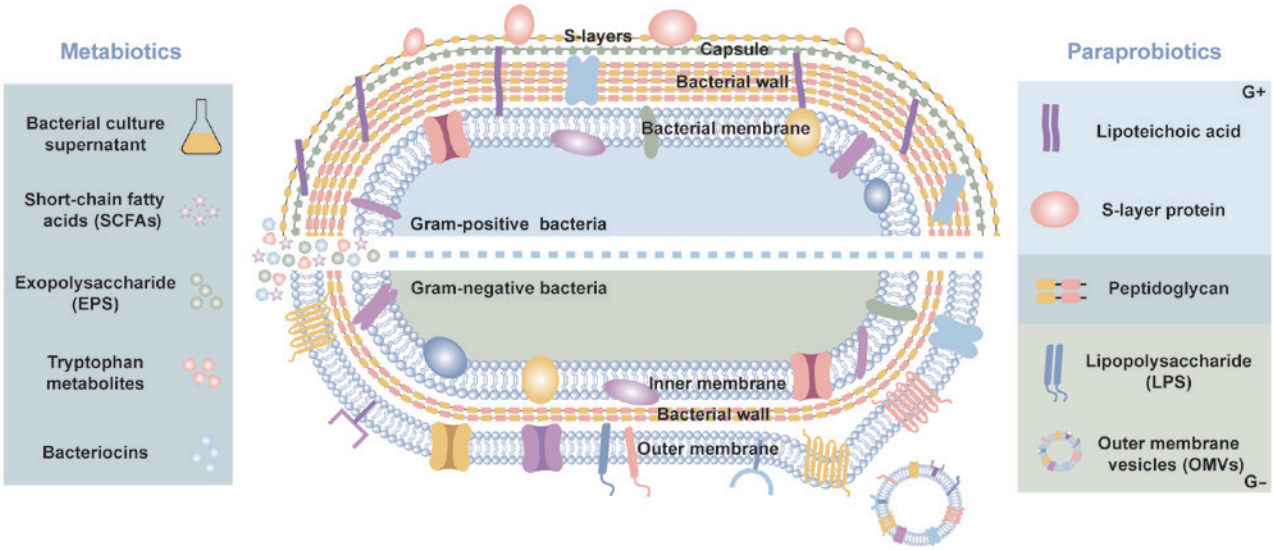


Figure 1 Schematic classification of postbiotics. Postbiotics are classified into metabiotics and paraprobiotics. Metabiotics derived from bacterial culture supernatants include a variety of bioactive compounds, such as short-chain fatty acids, exopolysaccharides, teichoic acids, tryptophan metabolites, and bacteriocins. Paraprobiotics comprise various structural and functional components, including lipoteichoic acid, S-layer proteins, peptidoglycans, lipopolysaccharides, and outer-membrane vesicles. EPS, exopolysaccharides; G+, gram-positive bacteria; G−, gram-negative bacteria; LPS, lipopolysaccharides; OMVs, outer-membrane vesicles; SCFAs, short-chain fatty acids. (This figure was created with Adobe Illustrator.)

bacterial cell structure components, cell lysates, and bacterial fractions such as surface proteins and outer-membrane vesicles (OMVs). These entities act as innate immune adjuvants by engaging pattern-recognition receptors and subsequently boosting anti-tumor immunity. They are increasingly used as adjuvant options in modern cancer treatments[17].

Antitumor mechanisms of postbiotics

The specialized barrier architecture of malignant neoplasms prevents efficient drug delivery to neoplastic cells[18,19], whereas the immunosuppressive milieu of the tumor microenvironment (TME) restricts infiltration by inflammatory and immune effector cells. This limitation decreases the efficacy of immunotherapeutic modalities[20]. As successors to probiotics, postbiotics directly regulate oncogenic signaling pathways, remodel the TME, and enhance antitumor immunity, while simultaneously reprogramming tumor metabolism. At a deeper level, postbiotic nanostructures, such as bacterial OMVs and metabolite-assembled nanoparticles, constitute the fundamental material basis for antitumor activity. These naturally derived nanocarriers exhibit inherent tumor tropism and exceptional biocompatibility, thereby enabling intelligent, site-specific drug delivery to neoplastic lesions. When used as adjuncts to existing antineoplastic regimens, they provide synergistic efficacy benefits and mitigate treatment-related toxicities (**Figure 2**).

Intervened in the main pathways that regulate tumor growth and metastasis

The most frequently used pharmacological strategy for suppressing tumor growth is direct activation of tumor-cell apoptotic pathways to trigger cell death. EPS are metabiotic carbohydrate macromolecules secreted outside the microbial cell wall during active growth and metabolism; they may remain attached to the cell surface as capsular polysaccharides or disperse into the extracellular environment as mucilaginous polysaccharides. Sun et al. have demonstrated that crude EPS from *Lactobacillus plantarum* 12 inhibit HT-29 cell proliferation in a time-dependent manner; induce apoptosis by up-regulating pro-apoptotic Bax, Caspase-3, and Caspase-9; and concurrently down-regulate anti-apoptotic Bcl-2[21]. Similarly, the antimicrobial peptide Plpl_18 produced by *Lactobacillus plantarum* is a metabiotic that destabilizes the p38/NF-κB signaling pathway in oral squamous cell carcinoma (OSCC) through direct molecular interactions, thereby suppressing tumor proliferation[22]. Postbiotics also demonstrate strong anti-metastatic effects. *Lactobacillus*-derived EPS disrupt tumor cell–fibronectin adhesion and inhibit invadopodia formation. In mouse models, this intervention has been found to decrease pulmonary breast

Table 1 Characteristics of postbiotics

Types	Metabiotics					Paraprobiotics		
Name	Aseptic clarified medium filtrate	Short-chain fatty acids	Exopolysaccharides	Tryptophan metabolites	Bacteriocins	Thallus	Outer membrane vesicles	Lipoteichoic acid
Composition or structure	A sterile, cell-free supernatant rich in microbial metabolites	Saturated fatty acids comprising one to six carbon atoms	A homopolysaccharide comprising a single monosaccharide or a heteropolysaccharide containing two or more different monosaccharides	Indole-3-propionic acid	–	Inactivated bacteria	50–200 nm membrane vesicles released by Gram-negative bacteria that retain an outer membrane structure similar to that of the parent cell	An amphiphilic molecule traversing the peptidoglycan layer of the bacterial envelope
Parent bacteria	*Lacticaseibacillus casei*	*Bifidobacterium*, *Lactobacillus*, *Clostridium butyricum*	*Lactiplantibacillus plantarum*, *Lacticaseibacillus paracasei*, *Bifidobacterium*, *Enterococcus faecium*, *Enterococcus hirae*, *Bacillus amyloliquefaciens*	*Bifidobacterium*, *Clostridium*, *Lactobacillus*	*Lactobacillus*, *Bifidobacterium*, *Clostridium*	–	*Escherichia coli*·Nissle 1917 (EcN), *Akkermansia muciniphila*, *Bifidobacterium longum*, *Roseburia intestinalis*	*Lactobacillus*, *Bifidobacterium*, *Bacillus*
Production	Bacterial culture medium	Dietary polysaccharides, such as starches and fibers, that avoid host enzymatic hydrolysis and are fermented by bacteria within the gut lumen	Secondary metabolites produced by microorganisms during active growth and metabolism	Bacterial metabolites	Bacterial secretome	Thermal sterilization achieved through lethal heat exposure to eliminate bacterial viability	Active bacterial secretion	Bacterial metabolites
Proposed anti-tumor mechanism	Mechanism involves regulation of intestinal flora and inhibition of colon tumor growth	Augmenting CCL20 expression in pulmonary endothelial cells recruits Th17 cells to the lung and thereby curtails melanoma metastatic seeding	Postbiotic exposure alters the steady-state level of hTERT mRNA, modulates intracellular Ca^{2+} flux, and thereby restrains gastric tumor-cell growth, while simultaneously throttling the DNA-synthesis rate and curtailing proliferative ability	AhR activation sustains the stem-like properties of $CD8^{+}$ T cells, thereby preserving their self-renewal and multipotency	The tumor cell membrane is directly lysed	Remodeling of the tumor microenvironment reactivates innate anti-tumor immunity	Macrophage repolarization toward the pro-inflammatory M1 phenotype reshapes the tumor immune microenvironment	Activation of dendritic cells and T cells initiates a tumor-directed adaptive immune response
References	5,6	7	8	9	10	11,12	13	14,15

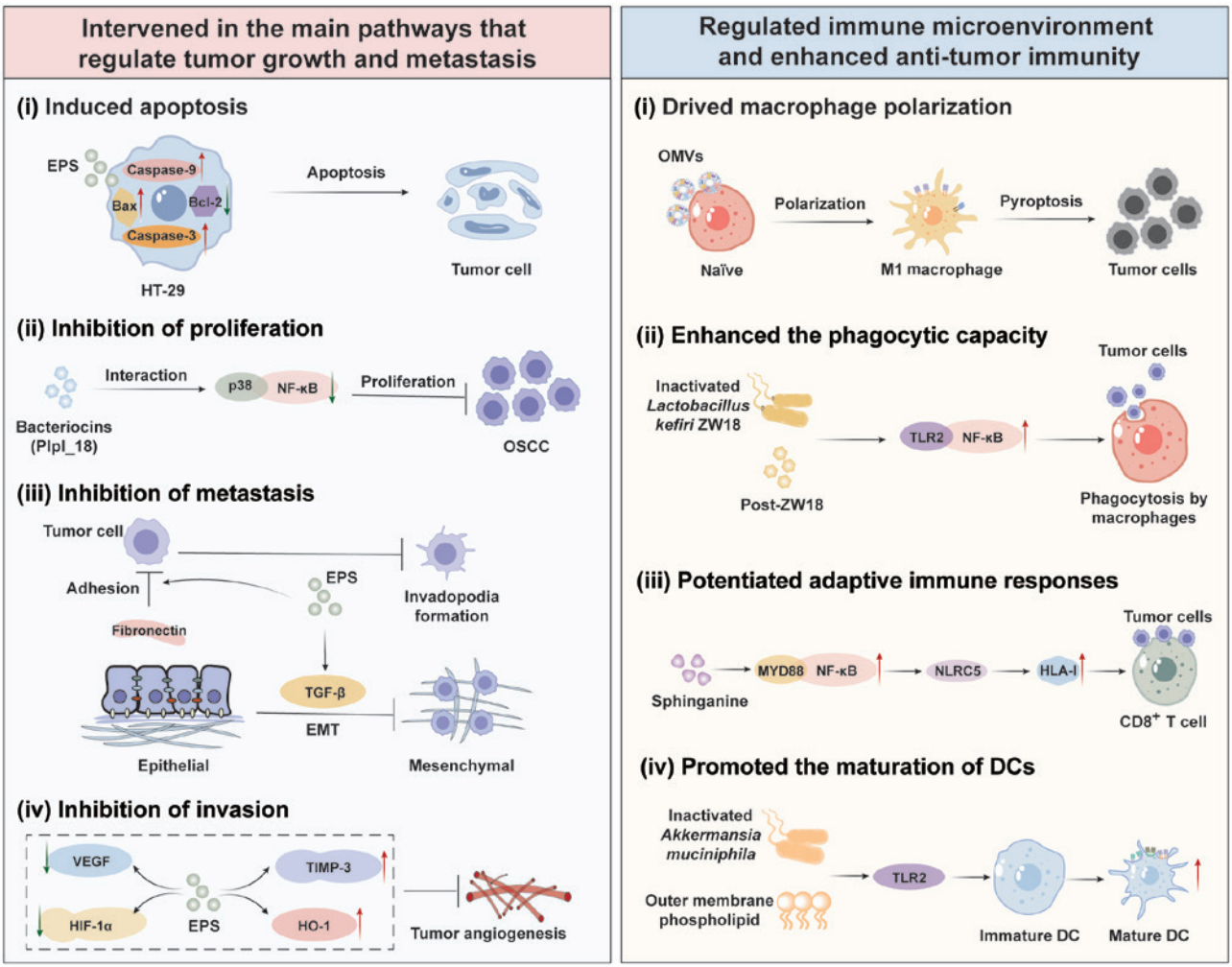


Figure 2 Continued

cancer metastases by 73% and to block TGF-β-driven epithelial-to-mesenchymal transition[23]. Furthermore, Deepak et al. have demonstrated that EPS suppress tumor angiogenesis and survival-gene expression by down-regulating VEGF and HIF-1α while up-regulating TIMP-3 and HO-1[24]. Future research should focus on how different structural types of postbiotics inhibit tumor growth and metastasis through distinct mechanisms. Collectively, postbiotics directly target tumor cells *via* non-immune-dependent pathways, thereby orchestrating proliferation, apoptosis, invasion, and metastasis across multiple biological axes.

Regulated immune microenvironment and enhanced anti-tumor immunity

Aberrant tumor vasculature, a lack of lymphatic drainage, and high interstitial pressure collectively inhibit pro-inflammatory immune cell activity and limit the infiltration of effector T cells into the tumor core, thus promoting immune evasion and preventing immune-mediated tumor cell detection and destruction. Notably, certain postbiotics retain the immunogenicity of their probiotic progenitors, and consequently remodel the tumor immune microenvironment and trigger anti-tumor immunity through multiple mechanisms. Li et al. have demonstrated that lipopolysaccharide-bearing OMVs derived from *Escherichia coli* DH5α induce macrophage polarization toward a proinflammatory M1 phenotype and initiate pyroptosis, thereby enhancing anti-tumor immunity[25]. This formulation comprising heat-killed bacteria and metabolites (Post-ZW18) from *Lactobacillus kefiri* ZW18 activates the Toll-like receptor 2 (TLR2)/NF-κB pathway and significantly increases the phagocytic ability of RAW264.7 macrophages[26]. Postbiotics additionally enhance antigen presentation and adaptive immune responses. Specifically, the sphinganine metabolite secreted by *Lactobacillus paracasei* CNCM I-5220 activates the MYD88/NF-κB pathway and consequently the transcription factor NLRC5, thereby increasing HLA-I expression on tumor cells and enhancing the recognition and killing ability

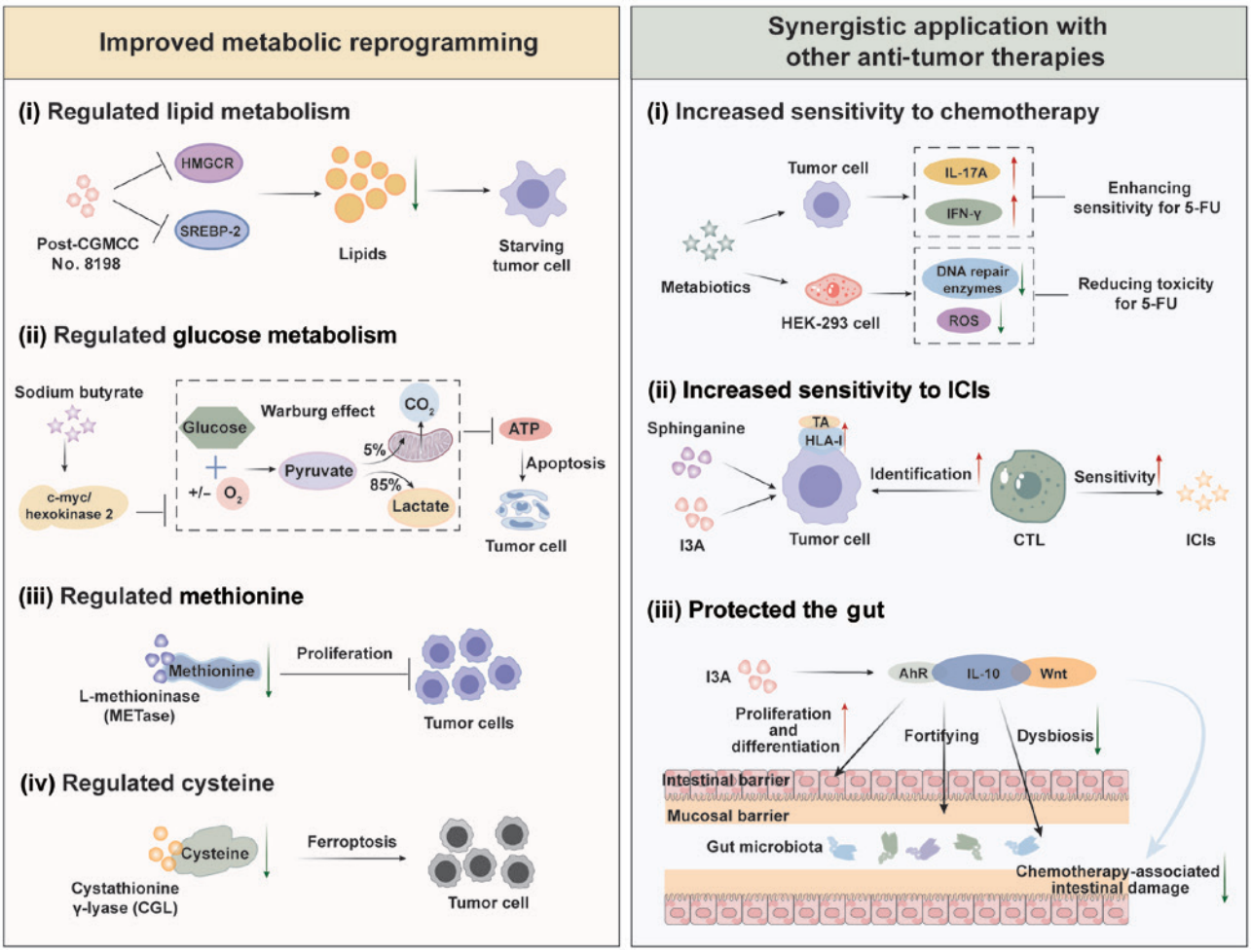


Figure 2 Anti-tumor mechanisms of postbiotics. **Interventions targeting major pathways regulating tumor growth and metastasis:** (i) EPS induce apoptosis by upregulating the expression of Caspase-3, Caspase-9, and Bax, while simultaneously downregulating Bcl-2 expression. (ii) Bacteriocins (Plpl_18) inhibit tumor proliferation in OSCC by interfering with the p38/NF-κB signaling pathway. (iii) By disrupting tumor cell–fibronectin adhesion, inhibiting invadopodia formation, and blocking TGF-β-driven epithelial-to-mesenchymal transition, EPS collectively suppress tumor cell metastasis. (iv) EPS suppress tumor angiogenesis by downregulating the expression of VEGF and HIF-1α and upregulating the expression of TIMP-3 and HO-1. **Regulated immune microenvironment and enhanced anti-tumor immunity:** (i) OMVs drive macrophage repolarization toward the M1 phenotype, thus reshaping the tumor immune microenvironment and inducing pyroptosis. (ii) Heat-killed bacteria and metabolites (Post-ZW18) from *Lactobacillus kefiri* ZW18 activate the TLR2/NF-κB pathway and significantly increase the phagocytic capacity of macrophages. (iii) Sphinganine produced by *Lactobacillus paracasei* CNCM I-5220 engages the MYD88/NF-κB axis, thereby inducing the transcriptional upregulation of NLRC5, enhancing HLA-I display on malignant cells, and facilitating more efficient recognition and cytolysis by tumor-reactive $CD8^+$ T cells. (iv) Inactivated *Akkermansia muciniphila*, together with its outer-membrane phospholipid (a15:0-i15:0 PE), reprograms the activation threshold of DCs *via* TLR2 signaling, thus promoting their maturation and potentiating anti-tumor immune responses. **Improved metabolic reprogramming:** (i) Postbiotic factors from *Lactobacillus plantarum* CGMCC 8198 suppress the key cholesterol-biosynthetic regulators HMGCR and SREBP-2, thereby limiting intracellular lipid accrual and restricting tumor cells' access to critical lipid substrates. (ii) Sodium butyrate generated by *Firmicutes* constrains aerobic glycolysis in hepatocellular carcinoma *via* the c-Myc/hexokinase-2 axis, decreases ATP output, and ultimately triggers apoptosis in malignant cells. (iii) An attenuated *Salmonella* strain (SGN1) engineered to overexpress L-methioninase (METase) selectively depletes methionine in the tumor microenvironment, thereby curbing malignant cell proliferation. (iv) Engineered bacteria expressing cystathionine-γ-lyase (CGL) selectively drain cysteine and block its downstream metabolic flux, thereby heightening tumor cell susceptibility to ferroptotic cell death. **Synergistic application with other anti-tumor therapies:** (i) Metabolites from *Limosilactobacillus fermentum* and *Lactiplantibacillus plantarum* isolated from mule milk markedly increase 5-FU sensitivity in colorectal cancer cells, and concurrently attenuate 5-FU-associated cytotoxicity in HEK-293 cells. (ii) Bacterial metabolites can transcriptionally increase the abundance of TA and HLA-I on malignant cells, thereby increasing their susceptibility to tumor

antigen-specific CTL killing *in vitro* and *in vivo*, potentiating ICI efficacy, and yielding synergistic antitumor activity. (iii) The microbial metabolite I3A engages the AhR/IL-10/Wnt cascade, thus driving epithelial proliferation and differentiation; reinforcing mucosal barrier integrity; and mitigating radiation-induced enteropathy/dysbiosis while also decreasing chemotherapy-associated intestinal injury. 5-FU, fluorouracil; AhR, aryl hydrocarbon receptor; ATP, adenosine triphosphate; CO_2, carbon dioxide; CTL, cytotoxic T-lymphocyte; DC, dendritic cell; EPS, exopolysaccharides; HIF-1α, hypoxia inducible factor-1α; HLA-I, human leukocyte antigen class I; HMGCR, 3-hydroxy-3-methyl-glutaryl-CoA reductase; HO-1, heme oxygenase; I3A, indole-3-aldehyde; ICIs, immune-checkpoint inhibitors; IL-10, interleukin-10; MYD88, myeloid differentiation primary response gene 88; NF-κB, nuclear factor-k-gene binding; NLRC5, NOD-like receptor caspase recruitment domain-containing 5; O_2, oxygen; OMVs, outer-membrane vesicles; OSCC, oral squamous cell carcinoma; SREBP-2, sterol regulatory element-binding protein 2; TGF-β, transforming growth factor-β; TA, tumor-antigen; TIMP-3, tissue inhibitor of metalloproteinases-3; TLR2, toll like receptors 2; VEGF, vascular endothelial growth factor. (This figure was created with Adobe Illustrator.)

of tumor-specific CD8+ T cells[27]. Furthermore, postbiotics influence immune cell differentiation. Luo et al. have demonstrated that heat-killed *Akkermansia muciniphila* combined with its outer-membrane phospholipid (a15:0-i15:0 PE) resets the activation threshold of dendritic cells through TLR2 signaling, thus leading to dendritic cell maturation and enhancing anti-tumor immunity[28]. Future research should focus on harnessing postbiotics to regulate the gut–tumor axis and improve cancer immunotherapy. In particular, targeted delivery approaches and rational selection of postbiotic types that precisely manipulate the gut microbiota might potentiate antitumor immune responses and beneficially reprogram the tumor immune microenvironment. Collectively, postbiotics not only have direct cytotoxic effects on tumor cells but also modify the TME and activate both innate and adaptive immune responses, thereby reversing the tumor's immunosuppressive environment and providing a promising addition to improve cancer immunotherapy.

Improved metabolic reprogramming

In tumor cells, reprogramming of the metabolic circuitry significantly increases flux, thereby ensuring the ATP and biomass needed for rapid growth. This heightened metabolic state not only facilitates tumor growth but also shapes the TME, a complex ecosystem comprising malignant cells, vasculature, secreted factors, and extracellular matrix. The resultant metabolic hyperactivity creates specific physicochemical constraints in the TME, including hypoxia, acidosis, and an increase in reactive oxygen species[29]. Given the crucial role of tumor metabolism, targeting metabolic pathways has become a primary therapeutic strategy. Among these pathways, abnormal lipid metabolism is a major change occurring in cancer. Wang et al. have demonstrated that postbiotics derived from *Lactobacillus plantarum* CGMCC NO. 8198 downregulate the master transcriptional regulators of cholesterol biosynthesis 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR) and sterol regulatory element-binding protein 2 (SREBP-2), thereby blocking intracellular lipid accumulation and depriving malignant cells of essential lipid resources[30]. Furthermore, sodium butyrate produced by *Firmicutes* inhibits aerobic glycolysis (the Warburg effect) in hepatocellular carcinoma cells through the c-myc/hexokinase 2 pathway, thereby decreasing ATP production and ultimately inducing apoptosis in tumor cells[31]. The metabolic pathway of methionine, an essential amino acid for tumor cell growth, is significantly upregulated in neoplastic cells. Zhou et al. have engineered an attenuated *Salmonella* strain (SGN1) to overexpress L-methioninase, thereby selectively depleting methionine within the TME and effectively decreasing tumor cell proliferation[32]. Cysteine is the essential precursor for glutathione, coenzyme Q10, and tetrahydrobiopterin, which are crucial antioxidants in the ferroptosis defense network. Engineered bacteria expressing cystathionine γ-lyase selectively deplete cysteine and completely block its downstream metabolism, thereby increasing tumor cells' sensitivity to ferroptosis cell death[33]. Collectively, postbiotic-mediated targeting of tumor metabolic reprogramming and its resultant TME through nutrient-deprivation strategies offers a new therapeutic approach for fighting tumor growth.

Synergistic application with other antitumor therapies

Postbiotics not only exhibit direct antitumor activity but also synergize with various anticancer treatments through multiple mechanisms; therefore, they have potential to improve therapeutic effectiveness while decreasing adverse effects. Salek et al. have shown that metabolites from *Limosilactobacillus fermentum* and *Lactiplantibacillus plantarum*, isolated from mule milk, significantly sensitize colorectal cancer cells to 5-fluorouracil (5-FU) and importantly decrease 5-FU-induced cytotoxicity in human embryonic kidney cells (HEK-293)[34], thus underscoring their dual ability to potentiate chemotherapy efficacy and control off-target toxicity. Postbiotics upregulate antitumor cytokines, including IL-17A and IFN-γ, thereby enhancing the sensitivity of cancer cells to 5-FU. In normal HEK-293 cells, the postbiotics mitigate 5-FU-induced cytotoxicity by upregulating DNA repair enzymes and scavenging reactive oxygen species, thus ultimately preserving cell viability and decreasing apoptosis. Emerging evidence indicates that postbiotics heighten sensitivity to immune-checkpoint inhibitors (ICIs). ICI efficacy depends on tumor-antigen (TA)-specific cytotoxic T-lymphocyte (CTL) activity, which in turn requires TA presentation *via* cancer-cell HLA-I. Tumor cells

often evade recognition by down-regulating HLA-I, thereby decreasing CTL responses and IC responsiveness. Bacterial metabolites such as phytosphingosine have recently been shown to transcriptionally increase tumor-cell HLA-I expression[35]. Consequently, the increased tumor cell vulnerability to TA-specific CTL lysis *in vitro* and *in vivo* enhances ICI efficacy and elicits synergistic antitumor responses[27]. Bender and colleagues have further demonstrated that indole-3-aldehyde (I3A), a metabolite released by *Lactobacillus reuteri*, enhances ICI effectiveness[36]. Furthermore, Xie et al. have shown that I3A activates the AhR/IL-10/Wnt signaling pathway, thereby promoting intestinal epithelial proliferation and differentiation, strengthening the mucosal barrier, and effectively preventing radiation-induced enteropathy and dysbiosis while decreasing chemotherapy-related intestinal damage[36]. Collectively, postbiotics work together with existing anticancer approaches by increasing chemotherapy effectiveness, reprogramming the immune microenvironment to enhance immunotherapy, and protecting normal tissues against therapy-related toxicities, thus highlighting their important translational potential. However, the synergistic application of postbiotics with other antitumor therapies remains largely in preclinical stages, with limited mechanistic investigations and a lack of high-quality clinical evidence.

Progress in clinical research and industrialization

The mechanisms of postbiotics in anti-tumor therapy have been increasingly clarified in terms of signaling pathway regulation, immune regulation, and metabolic intervention. The production process has become more precise and standardized, including extraction, purification, activity stability, and quality control. Basic research and translational application systems in this field have progressively improved as research has advanced and matured.

Postbiotic formulation MS-20 is a multi-strain metabolite consortium derived from probiotic bacteria and yeasts. When co-administered with an anti-PD-1, MS-20 increases gut microbial diversity, promotes effector $CD8^+$ T-cell expansion, and downregulates PD-1 expression, thereby reconfiguring the TME. In mouse xenograft models, this combination elicits significant growth inhibition of colorectal and lung tumours[37]. Notably, MS-20 is the first postbiotic preparation to receive U.S. FDA Generally Recognized as Safe status for oral use as an adjunct cancer therapy. It is compatible with standard-of-care agents, thereby offering a safe and effective option for patients[13]. Phase III trials evaluating MS-20 as an adjuvant treatment for non-small cell lung carcinoma (NSCLC) are currently underway[38]. The study enrolled patients diagnosed with unresectable stage IIIB–IV metastatic NSCLC, including those with metastatic non-squamous carcinoma with wild-type EGFR/ALK/ROS1 genes, as well as patients with squamous cell carcinoma with wild-type EGFR/ALK genes. Eligible participants received an oral solution of the study drug at a dose of 4 c.c. twice daily for 48 weeks, and treatment efficacy was assessed according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). The objective response rate was defined as the proportion of patients achieving a predefined decrease in tumor size sustained for a minimum duration, encompassing both complete response and partial response. The MS-20–Keytruda combination group achieved an objective response rate of 75%, a value three times the 25% observed in the Keytruda monotherapy group. Moreover, the median progression-free survival was extended from 4.5 months in the control group to more than 12 months in the MS-20 group. A complete response was observed in 12.5% of patients receiving the combination therapy. These results support the potential of MS-20 to modulate the gut microbiome and enhance the clinical efficacy of Keytruda in advanced NSCLC. Orally administered *Clostridium butyricum* cells display surface-expressed SecD, which specifically binds the tumor-restricted receptor GRP78 on colorectal cancer cells. This binding inhibits downstream PI3K/Akt–NF-κB signaling, thus decreasing the secretion of the immunosuppressive cytokine IL-6 and alleviating $CD8^+$ T cell inhibition. Consequently, enhanced T-cell receptor signaling, as indicated by increased phosphorylation of LCK/ZAP70, leads $CD8^+$ T cells to release effector molecules (IFN-γ, TNF-α, and granzyme B). Simultaneously, tumor-associated macrophages are prevented from adopting the immunosuppressive M2 phenotype. Collectively, these effects remodel the tumor immune microenvironment and offer a clinically translatable approach to address resistance to immune-checkpoint blockade in microsatellite-stable colorectal cancer[39]. Sudheer et al. have demonstrated that the postbiotic 2,4-di-tert-butylphenol, a bioactive small-molecule metabolite produced by *Lactobacillus plantarum*, disrupts carbohydrate metabolism and induces a metabolic shift toward lactose utilization, while simultaneously engaging the oral-squamous-cell-carcinoma-associated signaling proteins p38 and NF-κB[22]. To accelerate clinical translation, researchers should delineate specific protein–protein interaction networks and core molecular mechanisms of postbiotics, to establish a foundation for the precise prediction and screening of highly effective therapeutic candidates. In addition, innovative targeted delivery technologies should be developed to expand the multitarget synergistic network of postbiotics in combination with radiotherapy, targeted therapy, and engineered bacterial therapy. Large-scale clinical investigations in diverse cancer types including breast and lung cancers should also be promoted to strengthen the evidence base with high-quality clinical data. Furthermore, individualized therapeutic regimens for postbiotics should be optimized, and standardized efficacy evaluation systems should be established.

Postbiotics have progressed to industrial-scale production as complementary agents in cancer treatment. A postbiotic nutritional solution has been found to counteract cyclophosphamide-induced myelosuppression, thereby promoting strong recovery of white blood cell and platelet counts after chemotherapy, and decreasing irinotecan-associated diarrhea by 60%. Mechanistically, the formulation enhances intestinal barrier function by increasing the expression of the tight junction proteins ZO-1 and occludin. This supportive therapy consequently decreases both immunosuppression and gastrointestinal toxicity. Similarly, the same group has developed a multi-strain *Bifidobacterium longum* preparation that effectively inhibits the growth of the mouse hepatocellular carcinoma line H22. When combined with botanical compounds from *Astragalus mongholicus* and *Polygonatum sibiricum*, it lessens tumor-related inflammatory responses[40].

Although several postbiotic formulations have entered clinical trials, and a subset have received regulatory approval as adjuvant therapeutics, their large-scale industrial manufacture faces many obstacles. At the process level, current inactivation protocols remain suboptimal: thermal inactivation frequently degrades functional moieties, thus resulting in fluctuating lot-to-lot potency. Stabilization technologies are equally limited: spray-drying, for example, retains only 68%–72% of the initial bioactivity and compromises storage stability. In quality control, the substantial variability (as much as ±35%) *in vitro* immunostimulation assays highlights the lack of a standardized framework for potency assessment and hinders meaningful cross-batch comparability. Another challenge is determining appropriate dosages for postbiotics. The dose-response relationship for inactivated lactic acid bacteria often follows a biphasic, U-shaped curve, wherein bioactivity is absent at low doses and suppressed at high doses, thereby posing substantial challenges in defining a safe and effective therapeutic window[41].

Challenges and prospects

Postbiotics are non-viable cellular fractions and metabolites derived from probiotic organisms. Both types of postbiotics specifically target oncogenic signaling pathways and consequently exert tumor-suppressive effects, while simultaneously regulating the immune microenvironment and enhancing the effectiveness of anti-tumor immunity. Additionally, postbiotics reprogram tumor metabolism and, when used as adjunctive therapies alongside existing cancer treatments, improve therapeutic outcomes and decrease treatment-related toxicities. Their chemically diverse and bioactive profiles enable multiple synergistic anticancer mechanisms.

Although postbiotics' established safety profiles and the ability for scale-up with standardized manufacturing provide a foundation for translation, their clinical applications remain limited by several major challenges. Postbiotic is a loosely defined term, and products from different taxa or manufacturing processes exhibit markedly differing bioactivities. No quality control framework is currently universally accepted. Advancing mechanistic understanding of probiotic activity is driving the diversification of the quality standard framework for postbiotic formulations. For example, paraprobiotic preparations composed primarily of intact, heat-inactivated probiotics can be quality-controlled through well-defined physicochemical metrics, such as the numerical count of microbial bodies and culture pH. Metabiotics comprising secreted metabolites are monitored by targeted identification and quantification of bioactive moieties such as short-chain fatty acids and bacteriocins. Omics platforms now furnish high-resolution routes for postbiotic taxonomic authentication and quality framework construction: metabolomics comprehensively maps the secreted metabolite landscape, proteomics defines the proteinaceous signature of paraprobiotic biomass, and genomics provides unambiguous taxonomic authentication plus early exclusion of virulence or antimicrobial-resistance determinants, thereby enabling the establishment of rigorous quality specifications. Additionally, the therapeutic effectiveness of postbiotics depends on host microbiota composition, genetic background, and tumor type, and substantial variability is observed among individuals. To address this challenge, integrating patient tumor genomic profiles with genomic fingerprints of postbiotic strains would enable precise estimation of host strain compatibility, thereby providing a rational basis for personalized regimen design and enhancing therapeutic precision and efficacy. Similarly, because mechanistic understanding of the anti-tumor effects of postbiotics has come primarily from animal studies, their targeting efficiency in humans and long-term safety remain to be addressed. Moreover, only few postbiotics have advanced to clinical trials, most of which have been limited by small sample sizes and have lacked randomized controlled designs. The optimal administration method, considering dose and timing for adjuvant therapy, remains to be determined.

Given their polypharmacological anti-tumor mechanisms and favorable safety margins, postbiotics are a valuable therapeutic approach. Future directions should include: (i) synthetic-biological consortia that combine probiotics and prebiotics to increase postbiotic bioavailability; (ii) development of precision-medicine algorithms that incorporate microbiota profiling to identify responders and provide personalized supplementation of the specific postbiotic components each needs; and (iii) engineered delivery platforms in which synthetic-biology circuits control tumor-microenvironment-responsive release, thereby enhancing on-target effectiveness.

Grant support

This work was supported by the National Natural Science Foundation of China (Grant Nos. 32271456 to LJ and 52333003 to XJ).

Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Xiqun Jiang, Lei Jiang.
Collected the data: Lei Jiang, Sihan Li, Fashun Li.
Contributed data or analysis tools: Xiqun Jiang, Lei Jiang, Jiasheng Tu.
Performed the analysis: Sihan Li, Fashun Li.
Wrote the paper: Lei Jiang, Sihan Li, Fashun Li.

References

1. Salminen S, Collado MC, Endo A, Hill C, Lebeer S, Quigley EMM, et al. The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics. Nat Rev Gastroenterol Hepatol. 2021; 18: 649-67.
2. de Deus C, Duque-Soto C, Rueda-Robles A, Martínez-Baena D, Borrás-Linares I, Quirantes-Piné R, et al. Stability of probiotics through encapsulation: comparative analysis of current methods and solutions. Food Res Int. 2024; 197: 115183.
3. Zagato E, Pozzi C, Bertocchi A, Schioppa T, Saccheri F, Guglietta S, et al. Endogenous murine microbiota member Faecalibaculum rodentium and its human homologue protect from intestinal tumour growth. Nat Microbiol. 2020; 5: 511-24.
4. Nataraj BH, Ali SA, Behare PV, Yadav H. Postbiotics-parabiotics: the new horizons in microbial biotherapy and functional foods. Microb Cell Fact. 2020; 19: 168.
5. Cizkova D, Cizek M, Maloveska M, Kmetova M, Kmet V, Bujnakova D. Cell-free *Lactobacillus casei* 21L10 modulates nitric oxide release and cell proliferation/cell death in lipopolysaccharide-challenged HT-29 cells. Inflammation. 2021; 44: 2419-28.
6. Kim MJ, Song M-H, Ji Y-S, Park JW, Shin Y-K, Kim S-C, et al. Cell free supernatants of *bifidobacterium adolescentis* and *bifidobacterium longum* suppress the tumor growth in colorectal cancer organoid model. Sci Rep. 2025; 15: 935.
7. Chen L, Zhou X, Wang Y, Wang D, Ke Y, Zeng X. Propionate and butyrate produced by gut microbiota after probiotic supplementation attenuate lung metastasis of melanoma cells in mice. Mol Nutr Food Res. 2021; 65: 2100096.
8. Riaz Rajoka MS, Wu Y, Mehwish HM, Bansal M, Zhao L. *Lactobacillus* exopolysaccharides: new perspectives on engineering strategies, physiochemical functions, and immunomodulatory effects on host health. Trends Food Sci Technol. 2020; 103: 36-48.
9. Jia D, Wang Q, Qi Y, Jiang Y, He J, Lin y, et al. Microbial metabolite enhances immunotherapy efficacy by modulating T cell stemness in pan-cancer. Cell. 2024; 187: 1651-65.
10. Ebrahimzadeh S, Ahangari H, Soleimanian A, Hosseini K, Ebrahimi V, Ghasemnejad T, et al. Colorectal cancer treatment using bacteria: focus on molecular mechanisms. BMC Microbiol. 2021; 21: 218.
11. Li Q, Luo W, Xiao L, Xu X, Peng X, Cheng L, et al. Microbial manipulators: *Fusobacterium nucleatum* modulates the tumor immune microenvironment in colorectal cancer. J Oral Microbiol. 2025; 17: 2544169.
12. Zhang J, You Z, Li X, Hu J, Li J, Jing Z. Harnessing intratumoral microbiota: new horizons in immune microenvironment and immunotherapy. J Transl Med. 2025; 23: 897.
13. Chai Q, Li D, Zhang M, Gu Y, Li A, Wu X, et al. Engineering nanoplatforms of bacterial outer membrane vesicles to overcome cancer therapy resistance. Drug Resist Updat. 2025; 83: 101277.
14. Friedrich AD, Leoni J, Paz ML, González Maglio DH. Lipoteichoic acid from *lacticaseibacillus rhamnosus* GG modulates dendritic cells and T cells in the gut. Nutrients. 2022; 14.
15. Pradhan D, Gulati G, Avadhani R, Rashmi HM, Soumya K, Kumari A, et al. Postbiotic lipoteichoic acid of probiotic lactobacillus origin ameliorates inflammation in HT-29 cells and colitis mice. Int J Biol Macromol. 2023; 236: 123962.
16. Ragavan ML, Hemalatha S. The functional roles of short chain fatty acids as postbiotics in human gut: future perspectives. Food Sci Biotechnol. 2024; 33: 275-85.
17. Lee NK, Park YS, Kang DK, Paik HD. Paraprobiotics: definition, manufacturing methods, and functionality. Food Sci Biotechnol. 2023; 32: 1981-91.
18. Gong N, Zhong W, Alameh MG, Han X, Xue L, El-Mayta R, et al. Tumour-derived small extracellular vesicles act as a barrier to therapeutic nanoparticle delivery. Nat Mater. 2024; 23: 1736-47.
19. Wang Q, Liang Q, Dou J, Zhou H, Zeng C, Pan H, et al. Breaking through the basement membrane barrier to improve nanotherapeutic delivery to tumours. Nat Nanotechnol. 2024; 19: 95-105.
20. Mair F, Erickson JR, Frutoso M, Konecny AJ, Greene E, Voillet V, et al. Extricating human tumour immune alterations from tissue inflammation. Nature. 2022; 605: 728-35.
21. Sun M, Liu W, Song Y, Tuo Y, Mu G, Ma F. The effects of *Lactobacillus plantarum*-12 crude exopolysaccharides on the cell proliferation and apoptosis of human colon cancer (HT-29) cells. Probiotics Antimicrob Proteins. 2021; 13: 413-21.
22. Sudheer A, Taj Z, Nidhin IK, Chattopadhyay I. Unraveling the transcriptomic adaptations of *Streptococcus mutans* biofilm to the post-biotic impact of *Lactiplantibacillus plantarum*. APMIS. 2025; 133: e70054.
23. Liu J, Luo F, Wen L, Zhao Z, Sun H. Current understanding of microbiomes in cancer metastasis. Cancers (Basel). 2023; 15: 1893.
24. Deepak V, Ramachandran S, Balahmar RM, Pandian SR, Sivasubramaniam SD, Nellaiah H, et al. *In vitro* evaluation of anticancer properties of exopolysaccharides from *Lactobacillus*

acidophilus in colon cancer cell lines. In Vitro Cell Dev Biol Anim. 2016; 52: 163-73.
25. Li Y, Wu J, Qiu X, Dong S, He J, Liu J, et al. Bacterial outer membrane vesicles-based therapeutic platform eradicates triple-negative breast tumor by combinational photodynamic/chemo-/immunotherapy. Bioact Mater. 2023; 20: 548-60.
26. Xu H, Li X, Geng W, Jia L, Wang Y, Wang J. Immunoenhancing effect of *Lactobacillus kefiranofaciens* ZW18 postbiotic on cyclophosphamide-induced immunosuppressed mice. Probiotics Antimicrob Proteins. 2025. doi: 10.1007/s12602-025-10630-2.
27. Ferrari V, Lo Cascio A, Melacarne A, Tanasković N, Mozzarelli AM, Tiraboschi L, et al. Sensitizing cancer cells to immune checkpoint inhibitors by microbiota-mediated upregulation of HLA class I. Cancer Cell. 2023; 41: 1717-30.e4.
28. Luo Y, Lan C, Li H, Ouyang Q, Kong F, Wu A, et al. Rational consideration of *Akkermansia muciniphila* targeting intestinal health: advantages and challenges. NPJ Biofilms Microbiomes. 2022; 8: 81.
29. Martínez-Reyes I, Chandel NS. Cancer metabolism: looking forward. Nat Rev Cancer. 2021; 21: 669-80.
30. Wang C, Zhang L, Zhang T, Luo X. *Lactobacillus plantarum* CGMCC8198 exerts prevention and treatment of liver cancer effects by intervening in lipid metabolism disorders. Microbiol China. 2021; 48: 3054-64.
31. Yu Q, Dai W, Ji J, Wu L, Feng J, Li J, et al. Sodium butyrate inhibits aerobic glycolysis of hepatocellular carcinoma cells via the c-myc/hexokinase 2 pathway. J Cell Mol Med. 2022; 26: 3031-45.
32. Zhou S, Lin Y, Zhao Z, Lai Y, Lu M, Shao Z, et al. Targeted deprivation of methionine with engineered salmonella leads to oncolysis and suppression of metastasis in broad types of animal tumor models. Cell Rep Med. 2023; 4: 101070.
33. Qiao C, Wang L, Huang C, Jia Q, Bao W, Guo P, et al. Engineered bacteria manipulate cysteine metabolism to boost ferroptosis-based pancreatic ductal adenocarcinoma therapy. Adv Mater. 2025; 37: 2412982.
34. Salek S, Moazamian E, Mohammadi Bardbori A, Shamsdin SA. The anticancer effect of potential probiotic L. fermentum and L. plantarum in combination with 5-fluorouracil on colorectal cancer cells. World J Microbiol Biotechnol. 2024; 40: 139.
35. Bender MJ, McPherson AC, Phelps CM, Pandey SP, Laughlin CR, Shapira JH, et al. Dietary tryptophan metabolite released by intratumoral *Lactobacillus reuteri* facilitates immune checkpoint inhibitor treatment. Cell. 2023; 186: 1846-62.e26.
36. Xie LW, Cai S, Lu HY, Tang FL, Zhu RQ, Tian Y, et al. Microbiota-derived I3A protects the intestine against radiation injury by activating AhR/IL-10/Wnt signaling and enhancing the abundance of probiotics. Gut Microbes. 2024; 16: 2347722.
37. Lee PJ, Hung CM, Yang AJ, Hou CY, Chou HW, Chang YC, et al. MS-20 enhances the gut microbiota-associated antitumor effects of anti-PD1 antibody. Gut Microbes. 2024; 16: 2380061.
38. National Library Medicine. A randomized, placebo controlled study to evaluate the safety and potential efficacy of MS-20 in combination with pembrolizumab for the treatment of non-small-cell lung cancer. 2021.
39. Xie M, Yuan K, Zhang Y, Zhang Y, Zhang R, Gao J, et al. Tumor-resident probiotic *Clostridium butyricum* improves aPD-1 efficacy in colorectal cancer models by inhibiting IL-6-mediated immunosuppression. Cancer Cell. 2025; 43: 1885-901.e10.
40. Rui-Zhi T, Hui D, Jian-Chun L, Xia Z, Xiao-Jia W, Dan W, et al. *Astragalus mongholicus* bunge and panax notoginseng formula (a&p) combined with bifidobacterium contribute a renoprotective effect in chronic kidney disease through inhibiting macrophage inflammatory response in kidney and intestine. Front Physiol. 2020; 11: 583668.
41. Zhong Y, Wang T, Luo R, Liu J, Jin R, Peng X. Recent advances and potentiality of postbiotics in the food industry: composition, inactivation methods, current applications in metabolic syndrome, and future trends. Crit Rev Food Sci Nutr. 2024; 64: 5768-92.

Cite this article as: Li S, Li F, Tu J, Jiang L, Jiang X. Postbiotics: emerging bioactive agents in cancer therapy. Cancer Biol Med. 2026; 23: 470-479. doi: 10.20892/j.issn.2095-3941.2025.0511